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USER-PERCEIVED EFFECTIVENESS AND SAFETY OF PAEDIATRIC COMPLEMENTARY & ALTERNATIVE MEDICINES: PERSPECTIVES FROM INTERNATIONAL, BRITISH AND LOCAL SCOTTISH OUTCOMES STUDIES

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BPharm.; MPharm. (Pharmacology); PgCert (Research Methods)

A thesis submitted in partial fulfilment of the
requirements of the
Robert Gordon University
for the degree of Doctor of Philosophy

JUNE 2015

Declaration of Authorship

I, Okechukwu Obisike Ndu, declare that this thesis titled, 'USER-PERCEIVED EFFECTIVENESS AND SAFETY OF PAEDIATRIC COMPLEMENTARY & ALTERNATIVE MEDICINES: PERSPECTIVES FROM INTERNATIONAL, BRITISH AND LOCAL SCOTTISH OUTCOMES STUDIES ' and the work presented in it are my own. I confirm that:

- This work was done wholly or mainly while in candidature for a research degree at this University.
- Where I have consulted the published work of others, this is always clearly attributed.
- Where I have quoted from the work of others, the source is always given. With the exception of such quotations, this thesis is entirely my own work.
- I have acknowledged all main sources of help.
- Where the thesis is based on work done by myself jointly with others, I have made clear exactly what was done by others and what I have contributed myself.

Signed: _____

Date: _____

"The end of a thing is better than its beginning"

Eccl. 7:8a (NKJV)

Abstract

In the light of the current patient-centred approach to healthcare delivery, this research investigated the effectiveness and safety of paediatric complementary and alternative medicines (CAMs) from the users' perspective in order to generate suitable data to inform healthcare policy and planning. The research was in three parts: a systematic review (SR), a database analysis and a survey.

The SR of papers published on the topic from 2000 to July 2011 identified 46 eligible studies conducted predominantly in the USA (14; 30%); with only 5 UK studies (11%), of which 2 were Scottish. Generally, their findings indicated a high report of positive health outcomes by CAM users, and a low report of adverse outcomes. Critical appraisal, however, highlighted the low methodological quality of most studies; with an overall quality rating of 45%, and only 9 studies (20%) possessing up to 8 of 12 quality indices. A tendency towards selective outcome reporting bias was also observed.

The database research explored the suspected adverse reactions (ADRs) associated with paediatric use of natural health products (NHPs) as reported on the Yellow Card Scheme (YCS) from its inception until July 2012. The YCS data was mined to estimate the frequency and seriousness of the ADRs reported. NHPs were found to have contributed <1% of ADR reports within the period, with paediatric subjects contributing 8.6% of NHP reports (192 reports). These profiled 332 specific ADRs, 30% of which were described as serious. Female subjects contributed marginally more ADRs than males (51.5%). Rash and other skin and subcutaneous disorders were the most common ADRs. Herb-drug combination products were found to generate the most ADRs, with the senna-piperazine combination being the most frequently reported (89 ADRs). The product most associated with fatalities was soybean oil (5 reports). Generally, however, NHP-related ADRs reported for paediatric subjects in the YCS were found to be relatively few, and of low severity (6%) and fatality (2%); with over 75% resolution, and mostly within 3 days (68%).

The survey component of the research was a bi-modal analytic cross-sectional survey of parents in Aberdeen, and aimed to determine the nature and demography of the use and user-reported outcomes of CAM among children in Aberdeen. Consenting parents recruited from the general population were invited to complete online or paper versions of a validated questionnaire. 212 parents of 391 children completed the survey, of which 143 reported CAM use in their children (67.5%). Participants were mainly mothers (73.6%); Caucasian (84.4%); aged 30-44 years

(59.7%); and educated beyond secondary level (85.3%). 213 children had ever used CAM, 64.3% of which had always used CAM; while 21.1% had only used CAM within the last 12 months, and 14.6% had used it only previously. 53.1% of child CAM users were female. Parental self CAM use was found to be the strongest predictor of paediatric CAM use. 102 of the 123 parents that rated their children's CAM use (82.9%) perceived them as helpful; 76 of which said they helped "a lot". Finding personal CAM use helpful was the only factor found to significantly predict perceived effectiveness for paediatric CAM use. 9 parents reported adverse outcomes, mainly allergic skin reactions.

In all, this research featured the first SR of user-perceived effectiveness and safety outcomes of paediatric CAMs; the first analysis of NHP-associated ADR reports on the YCS; and the first population-based Scottish study of paediatric CAM use. A triangulation of the results from these three strands validated the key finding that CAM is used widely among children, with high perceived effectiveness and safety outcomes. The implications of this finding for healthcare policy and planning were highlighted.

Keywords: Complementary and alternative medicine; perceived effectiveness; safety; children; parents; outcomes; Yellow Card Scheme; pharmacovigilance; systematic review; natural health products; Aberdeen; Scotland

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My PhD journey was an exceptional one in many respects; and I am overjoyed to see it come to a successful end. I am so grateful to God for the opportunity to go through this immense training experience. It could easily have ended as an abandoned project; but, against all odds, HE has accomplished what HE promised. To HIM alone be all the glory.

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External Outputs

Journal publication

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Conference paper

Okechukwu Ndu, Alison Strath, Lesley Diack (2015). The use of complementary & alternative medicine among children in Aberdeen –an outcomes-based cross- sectional survey. (Poster presentation at CAMSTRAND –London, 2015.)

Other journal publications are at various stages of preparation.

Scholarship awards

I was awarded the Academic Staff Training & Development scholarship of the Education Tax Fund of the Federal Government of Nigeria (2010-2012)

Foreword

This thesis embodies the research I carried out over my four and half years of study at the Robert Gordon University, Aberdeen. Within that period, I explored the positive and negative experiences associated with the use of complementary and alternative medicines (CAMs) in children in Aberdeen.

Upon my graduation as a pharmacist from the University of Nigeria, Nsukka, Nigeria, I was retained by my home faculty of Pharmaceutical Sciences for the mandatory one-year pre-registration internship training as a graduate pharmacist. After my full registration with the Pharmacists' Council of Nigeria, I worked as a hospital pharmacist for a year; and thereafter spent two more years in community pharmacy practice. I then decided to return to my first love, the academia; and was employed as graduate assistant in the Department of Pharmacology & Toxicology of my alma mater. After completing a Master of Pharmacy programme in Pharmacology, I joined the teaching faculty as a Lecturer II, with the job description of undergraduate teaching and research. Over the years, I rose up the ranks, attaining the post of Senior Lecturer and Acting Head of Department in 2008, a post I held up until 2010 when I came to the UK for doctoral studies.

My interest in complementary and alternative medicines stemmmed from my years of research into the folkloric claims of various herbs used in traditional medicine in Nigeria. I commenced such research during my MPharm project, in which I investigated the hypotensive claims of petals of *Hibiscus sabdariffa* using laboratory animals. Encouraged by the findings of that study, I went on to investigate other related ethnomedicinal claims of the plant, as well as the pharmacological consequences of its use alone and in combination with various conventional anti-hypertensive drugs. I also explored its use in various physiological and pathological conditions. While the preliminary experiments yielded results that supported many of the ethnomedicinal claims, the studies on possible drug-herb interaction as well as its effects on physiological and pathological states produced conflicting results, highlighting the risk potential of its long-term use. These findings worried me in the light of the popular use of the herb in the community.

My first impressions of the high use of herbal medicines were to associate such with the combination of inadequate health care services and lack of health information by the public. A search of the literature, however, informed me better, as it revealed the global nature of high use of herbal medicines –even in economically advanced countries. I also noted with alarm their reported high use in children; which birthed in me the desire to investigate the outcomes of such herbal

medicinal product use in paediatric populations. As a pharmacist, I was particularly interested in patient safety; hence my emphasis on pharmacovigilance. Further internet search led me to reach out to my first principal supervisor; and ultimately resulted in my acceptance for doctoral training. Further discussions with him helped broaden my research outlook to focusing not only on paediatric herbal medicinal product use, but also on the use of complementary and alternative medicinal products generally in that demographic.

The last four years of doctoral research training have given me insight into the psycho-social and legal issues surrounding not only the use of CAMs, but also paediatric research in general. I have also come to appreciate the immense challenges and benefits of health services research generally. I look forward to honing the skills I have now acquired through the practice that makes perfect; so that one day I can effectively help others achieve what I have been enabled to achieve over the last few years.

List of Abbreviations

95 % C I	95 % confidence interval
ADHD	Attention deficit hyperactivity disorder
ADR	Adverse drug reaction
AE	Adverse effect
AERS	Adverse Event Reporting System
AMED	Allied and Complementary Medicine Database
ASD	Autism spectrum disorders
ATC	Anatomical, therapeutic and class
BCPNN	Bayesian Confidence Propagation Neural Network method
BNFC	British National Formulary for Children
CAM	Complementary and Alternative Medicine
CAMEOL	Complementary and Alternative Medicine Evidence Online
CAMs	Complementary and Alternative Medicines (i.e. Medicinal product CAM)
CASP	Critical Appraisal Skills Programme
CE	Clinical effectiveness
CINAHL	Cumulative Index to Nursing and Allied Health Literature
CIOMS	Council for International Organisations of Medical Sciences
CONSORT	Consolidated Standards of Reporting Trials
CRD	Centre for Reviews and Dissemination
CSD	Committee on Safety of Drugs
DEF	Data extraction form
Diet.	Dietitician
EBM	Evidence-based medicine
EBPH	Evidence-based public health
ED	Emergency department
edCAM	Pediatric Complementary and Alternative Medicine
EMA	European Medicines Agency
EQUATOR	Enhancing the QUAality & Transparency Of health Research
F2f	Face-to-face

FDA	Food and Drug Administration
GDASI	General disorders and administrative site injuries
GID	Gastrointestinal disorders
HCP	Health care professional
HEENT	Head, eyes, ear, nose and throat
HRQoL	Health-related quality of life
HTA	Health Technology Assessment
IBD	Inflammatory bowel disease
IBIDS	International Bibliographic Information on Dietary Supplements
ICD	International classification of diseases
ICSR	Individual case safety report
IPPC	Injury, poisoning & procedural complications
ISD	Information Services Division (of the Scottish NHS)
ISPOR	International Society for Pharmaco-economics and Outcomes Research
JIA	Juvenile idiopathic arthritis
ME	Medication error
MedDRA	Medical Dictionary for Regulatory Activities
MGPS	Multiple gamma-poisson shrinkage method
MHRA	Medicines and Healthcare products Regulatory Agency
NAPRALERT	Natural products Alert
NCCAM	National Centre for Complementary and Alternative Medicine
NCCIH	National Centre for Complementary and Integrative Health
NDS	Nervous system disorders
NHP	Natural Health Product
NHS	National Health System (of the UK)
NICE	National Institute for health and Care Excellence
NIMH	National Institute of Medical Herbalists
norphCAM	Network of Researchers in the Public Health of CAM
NP-CAM	Natural Product CAM
NR	Narrative review
O. T.	Occupational Therapist
OPD	Outpatient department
OR	Outcomes research
OR:	Odds ratio
PBRR	Population-based reporting ratio
PCORI	Patient-centered Outcomes Research Institute
PD	Psychiatric disorders
PE	Perceived effectiveness

Pharm.	Pharmacist
PICOS	Population; Intervention; Comparators; Outcomes; Study design
POEM	Patient-Oriented Evidence that Matters
PRISMA	Preferred Reporting Items for Systematic reviews and Meta-Analysis
PROM	Patient-reported outcomes measure
PROs	Patient-reported outcomes
PRR	Proportional reporting ratio
Psych.	Clinical psychologist
PV	Pharmacovigilance
RCPCH	Royal College of Paediatrics and Child Health
RCT	Randomized controlled trial
REC	Research Ethics Committee
REC:	Recommendation
RedHot	Reporting data on Homeopathic treatments
RN	Registered Nurse
RR	Response rate
RTMD	Respiratory, thoracic & mediastinal disorders
rym	Reports per year per million
SOC	System-organ class
SPSS	Statistical Package for Social Sciences
SR	Systematic review
SRS	Spontaneous reporting scheme
SSD	Skin and subcutaneous tissue disorders
STROBE	STrengthening the Report of OBservational studies in Epidemiology
T& CM	Traditional and Complementary Medicine
TCM	Traditional Chinese medicine
TM	Traditional medicine
UMC	Uppsala Monitoring Centre
UNICEF	United Nations Children's Fund
UPE	User-perceived effectiveness
UPES	User-perceived effectiveness and safety
WHO	World Health Organisation
YCS	Yellow Card Scheme

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Chapter 1

General Introduction

1.1 Complementary and Alternative Medicine (CAM)

This doctoral research is on the effectiveness and safety outcomes associated with the use of complementary and alternative medicines (CAM) in children. This introductory chapter seeks to provide a contextual definition of each of the key concepts associated with the research. This first section introduces CAM therapies in general, as well as outlines the key aspects relevant to the research.

1.1.1 CAM: Definition and classification

There is no commonly agreed definition for CAM among the several proposed in literature [1, 2]. While it can broadly be described as non-conventional medicine that is used either along with (complementary) or in preference (alternative) to conventional medicine [3], the specifics of what it embodies vary depending on the perspective from which it is viewed. For instance, the World Health Organisation (WHO) regards CAM somewhat as a new improved version of traditional medicine (TM), in that it originated from it and shares many of its features; differing only in the context within which it is used. Thus, while it defines TM as 'the sum total of knowledge, skills and practices based on the theories, beliefs and experiences indigenous to different cultures, whether explicable or not, used in the maintenance of health as well as in prevention, diagnosis, improvement or treatment of physical and mental illnesses' [4], it defines CAM in the same document as 'a broad set of health care practices that are not part of a country's own tradition and are not integrated into the dominant health care system'. The WHO therefore sees TM and CAM as different sides of the same coin, preferring to use the acronym TM/CAM [5] or T&CM [6] to either separate term. The Cochrane Collaboration, however, while adopting an essentially similar theoretical definition for CAM as the WHO, qualified it with a caveat. It defined CAM

as "a broad domain of healing resources that encompasses all health systems, modalities, and practices and their accompanying theories and beliefs, other than those intrinsic to the politically dominant health system of a particular society or culture in a given historical period"; but then added: "CAM includes all such practices and ideas self-defined by their users as preventing or treating illness or promoting health and well-being" [7, 8]. This definition was also adopted by the Institute of Medicine in 2005 with a slight amendment in the caveat, replacing "...as preventing or treating illness or promoting health and well-being" with "...as associated with positive health outcomes" [9, 10]; and is the definition most widely accepted by CAM researchers.

Due to the broad and ambiguous nature of these theoretical definitions, there was the need for operational definitions and classification schemes that utilise explicit and transparent criteria to clarify the scope of CAM [1, 2]. In line with this, the WHO categorized T&CM broadly into medication-based (or product-based) therapies -if they involve use of herbal medicines, animal parts and/or minerals; or non-medication-based (or practitioner-based) therapies—if carried out primarily through the agency of a specific therapist or practitioner, usually without the use of natural products, as in the case of acupuncture, manual therapies and spiritual therapies [5]. While there are several other such classification schemes for CAM, the most popular one among CAM researchers, and the one also adopted by the Cochrane Collaboration CAM Field, is that provided by the US National Centre for Complementary and Integrative Health (NCCIH), which initially categorised CAM in into five specific classes [2]. In March 2015, NCCIH updated its categorisation of CAM from the initial five classes to three broader ones [11, 12], as follows (1) natural products (formerly biologically-based therapies); (2) mind and body practices (a combination of the former manipulation and body-based methods and mind-body interventions classes); and (3) other complementary health approaches (an amalgamation of the initial alternative medical systems and energy therapies classes). The details of this classification system and the relevance of each of the categories to the research reported in this thesis are summarized in Table 1.1.

Generally, medication-based therapies are called CAM products; while non-medication-based therapies are called CAM practices [13]. Although the classical CAM products include herbal medicines, Bach flower remedies, dietary supplements, megavitamins and special diets; the ambit of CAM products can be broadened to include homeopathic products and essential oils. While these products are utilised as part of such CAM practices as aromatherapy, homeopathy and various forms of massage, they still are essentially medication-based therapies in their own right. Described as such, some authors [14, 15] have more aptly identified these therapies as Natural Product CAM (NP-CAM), Pharmaceutical-type Complementary and Alternative Medicines (PT-CAMs), or simply Complementary and Alternative Medicines (CAMs). In view of the practical impossibility of studying all CAM types in-depth within the time frame of the doctoral research and the pharmaceutical background of the student this research is largely restricted to CAM products or CAMs, except where the exigencies of a given aspect of the research dictate otherwise.

TABLE 1.1: NCCIH categorisation of CAM therapies and relevance to current research

NCCIH categorisation of CAM		Sub-types	General comments	Relevance to current research
Current	**Initial**			
1. Natural products	1. Biologically-based therapies	Bach flower therapy Chelation therapy Dietary supplements Essential oils Herbal medicines Home remedies Hydrotherapy Megavitamins & minerals Prolotherapy Special diets	Essentially medication-based therapies Primarily entail the use of medicinal products (natural products)	Will be the sole focus of the research reported in chapters 2 and 3; and the major aspect of the research reported in chapter 4
2. Mind and body practices	2. Mind-body interventions	Acupuncture Art therapy Aromatherapy* Bio-feedback Breathing techniques Dance therapy Guided imagery Humour therapy Hypnotherapy Meditation techniques Music therapy Play therapy Prayer therapy Yoga	Essentially non-medication-based except for *. Some may stand alone or form part of another sub-type *This involve the use of essential oils, which often have medicinal properties (natural products)	Will be considered only in the research reported in chapter 4; but essential oils will also form part of the research reported in chapters 2 and 3
	4. Manipulation & Body-based methods	Acupressure Alexander technique Chiropractic Feldenkrais Massage Osteopathy Reflexology Rolfing Therapeutic touch Trager approach	Essentially non-medication-based Some of these may stand alone or form part of another sub-type	Will be considered only in the research reported in chapter 4
3. Other complementary health approaches	4. Alternative medical systems	Acupuncture† Anthroposophy* Ayurveda* Homeopathy* Naturopathy* Traditional Chinese Medicine (TCM)* Kampo* Other indigenous traditional health practices*	Essentially non-medication-based except for * *These may also involve the use of medicinal (or natural) products †May also be part of categories 2 and/or 4	The natural product components (*) will be specifically focused on in the research reported in chapters 2 and 3; but all sub-types will be included in the research reported in chapter 4
	5. Energy therapies	**- Bio-field therapies**: Healing (Faith, distant, etc.) Qi gong Reiki Tai chi **- Bio-electromagnetic-based therapies:** Involves the unconventional use of pulse, magnetic, alternating or direct current fields	Essentially non-medication-based Some of these may stand alone or form part of another sub-type	Will be considered only in the research reported in chapter 4

This exception, however, applies to a significant degree only to the aspect of the research reported in chapter four of this thesis. For clarity, therefore, the terms CAM product(s) or CAMs are used inter-changeably throughout this thesis to distinguish natural product pharmaceutical-type CAM therapies from CAM practices in particular, or all CAM therapies in general.

1.1.2 CAM as a public health intervention

The role of CAM in public health has been increasingly acknowledged in recent times, and underpins the WHO's efforts towards the acceptance and integration of CAM therapies into health care systems globally [16–19]. As the field of Public Health is "the science and art of preventing disease, prolonging life and promoting health through the organized efforts and informed choices of society, organizations, public and private, communities and individuals" [20]; and CAM has been defined as 'the sum total of knowledge, skills and practices based on the theories, beliefs and experiences indigenous to different cultures, whether explicable or not, used in the maintenance of health; as well as in the prevention, diagnosis, improvement or treatment of physical and mental illnesses'[4]; their shared attributes and intersecting paradigms are quite obvious [21]. Public health interventions are focused at preventing and managing diseases, injuries and other health conditions through such simple and often non-medical methods as surveillance of cases and health promotion at the personal, community and global levels. The optimization of self-care capabilities of individuals and families through case management [22], a key aspect of public health interventions, has been the cornerstone of CAM use in various health conditions [23–27]. Some other aspects of public health interventions that are also applied in CAM research include adverse event surveillance [28–30]; population screening and case finding to determine prevalence and characteristics of use [31–33]; and collaboration and coalition building to enhance CAM research. Such collaboration has resulted in various networks such as the Network of Researchers in the Public Health of CAM (norphCAM) [18] and CAMbrella, a 3-year pan-European, EU-funded project that investigated the state of CAM use and research in Europe [19, 34, 35]. The CAMbrella project culminated in the release of a road map for CAM research in Europe [36], key aspects of which include:

(i.) the identification of CAM as a neglected research area in Europe;

(ii.) the need for research methods that reflect real-world health care settings in Europe;

(iii.) the need for an EU research strategy for CAM that prioritizes an approach that reflects the needs of its citizens and providers of CAM.

The current work builds on these public health aspects of CAM research.

1.1.3 CAMs: Popularity, effectiveness, and safety

In virtually all surveys of CAM use world-wide, CAM products have consistently been found to be the most popular CAM type used –even among paediatric populations [37, 38]. Also, against the back-drop of the limited evidence for the effectiveness of CAM therapies generally, CAM products, with the notable exception of homeopathic remedies, are generally associated with a significantly greater basis of evidence than many CAM practices [39]. This is particularly true for many herbal medicinal products [40], the ethno-medicinal claims and efficacy of many of which have been validated and affirmed in literature reports of experimental and quasi-experimental, pre-clinical and clinical studies –including randomized controlled trials, RCTs [15, 41, 42]. In spite of these advantages, however, CAMs –especially herbals- are plagued with the problems of large-scale adulteration [43–45], and a high tendency of often unfavourable interactions with conventional drugs [46, 47]. Homeopathic products, on the other hand, despite many clinical trials in various health conditions, are still plagued with the problem of controversial efficacy [48, 49], although widely acknowledged as safe [50, 51]. These drawbacks have grave implications for patient safety, and have raised concerns as to the over-all safety and effectiveness of these unconventional medicines. These concerns have been the subject of various studies [52, 53], and have also been highlighted for their use in paediatric subjects [28, 29].

In spite of many negative reports about the hazards of unguided and/or misguided CAM use, literature reports highlight their continued and increasing use world-wide in both adults and children [54, 55], suggesting that public opinion on CAM use has not been adversely affected. Moreover, studies have consistently associated high CAM use with both higher education and higher economic status [56, 57]; which finding undermines the allegations of ignorance or poverty as chief contributing factors to increased CAM use. Whether the continued popular use of these products is purely based on their widely reported anecdotal claims; or due to some hitherto unrecognised positive outcomes they yield to their users, is still the question of debate in various sectors. Also, even in the instance of an unrecognised positive benefit in terms of user-perceived effectiveness, one further wonders if these therapies are actually safe. While various studies have documented the high rates of adverse drug events associated with the widespread unlicensed and off-label medication use in children [58, 59], very little work has been published on paediatric CAM safety –particularly in the UK. This informed this doctoral research to determine the bases for -and implications of- this popularity by assessing user-focused outcomes in terms of effectiveness and safety in Scotland.

1.2 Outcomes research

1.2.1 Definition, history and scope

Health service outcomes have been described as the effects of health services on patients' health, as well as patients' evaluation of their health care [60]. As the well-being of the patient is the goal of all health services and interventions, outcomes research (OR) focuses to a large extent on patient-reported end-results of health services and interventions by identifying and analysing the patient's experiences, preferences and values [61, 62]. There is, therefore, a de-emphasis on the biomarkers and surrogate end-points that have traditionally characterised clinical medicine, in preference for the perceptions and preferences of treated patients. It is one of the dividends of the WHO's definition of health as 'a state of complete physical, mental and social well-being, and not merely the absence of disease or infirmity' [63].

Although first recognized in the 1850s through the work of Florence Nightingale on mortality rates following medical interventions, modern OR was founded by Avedis Donabedian when, in 1966, he published the landmark essay on evaluating quality of medical care [64]. He stated that 'outcomes, by and large, remain the ultimate validation of the effectiveness and quality of medical care'. Building on Donabedian's work, Ellwood later introduced the term 'outcomes management' [65], in which he suggested that patient management should be driven by the experience of how similar patients fared following alternative therapies. In its present form, OR aims at generating evidence for best practices and policies for the benefit of all stake-holders in medical care, by providing evidence on which interventions are best suited for each patient and/or circumstance [66, 67].

While OR emphasizes patient outcomes such as readmission or mortality rate, as well as patients' healthcare experiences or cost, system-related outcomes that can affect the patient experience –such as patient access to health care (waiting times), training of health professionals, or implementation of health care policies- are also studied. All these frontiers are embodied in the seven themes of OR as recognized by the Institute of Medicine -safety, effectiveness, patient-centeredness, system responsiveness, timeliness, efficiency and equity [67, 68]. These themes have been studied by means of primary epidemiological studies (such as RCTs, cross-sectional observational studies, etc.) or secondary epidemiological data from either published studies (systematic reviews and/or meta-analyses) or patient/consumer electronic health records (database studies) [69, 70]. The research reported in this thesis applies aspects of both of these methods to focus on the first 2 themes of OR in the context of CAM use among children in the Aberdeen area of North-east Scotland.

1.2.2 Health outcomes measurement

Health outcome measurement focuses on the results of health care –or the effects of a health care intervention- on the overall health, morbidity, disability and/or quality of life of the patient [71]. Described as such, it is intricately related to the health-related quality of life (HRQoL) of patients, as it focuses on their perceptions on their health status within the context of other aspects of their life in terms of changes in their symptoms and functioning, and their preferences and values, as well as their satisfaction with their treatment [66, 72]. In epidemiological studies, such outcome measures are determined essentially by means of either generic or (disease-, condition-, function-, population-, or treatment-) specific patient questionnaires [73, 74], usually based on the item-response theory [75, 76]. Such questionnaires are usually multi-dimensional in order to cover the various components considered important to patients, which can also affect them positively or negatively [77]. These components are often determined from the patients and care-givers directly, usually through one-on-one in-depth interviews and/or focus group discussions. The inputs from the patients are then combined with general findings from literature into a draft questionnaire that is deemed capable of assessing the outcome concerned [78, 79] –thus achieving face validity. The resulting instrument is then pre-tested in a purposive sample, not only to identify areas that could be unclear or difficult to understand, but also to ensure that the data eventually realised would meet the objectives of the survey. This is achieved conventionally by simply piloting the instrument; but other more in-depth methods, such as cognitive interviews, behaviour coding, response latency, vignette analyses and statistical modelling, have also been used [80, 81]. By these means the content validity of the items is determined.

Following pre-testing, the questionnaire is revised appropriately and subjected to item reduction, and, for health status outcomes instruments, further subjected to detailed psychometric analyses to determine its construct and criterion validity, reliability and sensitivity to change [79]. Conventionally, item reduction is achieved through expert review of the pool of items initially generated following feedback received from a field test to determine the acceptability of the instrument [82]. However, it could also be achieved by testing scaling assumptions, conducting a component factor analysis and determining the internal consistency of the various scales in the instrument [83]. As it is not the objective of this doctoral research to measure specific health status in patients with particular health conditions, a generic outcomes instrument is utilised in the aspect of the research reported in chapter four of this thesis, and detailed psychometric analyses are not conducted. Also conventional methods of validation are employed as applicable.

1.2.3 Outcomes measures instruments in CAM research

The theories and philosophies that under-pin CAM use are different from those associated with conventional medicine [84, 85]. It is, therefore, not strange that applying the same methodologies

that have been found useful in the assessment of the effectiveness of conventional medicines has not yielded much positive evidence for CAM therapies [86, 87]. In recent years, there have been repeated calls and proposals for the development of different strategies for the validation of CAM therapies as well as whole systems of integrative medicine [88–91]. As CAM use is primarily patient/user-driven [92–96], an emphasis on the reliance on patient-reported outcomes (PROs) -a conceptual framework of outcomes that reflect patients' lived experiences- is central to the strategies proposed for its proper evaluation [97]. Also proposed is a system of research that emphasizes the relevance of the context of the treatment –that aims at answering the question: "*Which treatment works for whom, when and why?*", rather than the traditional question: "*Which treatment works?*" [98]. In view of this emphasis on patient-specific outcomes, a variety of novel methodologies has been proposed, such as the inclusion of qualitative methods in RCTs [99, 100], whole systems research (WSR) [89], aptitude-treatment interaction (ATI) research [98], CAM systems research [101], and complex interventions research [102, 103], among others. One consistent theme that runs through all these designs is the combination of appropriate qualitative and quantitative methods in CAM research methodology [104, 105]. The research reported in chapter four of this thesis follows that same approach in line with recent research on CAM use [106].

1.3 Effectiveness of health interventions

1.3.1 Definition, classification and assessment

Efficacy and effectiveness are two closely related terms used in the evaluation of healthcare interventions. Historically, efficacy studies were the backbone of clinical research, being accepted as the 'gold standard' for determining whether or not a treatment worked [107]. From the turn of the 21st century, however, there has been a shift of emphasis towards effectiveness studies, which differ from efficacy studies in that they focus on real-world use of interventions as against an ideal-setting perspective [108, 109]. In other words, efficacy studies can be described as explanatory, and effectiveness studies as pragmatic [110, 111]. Despite these distinctions, there is still sufficient confusion among researchers over the right terminology to warrant mislabelling of some 'effectiveness' studies as 'efficacy' studies, and vice versa. As a result, many systematic reviews of 'effectiveness' studies often mistakenly include studies that are actually 'efficacy' studies. To guard against this common error, Gartlehner et al, in a research carried out for the Agency of Healthcare Research and Quality of the US Department of Health and Human Services, have identified six criteria by which effectiveness studies can be distinguished with high specificity and sensitivity from efficacy studies during systematic reviews [112, 113].

The effectiveness of a health intervention can be evaluated from two major perspectives –objectively: from the clinician's/experimenter's perspective (clinical effectiveness, CE), or subjectively: from a patient's/consumer's perspective (perceived effectiveness, PE) [114, 115]. The cost-effectiveness/cost-benefit of the intervention can then be obtained by deducing the economic implications of achieving or improving the effectiveness data realised from these two perspectives relative to those for another intervention [116, 117]. While CE focuses on the attainment of clinical/therapeutic outcomes/goals/end-points –and is best judged by carefully designed and well conducted pragmatic 'real world' randomized (controlled) trials (RCTs), PE focuses on the attainment of humanistic outcomes through assessing the receiver's own perception of –satisfaction/ contentment with- the treatment, or his own assessment of his health-related quality of life (HRQoL) following the treatment. It is best assessed using observational studies –essentially cross-sectional surveys, cohort or case-control studies, and qualitative research.

Although evidence obtained from well-conducted RCTs is generally accorded greater recognition by healthcare scientists and professionals, and is placed on a higher level in the popular hierarchies of evidence in the evaluation of healthcare interventions [118], studies have shown that observational studies are not particularly inferior to randomized trials in methodological quality [119, 120]. Rather, observational studies have been found to actually be superior to them in studies where opinions, attitudes and perceptions about interventions are being investigated [121, 122]. As the current research focuses on effectiveness from the users' perspective, an observational approach is, therefore, justified.

1.3.2 Importance of the patient/user's perspective

Conventionally, the effectiveness of a treatment or other health intervention is determined with respect to physiological and/or clinical end-points, such as infection/disease control, results of laboratory tests, and survival. While such objective measures yield very useful and accurate evidence on the effectiveness of interventions in many circumstances, there are other conditions –such as pain, fatigue, or visual acuity- in which objective measures are not either feasible or reliable. Determining effectiveness of interventions in such circumstances, therefore, has to rely on subjective data from the patient [123, 124]. Moreover, even in circumstances where objective measures are feasible and reliable, situations often arise where improvement in physiological indices do not translate into (significant) clinical response; or where clinical response does not result in patient satisfaction vis-a-vis the peculiarities of the patient's external circumstances [125]. In such circumstances, the patient has the final say; as the relevance of physiological and clinical measures ultimately diminish in view of the patient's perception of changes in his/her health status, and the effect of such changes on quality of life [126]. Another scenario in which the importance of the patient's judgement cannot be over-emphasized is in comparative effectiveness

studies [62], where there is need to determine which of two or more effective treatment options gives the greatest overall benefit to the patient. In coming to this decision, not only the direct benefit of the intervention is considered, but also the patient's perception of any adverse events that may be associated with it [127].

In view of the above, the patient is ultimately the best judge of the impact of health interventions, and, thus, absolutely relevant in the assessment of their effectiveness. The recognition of this has resulted in a shift of emphasis in healthcare delivery, assessment, and research in various parts of the world. Patient-reported outcome Measures (PROMs) have become incorporated into the NHS since April 2009 [128]. Also, NHS regulations are now based on national surveys of patient experiences [129]. In 2009, the US Food and Drug Administration, following a draft guideline in 2006, finally released definitive guidance on the use of patient-reported outcomes (PROs) to support labelling claims [130]. Also, the drug industry has now recognized the value of including PROs in labelling efficacy claims in improving consumer-targeted marketing [131]. All these reflect a realization of the profound impact of patient-centred care on the outcome of healthcare delivery, and have opened up a new field in healthcare research. The US Patient-centered Outcomes Research Institute (PCORI), a non-governmental institute charged with examining the 'relative health outcomes, clinical effectiveness and appropriateness' of different medical treatments by evaluating existing studies and carrying out its own, is a notable example. It is similar to the NHS National Institute for Health and Care Excellence (NICE) in England and Wales. However, PCORI differs from NICE in its de-emphasis on the cost-effectiveness of health interventions in establishing a recommendation. The data mining of (usually) health outcomes-related patient data and healthcare information systems represents another novel research method that is especially appealing due to its low cost [132, 133]. In addition to applying this novel approach, the research reported in this thesis follows the PCORI approach by placing the patient squarely at the centre of the study, while de-emphasizing the cost implications of the interventions concerned.

1.3.3 CAM effectiveness -resolving the controversy

As earlier stated, despite their high popularity, and in spite of the calls by the WHO for their integration into national health systems world-wide, there is still a lot of controversy surrounding the effectiveness of many CAM therapies. This is so even for such CAMs as herbal medicines that have been found to have some evidence base [134]. Generally, there is a great divide among medical practitioners and researchers on CAM effectiveness, and the rationale for their clinical use. While studies have shown that more than 70% of GPs recommend and/or refer their patients to some therapies [135–137], a qualitative study has shown that scepticism and uncertainty are prominent among medical doctors with a dual academic and clinical role [138]. Studies have also shown a similar attitude among medical students, with the scepticism growing as they progress in

pre-medical training [139, 140]. The views of other health professionals are generally more positive [141–143]. Although there are a number of studies to the contrary [144, 145], the primary basis for the scepticism and uncertainty among medical practitioners is the little, ambiguous, or outright lack of empirical evidence on the clinical efficacy of CAM therapies based on RCTs [146–148].

On the other hand, practitioners of, and many researchers in, complementary medicine contend that the various peculiarities of the philosophy and practice of CAM do not recommend them to assessment using RCTs [149], as proposed by the evidence-based medicine paradigm. They recommend instead the use of different and novel methodologies that take into consideration some of the dimensions over-looked in randomized trials. The common distinctive features of the new methodologies proposed are the reliance on real life, observational effectiveness studies and a greater consideration and incorporation of the perspectives of patients that use CAM in the assessment process, as well as the introduction of a holistic perspective in CAM use [86, 150]. A recent survey of clinicians and primary care trust managers in the NHS has shown, however, that clinical research evidence, rather than patient perspectives, is a greater factor in their professional decisions on their patients [151].

With the continued and growing popularity of CAM use, however, the importance of resolving the on-going controversy cannot be over-emphasized. This is especially so since the greatest casualties of the conflict are the patients, who are continually barraged from all sides with different 'expert' opinions [152]. While each side of the argument has its own merits, it is obvious that practical utility should not be marginalised in deference to dogma, as has been canvassed by various authors in recent times [152–154]. The advent of comparative effectiveness studies and patient-centred healthcare research, therefore, avails healthcare professionals and researchers on both sides a good opportunity to resolve the controversy by adopting a balanced and more tolerant, patient-focused approach [155, 156]. In other to achieve such balance, epidemiological outcome studies of subjective patient-reports can be compared with database outcomes studies of CAMs and other patient hospital records [157–159]. With many CAMs having been reported to be efficacious in specific disease conditions, the importance of patient-centred effectiveness studies in assessing their over-all usefulness cannot be over-emphasized. This is especially important for homeopathic products, as patient-centred effectiveness studies can help to resolve the controversies generated by the many conflicting results of efficacy studies. Only in this way can a truly patient-led healthcare system be achieved. The research embodied in this thesis, particularly the triangulation of research findings reported in chapter five, contributes towards this.

1.4 Medication safety and pharmacovigilance

1.4.1 Introduction and basic principles

Despite great advances in the field of surgery, the use of medications remains the most common intervention in allopathic medicine, being the preferred initial intervention in most health conditions, as well as an essential component of post-surgical management. Understandably, therefore, adverse outcomes following medicine use constitute the greatest proportion of medical errors in both adults and young people [160, 161]. These include the generally preventable medication errors (MEs) and the not always predictable adverse drug reactions (ADRs). Although the importance of reducing MEs is well noted, the key factor in the achievement of medication safety is the early detection and subsequent prevention of ADRs. This involves the use of not only hospital-based medication safety assessment techniques, but also the broader principles of pharmacovigilance (PV) techniques [162, 163].

Originating in the 1960s as a concerted response to the thalidomide disaster, PV is the pharmacological science that focuses on the detection, assessment, understanding and prevention of ADRs [162, 164]. Its ultimate goal is to ensure a rational and safe use of medicines, which is generally achieved via monitoring for, collecting, characterizing, assessing and evaluating information on adverse effects of medications and related health products both during the drug development process and after regulatory approval (post-marketing surveillance). Such information is obtained through various means, including spontaneous reporting, prescription event monitoring, record linkage, case-control surveillance, and cohort follow-up studies, among others [162, 165], New regulatory and scientific processes, such as conditional approval, risk management plans, transparency and increased patient involvement in suspected ADR reporting have also been introduced to improve effectiveness [164]. It is, however, not clear how these have affected the PV of CAMs.

In spite of these varieties of methods and policies, surveillance schemes based on national spontaneous reporting system databases, such as the Yellow Cards Scheme (YCS) of the Medicines and Healthcare products Regulatory Agency (MHRA), have become the cornerstone for the early detection of hints that suggest the possibility of hitherto unknown ADRs. Such hints are called 'signals'; and refer to a set of clinical, pharmacological, pathological, or epidemiological data that supports a hypothetical argument for a significant public health risk [166, 167]. They are identified by statistical analysis of the data generated in the database over a given period. Various methods have been utilised in signal generation, including frequentist and Bayesian statistical measures of association, such as Chi squared (Yates correction, X^2), proportional reporting ratio (PRR), reporting odds ratio (ROR), Yule's Q measure (Q), Poisson probability, sequential probability ratio test (SPRT), information component (IC), empirical Bayes method, and alternative generation criterion for the empirical Bayes method (EBP) [168]. Using two-by-two contingency

tables, these quantitative methods essentially measure the disproportionality (or 'unexpectedness') in the frequency of the report of a given ADR in association with a particular drug relative to the totality of the reports of that ADR in the database [169–171].

Variations (or combinations) of these methods have been used in different national and international pharmacovigilance agencies. For instance, while the WHO Collaborating Centre for International Drug Monitoring in Uppsala, Sweden, uses the Bayesian Confidence Propagation Neural Network method (BCPNN) to measure the IC of drug-event combinations; the US FDA's Adverse Event Reporting System (AERS) employs the multiple gamma-poisson shrinkage (MGPS) method [172, 173]. On the other hand, a combination of PPRs and Yates X^2 have been utilised in the UK's YCS database [174, 175]; while RORs and logistic regression have been used in Dutch Lareb centre [176]. While comparative studies have not found any particular measure to yield significantly better results [177], it has been reported that sensitivity is generally higher when point estimates (PPR, ROR, Yule's Q, etc.) are used in combination with estimators of the precision of point estimates (X^2, the lower limits of the 95% confidence intervals of point estimates, etc.) [169]. Although the objective of the doctoral research is not to generate signals for CAM products, these statistical principles are applied to PV data on CAMs in the research reported in chapter three of this thesis so as to provide a standard descriptive summary of suspected ADRs reported for CAM products in our target population.

1.4.2 Importance of patient-reporting of adverse drug reactions

In appraising the various methods that have been utilised in the detection of adverse effects and measurement of medication safety in adults and children, several studies have highlighted the importance of surveillance methods involving interaction with in-patients and outpatients [178, 179]. Apart from cases where diagnosis was required, or where patient consciousness, judgement or communication was impaired [180, 181], the information realised from such interaction –essentially through patient interviews and surveys- was found to be not only in concord with that reported by clinicians, but also complementary to it [182, 183]. In addition to the improved generation of information about the experiences of past patients for the benefit of future patients in both hospital and community settings, potential advantages of such methods include earlier detection of adverse effects, and additional toxicity data to compare with efficacy during regulatory review [184]. A 2011 HTA of patient-reporting of ADRs in the UK's YCS [185] found that patient reports contained a higher median number of suspected ADRs per report, and described reactions in greater detail, often including the effects of reported ADRs on their quality of life. Although it noted that patient reports were better at potential signal generation when used in combination with those from healthcare professionals, it concluded that ADR reporting by patients or consumers has a great potential to add value to pharmacovigilance in various interesting

respects. An earlier literature review of patient-reporting of ADRs [186], and another study in Sweden [187] also arrived at similar conclusions.

Thus, in spite of initial criticism and scepticism [188, 189], the active role of 'users' or 'consumers' in the assessment of healthcare quality has become firmly established as a '*sine qua non*' not only in the achievement of individual patient medication safety, but also in the improvement of pharmacovigilance efforts for entire populace [190, 191]. However, the general reluctance of patients to voluntarily report adverse drug events [192, 193], greatly emphasizes the need for frequent, well-designed and innovative epidemiological studies with a view to eliciting ADE reports, as such specific proactive projects have been shown to yield more comprehensive results than the spontaneous reporting scheme (SRS) activities of pharmacovigilance centres [194, 195]. Apart from this intensive monitoring of both hospitalized and out-patients as well as consumers, the utilization of database studies on adverse drug events based on retrospective medication and hospitalization-related patient data represents another avenue for quick and inexpensive generation of additional ADR data [159, 196]. The current work explores these two avenues in the context of paediatric CAM use.

1.4.3 Pharmacovigilance of CAMs

CAMs are generally promoted as being as effective as -or even more effective and less toxic than- conventional medicines [197]. Although there is limited information on the safety profiles of most CAMs, there is documented evidence of better safety profiles for some herbal products and dietary supplements relative to standard conventional drugs for the specific conditions concerned [198, 199]. Also, various studies have associated homeopathic medicines with low frequencies of adverse effects [50, 200]. However, there is also evidence of the association of many widely used CAMs with both serious and non-serious ADRs [201, 202]. Therefore, in view of the widely held view that CAMs are natural, and, thus, safe, there is great need to ensure the screening of CAMs for ADRs. This need is further emphasized by other complicating factors, such as the lack of standardization of products, the high degree of adulteration of botanicals, and the high risk of interaction with conventional drugs; as well as the high degree of under-reporting of ADRs due to CAM use [203, 204]. In Europe, this need has been further underlined by the EU directive on herbal medicines (established in 2004, but fully effective as from May, 2011) banning the sale of unlicensed traditional herbal medicinal products within the region (Directive 2004/24/EC). Another significant development in this regard is the European Medical Agency (EMA)'s four-year programme (2012-2015) for review of herbal medicines by its Committee on Herbal Medicinal Products [205].

In spite of these significant milestones, the development of PV practices for CAMs has been beset by various challenges. A 20-year retrospective analysis of the suspected herbal ADRs

reported to the WHO Uppsala Monitoring Centre (UMC) published in 2000 highlighted the problem of confusion over the nomenclature, classification and content of the herbal products involved, and emphasized the need for international cooperation in ensuring the use of a precise and consistent nomenclature in national pharmacopoeias [206]. Barnes [207] further highlighted the problems of public perception, source, utilization, and regulation of herbal medicines, as well as the difficulties with applying the traditional PV methods to herbal medicines, In addition to proposing the institution of stricter regulations, and the development of modified methods and/or new tools for monitoring the safety of herbal medicines, the need to improve public communication on herbal medication safety, as well as the advantages of widening the reporter base for herbal ADRs to include herbal medicine practitioners and patients/consumers were also highlighted. The conclusions of these studies have led to an increase in PV efforts in CAMs world-wide -even in such areas as Korea and India that have been greatly associated with their long-term use; and where they enjoy high degrees of acceptance. Among the methods that have been proposed and utilised in the monitoring and detection of ADRs in CAMs are assessing historical use [208], controlled clinical trials, systematic and narrative reviews [209], SRS [210], epidemiological investigations, including primary and secondary data outcomes studies [211], and new signal detection tools [199]. This doctoral research focuses on the safety outcomes of CAM use in children as determined from both primary and secondary epidemiologic data.

1.5 Paediatric research

1.5.1 Introducing the paediatric patient

Providing a globally acceptable definition of the paediatric age group has proved difficult. While paediatrics is defined as the branch of medicine that deals with the medical care of infants, children, and adolescents/young people [212, 213], there is no general consensus on the upper paediatric age limit. Generally, based on the guidelines of international health bodies, the age limit ranges from as low as 14 years to as high as 24 years; with many national paediatrics associations preferring not to state a specific cut-off age. While the WHO states that the paediatric population is typically considered to be between 0 and 14 years of age [214], and the European Medicines Agency's Paediatric Committee defines "paediatric population" as "the part of the population aged between birth and 18 years" [215]; the UN specifies a much higher age limit for them, defining "youth" as subjects aged 15-24 years, and "young people" as adolescents and youth aged from 10 to 24 years [216]. The UN definition for "young people" is striking in view of the definition of "paediatrics" by the Royal College of Paediatrics and Child Health (RCPCH) as "a medical specialty that manages health conditions affecting babies, children and young people" [217]. While the RCPCH does not specify an upper age limit for the "young people" included

in the definition, it is generally understood to cover adolescents up until their 18th birthday, probably based on the age of majority in the UK and most parts of the world. This traditional understanding largely agrees with the definition of the United Nations Children's Fund (UNICEF) in its Convention on the Rights of the Child, where it defines a child as 'every human being below the age of 18 years, unless, under the law applicable to the child, majority is attained earlier' [218]. It, however, slightly disagrees with the paediatric age specified on the NICE website for the British National Formulary for Children (BNFC), on which it states that the BNFC "covers the use of drugs in children of all ages from new-born infants, including those born prematurely, to individuals aged 18 years" [219].

To manage this controversy for the purposes of this research report, the term "paediatric" will, in line with the traditional definition, be used to describe "infants, children and adolescents from birth to age 17 years", or "up until their 18th birthday". This position is in line with many paediatric studies in literature [220–224]. The only exception to the application of this rule in this thesis is in the aspect of the research reported in chapter two of this thesis, where the word is used to refer to subjects aged up to 21 years. As that chapter reports the systematic review of current literature on the perceived effectiveness of paediatric CAM use, this exception is justified by the goal of not automatically excluding "paediatric" studies conducted in settings where a broader definition of the word applies.

1.5.2 Identifying the "user" of paediatric medicines

Although medicines are 'used' for the basic purpose of improving health, the 'user' varies depending on the type of medication and the context in which it is used. While prescribers must take the decision to 'use' prescription drugs to improve the health status of their patients (clients), the patients themselves at the same time must accept to 'use' them by taking them as prescribed, for their own personal benefit. Any deviation from this pattern would be termed a misuse or an abuse of prescription drugs, as appropriate [225]. For non-prescription or self-prescribed over-the-counter medicines or medicinal products such as CAMs, however, the decision to 'use' them often lies invariably with the consumer, who then goes ahead to also purchase and take them as s/he deems fit [226, 227]. Here also, the potential for abuse and misuse exists [228, 229]. While this pattern generally holds true for all adults and some late adolescents, a slightly different pattern obtains in the context of paediatric subjects. Here, for most infants and young children, the decision to 'use' medicines lies more-often-than-not with the parents/guardians, usually the mothers, rather than the children who actually take them [230, 231]. Various factors buttress this trend. For one, because paediatric subjects, irrespective of their actual age, have not reached the "age of consent", they are not usually considered "old enough" to take important health care decisions for themselves [232]. Also, because most paediatric patients are still the responsibilities of their

parents/guardians, psychological factors and pragmatic considerations by parents play significant roles in child health decision-making [233, 234]. Additionally, as young paediatric subjects are still trying to develop their own identifies, their views and perceptions are often coloured by those of their parents/guardians [235, 236]. With the transition from childhood to adolescence and early adulthood, however, due to the growing influence of peer pressure and self-efficacy, young people tend to gradually become more self-opinionated and assertive; and usually come to the point where they assume full responsibility of their health care decisions [237, 238]. But even at such a "mature" stage in life, many have been found to still be influenced by the 'health culture' established by their parents and families [239, 240]. In view of these trends, in this thesis, the term 'user', while referring where ever possible to the young person actually using the CAM, will largely refer to the parents/guardians or carers of the paediatric-aged CAM users. This pattern is in line with literature reports of similar studies in this demographic [241–243].

1.5.3 Specific application to current study

In view of the above, the current research aims at systematically determining the perceived effectiveness and safety outcomes of CAM use among children in the general population within and around Aberdeen metropolis through parent users. Also, to get an unbiased view of the general inclination of parent residents within the Aberdeen metropolitan area towards child CAM use, their views, opinions and attitudes on/towards CAM use in children are determined irrespective of their use of CAM in their children. To improve the validity of the findings, and also properly situate them with respect to current realities, the data reported is generated from both primary and secondary epidemiologic sources in line with standard public health research methodologies.

1.6 Purpose and plan of study

1.6.1 Research questions

The goal of the research embodied in this thesis is to provide adequate answers to the following research questions:

1. What is the strength and quality of published literature relating to user-reported effectiveness and safety outcomes of paediatric CAM product use in terms of methodologies, methods and models?

2. What are the key findings of published literature on the impact of paediatric CAM product use in terms of user-reported effectiveness and safety outcomes?

3. What is the extent and nature of the pharmacovigilance data on paediatric CAM product use in the UK?

4. What is the nature and demography of the use and user-reported outcomes of paediatric CAM products and practices in the Aberdeen area of NE Scotland with respect to perceived effectiveness and safety?

5. What implications do the findings have for research and/or health policy and planning in Scotland?

1.6.2 Aims and objectives of the study

The specific objectives developed to achieve these aims include the following:

1. to identify and systematically review all published literature on user-reported effectiveness and safety outcomes of paediatric CAM products, using clear inclusion/exclusion criteria;

2. to determine and characterise the MHRA data on paediatric CAM product use with a view to deducing the associated safety outcomes;

3. to develop suitable and validated user-reported outcomes measures instruments for the study;

4. to carry out a survey on paediatric CAM use in Aberdeen metropolitan area using the pre-tested instruments;

5. to carry out descriptive and inferential statistical and regression analyses of the data obtained, as appropriate;

6. to tie together the findings of the various aspects of the research in order to generate valid consolidated study outcomes; and

7. to draw out conclusions and recommendations from the findings of the study.

1.6.3 General outline of the thesis

This doctoral research is in three sections. The first section reported in chapter two features a systematic review of the current literature in the field. It sets the global context on the area of research to provide standard parameters against which the findings of the more local studies will be compared. The second section documented in chapter three is a report of an exploratory database analysis of PV data on paediatric CAM product use in the UK. Chapter four details the findings of the last major aspect of the research, a cross-sectional survey of parents within

the Aberdeen metropolitan area on the user-perceived and safety outcomes of paediatric CAM use. Finally, after a triangulation of the findings of these separate strands of the research in chapter five, the thesis concludes in chapter six with an outline of the associated and resultant key recommendations of the study for health care policy and planning in Aberdeen, as well as the whole of Scotland.

Chapter 2

User-Perceived Effectiveness and Safety Outcomes of Paediatric Complementary & Alternative Medicines - A Systematic Literature Review

2.1 Introduction

The growing popularity of CAM use world-wide has resulted in a surge in the number of publications on the subject in recent years. As studies focused specifically on CAM use in paediatric populations are fewer than those for adult populations, there have also been much fewer systematic reviews (SRs) on paediatric CAM use studies. On the specific subject of the user-perceived effectiveness and safety (UPES) outcomes of CAM use in paediatric populations, there is no SR as yet, as the available SRs have focused mostly on prevalence of CAM use. This chapter aims at filling this knowledge gap. The SR was mainly aimed at determining the quantity and quality of available evidence on the outcomes associated with the use of paediatric CAM products (or CAMs) as published in the English Language in peer-reviewed journals from January 2000 to July 2011. Special emphasis was placed on the methods used in identified studies with a view to informing further phases of the doctoral research.

After a general introduction to SR methodology, the peculiarities of SRs of public health interventions in general are highlighted; before narrowing down to an overview of SRs on CAM use as a specific public health intervention. The specific aims and objectives of the current SR are then

outlined, followed by a detailed description of the methods followed in the SR process. Finally, the findings are reported and discussed in detail. In line with section 1.5 above, so as not to exclude studies carried out in parts of the world that have a broader definition of the paediatric population, an upper paediatric age limit of 21 years is used in the SR. Thus the term "paediatric" is used in this chapter to refer to infants, children and adolescents aged up to 21 years.

An overview of the findings of this first SR on UPES outcomes generally indicates a low methodological quality profile among the 46 eligible studies identified, which studied a cumulative population of 9,087 paediatric subjects. The low methodological quality profile identified was found to be due to a preponderance of study designs with a high tendency to bias and confounding, and scant use of piloted or standardized data collection tools. Most of the studies included were primarily descriptive and hospital-based, and utilised mainly self-completion or face-to-face interview methods to collect data usually by proxy report. In addition to the wide variety of definitions used for CAM therapies among the studies, many different and non-specific constructs were also used to describe UPES outcomes. While these factors complicated a meta-analytic synthesis of the outcomes findings reported, an overview of the findings reported indicated a high report of positive health outcomes by majorities of CAM user sub-populations among the studies (with the notable exception of three of the five the UK studies included), as well as a low report of adverse outcomes. These generally positive findings were, however, not evident in the conclusions and recommendations made by many studies, as study findings on outcomes were often either disregarded altogether, or reported partially or in negative light. One reason for this could be the observed high degree of non-application of inferential statistics to UPES outcomes data, even where such were used for the non-outcomes data reported by the same studies, and for the same study samples, suggesting a possible selective reporting and/or confirmation bias among study authors. While the various limitations acknowledged by study authors are note-worthy, the apparent tendency to selective reporting and/or confirmation bias in the studies could imply that the opinions and perspectives of patients who use CAM are probably not being given sufficient consideration by health care providers with respect to their (the users') health-related quality of life. This raises important ethical issues for social research generally; but more so in the light of the current global trend towards patient-centred health care. The high report of positive health outcomes for paediatric CAM use, however, highlight various implications for future research and clinical practice, as were indicated in a summary of the Patient-Oriented Evidence that Matters (POEM)-based recommendations made by many of the studies. These recommendations centred on the need for greater cooperation in decision-making and collaboration in research between health care providers and paediatric patients and/or their parents, as well as the need for greater integration of CAM into conventional care settings. All in all, the findings of this review emphasize the need for more rigorous, methodologically superior, and user-focused research into the UPES outcomes of paediatric CAM interventions -particularly in the UK; thus justifying the inclusion of a survey component in the current doctoral research.

2.1.1 Systematic Literature Reviews –from First Principles

A literature review in its simplest sense is a summary of the field of a subject that helps to support the identification of specific research questions [244]. Thus, in addition to demonstrating a reviewer's knowledge about a particular field of study [245], literature reviews indicate the directions for future research by highlighting the gaps in literature [246–248]. There are various types of literature reviews depending on the perspective from which they are viewed or the purpose for which they were intended [249]. Methodologically speaking, however, there are essentially two types of literature reviews –the traditional narrative reviews (NRs) and the more recent SRs [250–252]. (The other two main types of reviews –meta-analyses [253]and meta-synthesis [254]- are actually special forms of SRs.). While the traditional NRs are often at best expert opinions given based on a collection of studies selected and summarized by the author to buttress or showcase a certain viewpoint, SRs are carried out through a much more objective and rigorous process [255, 256].

The Cochrane Handbook for Systematic Reviews of Interventions [257] defines a SR as a collation of all empirical evidence that fits pre-specified eligibility criteria in order to answer a specific research question. A SR uses explicit, systematic methods that are selected with a view to minimizing bias and providing reliable findings from which conclusions can be drawn and decisions made [258, 259]. Such methods generally include the following series of steps: formulating the research question(s); specifying the inclusion and exclusion criteria and search strategy in a detailed peer-reviewed protocol; searching for studies on the subject using the pre-defined search strategy; screening identified studies using the pre-defined inclusion and exclusion criteria so as to select the studies to be included in the review; extracting all relevant data from included studies; assessing included studies for methodological quality; critically analysing results and synthesizing new data from them either quantitatively (in meta-analyses) or narratively; and finally, making recommendations for practice or future research [260–262]. Thus, a SR differs from the traditional NR essentially in the robust and methodical manner in which the studies included in it are identified, and their findings collated, analysed and synthesized in order to answer the research question(s) that informed the process [263, 264].

SRs were developed as a way to make sense of the numerous publications of the results of various interventions within the last 50 years. Following Archibald Cochrane's proposal in 1972 that, in view of the scarcity of resources, medical care should focus on interventions that have been shown to work best, based on available evidence [265], it became necessary to develop ways of achieving a critical appraisal and synthesis of research data on health interventions in order to determine evidence-based best practices. The first result of such efforts was the development of the method of meta-analysis in 1975, which statistically integrated data from several independent "combinable" studies to enable a summary conclusion [266–268]. This method was first applied

by Glass et al to research in the fields of education [269, 270] and psychotherapy [271]. Cochrane's continued calls for systematic reviews in medicine and health, were strengthened by Sackett and colleagues' formal definition of evidence-based medicine (EBM) in 1986 [272], and finally resulted in the opening of the Cochrane Collaboration centre at Oxford in 1992 for the specific purpose of "preparing, maintaining and disseminating systematic reviews of the effects of health care" [273]. Although the Cochrane Collaboration has continued to promote and provide guidelines for SRs of the effects of various health care interventions, with special emphasis on the use of RCT study designs, the basic principles of SR methodology have come to find application in various fields of research out with medical or effectiveness research. In each case, the main rationale behind the application of the SR methodology is to efficiently integrate existing information and provide data for the guidance of health care providers, researchers, and policy makers in rational decision making [274–277]. As one of the objectives of the current research is to inform health policy and planning in the context of CAM as a public health intervention, a SR of the subject was considered relevant. Primarily, however, the SR was expected to set the context for the whole doctoral research, by identifying and highlighting the global standards against with the data generated from the ensuing research would be compared.

2.1.2 Systematic reviews of public health interventions –RCTs vs. observational studies

This section explains the rationale for not excluding cross sectional studies in the systematic review: because of their high recognition in the evaluation of public health interventions.

Evidence-based public health (EBPH) differs from EBM in a number of ways, the most significant of which are the study designs used and the settings in which the intervention is applied [278]. Medical research studies rely essentially on RCTs, which are considered the "gold standard" for evaluation of efficacy or clinical effectiveness [279]; while public health interventions tend to rely a lot more on observational studies (cross-sectional, case-control, cohort, and case series). While SRs focusing on RCT study designs have generally been accorded the highest recognition in the standard hierarchy of evidence, the importance of observational study designs has become increasingly recognized in recent times [280]. Apart from their utility in scenarios where experimentation may be unnecessary, inappropriate, impossible, or inadequate [281], some comparative pooled studies have also shown them to yield statistically similar outcomes as RCTs in some cases[282–284]. Also, because RCTs tend to have high internal validity but low external validity, the applicability of their findings to real life practice (generalisability) is often limited [285–287]. Observational study designs therefore afford the opportunity to close the gap between theory and practice -between what works in ideal conditions (efficacy) and what actually works

in real life (effectiveness) [288, 289]; so they can supplement the findings of RCTs in this respect [280, 290, 291]. In recognition of this potential contributions of observational studies in the generation of comprehensive evidence, their inclusion in SRs of health interventions has been encouraged wherever possible [292–294].

While the contributions of observational studies in general to SRs have been recognized [295], longitudinal study designs (cohort and case-control) have generally been preferred to cross-sectional studies and case series for most medical decisions [296, 297]. As such, studies comparing observational studies with RCTs [282–284] have focused on longitudinal studies, which are ranked just below RCTs in the hierarchy of evidence [298], rather than on cross sectional studies, which are placed further down [299]. In EBPH, however, a different scenario obtains [278], as adequacy and plausibility assessments of public health interventions using cross sectional study designs have been shown to yield sufficient data to inform health policy decisions at local and/or international levels [300–302]. Since the major objective of the assessment of the impact of public health interventions is to inform public health policy [303, 304], cross sectional studies are accorded greater recognition in EBPH than in EBM [305, 306]. In view of this, a strict adherence to a standard hierarchy of evidence irrespective of study context has been severally discouraged [121, 307, 308]. These considerations informed the inclusion of cross sectional and other observational studies in the present review.

2.1.3 Systematic Reviews of CAM Interventions –An Overview

While there has been an upsurge in the publication of SRs on CAM interventions in recent times, very few of them have been focused on paediatric studies. A scoping search of articles indexed in Google Scholar conducted by the student in March 2014 shows that of the 62 SRs on non-specific CAM use, only one was published before 2000; while 16 were published between 2000 and 2009, and the rest (45) were published between 2010 and March 2014. Also, only 6 of the 62 SRs were focused on paediatric studies. In addition, although about 60% of the SRs (37 out of 62) focused on surveys, with most of them (27) summarizing research on prevalence of CAM use in various countries, regions, and/or patient populations, none of them focused on user-perceived effectiveness and safety (UPES) outcomes of CAM use. This same pattern of findings was obtained when a scoping search of SRs on specific CAM products was conducted. While the SRs identified for herbal medicines, Bach flower therapies, probiotics, and dietary supplements focused predominantly on CAM efficacy or clinical effectiveness, also with much fewer studies for paediatric subjects in each case; none focused on UPES outcomes of CAM use. The lack of summary evidence on this aspect of CAM use is very significant considering the pivotal role of perceived effectiveness (PE) as a global driver of CAM use through relationship marketing and peer-to-peer reports [309–312]. Also, considering the greater vulnerability associated with

paediatric populations in health and disease [313–315], as well as their significance as the future generation [316–318], the observed paucity of SRs in that population is obviously troubling.

The above considerations informed the decision to conduct a SR of recent findings on UPES outcomes of paediatric CAM use as part of the doctoral research on the outcomes associated with paediatric CAM use. The SR was conducted in August 2011. To ensure a manageable, contemporary and globally relevant study, the SR was proposed to focus on CAM products used in infants, children and adolescents aged up to 21 years as published in English in peer-reviewed journals in the period between January 2000 and July 2011. The specific findings sought to be summarized by the SR were detailed to include user reports of the perceived outcomes of their use of paediatric CAMs. More specifically, this included their experiences of paediatric CAM use with respect to perceived effectiveness or other positive health outcomes (in terms of perceived helpfulness, usefulness, satisfaction, benefits, improvement, etc.); as well as the adverse experiences reported as encountered during such CAM use (in terms of user-reported toxic and/or adverse effects, discomfort, harm, etc.). The study sought to answer the following questions:

1. What is the strength and quality of published literature relating to UPES outcomes of CAM use in infants, children and adolescents aged up to 21 years in terms of methodologies, methods and models?
2. What are the key findings of published literature on UPES outcomes of paediatric CAM use?

In order to answer these questions, the following specific objectives were developed:

- To determine, outline and compare the strengths and weaknesses of all identified studies on UPES outcomes of paediatric CAM use published in peer-reviewed journals in terms of methodological quality and consistency of findings;
- To summarize and discuss key findings of the studies identified;
- To identify gaps in the literature to inform further phases of the doctoral research;
- To inform the most appropriate methodological approaches in further research;
- To obtain standard reference data on the subject with which to compare the findings of the proposed research.

2.2 Methods

2.2.1 Review Protocol

A review protocol was drafted for the review, and after under-going internal and external review and a number of amendments, a final copy was adopted for the SR. The protocol was drawn up in line with standard recommendations for SR as outlined in the guidelines by Centre for Reviews and Dissemination, University of York [319], taking into consideration the limitations associated with the doctoral research process [320]. While a full version of the review protocol including the detailed search strategy used is provided in Appendix (i), a summary of the inclusion and exclusion criteria of the SR outlined in the standard PICOS format is as follows:

Inclusion criteria

- *Populations*:

  CAM studies focusing on paediatric subjects aged up to 21 years irrespective of health status, and/or their parents.

- *Interventions*:

  Studies that assessed natural product-based CAM (NP-CAM) modalities or complementary and alternative medicines (CAMs) alone or in combination with other CAM types were included. The specific modalities of interest included -herbal medicines, animal parts and/or minerals, homeopathic medicines, dietary supplements, essential oils, probiotics, Bach flower remedies, vitamin and mineral supplements, special diets, etc. Traditional Chinese Medicine was also included as it involves a high application of Chinese medicines.

- *Comparators*:

  No specific comparators or control groups were required for inclusion.

- *Outcomes*:

  Studies reporting any views, opinions, perspectives and perceptions shared, given, or expressed by users of CAMs in children and adolescents (i. e. the subjects themselves and/or their parents, guardians or carers) on the effectiveness (helpfulness, benefits, usefulness, etc.) and safety (adverse or side effects, discomfort, harmfulness, etc.) outcomes of their CAM use were included.

- *Study designs*:

  Essentially survey, cohort and other observational studies were included, irrespective of whether they were prospective/retrospective, or quantitative/qualitative in nature; provided

they were published as full papers in the English language between January 2000 and July 2011.

Exclusion criteria

- Perception studies that focused only on health professionals or other non-user/consumers;
- Studies that focused on the general views, opinions, perspectives and perceptions of CAM users as to the effectiveness and safety outcomes of NP-CAM, but did so from the perspective of their expectations, reasons for use, or beliefs, rather than based on their experiences of using them; and
- Perception studies that did not focus on user perspectives on CAM use, but rather on the decision-making process involved

2.2.2 Identification and Selection of Studies

Three mega-databases were used to search for papers to be included in the review: the Knowledge Network, EBSCO Host, and Pediatric Complementary and Alternative Medicine (PedCAM). These three were selected because together they were found to hold articles indexed by the major CAM databases, viz: Allied and Complementary Medicine Database (AMED), Alt HealthWatch, Cumulative Index to Nursing and Allied Health Literature (CINAHL), CAB Abstracts, International Pharmaceutical Abstracts (IPA), MEDLINE, EMBASE, PsychINFO, Complementary and Alternative Medicine Evidence Online (CAMEOL), CAM on PubMed, International Bibliographic Information on Dietary Supplements (IBIDS), Medicines Complete, and Natural products Alert (NAPRALERT). The databases were searched from January 2000 to July, 2011 using the following search terms in various combinations as detailed in the review protocol: "alternative medicin*", "bach flower", "Chinese medicin*", "complementary medicin*", "dietary supplement", "herbal medicin*", "herbal remed*"", "herbal supplement", "holistic health", "integrative medicin*", "natural product", "natural remed*", "nonconventional medicin*", "hom?eopath*", "megavitamin", "traditional medicin*", "unconventional medicin*", "adolescen*", "baby", "child", "father", "infant", "minors", "mother", "p?ediatric" "parent*", "teen*", "youth", "adverse", "benefi*", "discomfort", "effect*", "efficacy*", "harm*", "help*", "improve*", "opinion", "perceive", "perception", "perspective", "outcome", "safe*", satisf*", "use*", and "view".

At the conclusion of the search, the student screened the titles and abstracts of identified studies in a step-wise sequential process to identify and select studies that met the pre-specified inclusion criteria. One research supervisor independently reviewed a random sample of identified studies at

each stage of the process, after which the results were compared with the student's for inter-rater agreement. Cases where there was lack of consensus were settled either by discussion or by the opinion of a second supervisor. Where lack of consensus still persisted, the paper concerned was retained for the next stage of the process. Duplicate studies were removed from the resulting pool of studies, and a citation search was then carried out by title-screening the reference lists of the studies for potentially relevant CAM studies. These were then searched for and abstract-screened; and those that met the inclusion criteria were added to the pool of studies already selected for full paper screening. Full papers of all studies in the cumulative pool were then assessed for eligibility based on the pre-specified exclusion criteria. Ineligible studies were excluded from the final list of studies for data extraction and critical appraisal.

2.2.3 Data Extraction

A data extraction form was developed by the student for the extraction of relevant details from the selected papers, and was subsequently reviewed for completeness and utility by the review team. The final version enabled the extraction of 27 different items from each included study. The items were selected following a consideration of the recommendations in CRD's guidance for undertaking reviews in healthcare [319] and an overview of the items included in a random selection of SR papers on CAM-related topics. The extracted items were of 5 distinct categories. First, general information on each study was extracted, including the first author's name and publication year, the primary/corresponding author's profession and the place (country) of the study, along with its setting, geographical spread and duration. Then study sample-related data was collected, including the target and eventual sample size and the sampling method used, the associated sample size justification and response rate (RR) data; as well as the type of study participants and age range of the paediatric subjects involved. The study design & procedure-related data gathered included the study design, data collection method used, the level of adherence to ethical considerations, and the transparency of participant recruitment and data collection methods; as well as the associated study limitations acknowledged by the authors. Then the following CAM-related data were extracted: level of standardization of the CAM data collection tool; the type and description of the CAM therapies studied and the prevalence of their use among the participants; the specific aspects or dimensions of user-perceived effectiveness outcomes focused on in the study, with their associated level(s) of measurement; and the type of reporter involved. Finally, the following results-related information was obtained: the specific findings reported for UPES outcomes, and the level and type of statistical analysis conducted on the data; as well as whether a valid summary of results and conclusion was provided for such data. Any recommendations made based on the study findings on UPES outcomes were also recorded. To ensure an ordered and systematic entry and summary, a specific range of coding categories was drawn up for each item based on standard and expected report formats for observational studies.

Any feature encountered in the course of the extraction process that had not been included in the range of codes originally drawn up for the item concerned was discussed by the review team, and a final decision was reached on either a suitable existing code or to create an extra one to accommodate the new feature. The student extracted these data from the selected studies and entered them into the extraction form; the entries were cross-checked and ratified by a supervisor.

2.2.4 Critical Appraisal & Methodological Quality Assessment

An initial 21-item checklist was developed for critical appraisal of included studies. It comprised generally broad items drawn from various sources, including the guidelines published by CASP (Critical Appraisal Skills Programme) and the CRD [319]; standard recommendations of the STROBE (STrengthening the Report of OBservational studies in Epidemiology), ISPOR (International Society for Pharmaco-economics and Outcomes Research) statements, and updated PRISMA statements [321–323]; and the findings of a recent SR of the reporting of key quality criteria for survey research in 117 recently published reports of self-administered surveys [324]. After further review by the team, a shortened checklist of 12 assessment criteria specific for observational studies was adopted for methodological quality assessment of included studies in line with current recommendations [325, 326]. It comprised 12 fine-grained questions selected from the 21 questions in the critical appraisal checklist, each of which aimed at determining the risk of bias associated with various aspects of the study and its findings based on acceptable standards reported in literature for observational studies. The 12 questions selected for methodological quality assessment and the type of bias or quality criterion assessed by each are outlined in the table 2.1.

TABLE 2.1: List of criteria used for methodological quality assessment during critical appraisal

QUALITY ASSESSMENT INDEX	TYPE OF BIAS/QUALITY CRITERION ASSESSED
Is the study design associated with a low tendency to bias and confounding?	Internal validity
Were study participants defined by clear inclusion/exclusion criteria?	Selection bias; External validity
Was a clear systematic method used for sampling/recruitment?	Selection bias
Were there efforts to obtain a representative sample?	Selection bias; generalisability
Was the sample size justified or ≥300?	Selection bias
Was a response rate ≥60 % achieved?	Selection bias; Generalisability
Was a standard, validated, or piloted (n≥12) CAM tool used?	Information bias; internal validity
Were UPES outcomes data analysed for inference or confounding?	Confounding (External validity)
Was a valid summary of UPES outcomes data provided?	Selective outcome reporting (Confirmation bias)
Was the generalisability of findings on UPES outcomes discussed?	Generalisability/Applicability (External validity)
Were valid conclusions drawn from study findings on UPES outcomes?	Confirmation bias/Conclusion validity (External validity)
Was any POEM bottom line recommendation) made based on UPES outcomes data?	Practical relevance (Usefulness)

The primary factor considered in determining the acceptable standards selected for quality assessment was evidence from literature. Such acceptable standards were particularly relevant for

the determination of a minimum sample size for a pilot study [327, 328]; and the RR threshold [329, 330]. For the study sample size, the threshold of 300 participants was selected based on the calculated sample size of 306 for a minimum study population estimate of 1500 at 95% confidence interval with a 5% margin of error and 50% response distribution. However allowance was made for smaller sample sizes provided a clear statistical justification was provided for its use. Efforts considered indicative of the representativeness of the sample used included the use of multiple centres [331, 332] or a population-based approach [333, 334], the use of a broad/large database (rather than a local one) for participant recruitment for mail surveys [335]; and/or continuous recruitment for at least 12 months [336, 337] to account for possible year-round variations. The demonstration of the empirical generalisability of study findings was judged by the discussion of the consistency or otherwise of the findings of the study to those of similar studies conducted by other researchers [338]. The validity of the results summary or conclusion was based simply on their being in line with the outcomes data reported in the study, with a view to detecting confirmation bias [339, 340] or selective outcomes reporting bias [341, 342]. Such forms of bias have been found to be common in controversial topics like CAM [343–345]; and their report in systematic reviews is also required in the PRISMA updated guidelines [323]. Finally, as future research and practice is usually informed by the main findings of previous studies, the report of patient- and/or practitioner-oriented "bottom line" recommendations based on study findings on UPES outcomes was considered important for the practical relevance and usefulness of study findings in the context of Patient-Oriented Evidence that Matters (POEMs) [346, 347]. In this vein, to align with the focus of the current SR, research-oriented recommendations were deemed acceptable only where patient views/opinions were included.

The student and at least one supervisor critically appraised the selected studies in line with the adopted checklists; and afterwards cross-checked their ratings to ensure inter-rater agreement. In any case of variance, the case was reviewed together to facilitate an accord. Although each question had two categorical response options, either YES or NO, in cases where there was difficulty or lack of clarity in determining an unequivocal response with three assessors, the basis for the difficulty was entered qualitatively for the given criterion instead of a categorical response. As such only consensus ratings were reported. To enable a comparison of the quality of included studies, the number of criteria met by each study was recorded. In line with current recommendations [325, 326], an arbitrary standard of meeting a minimum of 67% of the quality criteria (i. e. any 8 of the 12 criteria) was considered indicative of high methodological quality.

2.2.5 Data Analysis and Synthesis

To facilitate a narrative synthesis of the findings of this review, aspects of the extracted data deemed relevant for addressing the specific objectives of the review were entered into SPSS

(IBM® SPSS® Statistics Data Editor Version 21) for statistical analysis. Inter-rater agreement during the screening stage was determined by Cohen's Kappa. To highlight the similarities and differences inherent in the selected studies, key characteristics were summarised using appropriate descriptive and/or univariate statistics. To determine whether research on the subject has changed significantly over the years, any differences in study characteristics as well as methodological quality between studies published by and after 2005 (the mid-point of the review period) were analysed for statistical significant difference using univariate and bivariate statistics. Additionally, the various factors associated with methodological quality were determined by appropriate bivariate analysis. Since the conclusions that would be reached by authors from the findings of their study would be mainly dependent on the way they summarised the findings of their study, which in turn would be dependent on the way the findings were analysed statistically, odds ratios were used to explore any tendency to confirmation bias by separately determining the strength of any association between the use of inferential statistics for CAM outcomes and non-outcomes data within the included studies, as well as the likelihood of the authors drawing a conclusion in line with the data provided when the majority rating was positive or not. Studies with a majority "positive" rating was described as those in which $> 55\%$ of the users surveyed reported positive health outcomes. Similarly, a majority "negative" rating was associated with studies where $< 45\%$ of the users reported positive health outcomes; while a "borderline" rating was reserved for those with a PE rating of 45-55%. Percentage scores were rounded off to one decimal place; and related pairs were compared for statistically significant differences, as appropriate, using the 2P (2 proportion) Binomial test in MiniTab® (MiniTab 16). For comparisons, statistical significant differences were tested for at $p \leq 0.05$.

2.3 Results

2.3.1 Study search and selection

A primary search of the 3 selected mega-databases using the specified search terms and combinations yielded a total of 2982 hits. Outputs of two searches made on EBSCO Host database in August 2011 are provided in Appendix (ii). 21 additional papers were later identified from other sources -a citation search of the studies initially selected after abstract screening (n=19) and recommendation from members of the review team (n=2). Following the sequential screening of titles and abstracts of the 3003 studies cumulatively identified, and the removal of duplicates, 67 papers were retained for full paper eligibility assessment, leading to the exclusion of 21 papers for various reasons, as outlined in figure 1. The remaining 46 papers were included in the review for data extraction and critical appraisal. The PRISMA flow chart summarising the study selection process is outlined in figure 2.1. A Kappa coefficient of 0.91 was obtained for inter-rater agreement for the 100 randomly selected papers screened at the abstract screening stage.

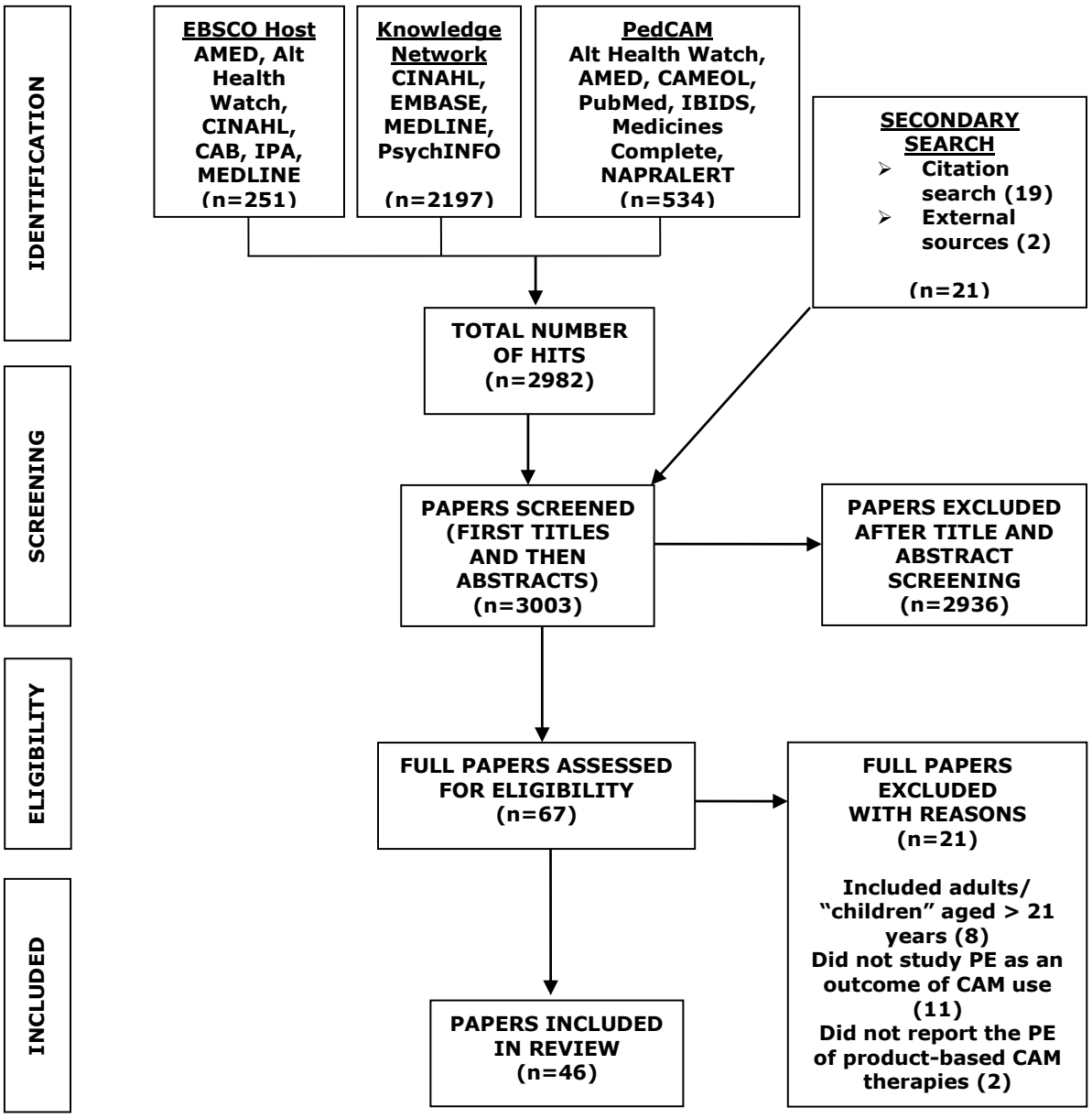

FIGURE 2.1: PRISMA Flow Chart for Identification Of Papers For Critical Appraisal

2.3.2 Data Extraction

The 5 categories of items extracted from the included studies are summarised in tables 2.2 to 2.6; while the completed data extraction form (DEF) is presented in table 2.12 at the end of the chapter. However, the ID numbers of studies with specific distinctive features are provided in tables 2.2 to 2.6 to facilitate a cross reference with the DEF. The ID numbers correspond to the serial numbers of the studies in the DEF.

2.3.2.1 General information on included studies

The 46 studies identified for critical appraisal were contributed by 43 different primary authors based in 16 different countries in 5 continents of the world. Except for 3 primary authors (April, K. T. (Canada); Day, A. S. (Australia); and Sawni-Sikand, A. (USA)) who contributed 2 studies each to the pool of included studies, each primary author contributed a single paper. Most of the primary or corresponding authors were medical doctors, which profession contributed 32 (70%) of the 46 included studies. While there was no eligible study published in the year 2000, and the year 2008 contributed most of the studies (9 studies), included studies were generally uniformly distributed across the period of review (X^2=9.478; df=10; $p > 0.05$). However, many more studies (29; 63.0%) were published after the mid-point year of 2005 (X^2 =3.130; df =1; p=0.077). The included studies also differed significantly with respect to the country (X^2=58.348; df=15; p¡0.001) and continent (X^2=28.348; df=4; p¡0.001) in which the studies were carried out; with the USA, Canada and Mexico contributing among themselves 21 (46%) of the included studies, skewing the continental distribution towards North America. The UK contributed 5 studies [348–352], which total was the highest among European countries. However, only 2 of these studies (and the only ones carried out in Scotland) [351, 352], were published after the year 2005, with the latest published in 2008 [352]. Most of the included studies (38, 83%) were carried out in clinic-based settings (X^2=19.565; df=1; $p < 0.001$), with 74% of such studies (28 studies) being carried out in outpatient departments. Only a few studies (12; 26%) recruited participants from multiple centres/cities or broad databases (X^2=10.552; df=1; p=0.001); and although the recruitment period was not reported in many cases (14 studies; 30%), among the studies where it was reported, the median study duration was shown to be six months [inter-quartile range (IQR): 2.6-9 months]. These facts are summarised in table 2.2.

2.3.2.2 Study sample-related data

Most of the sample-related data extracted were skewed; with 57% of actual sample size data (26 studies) being skewed towards lower limits of at most 200 respondents, while 65% of the studies included paediatric subjects aged above 16 years. Also, 28 studies (61%) attained response rates above 60%, with a mean RR of 78% among the 34 studies that reported such data. Skewing was also observed with respect to the sampling method used, as well as the provision of a statistical justification for the sample sizes used. While only 2 studies [348, 353] used the random sampling method (4%; X^2=17.913, df=1; $p < 0.001$), only 3 studies [348, 354, 355] provided statistical justification for the sample size used (7%; X^2=34.783, df=1; $p < 0.001$). Although cancer was the health condition most studied (8 studies; 17%), the studies were uniformly distributed across the 10 WHO ICD categories studied (X^2 =12.143; df=9; p=0.217). However, only 2 studies (4%)

TABLE 2.2: General characteristics of included studies

Study parameter	Categorical distribution	Frequency n (%)	Statistical analysis (Descriptives/X^2 statistic & p value)	Study ID number in data extraction form (DEF)
Annual publication frequency	2000	0 (0.0)	Modal year of publication: 2008 (9 studies); Study distribution around mid-point year (2005): By -17 (37.0 %); After -29 (63.0 %) [X^2 =3.130; df =1; p=0.077]	-
	2001	3 (6.5)		33;36;37
	2002	3 (6.5)		22;29;41
	2003	4 (8.7)		4;10;17;19
	2004	2 (4.3)		21;38
	2005	5 (10.9)		1;6;16;25;28
	2006	3 (6.5)		7;12;40
	2007	6 (13.0)		5;13;16;23;26;30
	2008	9 (19.6)		2;9;20;31;34;35;42;43;46
	2009	3 (6.5)		11;14;15
	2010	5 (10.9)		3;32;29;44;45
	2011 (July)	3 (6.5)		8;24;27
First/corresponding author profession	Medical doctor	32 (69.6)	Modal author profession: Medical doctor (32 studies)	See DEF
	Other core HCPs [Pharm. -2; RN -3]	5 (10.9)		Pharm.: 2;18 RN: 31;32;38
	Allied HCPs [Psych. -3; O. T.-2; Diet. -2]	7 (15.2)		Psych.:13;30;39 ; O. T.: 14;15, Diet.: 33;43
	Unclear	2 (4.3)		3;37
Study distribution by continent & country	Africa [Nigeria (1)]	1 (2.2)	Modal continent: North America Comparison across continents: X^2 =28.348; df=4; p=0.000 Modal country: USA Comparison across countries: X^2 =58.348; df=15; p=0.000	9
	Asia [Hong Kong (1); Israel (1); Jordan (1); Singapore (2); Turkey (3)]	8 (17.4)		Hong Kong: 1, Israel: 40, Jordan: 32, Singapore: 11;12, Turkey: 3;8;31
	Australia [Australia (3)]	3 (6.5)		16;21;22
	Europe [Denmark (1); Ireland (1); Switzerland (1); Italy (2); Germany (3); UK (5)]	13 (28.3)		Denmark: 10, Ireland: 18, Swiss: 45, Italy: 24;44, Germany: 20;42;46, Scot: 26;43. Engld: 19;36;38
	North America [Mexico (1); Canada (6); USA (14)]	21 (45.7)		Mexico: 23, Canada: 6;7;14;15;28;37 USA –See DES
Type of study setting	Clinic-based [OPD (28); ED (3); Hospital records (6); Hospital-based health centre (1)]	38 (82.6)	Comparison across type of study setting: X^2 =19.565; df=1; p=0.000 Modal study setting: Outpatient clinics (28 studies)	OPD: See DEF, ED: 5;28;45: Records: 3;15;21;34;35;38; Health centre: 12
	Non clinic-based (Registry (4); Online/web database (2); Health management centre (1); School (1)]	8 (17.4)		Registry: 33;36;37;42; Online: 3;39 Health centre: 20; School: 29
Geographical spread of recruitment	Single centre/local database	34 (73.9)	X^2 =10.552; df=1; p=0.001	See DEF
	Multi-centre/broad database	12 (26.1)		3;7;14;15;20;33;36;37;39;41;42;46
Study duration (Length of participant recruitment)	Up to 6 months	18 (39.1)	Median: 6 months; [Range: 0.5-120 month; IQR: 2.63-9 month]	See DEF
	6.5-12 months	10 (21.8)		2;4;5;14;19;24;28;31;32;42
	More than 12 months	4 (8.7)		20;43;44;46
	Not stated	14 (30.4)		See DEF

HCP –health care professional; Pharm. –pharmacist; RN: nurse; Psych. –clinical psychologist; O. T. –occupational therapist; Diet,: -dietitician; Scot. –Scotland; Engld. –England; OPD –outpatient department; ED –emergency department;

were conducted irrespective of participant health condition. These facts are summarised in table 2.3.

TABLE 2.3: Study sample-related data of included studies

Study parameter	Categorical distribution	Frequency n (%)	Statistical analysis (Descriptives/ X^2 statistic & p value)	Study ID number in data extraction form (DEF)
Target sample size (Number of people invited to participate)	Up to 200 participants	20 (43.5)	Median: 200 participants; [Range: 39-1595; IQR: 101-350]	See DEF
	201-400 participants	10 (21.7)		2;6;8;13;14;15;17;20;39;44
	401-1000 participants	6 (13.0)		5;10;24;26;27;28
	>1000 participants	3 (6.5)		36;41;42
	Not stated	7 (15.2)		1;3;4;9;10;40;45
Number of respondents (Actual sample size attained)	Up to 200 respondents	26 (56.5)	Median: 119 respondents; [Range: 36-994; IQR: 78.75-276]	See DEF
	201-400 respondents	11 (23.9)		1;4;8;9;11;15;17;20;26;27;39
	401-1000 respondents	5 (10.9)		5;10;24;28;36
	Not stated	4 (8.7)		41;42;45;46
Justification of sample size used	Provided	3 (6.5)	X^2=34.783; df=1; p=0.000	32;35;37
	Not provided	43 (93.5)		See DEF
Response rate attained	21-40 %	1 (2.2)	Mean (±SD) (n=34 studies): 78.06 % (±16.655);	13
	41-60 %	5 (10.9)		2;6;26;38;44
	61-80 %	13 (28.3)		See DEF
	81-100 %	15 (32.6)		See DEF
	Insufficient data	9 (19.6)		1;3;4;9;11;40;41;42;45
	Not applicable	3 (6.5)		34;39;46
Sampling method used	Consecutive	24 (52.2)	Modal method: Consecutive (24 studies)	See DEF
	Random	2 (4.3)		33;36
	Not described	20 (43.5)		See DEF
Upper age limit of paediatric subjects	<16 years	7 (15.2)	Modal upper age limit: 16-18 years (27 studies)]	12;15;23;24;37;42;44
	16-18 years	27 (58.7)		See DEF
	19-21 years	3 (6.5)		2;35;39
	Not stated	9 (19.6)		1;4;9;13;27;31;40;41;45
Disease conditions studied [International classification of diseases (ICD) classification]	Neoplasms	8 (17.4)	Modal ICD category: Neoplasms (8 studies) Comparison across the 10 valid ICD classes (n=35 studies): X^2 =12.143; df=9; p=0.217	12;23;32;33;37;38;40;42
	Endocrine, nutritional and metabolic diseases	3 (6.5)		2;20;31
	Mental & behavioural diseases	6 (13.0)		3;7;13;16;34;39
	Nervous system diseases	2 (4.3)		6;17
	Ear & mastoid process diseases	1 (2.2)		24
	Respiratory system diseases	3 (6.5)		4;29;44
	Digestive system diseases	3 (6.5)		21;22;43
	Skin & subcutaneous tissue diseases	4 (8.7)		1;18;19;46
	Musculoskeletal & connective tissue diseases	4 (8.7)		14;15;30;35
	Genitourinary system diseases	1 (2.2)		25
	Nonspecific/mixed	9 (19.6)		5;9;10;11;26;27;28;45
	No health condition	2 (4.3)		8;36

2.3.2.3 Study Design & procedure-related data

The study design and procedure-related data of included studies are summarised in table 2.4. Although most of the included studies (40; 87%) were cross sectional studies, three prospective longitudinal studies [356–358], a case-control study [359], and a case series [360] were also included. There was also a secondary study that analysed paediatric data from an on-going, broader online

survey on autism spectrum disorders [361]. While a variety of data collection methods was used, face-to-face self-completion questionnaires (19 studies, 41%) and interviews (12 studies, 26%) were particularly favoured. Although there was high report of adherence to ethical considerations among included studies, with only 2 studies (4%) [354, 362] not reporting any such considerations whatsoever, only 14 studies (30%) showed evidence of fully considering the 3 basic ethical factors required for health and social research involving children –Research Ethics Committee (REC) approval, informed consent and confidentiality/anonymity [363]. Many studies, however, reported only obtaining REC approval and informed consent from participants (18 studies; 39%). Also, only about a third (35%) of the studies transparently reported participant recruitment and data collection methods, another ethical requirement for research integrity [364].

TABLE 2.4: Study design and procedure-related data of included studies

Study parameter	Categorical distribution	Frequency n (%)	Statistical analysis (Descriptives/X^2 statistic & p value)	Study ID number in data extraction form (DEF)
Study design	Longitudinal study [Prospective]	3 (6.5)	X^2= 129.217; df=4; p=0.000; Modal design: Cross sectional study	14;44;46
	Case-control study	1 (2.2)		7
	Cross sectional study	40 (87.0)		See DEF
	Case series	1 (2.2)		34
	Secondary study (data analysis)	1 (2.2)		39
Data collection method	Interview [f-2-f -12; telephone -4; medical consultation –1]	17 (37.0)	X^2=20.652; df=2; p=0.000 Modal method: Self-completion questionnaire	F2f –See DEF; Telephone: 7;12;33;37, Medical consultation: 44
	Self-completion questionnaire [f-2-f -19; postal -7; Online -1]	27 (58.7)		F2f –See DEF; Online: 3, Postal: 13;14;21;35;36;38;42
	Other methods [Patient medical records -1; data analysis -1]	2 (4.3)		Patient medical records: 34 data analysis: 39
Transparency of data collection procedure	Who did it? How? Where exactly? When? & For how long?)			
	Transparent (Fully described)	16 (34.8)	X^2= 4.261; df=1; p=0.039	See DEF
	Not transparent (Partially described)	30 (65.2)		
Level of report of adherence to ethical requirements	None reported	2 (4.3)	X^2=19.652; df =4; p=0.001	12;37
	No REC approval but some others reported [informed consent -5; anonymity/confidentiality -2; Both -1 study]	8 (17.4)		Informed consent: 2;3;18;26;44, anonymity/confidentiality: 11;13, Both: 27
	REC approval only	4 (8.7)		1;8;29;34
	REC approval & informed consent only	18 (39.1)		See DEF
	Fully considered all ethical considerations above	14 (30.4)		See DEF

f2f –face-to-face: REC –research ethics committee

2.3.2.4 CAM-related data

Although CAM was described to study participants mostly by providing examples or a list of therapies (28 studies), various definitions were used among the studies. However, in 7 studies (15%) [349, 355, 365–369], there was no report whatsoever of any CAM definition or description being provided to participants. Although many studies reported a previous use or pilot of the CAM outcomes data collection tool used, with 17 of them (37%) reporting a revision of the tool

after a pilot, only 4 studies [355, 358, 370, 371] utilised validated instruments for collecting CAM outcomes data. However, 21 studies (46%) provided no information whatsoever on the level of standardisation of the instrument used. Although various different terms were used to describe the positive health outcomes studied, the most popular terms were perceived improvement (14 studies; 30%), perceived effectiveness/efficacy (10 studies; 22%) and perceived helpfulness (8 studies; 17%). Although outcomes were reported predominantly by proxy (37 studies; 80%), and were measured mostly at a nominal and/or ordinal levels (23 studies; 50%), higher levels of measurement as well as more direct forms of outcome report were also used. These characteristics of the studies are summarised in table 2.5.

TABLE 2.5: CAM-related data of included studies

Study parameter	Categorical distribution	Frequency n (%)	Statistical analysis (Descriptives/X^2 statistic & p value)	Study ID number in data extraction form (DEF)
CAM definition /description to participants	None reported	7 (15.2)	X^2=42.304; df =2; p<0.001	18;19;28;30;31;32;45
	Definition provided [Only defined -8; examples/list of therapies also provided -28]	36 (78.3)		See DEF
	No definition needed	3 (6.5)		1;44;46
Dimension of perceived effectiveness measured	Effectiveness/efficacy	10 (21.7)	X^2=17.913; df=6 p=0.007	2;4;20;21;24;26;29;38;43;45
	Helpfulness	8 (17.4)		6;13;16;27;28;30;35;36
	Usefulness	2 (4.3)		8;23
	Satisfaction	4 (8.7)		5;31;37;41
	Improvement	14 (30.4)		See DEF
	Benefits	6 (13.0)		7;9;14;15;25;32
	Positive effects/experiences	2 (4.3)		10;17
Level of standardization of CAM outcomes data collection tool	No report of pilot or validation	21 (45.7)	X^2=51.565; df=5; p=0.000	See DEF
	Tool previously used	2 (4.3)		5;8
	Developed and reviewed	2 (4.3)		21;22
	Piloted & revised	17 (37.0)		See DEF
	Piloted & validated	3 (6.5)		17;20;32
	Standard tool	1 (2.2)		44
Level of outcome measurement	Not described	18 (39.1)	X^2=44.931; df=6; p=0.000	See DEF
	Nominal scale	8 (17.4)		1;6;8;13;19;23;26;36
	Ordinal scale	14 (30.4)		See DEF
	Interval scale	2 (4.3)		38;44
	Ratio scale	2 (4.3)		35;46
	Mixed [Nominal & Ordinal]	1 (2.2)		3
	Qualitative report	1 (2.2)		37
Type of UPES outcomes report	Not stated/Unclear	3 (6.5)	X^2=105.739; df=4; p=0.000	2;36;44
	Self-report	1 (2.2)		29
	Proxy report	37 (80.4)		See DEF
	Mixed report	4 (8.7)		10;19;40;46
	Joint report	1 (2.2)		35

2.3.2.5 Results-related data

Except in 3 studies (7%) in which study findings on UPES outcomes were reported as mean ratings of PE and AE of therapies [350, 357, 372], outcomes findings were reported mainly as percentages of users rating PE or AE. While in most cases, these percentages were presented for overall CAM use by participants, in 13 studies, they were more specifically presented either for the individual CAM therapies used [220, 353, 359, 361, 373–376], or for the episodes/experiences of

CAM use [348, 349, 356, 371, 377]. One study [378], however, reported PE outcomes based on both user percentage and the therapies used; while another study [361], in addition to presenting PE outcomes as percentages of the degrees of user ratings for respective therapies, also distinctively applied odds ratios to determine the general direction of PE ratings for respective therapies, in terms of the degree of improvement reported by users.

The results-related data of included studies are summarised in tables 2.6 and 2.7. Table 2.6 shows that, the proportion of users reporting positive outcomes following CAM use ranged from as low as 35% [349] to as high as 99% [379], with a median PE rating of 72.5%. Discounting the 3 studies that utilised mean PE ratings, the outcomes of CAM use were generally perceived as positive by over 55% of users in 34 of 43 studies (79%). While AE outcomes were not studies in 27 of the studies (59%), of the 19 studies that studied it, the AE outcomes reported ranged from 0-11.9%, with a median of 4%, and a mean of 4.3%. While these outcomes data were validly summarised in 34 studies (74%), valid conclusions were reached in only 21 of the cases (46%), indicating a high degree of disparity. Detailed analysis based on study categorisation based on the majority outcomes rating by users suggests this disparity to be due to the disregard of positive outcomes reported by majority of the users sampled. With respect to providing a valid summary of the outcomes data reported, for instance, 92% of the 12 studies in which outcomes data were either not summarised at all or not validly summarised (11 studies) reported positive outcomes by a majority of CAM user samples surveyed. Similarly, 22 of the 25 studies (88%) which either did not provide any conclusion based on the outcomes data reported or made ambivalent or misleading conclusions also reported positive outcomes by $> 55\%$ of CAM users in the study samples.

Table 2.6 also shows that there was a disparity in the type and degree of statistical analyses applied to the outcomes and non-outcomes data reported in the studies. While there was a uniform spread in the level of statistical analyses used for non-outcomes data in included studies (X^2=4.957; df=3; p=0.175), with a generally high use of inferential statistics; the statistical analyses applied to outcomes data in the studies were highly skewed towards descriptive statistics (X^2=68.783; df=4; p=0.000), with scant use of inferential statistics. Thus, while CAM UPES outcomes data were mostly presented using only descriptive statistics (31; 67%), non-outcomes data were mostly presented using inferential statistical analyses (40 studies; 87%). Also, among the 15 studies in which multivariate analyses were applied to non-outcomes data, such analyses were extended to UPES outcomes data in only 3 cases [357, 358, 370]. A comparative analysis reported in table 2.7 confirms the statistical significance of these observations, as the application of inferential statistics was found to differ significantly between outcomes and non-outcomes data (87% vs. 30%; z = 6.72; $p < 0.001$). Table 2.7 also highlights the statistically significant disparity between the proportion of studies that validly summarised the outcomes data reported and the proportion that provided a valid conclusion for the study based on the outcomes data they reported.

TABLE 2.6: Results-related data of included studies

Study parameter	Categorical distribution	Frequency n (%)	Statistical analysis (Descriptives/X^2 statistic & p value)	Study ID number in data extraction form (DEF)
Level & type of statistical analysis used for non-outcomes data	Only descriptive statistics	6 (13.0)	X^2=4.957; df=3; p=0.175	2;3;16;18;22;37
	Descriptive & univariate	15 (32.6)		See DEF
	Descriptive & bivariate	10 (21.7)		7;9;10;12;19;23;29;35;38;40
	Descriptive & multivariate	15 (32.6)		See DEF
Level & type of statistical analysis used for outcomes data	No statistical analysis	1 (2.2)	X^2=68.783; df=4; p=0.000	3
	Only descriptive statistics	31 (67.4)		See DEF
	Descriptive & univariate	9 (19.6)		1;5;8;10;23;24;35;38;45
	Descriptive & bivariate	2 (4.3)		29;43
	Descriptive & multivariate	3 (6.5)		17;44;46
Proportion of users reporting PE [Majority rating among users]	Data unclear or N/A (Uncl/NA)	4 (8.7)	Mean (SD): 71.1 (15.7) %; Median: 72.5 % [Range:35-99 %; IQR: 57.5-84.5 %] Modal category: >55 % [Mostly positive]	Unclear: 9; N/A: 35;38;46
	<45 % [Mostly negative (-VE)]	4 (8.7)		13;18;19;45
	45-55 % [Borderline (Bordl.)]	4 (8.7)		6;31;41;43
	>55 % [Mostly positive (+VE)]	34 (73.9)		See DEF
Proportion of users reporting AEs	0 % (none reported)	3 (6.5)	Mean (SD): 4.2 (3.3) %; Median: 4.0 % [Range: 0-11.9 %; IQR: 1.5-6.3 %] Modal category: Not studied	22;44;46
	1-5 %	6 (13.0)		6;8;25;27;34;42
	6-10 %	4 (8.7)		9;10;12;45
	>10 %	1 (2.2)		20
	Qualitative report	1 (2.2)		3
	Data unclear	4 (8.7)		33;35;37;43
	Not studied	27 (58.7)		See DEF
Validity of summary provided on outcomes data [Majority rating type]	No summary provided [+VE -8]	8 (17.4)	X^2= 34.609; df=2; p=0.000	4;10;11;28;29;36;40
	Not validly summarised in line with data provided [+VE -3; Uncl -1]	4 (8.7)		+VE: 5;;21;32; Uncl: 9
	Validly summarised in line with data provided [+VE -23; Bordl. -4; -VE -4; N/A -3]	34 (73.9)		+VE: See DEF; Bordl.: 6;31;41;43; -VE: 13;18;19;45; Not applicable: 35;38;46
Type of conclusion made on UPES findings [Majority rating type]	No conclusion provided [+VE 18; Bordl -2; -VE -1]	21 (45.7)	X^2= 12.565; df=2; p=0.002	+VE: See DEF; Bordl.: 41;43; -VE: 13
	Ambivalent or misleading [+VE -4]	4 (8.7)		2;3;7;39
	Valid conclusion in line with data reported [+VE -12; Bordl. -2; -VE -3; Uncl/NA -4]	21 (45.7)		+VE: See DEF; Bordl.: 6;31; -VE: 18;19;45; Uncl/NA: 9; 35;38;46
Type of POEM-based recommendation made based on outcomes data reported	None made [None on outcomes -18; None related to practice or outcomes research -7]	25 (54.3)	X^2= 21.652; df=3; p=0.000	See DEF
	Calling for (improved) outcomes research	6 (13.0)		3;9;30;35;40;46
	Directed at HCPs	6 (13.0)		1;16;24;28;38;44
	Both practice & research-oriented	9 (19.6)		7;13;14;15;17;20;32;33;37

PE –perceived effectiveness; AE –adverse effects; N/A –not applicable; UPES –user-perceived effectiveness & safety outcomes; HCP –health care professionals; POEM –patient-oriented evidence that matters; +VE rating –positive outcomes rating by >55 % of users; Bordl. Rating –positive outcomes rating by 45-55 % of users; -VE rating –positive outcomes rating by <45 % of users

TABLE 2.7: 2-Proportion Binomial test for disparities in some results-related data among included studies

Parameter tested	≠ of studies with parameter	≠ of studies tested	Proportions to be tested	Test for difference [z score]	95% CI for difference	P value
Valid summary of results	34	46	74 %	74 % vs. 46 %; [Z = 2.89]	(0.091-0.474)	0.004
Valid conclusion drawn	21	46	46 %			
Use of inferential/Multivariable statistics in paper	40	46	87 %	87 % vs. 30 %; [Z = 6.72]	(0.400 -0.730)	0.000
Use of inferential/Multivariable statistics for UPES outcomes	14	46	30 %			

Although the outcomes reported were validly summarised in 34 studies (74%), valid conclusions were made in only 21 studies (46%), with the 2 proportions differing significantly (74% vs. 46%;z =2.89; $p < 0.05$). Following from the results reported in table 2.7, the odds of drawing a valid conclusion based on the type of majority PE rating reported for the study was determined as a test of possible confirmation bias, and the output is displayed in tables 2.8 and 2.9.

TABLE 2.8: Cross-tabulation of the odds of drawing valid conclusions based on the type of majority PE rating reported in the study

Were valid conclusions drawn from outcomes data provided? * Was a POSITIVE majority rating of PE outcomes (PE >55 %) reported for the study? Cross-tabulation			Was a POSITIVE majority rating of PE outcomes (PE >55 %) reported for the study?		Total
			Yes	No	
Were valid conclusions drawn from outcomes data reported?	**Yes**	**Count**	**12**	**9**	**21**
		% within Were valid conclusions drawn from outcomes data reported?	57.1 %	42.9 %	100 %
	No	**Count**	**22**	**3**	**25**
		% within Were valid conclusions drawn from outcomes data reported?	88.0 %	12.0 %	100 %
Total		**Count**	**34**	**12**	**46**
		% within Were valid conclusions drawn from outcomes data reported?	73.9 %	26.1 %	100 %

TABLE 2.9: SPSS risk estimate output for test of confirmation Bias

PARAMETER TESTED	Value	Confidence Interval		Implication
		Lower	Upper	
Odds Ratio for: Were valid conclusions drawn from outcomes data reported? (Yes/No)	0.182	0.041	0.802	Significant association
Relative Risk for cohort: Was a POSITIVE majority rating of PE outcomes (PE >55 %) reported for the study? (Yes)	0.649	0.436	0.966	Significant association
Relative Risk for cohort: Was a POSITIVE majority rating of PE outcomes (PE >55 %) reported for the study? (No)	3.571	1.108	11.156	Significant association

Odds ratio estimates clearly show the much reduced odds of drawing valid conclusions from outcomes data reported by the studies (OR 0.18; 95 % C I: 0.041- 0.802). This finding was also shown to be associated with reduced chances of drawing valid conclusions when the majority PE rating was positive (P >55 %) (RR 0.649; 95 % C I: 0.436-0.966); and about 4-fold likelihood of doing same when the majority PE rating was not positive (RR 3.571; 95 % C I: 1.108-11.156)

-that is, when the majority PE rating was either borderline (PE= 45-55 %) or negative (PE <45 %).

Only 21 studies (46%) made POEM-based recommendations on the UPES outcomes findings they reported. The full extracts of all the recommendations made based on UPES outcomes are included in the data extraction form in table 2.12. A coherent synthesis of the POEM-based recommendations made by the various studies, however, goes as follows: in view of the predominantly positive UPES outcomes reported for CAM use in children, the time has come for healthcare researchers and providers not only to become sensitive to parental attitudes towards CAM [375] and respect their wishes to use CAM even if its efficacy is not yet proved [371], but also to aim to work together with parents who choose to use CAM [380] by adapting to and supporting their needs [354], and helping them to properly evaluate the benefits of CAM [365, 374, 375]. In this way, health professionals can practically evaluate the use of CAM in children [356, 377] with a view to identifying safe and potentially helpful therapies [354], and optimising the positive outcomes reported for such therapies [380]. While further research is needed to substantiate apparent benefits of CAM [359] in terms of improved clinical outcome or enhanced quality of life among pediatric patients [353], it should be understood that potential interactions and benefits of CAM cannot be determined without adequate information on patient and parent CAM behaviour [355]. As such, future research, rather than aiming to understand why patients turn to CAM in general [354], should focus instead on therapies that parents feel are helpful and low in side effects [372]; and must consider effectiveness in relation to users' expected outcomes [354]. In other words, clinical trials should be aimed at establishing the validity of parents' claims, and assessing the safety of CAM therapies for children [381]. While such research continues, the use of therapies with high safety profiles that have been found to be consistently associated with positive and beneficial effects [350] should be encouraged in conditions where they have been found useful [380]. This is particularly so for children with high health care needs [356, 377] such as recurrent conditions like acute otitis media [382] or paediatric respiratory ailments [358]; chronic conditions like physical disabilities [377], cerebral palsy [370]; or incurable conditions like cancer [350]. This would ensure that patients' (and parents') desires to "leave no stone unturned" [362] is considered, and that they are not denied any therapy that could prove helpful when integrated into their conventional treatments [350, 370]. To facilitate this integration process, health care providers need to gain some familiarity with CAM therapies most often reported as useful [382, 383], communicate with patients about various treatment options, and make referrals wherever appropriate [353]. Additionally, they should try to understand what factors make CAM modalities desirable and effective either directly, on their own [370], or indirectly, by differentially affecting the child's medical and psychological status and, thus, contributing to a positive outcome and optimal overall functioning [368]; so as to consider how these factors can be woven into the "standard care" that children currently receive [370].

2.3.3 Quality Assessment

The results of the quality assessment of included studies based on the 12 quality indices selected are outlined in table 2.10; while a summary of the overall performance of included studies presented is in table 2.11. Generally, included studies fared poorly in terms of methodological quality, with an overall quality rating of 45% (251/552 points) across the studies, and only 9 studies (20%) meeting the pre-set minimum of 8 quality indices indicative of high quality.

TABLE 2.10: Results of quality assessment of included studies

ID no	Low tendency to bias & confounding?	Clear inclusion/ exclusion criteria?	Clear systematic sampling method?	Efforts towards representative sample?	Sample size justified or ≥300?	RR ≥60 %?	CAM tool validated/ piloted (n=12)?	Inferential statistical analyses/ confounding?	Valid summary of outcomes data?	Discussed generalisability?	Valid conclusions drawn?	POEM recommendation?	QA Score (x/ 12)
1	No	No	No	No	No	NR	No	Yes	Yes	Yes	No	Yes	4
2	No	No	No	No	No	No	No	No	Yes	No	No	No	1
3	No	No	Yes	Yes	No	No	No	No	Yes	Yes	No	Yes	5
4	No	No	No	No	Yes	NR	No	No	No	No	No	No	1
5	No	Yes	No	No	Yes	Yes	Yes	Yes	No	Yes	No	No	6
6	No	Yes	No	No	No	No	No	No	Yes	Yes	Yes	No	4
7	Yes	Yes	No	Yes	No	Yes	No	No	Yes	No	No	Yes	6
8	No	No	No	No	No	Yes	Yes	Yes	No	Yes	No	No	4
9	No	Yes	No	No	Yes	NR	NR^{n}	No	No	Yes	Yes	Yes	5
10	No	Yes	Yes	No	Yes	Yes	No	Yes	No	No	No	No	5
11	No	No	No	No	Yes	NR	No	No	No	No	No	No	1
12	No	Yes	No	No	No	Yes	No	No	Yes	Yes	Yes	No	5
13	No	No	No	Yes	No	No	No	No	Yes	No	No	Yes	3
14	Yes	Yes	No	Yes	No	Yes	NR^{n}	No	Yes	Yes	Yes	Yes	8
15	No	Yes	No	Yes	No	Yes	No	No	Yes	Yes	Yes	Yes	7
16	No	Yes	No	No	No	Yes	No	No	Yes	Yes	No	Yes	5
17	No	Yes	Yes	No	No	Yes	Yes	Yes	Yes	No	Yes	Yes	8
18	No	No	No	No	No	Yes	No	No	Yes	Yes	Yes	No	4
19	No	Yes	Yes	No	No	Yes	No	No	Yes	Yes	Yes	No	6
20	No	Yes	No	Yes	No	Yes	Yes	No	Yes	Yes	Yes	Yes	8
21	No	No	Yes	Yes	No	Yes	NR^{n}	No	No	Yes	No	No	4
22	No	No	No	No	No	Yes	NR^{n}	No	Yes	Yes	No	No	3
23	No	No	Yes	No	No	Yes	NR^{n}	Yes	Yes	Yes	Yes	No	6
24	No	Yes	Yes	Yes	Yes	Yes	No	Yes	Yes	Yes	No	Yes	9
25	No	Yes	No	No	No	Yes	No	No	Yes	Yes	No	No	4
26	No	No	Yes	No	Yes	No	No	No	Yes	No	No	No	3
27	No	No	Yes	No	Yes	Yes	No	No	Yes	Yes	Yes	No	6
28	No	Yes	No	No	Yes	Yes	Yes	No	No	No	No	Yes	5
29	No	Yes	Yes	No	No	Yes	NR^{n}	Yes	No	No	No	No	4
30	No	Yes	Yes	No	No	Yes	No	No	Yes	No	Yes	Yes	6
31	No	Yes	Yes	Yes	No	Yes	No	No	Yes	No	Yes	No	6
32	No	Yes	No	No	Yes	Yes	Yes	No	No	No	No	Yes	5
33	No	Yes	Yes	Yes	No	Yes	No	No	Yes	Yes	No	Yes	7
34	No	Yes	Yes	No	No	NR.	No	No	Yes	No	Yes	No	4
35	No	Yes	Yes	No	No	Yes	No	Yes	Yes	Yes	Yes	Yes	8
36	No	Yes	Yes	Yes	Yes	Yes	NR^{n}	No	No	No	No	No	5
37	No	Yes	Yes	Yes	Yes	Yes	No	No	Yes	No	Yes	Yes	8
38	No	Yes	Yes	No	No	No	No	Yes	Yes	Yes	Yes	Yes	7
39	No	Yes	Yes	Yes	No	No	No	Yes	Yes	Yes	No	No	6
40	No	Yes	Yes	No	No	NR	No	No	No	Yes	Yes	Yes	5
41	No	No	No	Yes	Yes	Yes	NR^{n}	No	Yes	Yes	No	No	5
42	No	Yes	Yes	Yes	Yes	NR	No	No	Yes	Yes	No	No	6
43	No	Yes	Yes	Yes	No	Yes	Yes	Yes	Yes	Yes	No	No	8
44	Yes	No	Yes	Yes	No	No	Yes	Yes	Yes	Yes	Yes	Yes	9
45	No	Yes	No	No	Yes	NR	Yes	Yes	Yes	No	Yes	No	6
46	Yes	Yes	Yes	Yes	No	Yes	No	Yes	Yes	Yes	Yes	Yes	10
Total (%)	4 (8.7)	31 (67.4)	24 (52.2)	17 (37.0)	15 (32.6)	30 (65.2)	9 (19.6)	15 (32.6)	33 (71.7)	29 (63.0)	21 (45.7)	21 (46.7)	251 (45.5)

RR –response rate; NR –Not reported; NR^{n} - no "n" reported for pilot

Apart from the report of a valid summary of outcomes data (74%), the use of clear inclusion and exclusion criteria in participant recruitment (67%), the attainment of a RR $\geq$ 60% (65%), and

TABLE 2.11: Summary of quality indices attained by included studies

Quality assessment index	# (%) of studies meeting criterion (n=46)	X^2 statistic; p value	Pearson's correlation [r; p value]			Distinctive categories
			Possessing 8 or more quality indices)	Year of publication	Publication after mid-point year (2005)	
Is the study design associated with a low tendency to bias and confounding?	4 (8.7)	31.391; p=0.000*	r= 0.431; p=0.003*	r= -0.193; p=0.199	r= 0.076; p=0.614	Case-control -1; Prospective cohort -2; Prospective parallel cohort -1
Were study participants defined by clear inclusion /exclusion criteria?	31 (67.4)	5.565; p=0.018*	r= 0.226; p=0.131	r= 0.104; p=0.494	r=-0.052; p=0.730	
Was a clear systematic method used for sampling/recruitment?	24 (52.2)	0.087; p=0.883	r= 0.253; p=0.090	r= 0.082; p=0.590	r= -0.012; p=0.938	All eligible -14; Consecutive - 8; Simple random -2
Were there efforts to obtain a representative sample?	17 (37.0)	2.174; p=0.184	r= 0.391; p=0.007*	r= -0.079; p=0.600	r= 0.060; p=0.891	Recruitment period ≥ 1 year -9; Multi-centre/city -4; Broad/multi-centre database -5[a]
Was the sample size justified or ≥300?	15 (32.6)	5.565; p=0.018*	r= -0.109; p=0.470	r= 0.008; p=0.956	r= -0.044; p=0.772	Justified -3 Sample size ≥300 -13[a]
Was a response rate ≥60 % achieved?	30 (65.2)	42.174; p=0.000*	r= 0.263; p=0.077	r= 0.244; p=0.102	r= -0.244; p=0.102	
Was a validated, or piloted (n≥12) CAM use survey tool used?	9 (19.6)	19.304; p=0.000*	r= 0.253; p=0.090	r= -0.377; p=0.010*	r= 0.250; p=0.094	Standard -1; Validated -4; Piloted (n≥12) -4
Were UPES outcomes data analysed for inference or confounding?	15 (32.6)	5.565; p=0.018*	r= 0.358; p=0.014*	r= -0.167; p=0.266	r= 0.052; p=0.730	Univariate inferential analysis -9; Bi-/multivariate analysis -6
Was a valid summary of UPES outcomes data provided?	34 (73.9)	10.522; p=0.001*	r= 0.293; p=0.048*	r= -0.140; p=0.353	r= 0.161; p=0.287	For positive outcomes –31 For non-positive outcomes -3
Was the generalisability of findings on UPES outcomes discussed?	29 (63.0)	3.130 p=0.077	r= 0.151; p=0.318	r= -0.177; p=0.240	r= 0.160; p=0.287	
Were valid conclusions drawn from study findings on UPES outcomes?	21 (46 %)	0.348; p=0.555	r= 0.318; p=0.031*	r= -0.163; p=0.278	r= 0.340; p=0.021*	For positive outcomes –19 For non-positive outcomes -2
Was any POEM "bottom line" recommendation made based on outcomes data?	21 (45.7)	0.348; p=0.555	r= 0.428; p=0.003*	r= -0.088; p=0.560	r= -0.022; p=0.887	Research-oriented –23 Practice-oriented –10 Parent-oriented -2
Attained high quality status (8 or more indices)	9 (19.6)	-	1.00	r= 0.151; p=0.318	r= -0.153; p=0.311	

the discussion of the generalisability of the UPES outcomes data reported (63%), most of the included studies failed to meet the quality indices selected. Overall, the number of quality indices attained was normally distributed among included studies with two close modes of 5 and 6 indices attained by 10 studies apiece, a median of 5 quality indices, and a mean of 5.46. Individually, however, the quality of included studies ranged from as low as meeting only 1 quality index (3 studies) to meeting 10 indices (1 study). Bivariate analyses showed that 6 quality indices were significantly correlated with attaining high methodological quality status. Of these, the indices most significantly correlated were the type of study design used (r=0.431; p=0.003) and the presence of a POEM-based recommendation (0.428; p=0.003); while the indicator least significantly

correlated was the provision of a valid summary of CAM outcomes data (r=0.293; p=0.048). Only the use of a justified sample size or a sample size ≥ 300 was inversely correlated to attaining high quality status, albeit non-significantly (r=-0.109; p=0.47). As to how the studies fared across the years in the period of review, the only quality index significantly correlated with the year of study publication was the use of a validated or piloted tool for CAM data collection (r=-0.377; p=0.01); although it was also significantly correlated with the level of outcomes measurement (r=-0.316; p=0.033), one of the 27 items extracted from included studies (not shown in table). Being published after the mid-point year of 2005 was significantly correlated with only one quality index -drawing valid conclusions from outcomes data reported (r= 0.340; p=0.021). It was, however, inversely correlated with many of the quality indices, as well as attaining high quality status, but in all these cases, non-significantly.

2.4 Discussion

2.4.1 Summary of findings

This is the very first SR on UPES outcomes of paediatric CAM use. The systematic search strategy and step-wise screening process yielded 46 eligible studies that studied a cumulative population of 9,087 paediatric subjects aged up to 21 years. An overview of the findings of the review generally indicates a low methodological quality profile among studies, due mainly to a preponderance of study designs with a high tendency to bias and confounding, and scant use of piloted or standardized data collection tools. Most of the studies included were primarily descriptive and hospital-based, and utilised mainly self-completion or face-to-face interview methods to collect data usually by proxy report. Although about one-fifth of the studies did not study a specific health condition, the specific disease category for which CAM use was most studied was cancers, closely followed by mental & behavioural disorders. In addition to a variety of definitions used for CAM therapies among the studies, many different and non-specific constructs were also used to describe UPES outcomes. While these points make it difficult to draw a specific conclusion from the outcomes findings reported, a general overview indicates a high report of positive outcomes by majorities of CAM users in the studies (with the notable exception of the UK studies included), as well as a low report of negative outcomes. However, there was far less emphasis on the report of negative outcomes among the studies, as CAM-related adverse effects were not studied in more than half of the studies. These generally positive findings were, however, not evident in the conclusions and recommendations of many studies, as study findings on outcomes were either disregarded altogether, or reported partially or in negative light.

One reason for this is the high degree of non-application of inferential statistics to UPES outcomes data, even where such were used for the non-outcomes data reported by the same studies

and for the same study samples, suggesting some tendency to confirmation bias among study authors. While the various limitations acknowledged by study authors are note-worthy, the apparent tendency to confirmation bias in the studies suggests that the opinions and perspectives of patients who use CAM are probably not being given sufficient consideration by health care providers with respect to their (the users') health-related quality of life. This raises important ethical issues for social research generally; but more so in the light of the current global trend towards patient-centred health care. The high report of positive outcomes for paediatric CAM use, however, raises a number of implications for future research and clinical practice, as were prominently portrayed in the POEM-based recommendations made by the studies. These recommendations centred on the need for greater cooperation in decision-making and collaboration in research between health care providers and their patients and/or their parents, as well as the need for greater integration of CAM into conventional care settings.

2.4.2 General characteristics of studies

A comparison of the included studies by the geographical regions in which they were conducted indicates a relatively high concentration of research publications on outcomes of paediatric CAM use in North America, with the USA and Canada contributing more studies individually than any other country. In all, 5 of the 6 inhabited continents of the world were represented, with no publication included from South America, probably because of the language restriction in this review to the English Language. Also, as the languages most often affected by such restriction have been found to be German and French [384], the language bias in the present study may very likely have contributed to the relatively fewer publications retrieved from Europe, as well as other parts of the world. The importance of non-restriction in the language of publication in systematic reviews in general has already been noted in literature, particularly for CAM interventions [384, 385]. This is therefore an important recommendation for future systematic reviews on the subject.

The quality of research as well as its reporting is generally expected to improve with the passing years in line with the discovery of better techniques and the development of standard reporting standards. As the STROBE statement was published in 2007 with the aim of improving the quality of observational health research studies [386, 387], a significant positive difference in study quality was expected for studies published after 2005, the mid-point year of the review. The findings however indicate that the year of publication had no significant effect on the quality of included studies, being significantly correlated with only two study features, and even then only negatively. Table 2.5 suggests the negative correlation to be due to the high non-report of these two features in latter years. As the present study was not primarily aimed at evaluating the effectiveness of any reporting standard in influencing research quality, these findings can only

suggest the need for such evaluative research for the STROBE statement, as has been done for other standard checklists [388, 389]. They also emphasize the necessity of greater adherence to the STROBE checklist by study authors and journal editors, as has been noted for standard reporting guidelines in general [390]. This is especially needful in CAM outcomes research, where its adoption has been noted to be particularly relevant [391, 392].

The relative paucity of research on paediatric CAM interventions has already been acknowledged [393, 394]. However, the relative paucity of UK research studies on paediatric CAM outcomes found from the current review, and the fact that the latest eligible UK study (which also happens to have been carried out in Scotland) [352] was published in 2008, not only greatly emphasize the need for such research within the UK, but also the relevance of the current doctoral research. Also striking is the marked deviation of the UK studies included in this review from the generally reported predominantly positive outcomes of paediatric CAM use. Although the oldest UK study included [348] reported a high PE outcomes rating (85%), 3 of the remaining 4 studies reported poor to average PE ratings, including the poorest rating reported among included studies -35% [349]. A SR of prevalence of paediatric CAM use in the UK that included data on perceived effectiveness found an average PE of 48.3% (range 14-61%) for included studies [395]. Methodologically sound studies are therefore needed to determine a more reliable and current estimate of paediatric CAM UPES among the UK public.

2.4.3 Methodological Quality

Like has already been found in many systematic reviews of CAM interventions [48, 396, 397], most of the studies included in the current review were of poor methodological quality, with only 9 studies ($< 20\%$) meeting 8 (67%) of the 12 quality requirements assessed, the pre-set standard for high quality status. As the strongest predictors of high quality status were type of study design and the presence of a POEM-based recommendation, future studies on UPES outcomes need to give special consideration to these particular indices.

A significant difference has been demonstrated for the use of high quality study designs in paediatric research relative to adult research [398]. Because of the many ethical issues associated with paediatric research [399], observational effectiveness studies have many advantages over RCTs in that population [400, 401]. However, because of their high tendency to confounding and bias, cross sectional studies are lowly rated among observational effectiveness study designs used in outcomes research [299]. This is especially so when they are purely descriptive in design; instead of the analytical cross sectional studies that are sometimes considered an acceptable source of evidence for systematic reviews of health outcomes, alongside longitudinal and case-control studies [402, 403]. Such analytical studies are designed to facilitate the application of inferential and multivariable statistical analyses of outcomes data [404, 405]. The high proportion of cross

sectional studies with purely descriptive statistical analysis of outcomes therefore contributed to the low quality rating among the studies.

The importance of POEMs has been emphasized for health outcomes studies [347, 406], as the main objective of such studies is to optimise the delivery of quality patient care [407]. Understandably, this objective is especially important for user-led interventions like CAM [408]. The call for greater cooperation of health care providers with parents and patients in decision-making to optimise their use of CAM is justified, as various studies have pointed to its value and inadequacy in both conventional care hospitals [97, 409, 410] and pharmacies [411, 412]. The various barriers to such helpful interaction have also been reviewed [413, 414]. While patient collaboration in CAM outcomes research appears to have increased in recent years, as evidenced by the increased use of patient-reported outcomes (PRO) tools in the assessment of the outcomes of CAM interventions [415, 416], the poor clinical meaningfulness of the assessments made –that is, what effect they would really have on the quality of patient care, and/or any practical changes that are required to ensure better quality of patient care- has also been reported [416]. In the systematic review of methodological quality assessment in CAM interventions, Efficace et al [396], found that, although many PRO tools had been used among the 44 RCTs included in their review, only 20% of the studies reported on the clinical significance of their findings. This agrees with the 21% found in the current review. It is therefore clear that future studies need to place at least as much emphasis on the clinical significance of their findings as they do on their statistical significance [77, 417].

Another predictor of high quality status among included studies in the current review was the efforts made to achieve a representative population sample. While the relevance of the representativeness of a study sample is well recognized, as it is indicative of the generalisability of the resulting findings [418], its reporting in survey reports is generally poor. The current review found that only 37% of included studies (17 studies) demonstrated efforts to achieve a representative sample. Although this was a poor outcome that significantly contributed to the low quality of included studies, an overview of recent reviews indicates that this finding was better than for many. This could be because most reviews either did not specifically include or report this feature [395, 419, 420], or made it an inclusion criterion in order to improve the quality of included studies [421, 422]. However, for those that did report it, none was found that reported a better outcome than did the current review. The SR most related to the current, Bishop et al's review of prevalence of paediatric CAM use [423], reported that only 11% of included studies (3 studies) demonstrated efforts to achieve representative samples. Also, Bennett et al's SR [324] of the quality of reporting of key quality criteria for survey research in 117 reports of self-administered health care research surveys published in 34 high impact factor journals also reported that only 13 studies (11%) described the representativeness of the samples used. The best outcome encountered was for Blagojevic et al's review and meta-analysis of the risk factors for the onset

of osteoarthritis in older adults [424] which reported 32% population representativeness among included studies (27 studies). Clearly there is need for greater effort in this aspect of research quality.

2.4.4 Adherence to Procedural Research Ethics

Research ethics generally refer to a set of principles by which research should be conducted [425, 426]; or, more specifically, a set of methods, procedures, or perspectives for analysing complex problems and issues [427]. Adherence to research ethics is important for a study and its findings to be acceptable to the research community and other users of the research results. Such ethical considerations are particularly important for research involving vulnerable populations like children and their families [428]. In addition to obtaining approval for the study from an ethics board, typical ethical considerations relevant to social research involving children include informed consent during participant recruitment [429, 430], assurance of confidentiality of data [431, 432], and, more generally, transparency in reporting procedures, methods and findings [433].

Although there was high report of adherence to ethical considerations among included studies, only 14 studies (30%) reported them fully including assuring the maintenance of confidentiality/anonymity. Maintaining confidentiality or anonymity is important in any data collection [434], particularly in sensitive or controversial topics where social desirability factors could play a high role. This is the case for the use of unconventional medicine [392, 435, 436], especially when it is researched in a conventional health care setting. Moreover, its assurance (or the lack of such) has been shown to significantly affect the type and quality of responses gotten from paediatric public health surveys [437, 438]. Thus, the lack of emphasis placed on this ethical factor by authors of included studies is worrisome, as it could very well have impacted on the study outcomes. A SR on standards and ethics in e-health also found that much less emphasis was paid to assuring maintenance of confidentiality than in obtaining informed consent [439]. Although confidentiality matters seemed to be highly reported in Caplan et al's SR of ethics in rheumatology literature [440], that was only because it was not considered separately, but rather grouped along with informed consent as autonomy, based on Beauchamp and Childress' framework of ethical principles [441]. Future SRs need to consider this important aspect of ethics, especially in CAM use research.

About two thirds of included studies did not provide a transparent report of the participant recruitment and data collection methods used. The transparent report of research methods increases the reliability, utility, and impact of the research, the major objective of the EQUATOR (Enhancing the QUAality & Transparency Of health Research) network [442]. The lack of transparency among the studies is evidenced by the high degree of non-report of the sampling method used (20 studies, 43%) and the duration of data collection (14 studies, 30%), as well as significant

missing data in the target and actual sample sizes and RR (see table 2.3). The poor report of the procedures used to recruit participants and collect data further illustrates the fact that the impact of the standard reporting guidelines on improving study quality is happening slowly [388, 443]. As several calls have been made for greater transparency in research involving human participants [444–446], future SRs on clinical and social research need to focus on this neglected aspect of research ethics.

2.4.5 Tendency towards Non rigorous Research

Although the included studies were heterogeneous in many respects, an overview highlights a number of trends in paediatric UPES CAM research in the period of review. The most obvious trend is a tendency towards non-rigorous research, as is characterised by a high dependence on descriptive cross sectional study designs carried out mainly by medical doctors on conveniently accessible patient participants in mostly single-centre, hospital settings. Also, such studies tended to rely predominantly on proxy report of PE outcomes using non-validated instruments that gave with little emphasis to safety outcomes report. A less obvious trend is an apparent tendency towards confirmation bias against affirming benefit from CAM use, both in terms of unbalanced application of statistical methods within studies and selective reporting of positive outcomes.

Single-centre studies, while simple and inexpensive to execute, have been associated with several limitations [331]. Although the most obvious limitation associated with such studies is poor external validity, which reduces the generalisability of the findings [447], single-centre studies have also been found to show slightly larger intervention effects than multicentre studies when the outcomes were continuous [448]. Although most of the UPES outcomes reported in included studies were categorical rather than continuous, the high use of single-centre studies could belie the predominantly positive outcomes associated with the studies.

Over 80% of included studies were carried out in clinic-based settings. While the key attraction of hospital-based studies is convenient access to study participants, this is particularly so where at least one of the researchers is a medical doctor and affiliated with the healthcare setting concerned [449]. With the high representation of medical doctors among the primary/corresponding authors of included studies (table 2.2), the preponderance of hospital-based studies seen in the current SR is therefore not strange. A recent SR of prevalence studies on CAM use by paediatric patients between 2000 and 2011 identified 11 eligible studies covering 17,631 patients within the UK alone [395]. Hospital-based studies are, however, associated with a number of challenges. For one, they tend to overestimate the prevalence of CAM use [450, 451], essentially skewing the prevalence data obtained from them [452]. Also, and more relevant to the current study, hospital-based studies could affect the level of report of positive outcomes associated with CAM use [453]. This is especially so for self-care CAM therapies like CAM products [454], which are the focus of the

current SR. An underestimation of reported outcomes is understandable given the reported high level of nondisclosure of CAM use to medical doctors [455, 456], most probably due to social desirability issues [457]. In the current review, the lowest proportion of users reporting positive outcomes for CAM use (35%) was arrived at from interviews by the patients' doctors either before or during the course of their outpatient consultation [349]. Although the study authors reported efforts to assure participating patients of the confidentiality of their responses, as well as its not affecting their treatment, the fact that it still might have affected them cannot really be ruled out, a limitation that the authors duly acknowledged. However, those same factors could also account for an overestimation of the outcomes reported [458]. This could explain why the highest proportions of users rating CAM as effective in the current review (96% and 99%) were gotten from patients at a Homeopathic hospital [358] and a TCM clinic [379], respectively, in the course of their routine clinical visits. All these factors significantly compromise the external validity of the studies [459], making them inferior to population-based studies for such measures [460, 461]. Although this issue is mostly associated with face-to-face interview studies, and some of the studies tried to minimize the possibility by either using research assistants or avoiding the use of the participants' paediatricians [220, 377, 462], future studies need to concentrate on the general population (like [348]) so as to avoid these highlighted methodological flaws.

8 in every 10 of the included studies relied solely on proxy report for UPES outcomes measurement, with 5 other studies combining proxy report with self-report either as mixed or joint report (table 2.5). The high reliance on proxy report is understandable because of the ethical and other methodological challenges of surveying paediatric subjects [431, 463, 464]. However, while an earlier SR found that parent-proxy health assessments may agree with child self-reports with respect to observable health behaviours, the same study also found that that their assessments differ significantly in abstract issues like social and emotional health matters [465]. More recent primary studies have confirmed clinically significant differences between the perceptions of general health, frequency and amount of body pain, experience of mental health, and other measures of health status [466, 467], many of which concerns would have been considered in the PE outcomes ratings provided in included studies in the current review. The consensus, therefore, is that whenever a child can provide valid and reliable data, paediatric self-report should be used [468]. Studies have shown the youngest such age to be from 4-6 years [469, 470]. This recommendation was not followed in most included studies, the seriousness of which failure is particularly heightened by the fact that an upper paediatric age limit of at least 16 years was an inclusion criterion for about two thirds of included studies. This somewhat questions the credibility of the outcomes reported. This is further strengthened by the fact that parents have also been associated with greater social desirability bias than their children in certain contexts, including the report of child health matters [471–473]. Within the context of ethical provisions according "(every) child who is capable of forming his or her own views the right to express those views freely in all matters

affecting the child" [474], future studies need to seriously consider including child self-report at least for adolescents.

About 60% of included studies did not study patient-reported adverse effects. This is very striking, given that one of the cardinal ethical considerations in the practice of medicine is to "first do no harm" [475], a fact that has also been emphasized for CAM interventions [476, 477]. While the reasons for this development are not obvious, it certainly goes against the clarion call of the Institute of Medicine in its landmark 1999 report "To Err is Human: Building a Safer Health System" [478]. It also disregards the huge concerns for patient safety expressed about CAM therapies by several health professions and stakeholders over the years [479, 480], especially in the context of their use in children [481, 482]. This suggests that the positive impact of the publication of the IOM report on safety considerations in published literature reported by a previous SR [483] is yet to be significantly evident in paediatric CAM research.

2.4.6 Tendency towards Confirmation/Selective Reporting Bias

Significant differences were demonstrated between the application of inferential and multivariable statistics to outcomes and non-outcomes data within studies, as well as between providing a valid summary of outcomes findings and drawing valid conclusions from them. These suggest a subtle tendency to confirmation or selective reporting bias among study authors, as also buttressed by the odds ratio tests carried out. Confirmation/selective reporting bias describes the tendency for scientists to search for or interpret new information in such a way as to confirm their own prior beliefs or theories; or to steer clear of or ignore data or evidence that may contradict those prior beliefs [484, 485]. The occurrence of these biases in primary studies and SRs has been highlighted in various reviews [486–488]; and both traits were obvious in included studies.

A comparison of the likelihood of authors reaching a valid conclusion based on a valid summary of the findings reported for their study showed that authors were so much wary of drawing wrong conclusions that they often ignored valid ones. This tendency was observed much more when the findings were mainly positive –that is, in favour of CAM use- than in cases where the majority rating of perceived outcomes was either borderline or lower than 45% of users surveyed. This fact is buttressed by the fact that 11 of the 12 studies for which no valid summary of outcomes was provided were all associated with positive outcomes reported by 56-91% of CAM users surveyed. Likewise, of the 25 studies for which no valid conclusions were drawn, only in 3 instances [352, 374, 489] were positive outcomes reported by less than 55% of the participants surveyed. While many of the 12 studies without valid outcomes data summaries did not provide any summary whatsoever of the outcomes findings reported, and as such did not discuss the outcomes data reported further, 4 of them [355, 462, 490, 491] omitted key aspects of the study outcomes data in their summaries, resulting in their providing a negative data summary of the

positive outcomes findings they reported. Furthermore, except for 3 cases in which authors drew ambivalent conclusions from their findings [359, 361, 375], and a single case in which the authors drew a completely misleading one [492], most of the study authors drew no conclusions whatsoever from the findings of their studies on outcomes data, while drawing conclusions from other data obtained in their studies. As a researcher's ability to draw a conclusion from study findings is facilitated by the type of statistical analyses carried out on the data obtained [493, 494], the unbalanced application of inferential and multivariate statistical tests in the studies somewhat facilitated this trend.

While there are no obvious reasons for this development, a couple of possibilities exist. Firstly, as the prominence of scepticism and uncertainty about the value of CAM has been reported for medical doctors in general [138], the high proportion of medical practitioners among the authors could offer an explanation. This professional bias has also been observed at the student level, as nursing [495, 496] and pharmacy [497, 498] students have been reported to have more positive attitudes to CAM use and integration than medical students [499, 500]. However, CAM has been reported to be better appreciated by younger medical doctors [501], as well as with those who either use it themselves or practise one or more forms of CAM [138, 502]. This is obvious from the findings of this review, as the highest positive outcomes were reported by medical doctors practising TCM [379] and Homeopathy [358], respectively. Moreover, other health professional also contributed to the problem observed [355, 366, 492], indicating that it is not specific to the medical profession.

Another possibility is the study design used, or the various limitations in study design acknowledged by authors. While it is true that cross sectional studies are not highly regarded in EBM because they are usually fraught with many limitations, it would certainly be unfair to disregard the findings of a study because of the design used to elicit them. That would imply that the study had been designed to fail ab initio. While the findings of cross sectional studies are not regarded as evidence, they serve the purpose of formulating hypotheses that could be verified or otherwise by more internally valid study designs [305, 503]. Defaulting authors could therefore have formulated hypothesis from their findings, and called for more valid study designs to verify them –as many of the other authors did.

A possible explanation for the unbalanced application of statistical analysis between UPES outcomes and non-outcomes data could be that the sample sizes used in the studies were too small to support such detailed analyses. This view could be supported by the fact that 8 of the studies that applied inferential and/or multivariate analyses reported more than 100 CAM users [220, 358, 361, 369, 370, 382, 504, 505]. However, although up to 10 authors acknowledged small sample size as one of their study limitations [350, 353, 355, 359, 360, 362, 368, 371, 373, 492], only in one case [371] was this limitation attributed to the level of statistical analyses carried out. The relevance of sample size in statistical analyses has well established [506, 507], with the general

discouragement of using sample sizes less than 100 for certain tests, like the goodness-of-fit test [506]. However, certain exact statistical tests, like Fisher's test, for instance, have been designed specifically for small sample sizes [508, 509]. As such, 7 of the included studies were still able to carry out inferential statistical analyses even with CAM user sample sizes of 16-88 participants [350, 352, 357, 372, 383, 489, 510]. Also, some of the studies for which inferential statistical analyses were not carried out for UPES outcomes data also reported high CAM user sample sizes of more than 150 participants [348, 379, 489]. Finally, while small sample sizes may not yield statistically significant findings, they have been associated with more clinically significant results [511, 512], with well-designed but small studies having been shown to be sufficient for detecting meaningful change [513]. Thus, an argument for non-conclusion based on small population of CAM users does not really hold up to scrutiny.

Whatever the reason for the bias observed, its presence raises ethical issues; as it implies that the views and opinions of research participants –and patients- are not being given due consideration. The benefits of considering the perspectives, views and opinions of patients in the planning and development of healthcare, particularly for long-term health conditions, has been documented in earlier SRs [514–516]. Moreover, considering the inconveniences participants have to put up with in social/public health research, any disregard of their views would amount to a great travesty that could endanger future health research and practice [517–519]. This is particularly relevant in the context of the current patient-centred healthcare dispensation [520, 521].

2.4.7 Limitations of the Review

The current SR is associated with a number of limitations. The most obvious is the language bias due to the restriction to English language studies, which has been reported to be very significant for SRs of CAM interventions [384, 385]. This has also been confirmed by a recent SR [522]. However, since the exclusion of languages other than English from SRs of CAM interventions has been associated with a reduced positive outcomes [384], it is likely that a more inclusive SR would have yielded an even higher report of positive outcomes than observed in the current one. Another limitation could also be the non-inclusion of grey literature in this review. This has been reported to be associated with exaggerated estimates of intervention effectiveness [523]. Also, a recent SR has recommended the need to search for trials in both the published and grey literature in order to help minimise the effects of publication bias in health care intervention reviews [524]. Future SRs therefore need to take this into consideration.

Thirdly, there is the limitation of the datedness of the review relative to the completion of the manuscript of the doctoral thesis in which it is contained. As the SR was conducted in 2011 with the main purpose of informing further phases of the doctoral research, an update of the SR was not considered necessary during the final phase of the research. However, in order to keep

track of possibly eligible studies published in the intervening period, ZETOC® alerts were set up for key search terms, and have yielded 12 eligible studies based on title and abstract screening. An overview of the findings of these studies as reported in their abstracts does not indicate any deviation from the general trends observed in the studies included in the current review. That notwithstanding, the necessity of an updated SR on the subject cannot be denied.

2.5 Conclusion

The findings of this review generally emphasize the need for more rigorous research into the UPES outcomes of paediatric CAM interventions. While this is needed globally, it is needed particularly in the UK, which is behind her North American counterparts in this area of research. Such future studies should be suitably designed to reflect the practical uses of CAM by paediatric patients and their parents in real life circumstances, taking into consideration the peculiar objectives for such use. Greater emphasis should also be laid on identifying any negative outcomes associated with paediatric CAM interventions; as well as in always providing conclusions that are congruent with the reported perceptions of users. This would enable the verification of the predominantly positive outcomes generally reported by past studies, and prepare the way for a better appreciation of the benefits (if any) of CAM interventions and their possible integration into conventional care. It would also overcome the ethical and social issues highlighted in this review, and give patients their due recognition as partners in healthcare decision making. As the paucity of research on this subject in the UK and Scotland justifies the inclusion of a survey component in the current doctoral research, all these findings will be taken into consideration in the design of the study so as to avoid the many methodological flaws of past studies. Given that the UK studies included in this review varied widely in the PE outcomes reported -from as low as 35%, the lowest in the review, [349] to as high as 85% [348], with 2 of the remaining 3 UK studies reporting either borderline (48%) [352] or average (61%) [351] PE ratings, a major objective of that survey will be to determine what the current opinion of the UK public is on the UPES of paediatric CAM use.

Table 2.12: Completed data extraction form for included studies

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Study (Year) Country [Profession of primary/ corresponding author]	Sample size (of paediatric subjects where possible) Number of respondents [Response Rate, RR]	Type of participants [Age range of paediatric subjects] Sampling method [Justification of sample size used]	Study design [Data collection method used] Extent of validation of CAM data collection tool	Level of adherence to ethical considerations Study setting, distribution & spread [Study duration]	Type of CAM studied and the definition provided to study participants Prevalence of CAM use (type; number of users)	Specific type of CAM UPES outcome(s) studied Type of report (Self, Proxy, Mixed or Joint)	Type (level) of measurement scale used for UPES outcomes (Description) Type of statistics used for outcomes data	Proportion (number) of CAM users reporting PE (*OR Mean PE rating of CAM therapies by users) Proportion (number) of CAM users reporting AE (*OR Mean AE severity rating of CAM therapies by users)	Authors' summary of study findings/conclusions based on UPES outcomes data [Recommendations made based on UPES outcomes data] Limitations acknowledged
1. Hon et al (2005) [383] Conducted in Hong Kong [Profession of primary author - Medical doctor]	Sample size not stated	Caregivers of children with atopic dermatitis [Age range not stated]	Cross sectional study design used [Face to face interview method]	Ethics committee approval only obtained	Traditional Chinese Medicine; but no definition provided	Perceived improvement; AE not studied	Nominal scale: 3 categories (Yes/No/Not sure)	PE: 57 % (38 users); No significant difference (p=0.13) in PE with respect to disease severity	Findings on outcomes summarised, but no conclusions reported [REC: A number of studies have shown the usefulness of TCM in the treatment of common skin conditions such as eczema and psoriasis, and thus it is worthwhile for dermatologists throughout the West to gain some familiarity with this method]
	227 respondents [RR data not available]	Sampling method used not described [Sample size not justified]	No report of validation, pilot or previous use of CAM outcomes tool	Outpatient clinic; single centre [For 4 months]	Prevalence: 30 % (12-month; 67 respondents)	Proxy report	Descriptive (%) and inferential statistics (Pearson's χ^2, $p<0.05$); univariate analysis (frequency table)	AE not studied	No limitations acknowledged
2. Murray et al (2008) [492] Conducted in the USA [Profession of primary author - Pharmacist]	247 paediatric subjects	Patients and guardians of patients with cystic fibrosis [aged 0.49-19 years]	Cross sectional study design used [Face to face interview method]	Ethics committee approval & informed consent obtained	Dietary supplements; defined to participants; excluded multivitamin preparations or prescribed high calorie nutrition supplements	Perceived effectiveness; AE not studied	Type of outcomes measurement not described	PE: 50-90 % (15-27 users): {Somewhat effective - 40 % (12 users); Averagely effective - 30 % (9 users); Extremely effective – 20 % (6 users)}	Findings on outcomes validly summarised; but the conclusions were misleading: Dietary supplement use in paediatric patients with cystic fibrosis was common, although few perceived it as effective [No recommendations made on UPES outcomes data]
	121 respondents [RR 49 %]	Sampling method not described [Sample size not justified]	No report of validation, pilot or previous use of CAM outcomes tool	Outpatient clinic; single centre [For 7 months]	Prevalence: 25 % (ever used; 30 respondents): (19 % -current; 10 % -past)	Reporter type not stated	Descriptive statistics (%) only; outcomes data not statistically analysed	AE not studied	Limitations acknowledged: 1. Small sample size 2. Recall bias 3. Use of survey design 4. Interviewer bias 5. Lack of information on possible confounders

3. Senel (2010) [375] Conducted in Turkey [Profession of primary author unclear]	400-500 children	Parents of children with autism spectrum disorders (ASD) [aged 0-18 years]	Cross sectional study design [E-mail survey method]	Ethical issues not specifically described; but informed consent implied	A list of 18 specific CAM treatments (arranged alphabetically from acupuncture to yoga)	Perceived improvement; perceived benefits /positive changes; harmfulness	Ordinal and Nominal scales used: PE: (Ordinal rating) (Worse/ No change/ Little/ Great improvement); Positive changes: (Nominal rating) (Sleeps better/ Eats better/ behaves better/ Communicates better/ Healthier/ Other); Negative effects: (Nominal rating) (Nothing/ Difficult to use/ Harmful /Expensive /Other)	PE – No summary count for all CAM use PE for specific CAM products: Herbals- 7 of 10 users (70 %) Little: 5; Great: 2]; Vitamins/minerals- 27 of 32 users (84.4 %) [Little: 12; Great: 15]; Special diets- -24 of 30 users (80 %) [Little: 12; Great: 12]; Other dietary supplements- 15 of 19 users (78.9 %) [Little: 7; Great: 8] Positive effects: Most rated positive effects in decreasing order of report: Improved communication, learning, health, and behaviour	Findings on outcomes validly summarised; but the following ambivalent conclusion was reached: It can be said that the results showed that parents' ratings were optimistic. In general the results show that there is no treatment which brought 100 % improvement without any negative sides [REC: Parents should have realistic expectancy, and then to learn all the negative sides,… from large experienced groups before trying any CAM. For further research, meta-analysis should be considered for analysing the researches relevant to these treatments. It would be beneficial to study details of what kinds of negative sides or risks parents had experienced with any CAM, preferably through large sample of parent group]
	44 respondents [RR data not clear]	Convenience sampling (All eligible participants) [Sample size not justified]	CAM outcomes tool piloted and revised	E-mail communication support group for ASD; database coverage not described [For 2 months]	Prevalence: 86 % (ever used; 38 respondents)	Proxy report used	Neither descriptive nor inferential statistics used (Data simply stated)	Negative effects Most rated negative effects in decreasing order of report: Nothing; expensive; difficulty to use; harmful	Limitations acknowledged: 1. Questionnaire bias (possible linguistic barrier in comprehension) 2.Subjective report 3. Small sample size 4. Social desirability bias
4. Braganza et al (2003) Conducted in the USA [Profession of primary author - Medical doctor]	Target sample size not stated	Parents of children with asthma [Age range not specified]	Cross sectional study design [Face to face interview method]	Ethics committee approval and informed consent obtained. Anonymous?	A compiled list of 26 commonly available CAM therapies, especially those reportedly used for asthma	Perceived effectiveness; AE not studied	Type of outcomes measurement not described	PE: 59 % -at least as effective as asthma medicines; 44 % used CAM as first treatment of an asthma attack (number of users not provided)	Findings on outcomes not summarised; nor were any conclusions reported [No recommendations made on UPES outcomes data]
	310 respondents [RR data not available]	Sampling method not described [Sample size not justified]	No report of validation, pilot or previous use of survey	Inner-city outpatient clinic; single centre [For 7 months]	Prevalence: 89 % (12-month; 276 respondents)	Proxy report used	Descriptive statistics (%); outcomes data not statistically analysed	AE not studied	Limitations acknowledged: 1. Cross sectional study design 2. Social desirability bias 3. Non validation of instrument 4. Single centre

			CAM outcomes tool						
5. Sawni et al (2007) [462] Conducted in the USA [Profession of primary author - Medical doctor]	650 paediatric subjects	English-speaking parents/care-givers of children on emergency care [aged 0-18 years]	Cross sectional study design [Face to face interview method]	Ethics committee approval and informed consent	CAM defined as any therapy for a medical illness that the child's regular doctor did not prescribe, excluding OTC medications and multivitamins. Examples of CAM were also provided	Satisfaction with CAM therapy, alone and relative to conventional therapy; AE not studied	Type of outcomes measurement not described	PE: Satisfaction with CAM - 76 % (number of users not provided) Satisfaction relative to conventional therapy – 66 % used CAM along with conventional therapy, and 37 % felt results were best when both CAM and conventional medicine were integrated ($p<0.001$	Findings on outcomes partially summarised (data on satisfaction not reported), and no conclusions were reached on the data reported [No recommendations made on UPES outcomes data]
	602 respondents (93 %)	Convenience sampling (interviews conducted on random days and times) [Sample size not justified]	CAM outcomes tool piloted and previously used	Emergency department; single centre [For 7 months]	Prevalence : 15 % (ever used; 88 respondents)	Proxy report used	Descriptive (%) and inferential (p values) statistics; univariate analysis (Fisher χ^2; significance level not stated)	AE not studied	Limitations acknowledged: 1. Sampling bias (convenience sampling) 2. Use of proxy report 3. Exclusion bias (language) 4. Non-generalisability (non-diverse sample used) 5. Non validation of instrument
6. Soo et al (2005) [373] Conducted in Canada [Profession of primary author - Medical doctor]	228 eligible paediatric subjects	Families of children attending the neurology clinic [aged 2-18 years]	Cross sectional study design [Self-completion survey method]	Ethics committee approval and informed consent obtained; & confidentiality assured	Different CAM types were classified based on Tataryn's framework of body, mind, energy and spirit paradigm	Perceived helpfulness; Perceived AE	Nominal scale: 2 categories (Helpful/Not helpful)	PE for all CAM therapies: 54 % (57 of 106 users); PE for CAM products: Herbal remedies – 67 % (6 of 9 users); Dietary therapy – 77 % (10 of 13 users); Vitamins/Minerals – 43 % (3 of 7 users); Natural supplements – 14 % (1 of 7 users); Aromatherapy – 60 % (3 of 5 Users); Aqua therapy – 0 % 0 of 2 users); Homeopathy – 22 % (2 of 9 users)	Findings on outcomes validly summarised, and led to the following conclusion: The majority of caregivers found CAM to be helpful, and the positive aspects of CAM use were augmented by their infrequent side-effects. [REC: Further studies to investigate drug interactions, effectiveness, adverse effects, and cost benefits of CAM are required. With that foundation of knowledge it would be possible to advocate coverage of efficacious therapies and avoid unsafe therapies for patients]
	125 respondents [RR 55 %]	Convenience sampling (All eligible subjects)	No report of validation, pilot or previous use	Outpatients clinic; single centre [For 4 months]	Prevalence: 44 % (ever used; 46	Proxy report used	Descriptive statistics (%); univariate analysis of outcomes data	AE: 2 % (1 user)	Limitations acknowledged: 1. Small sample size 2. Low response rate 3. Possible non-response bias

		[Sample size not justified	of CAM outcomes tool				(frequency table)		
7. Wong and Smith (2006) [359] Conducted in Canada [Profession of primary author - Medical doctor]	108 paediatric subjects (Case=55; Control=53)	Parents of two sets of children, one diagnosed with ASD (case), and the other not (control) [aged 2-17 years]	Case-control study design [Interview method –by telephone & face to face]	Ethics committee approval and informed consent obtained	CAM was reported as defined to participants but definition not stated. All CAM types were included, except regular multivitamins. A list of CAM types was also provided	Perceived benefit; AE not studied	Type of outcomes measurement not described	PE reported for CAM therapies used: ASD group: 75 % (45 of 60 users of all CAM therapies; including 33 of 44 users of CAM products specifically); Control: 88 % (22 of 25 users of all CAM therapies; including 19 of 19 users of CAM products specifically) Results of statistical analysis not shown.	Findings on outcomes validly summarised with the this ambivalent conclusion: Although this study provides information about the attitudes of parents regarding the benefits and short-comings of various CAM therapies for their child, the study does not provide any objective evidence regarding the efficacy of these therapies [REC: While further research is needed to substantiate apparent benefits of CAM therapies, physicians need to be aware of the prevalence of use, and be sensitive to parental attitudes towards CAM. Also, several others –including parents]
	100 respondents (50 per group) [RR: Case -91 %; Control -94 %]	Sampling method not described [Sample size not justified]	No report of validation, pilot or previous use of CAM outcomes tool	Hospital-based; 4 centres in same city [Study duration not stated}	Prevalence: ASD group - 52 % (ever used; 26 respondents) Control group – 28 % (ever used; 41)	Proxy report used	Descriptive statistics (%); univariate analysis of outcomes data (frequency table)	AE not studied	Limitations acknowledged: 1. Small sample size 2. Non-generalisability (one geographical area studied)
8. Araz and Bulbul (2011) [505] Conducted in Turkey [Profession of primary author - Medical doctor]	350 paediatric subjects	Parents of children attending outpatient clinic [1 month – 17 years]	Cross sectional study design [Face to face interview method]	Ethics committee approval only obtained	CAM defined as practices and ideas which are outside the conventional treatment methods for preventing or treating illness, or promoting health; but no list/examples reported as provided	Perceived Usefulness (benefit); Perceived harmfulness	Type of outcomes measurement unclear: 5 categories (No benefit/ Slightly useful/ Fairly useful/ Just started/ Harmful)	PE for Herbal natural products: 76 % (119 users) {Slightly useful- 57.7 % (90 users, C I 27.93-39.23); Fairly useful- 18.6 % (29 users, C I 7.1-14.54)}	Report of outcomes findings unclear; also, no conclusions were made based on outcomes data reported [Further studies should analyse the…effectiveness, safety and side effects of frequently preferred CAM therapies.]
	68 respondents	Sampling method not	CAM outcomes	Outpatient clinic; single	Prevalence:59 % (12-month; 157	Proxy report used	Descriptive (%) and inferential	AE 4 % (0.47-4.01)	Limitations acknowledged: 1. Non-generalisability (Only one

	[RR 77 %]	described [Sample size not justified]	tool piloted in a previous study	centre [For 2 months]	respondents)		(C I) statistics; univariate analysis of outcomes data (frequency table)	(6 users)	region studied) 2. Hospital setting bias 3. Proxy report
9. Oshikoya et al (2008) [381] Conducted in Nigeria [Profession of primary author - Medical doctor]	Target sample size not stated	Parents of 122 subjects with epilepsy, 78 with asthma, and 122 with sickle cell disease [Paediatric age range not specified]	Cross sectional study design [Face to face interview method]	Ethics committee approval; informed consent obtained; & confidentiality assured	CAM defined according to National Institute of Health classification, and a list of commonly used biological CAM products and samples and pictures of other local CAM types were provided	Perceived benefits; perceived AE	Type of outcomes measurement not described	PE: 78 % (78 users): {Specific- 46 %; Inexplicable -32 %} (NB: Reported data unclear - 46 % vs. 78 %? And is 46 % for "specific" or "non-specific" benefits?)	Findings on outcomes partially summarised, resulting in the following conclusion: Parents considered CAM to be beneficial to their children REC: The fact that approximately half the parents reported some benefits of CAM to their children, albeit non-specific, calls for clinical trials of CAMs to establish parents' claims, and assess the safety of the therapy for children.]
	318 respondents [RR data not available]	Convenience sampling (Randomly on consecutive presentation) [Sample size not justified]	CAM outcomes tool pretested and revised	Outpatient clinics; single centre [For 3 months]	Prevalence: 31 % (ever used; 99 respondents); 26 % (6-month; 83 respondents)	Proxy report used	Descriptive statistics (%); outcomes data not statistically analysed	AE: 7 % (7 users)	Limitations acknowledged: 1. Cross sectional study design (no comparison /control group)
10. Madsen et al (2003) [220] Conducted in Denmark [Profession of primary author - Medical doctor]	674 paediatric subjects	Outpatients and hospitalized paediatric patients and their parents [aged 0-17 years]	Cross sectional study design [Face to face interview method]	Ethics committee approval; informed consent	CAM was categorized into Authorized herbal drugs (according to The Danish Medicines Agency), Alternative therapy), and Chiropractic. The herbal drugs category also included vitamin/mineral preparations, dietary supplements, and other mi8scellaneous preparations	Positive effects; unexpected effects; and side effects	Type of outcomes measurement not described	PE for all CAM therapies- Not available; PE for Product-based CAM: Positive effects– 56 % (45-66 %); Unexpected effects – 16 % (9-25 %) (number of users not provided)	Findings on outcomes not summarised; nor were any conclusions reported [No recommendations made on UPES outcomes data]
	622	Convenience	No report of	Paediatric	Prevalence: 53 %	Proxy report	Descriptive (%)	AE for all CAM therapies:	Limitations acknowledged:

	respondents [92 %]	sampling (All patients were asked to participate) [Sample size not justified]	validation, pilot or previous use of CAM outcomes tool	department of a university hospital; single centre [For 2 weeks]	(ever used; 327 respondents); 20 % (1-month; 121 respondents)	used for babies; Joint report used for children and adolescents	and inferential (95 % C I) statistics; univariate analysis (Pearson's χ^2 @ $p<0.05$)	6 % (8 of 121 users); <u>AE for Product-based CAM therapies:</u> 2 % (0-8 %) (number of users not provided)	1. Non consideration of duration of CAM use (information bias)
11. Loh (2009) [379] Conducted in Singapore [Profession of primary author - Medical doctor]	Target sample size not stated	Parents of paediatric subjects [aged 1-18 years]	Cross sectional study design [Self-administered survey]	No ethical considerations reported; but survey described as anonymous	Traditional Chinese Medicine, specifically acupuncture and herbal medicine, alone or in combination	Perceived improvement; AE not studied	Ordinal scale: 3 categories (No change /Some improvement /Much improvement)	<u>PE:</u> 99 % (number of users not provided) {Much improvement – 75 %; Some improvement – 24 %}	Findings on outcomes not summarised (emphasis rather placed on data from physician postal survey); no conclusions reported with respect to UPES outcomes [No recommendations made on UPES outcomes data]
	300 respondents [RR data not available]	Sampling method not described [Sample size not justified]	No report of validation, pilot or previous use of CAM outcomes tool	TCM outpatient clinic; single centre [Study duration not stated]	<u>TCM (as above)</u>: 87 % (ever used; 262 respondents); <u>Herbs:</u> 84 % (253 respondents); <u>Acupuncture</u> -3 % (9 respondents)	Proxy report used	Descriptive statistics (%); outcomes data not statistically analysed	AE not studied	<u>Limitations acknowledged</u>: 1. Selection bias (non-representative -limited to clinic attendees) 2. Reporting bias (tending towards affirmation of TCM)
12. Lim et al (2006) [362] Conducted in Singapore [Profession of primary author - Medical doctor]	73 paediatric patients in the CAM outcomes phase (Target sample size for the first phase not stated)	Primary caregivers of paediatric cancer patients [aged 1-14 years]	2-stage Cross sectional study design [Face to face Interviews, followed by telephone, interviews - for outcomes report]	No ethical considerations reported	All CAM types according to NCCAM classification, with a list of specific therapies	Perceived improvement/benefits on physical health, quality of life (QoL), control over situation, and sense of hope; overall satisfaction; perceived AE	Ordinal scale: Improvement in specific criteria rated based on degrees of agreement (Strongly agree /Agree /Disagree; Overall satisfaction (Very satisfied /Satisfied /Not satisfied); AE rating unclear	<u>Perceived benefits:</u> Improved Physical health - 88 % (Agree 64 %; Strongly agree 24 %); Improved QoL -65 % (Agree 47 %; Strongly agree 18 %); Improved Control -53 % (Agree 53 %); Improved psychological benefit (hope) -75 % (Agree 75 %) <u>Perceived satisfaction:</u> 94 % (Satisfied -77 %; Very satisfied -18 %) (number of users not provided in all cases)	Findings on outcomes validly summarised, with the following conclusion: CAM has a widening impact on every facet of the healthcare system and all specialties of medicine, including paediatric oncology [REC: Future research needs to clarify the distinction between potentially harmful alternative "cancer cures" and potentially beneficial complementary therapies employed as adjuncts to cancer treatment.]
	59 respondents (for the CAM	Sampling method not described	CAM outcomes tool piloted	Cancer centre of a local hospital; single	Prevalence: 67 % (for condition; 49 of 73 participants	Proxy report used	Descriptive statistics (%); univariate analysis	<u>AE:</u> 6.1 % (3 of 49 users). NB: % not specifically	<u>Limitations acknowledged</u>: 1. Small sample size 2. Non representative (so

	outcomes phase) [RR 81 %]	[Sample size not justified]	(in 10 patients) and revised	centre [For 3 weeks]	in stage 1)		of outcomes data (stacked bar charts)	stated: but reported in the discussion that "94 % of participants experienced no ill effects with CAM")	underpowered to detect regionally used therapies) 3. Recall bias 4. Exclusion bias (parents of deceased patients) 5. Single centre study
13. Hanson et al (2006) [374] Conducted in the USA [Profession of primary author - Psychologist]	325 paediatric subjects	Parents of 20 % of children with ASD seen 1997-2003 [Paediatric age range not specified]	Cross sectional study design [Postal survey]	No ethical considerations reported; but survey described as anonymous	CAM defined as all therapies used except Educational techniques, Sensory therapies, and Prescription drugs. A list was also provided. Multivitamins were excluded.	Perceived helpfulness; AE not studied	Nominal scale 3 categories (Helpful/ Harmful/ No change)	<u>PE for All CAM therapies:</u> Summary data not provided <u>PE for CAM product therapies:</u> Modified diet – 41 % (17 of 41 users); Vitamins/Minerals – 41 % (12 of 29 users); Food Supplements – 58 % (15 of 26 users); Herbals – 73 % (8 of 11 users); Secretin (supplements – 33 % (3 of 9 users)	Findings on outcomes validly summarised; but no conclusions reached on outcomes data reported [REC: Providers should be able to help families who decide to use CAM in how to evaluate treatment and treatment response. Future research would entail investigating more specific comparisons on the perceived efficacy/inefficacy of CAM for children with ASD]
	112 respondents [RR 35 %]	Sampling method not described [Sample size not justified]	No report of validation, pilot or previous use of CAM outcomes tool	Hospital patient records; local database [Study duration not stated]	<u>Prevalence:</u> <u>All CAM</u> – 74 % (prevalence type unclear; 83 respondents); <u>CAM Products</u> – 54 % (as above; 60 respondents)	Proxy report used	Descriptive statistics (%); univariate analysis (frequency table)	AE not studied	<u>Limitations acknowledged:</u> 1. Questionnaire bias (poor comprehension of questions) 2. Possible measurement bias (too few categories on scale) 3. Reporting bias (social desirability) 4. Low response rate 5. Possible nonresponse bias due to variation in participant interest 6. Lack of diversity of sample 7. Anonymous design, thus unable to verify parent report of diagnosis
14. April et al (2009a) [356] Conducted in Canada [Profession of primary author - Occupational therapist]	254 paediatric subjects (157 in Montreal, and 97 in Vancouver)	Parents of children with Juvenile idiopathic arthritis [aged 2-18 years]	Longitudinal (Prospective cohort) study [Self-completion and postal survey]	Ethics committee approval; informed consent	A list of CAM types provided to participants; details given	Perceived benefit; AE not studied	Ordinal scale: 4 categories (no Improvement/ benefit to much improvement/ very beneficial)	<u>PE:</u> 72 % of all episodes of CAM use (Somewhat beneficial – 23 %; Moderately to Highly beneficial -49 %)	Findings on outcomes validly summarised with this conclusion: This study showed that CAHC use is common in children with JIA and that it is often perceived as being beneficial. [REC: This makes it important for health practitioners to evaluate CAM use]
	182 respondents, [72 %]:	Sampling method not described	CAM outcomes tool piloted	Outpatient clinics; 2 centres in	51 % (past use); 36 % (study period):	Proxy report used	Descriptive statistics (%); outcomes data not	AE not studied	<u>Limitations acknowledged:</u> 1. Questionnaire bias (non-validation; possibly incomplete

	Montreal, 120 [76 %]; Vancouver, 62 [64 %]	[Sample size not justified]	and revised	different cities [Quarterly over a 12-month study period]	Montreal – 42 % (study period); Vancouver – 25 % (study period) (specific data not provided)		statistically analysed		CAM list) 2. Selection bias (only clinic attendees/non-CAM users) 3. Social desirability bias 4. Attrition (Migration bias) 5. Confounding -previous CAM use
15. April et al (2009b) [377] Conducted in Canada [Profession of primary author - Occupational therapist]	277 paediatric subjects	Parents of children with physical disabilities [aged 0-6 years]	Cross sectional study design [Face to face interview method]	Ethics committee approval; informed consent	A list of CAM types provided to participants; details given	Perceived benefit; AE not studied	Ordinal scale: 4 categories (no Improvement/ benefit to much improvement/ very beneficial)	<u>PE:</u> 83 % of episodes of use {(Slightly beneficial -30 %; Moderately beneficial -15 %; Highly beneficial -38 %)} (number of users not provided in each case)	Findings on outcomes validly summarised, with this conclusion: Parents of children with physical disabilities who used CAM tended to perceive it as being helpful. [REC: It may be important for health professionals to evaluate the use of CAM in children, and their parents' beliefs which led them to try it, especially if the child has high health needs]
	206 respondents [RR 74 %]	Sampling method not described [Sample size not justified]	No report of validation, pilot or previous use of CAM outcomes tool	Patients on waiting list on referral from 2 hospitals; multi-centre patients' database [Study duration not stated]	Prevalence: 15 % (ever used; 31 respondents)	Proxy report used	Descriptive statistics (%); outcomes data not statistically analysed	AE not studied	<u>Limitations acknowledged:</u> 1. Questionnaire bias (nonvalidation; possibly incomplete CAM list; CAM not well defined); 2. Recall bias 3. Lack of objective CAM use data 4. Unable to check for confounders
16. Sinha and Efron (2005) [380] Conducted in Australia [Profession of primary author - Medical doctor]	105 paediatric subjects	Parents of children with ADHD [aged 5-17 years]	Cross sectional study design [Postal survey]	Ethics committee approval and informed consent obtained	A list of therapies provided to participants; but its content not described.	Perceived helpfulness; AE not studied	Type of outcomes measurement not described	<u>PE for all CAM therapies</u>: 58 % (29 users) <u>PE for CAM products</u>: Herbals – 22 % (2 of 9 users); Homeopathy – 30 % (3 of 10 users); Health products – 36 % (4 of 11 users); Dietary supplement – 36 % (5 of 12 users); Vitamin/Minerals – 21 % (3 of 14 users); Modified diet – 42 % (14 of 33 users); Aromatherapy –	Findings on outcomes validly summarised, but no conclusion was drawn therefrom [REC: The authors believe that if the risk of harm from the use of CAM is small, then we should aim to work together with parents who use complementary (as opposed to alternative/replacing) therapies in an effort to optimise the outcome for their children. It is important to explain to parents that many of these therapies have not undergone research trials, and to be clear that we do not recommend ceasing prescribed

	Montreal, 120 [76 %]; Vancouver, 62 [64 %]	[Sample size not justified]	and revised	different cities [Quarterly over a 12-month study period]	Montreal – 42 % (study period); Vancouver – 25 % (study period) (specific data not provided)		statistically analysed		CAM list) 2. Selection bias (only clinic attendees/non-CAM users) 3. Social desirability bias 4. Attrition (Migration bias) 5. Confounding -previous CAM use
15. April et al (2009b) [377] Conducted in Canada [Profession of primary author - Occupational therapist]	277 paediatric subjects	Parents of children with physical disabilities [aged 0-6 years]	Cross sectional study design [Face to face interview method]	Ethics committee approval; informed consent	A list of CAM types provided to participants; details given	Perceived benefit; AE not studied	Ordinal scale: 4 categories (no Improvement/ benefit to much improvement/ very beneficial)	<u>PE:</u> 83 % of episodes of use {(Slightly beneficial -30 %; Moderately beneficial -15 %; Highly beneficial -38 %)} (number of users not provided in each case)	Findings on outcomes validly summarised, with this conclusion: Parents of children with physical disabilities who used CAM tended to perceive it as being helpful. [REC: It may be important for health professionals to evaluate the use of CAM in children, and their parents' beliefs which led them to try it, especially if the child has high health needs]
	206 respondents [RR 74 %]	Sampling method not described [Sample size not justified]	No report of validation, pilot or previous use of CAM outcomes tool	Patients on waiting list on referral from 2 hospitals; multi-centre patients' database [Study duration not stated]	Prevalence: 15 % (ever used; 31 respondents)	Proxy report used	Descriptive statistics (%); outcomes data not statistically analysed	AE not studied	<u>Limitations acknowledged:</u> 1. Questionnaire bias (nonvalidation; possibly incomplete CAM list; CAM not well defined); 2. Recall bias 3. Lack of objective CAM use data 4. Unable to check for confounders
16. Sinha and Efron (2005) [380] Conducted in Australia [Profession of primary author - Medical doctor]	105 paediatric subjects	Parents of children with ADHD [aged 5-17 years]	Cross sectional study design [Postal survey]	Ethics committee approval and informed consent obtained	A list of therapies provided to participants; but its content not described.	Perceived helpfulness; AE not studied	Type of outcomes measurement not described	<u>PE for all CAM therapies</u>: 58 % (29 users) <u>PE for CAM products</u>: Herbals – 22 % (2 of 9 users); Homeopathy – 30 % (3 of 10 users); Health products – 36 % (4 of 11 users); Dietary supplement – 36 % (5 of 12 users); Vitamin/Minerals – 21 % (3 of 14 users); Modified diet – 42 % (14 of 33 users); Aromatherapy –	Findings on outcomes validly summarised, but no conclusion was drawn therefrom [REC: The authors believe that if the risk of harm from the use of CAM is small, then we should aim to work together with parents who use complementary (as opposed to alternative/replacing) therapies in an effort to optimise the outcome for their children. It is important to explain to parents that many of these therapies have not undergone research trials, and to be clear that we do not recommend ceasing prescribed

								39 % (5 of 13 users)	therapies]
	75 respondents [RR 71 %]	Sampling method not described [Sample size not justified]	CAM outcomes tool developed from those used in previous studies; but no report of validation or pilot	Outpatients of Children's hospital; single centre [For 5 months]	Prevalence: 68 % (for condition; 50 respondents)	Proxy report used	Descriptive statistics (%); univariate analysis of outcomes data (frequency table)	AE not studied	Limitations acknowledged: 1. Cross sectional study design (no comparison /control group) 2. Unable to detect confounding (small sample size)
17. Hurvitz et al (2003) [370] Conducted in the USA [Profession of primary author - Medical doctor]	235 paediatric subjects	Families of children with cerebral palsy [aged 1-18 years]	Cross sectional study design [Self-completion survey]	Ethics committee approval; informed consent	CAM was defined according to NCCAM, and a list of common CAM types provided, with free text space for entry of other CAM therapies not listed	Perceived positive outcomes; AE not studied	Type of outcomes measurement not described	PE for all CAM therapies: 56 % (number of users not provided) Association Families of CAM users in which the primary caregiver had used CAM were more likely to be pleased with the outcome of CAM for their child than for those families where there had been no such prior use (71 % vs. 43 %, P <0.005 two-tailed) Regression Parental use of CAM was the only factor that was predictive of parental satisfaction with the child's CAM therapies (OR 3.3, 95 % C I 1.5 to 7.0)	Findings on outcomes validly summarised, with this conclusion: Parental use of CAM was highly associated with choosing CAM for the child, and for eventual satisfaction with the treatment. [REC: Further contemplation and research is required to determine what factors make CAM modalities desirable and effective, and to consider how these factors can be woven into the "standard care" that we give children with cerebral palsy, and indeed all children]
	213 respondents [RR 91 %]	Convenience sampling (Consecutive, eligible subjects were recruited) [Sample size not justified]	CAM outcomes tool was validated by undergoing reviews by paediatric professionals and primary caregivers of children (for readability and ease of	Outpatients at a university medical centre; single centre [Study duration not stated]	Prevalence: 56 % (for condition; number of respondents not provided)	Proxy report used	Descriptive statistics (%); univariate, (frequency table) bivariate (Pearson's χ^2 @ p<0.05, 2-tailed), and multivariate (step-wise logistic regression) analyses	AE not studied	Limitations acknowledged: 1. Clinic-based setting (might have caused the relatively low prevalence values seen)

			use); and also through cognitive interviews with families						
18. Hughes et al (2007) [366] Conducted in the Republic of Ireland [Profession of primary author - Pharmacist]	80 paediatric subjects	Parents of paediatric patients with atopic dermatitis [aged 2 months – 17 years]	Cross sectional study design [Self-completion survey]	No mention of ethics committee approval; but informed consent obtained	No description or definition of CAM presented; nor was any reported as provided to participants	Perceived improvement; AE not studied	Type of outcomes measurement not described	PE: 44 % (15 users) reported some improvement –most commonly a reduction in rash. Most treatments were reported to show no improvement (58 %).	Findings on outcomes validly summarised, with this conclusion: Alternative therapies are largely ineffective and may be very expensive [No recommendations made on UPES outcomes data]
	80 respondents [RR 100 %]	Sampling method not described [Sample size not justified]	No report of validation, pilot or previous use of CAM outcomes tool	Dermatology outpatient clinic in a university teaching hospital; single centre [Study duration not stated]	All CAM: 43 % (prevalence type unclear; 34 respondents) Herbals: 41 %; Homeopathy: 24 % (number of users not provided)	Proxy report used	Descriptive statistics (%); outcomes data not statistically analysed	AE not studied	Limitations acknowledged: 1. Ascertainment bias (selection of patients with moderate to severe eczema) 2. Demographic effects/bias (low economic status; education0
19. Johnston et al (2003) [349] Conducted in the UK [Profession of primary author - Medical doctor]	100 paediatric subjects	Children with atopic dermatitis accompanied by their parents or guardians [aged 0.6-17.1 years]	Cross sectional study design [Face to face interview]	Ethics committee approval and informed consent obtained; confidentiality assured	No description or definition of CAM mentioned, nor reported as given to participants	Perceived improvement; AE not studied	Nominal scale: 3 categories (Skin better /No change /Skin worse)	PE for episodes of CAM therapies[†] used: 35 % (26 of 74 episodes) {41 % of patients reported improvement}	Findings on outcomes validly summarised with the following conclusion: While majority felt that CAM was safer than orthodox medicine, they reported that it did not improve their skin, and that they would not recommend it to other patients with AD. However a significant minority reported benefits from Cam and would recommend it. [No recommendations made on UPES outcomes data]
	100 respondents [RR 100 %]	Convenience sampling (Consecutive, eligible subjects were recruited) [Sample size not justified]	CAM outcomes tool piloted (in 10 patients) and revised	Dermatology outpatient clinic of a referral hospital; single centre [For 9 months]	Prevalence: 46 % (for condition; 46 respondents)	Mixed report used: Self-report (older children); proxy report (infants and toddlers)	Descriptive statistics (%); outcomes data not statistically analysed	AE not studied; Skin condition reported as worse with 12 % (9 of 74) therapies	Limitations acknowledged: 1. Shorter disease chronicity 2. Parental oversight of care 3. Selection bias (convenience sampling; nonrandomised) 4. Secondary care setting (higher disease severity) 5. Non-generalisability (high ethnic minority composition)

									6. Differences between CAM users and non-CAM users 7. Recall bias 8. Medical interviewer effect
20. Dannemann et al (2008) [371] Conducted in Germany [Profession of primary author - Medical doctor]	346 paediatric subjects	Parents of children with type 1 diabetes mellitus [aged 1-18 years]	Cross sectional study design [Self-completion survey]	Ethics committee approval and informed consent obtained; anonymity maintained	Provided a list of 11 drug-based and 13 non-drug based therapies, as well as a free text area for others	Perceived efficacy (overall, and also relative to insulin); specific reported effects; reported AE or side effects	Ordinal and Nominal scales: <u>Overall PE – Ordinal scale:</u> 5 categories (Very good /Rather good /No effect /Rather poor /Very poor); <u>PE relative to Insulin -Nominal:</u> Smaller than /Equal to /Greater than; <u>Specific reported effects –Nominal scale:</u> Improved /No change /Deteriorated	<u>Overall PE:</u> 63 % {Very good -12.5 %; Rather good -50 %; (number not stated)} <u>PE relative to Insulin:</u> Greater than insulin – 3 % (1 user); Equal to insulin – 15 % (number of users not stated) <u>Perceived improvement of specific reported effects:</u> Well-being -68 %; Quality of life -43 %; Acceptance of diabetes -37 %; Daily coping -34 %; Emotional stability -33 %; Metabolic control -26 %; Dealing with stress -24 %	Findings on outcomes validly summarised, with this conclusion: Despite the lack of objective outcome, diabetic patients seem to show improvement in non-quantitative vital measures once beginning alternative medical care. [REC: Respecting parents' wishes to use CAM is important even if its efficacy is not proved and viewed with scepticism. ..Facing the limited evidence of efficacy, further prospective, randomized trials are required to determine the impact of alternative approaches on the personal burden and quality of life of type 1 diabetes patients]
	228 respondents [66 %]	Sampling method not described [Sample size not justified]	Face and content validity of the survey was carried out by a panel of experts; and a pre-test in volunteers (including people with diabetes) to test its performance, length and understand-ing	4 paediatric diabetes centres; multi-centre; multi-city [for 13 months]	Prevalence: 18 % (for condition; 42 respondents)	Proxy report used	Descriptive statistics (%); univariate analysis (frequency table)	<u>AE:</u> 11.9 % (5 users) {With these comments: "Only five patients experienced short-term side effects, such as increased blood glucose levels or tiredness…..However, in our study, no severe side effects were stated."]	<u>Limitations acknowledged:</u> 1. Small number of CAM users (limited the statistical analyses that could be carried out); 2. Lack of control group 3. Volunteer bias (self-selection) 4. Recall bias
21. Day et al (2004)	60 eligible paediatric	Parents of patients with	Cross sectional	Ethics committee	A list of CAM therapies	Perceived effectiveness;	Type of outcomes measurement not	<u>PE:</u> 62 % (16 of 26 users):	Findings on outcomes not validly summarised (only the top-most

[490] Conducted in Australia [Profession of primary author - Medical doctor]	subjects	inflammatory bowel disease (IBD) [aged 1-18 years]	study design [Postal survey]	approval obtained; informed consent implied & anonymity maintained	provided. Parents also requested to report awareness of therapies with potential roles in the management of IBD	AE not studied	described	(Very effective /Effective -12 % (3 users); Partially effective – 50 % (13 users)	band was included); no conclusions made on the data [No recommendations made on UPES outcomes data]
	46 respondents [RR 77 %]	Convenience sampling (All eligible subjects were recruited) [Sample size not justified]	CAM outcomes tool was developed from an earlier one, and then a few parents were asked to review random questions	Clinic booking records/ database; local database, single centre [Study duration not stated]	Prevalence: 72 % (current use; 33 respondents)	Proxy report used	Descriptive statistics (%); outcomes data not statistically analysed	AE not studied	No limitations acknowledged
22. Day (2002) Conducted in Australia [Profession of primary author - Medical doctor]	115 paediatric subjects	Parents accompanying children to their clinic appointments [aged 6 months – 16 years]	Cross sectional study design [Self-completion survey]	Ethics committee approval and informed consent obtained; anonymity maintained	Specific examples of CAM therapies were listed, with emphasis on probiotics	Perceived improvement/benefit; perceived detrimental effect	Type of outcomes measurement not described	PE for CAM: 83.3 % (22 users): {Improvement – 62.5 % (15 users); Slight/possible benefits – 20.8 % (5 users)} Several parents commented in further detail that probiotic therapies had proved to be beneficial for their children	Findings on outcomes validly summarised; but no conclusions made on the data [No recommendations made on UPES outcomes data]
	92 respondents [RR 80 %]	Convenience sampling (All eligible subjects were recruited) [Sample size not justified]	Developed CAM outcomes tool was reviewed by a random selection of parents, and then revised	Gastroenterology outpatient clinic; single centre [For 1 month]	Prevalence: CAM: 36 % (recent/current use; 33 respondents); Probiotics: 24 % (ever used; 20 of 85 respondents -1 past user and 19 regular users)	Proxy report used	Descriptive statistics (%); outcomes data not statistically analysed	AE: 0 % (No users reported detrimental effects due to the alternative agents)	Limitations acknowledged: 1. Study duration probably too short 2. Reporting bias 3. Non-use of interview method 4. Questionnaire bias (possible linguistic barrier in comprehension)
23. Gomez-Martinez et al (2007) [510] Conducted in Mexico	110 paediatric subjects	Parents/ guardians of paediatric cancer patients [aged 0.76	Cross sectional study design [Face to face interview]	Ethics committee approval and informed consent obtained	CAM defined as "any agent or practice initiated since diagnosis that does not constitute part of	Perceived usefulness /level of satisfaction; AE not studied	Nominal scale: 4 categories (Very useful /Useful /Non-effective /Do not know)	PE: 79 %: {Useful -26 %; Very useful -53 %; (number of users not provided)}. The proportion of users that rated	Findings on outcomes validly summarised with the following conclusion: This study demonstrates a high level of satisfaction with CAM. [No recommendations made on

[Profession of primary author - Medical doctor]		months – 15.6 years]			the standard of care for a child with cancer". A list of definitions for each CAM type was provided			CAM as useful was significantly (p=0.0001) different from those that either rated it as non-effective (8 %) or did not know (13 %)	UPES outcomes data]
	110 respondents [RR 100 %]	Convenience sampling (Consecutive, eligible subjects were recruited) [Sample size not justified]	Survey was piloted for 1 month, and revised based on parental feedback	Tertiary care hospital providing health coverage for Western region of Mexico; single centre [For 6 months]	70 % (for condition; 77 respondents)	Proxy report used	Descriptive (%) and inferential (p value) statistics; univariate analysis (χ^2 test @ $p<0.05$)	AE not studied	<u>Limitation acknowledged:</u> 1. Non-consideration of herb-drug interaction
24. Marchisio et al (2011) [382] Conducted in Italy [Profession of primary author - Medical doctor]	850 eligible paediatric subjects	Parents /guardians or care-givers of children with recurrent acute otitis media [aged 1-7 years]	Cross sectional study design [Self-completion survey]	Ethics committee approval and informed consent obtained	Homeopathy and herbal medicine; specified	Perceived effectiveness; AE not studied	Ordinal scale; 4 categories (Very good /Good /Moderate /Poor)	<u>PE:</u> 68 % (number of users not stated. Responses regarding good effectiveness were, for all CAM therapies studied, significantly more common than any other response. C I ranges not quoted.	Findings on outcomes validly summarised; but no conclusions made on the data [REC: Paediatricians need to be urgently involved in educational programmes specifically aimed at increasing their knowledge of evidence-based strategies for preventing AOM in order to reduce the number of new RAOM episodes in otitis-prone children]
	850 respondents [RR 100 %]	Convenience sampling (Consecutive, eligible subjects were recruited) [Sample size not justified]	No report of validation, pilot or previous use of CAM tool	Outpatient clinic of a medical referral centre; single centre [For 12 months]	Prevalence: 46 % (12-month; 391 respondents)	Proxy report used	Descriptive (%) and inferential (95 % C I) statistics; univariate analysis (χ^2 test @ $p<0.05$)	AE not studied	<u>Limitations acknowledged:</u> 1. Recall bias 2. Sampling bias 3. Non-generalisability (a single geographical area) 4. Narrow focus of study (not all CAM types/health conditions)
25. Super et al (2005) Conducted in the USA [Profession of primary author - Medical doctor]	117 eligible paediatric subjects	English-speaking parents/ guardians or care-givers of paediatric patients presenting at nephrology clinic [aged 0.5-18	Cross sectional study design [Self-completion survey]	Ethics committee approval; informed consent (implied) & anonymity	Cranberry (specifically asked, with product details)	Perceived benefit (alone, and in combination with antibiotics; perceived side effects	Ordinal scale: 4 categories (Provided a cure /Very beneficial /Somewhat beneficial /Neither helped or harmed /Harmful)	<u>PE Overall:</u> 83 % (25 of 30 users) {Cured -3 % (1 user); Very beneficial – 67 % (20 users); Somewhat beneficial– 13 % (4 users) <u>PE with antibiotics:</u> Nearly half of users felt that cranberry plus antibiotics combined were more	Findings on outcomes validly summarised; but no conclusions made on the data [REC: RCTs are urgently needed to assess the effectiveness of cranberry juice in preventing and treating paediatric urinary tract infections]

		years]						effective than either alone	
	117 respondents [RR 100 %]	Convenience sampling (but the exact method not described) [Sample size not justified]	Survey was piloted (in 10 patients) and revised to simplify language	Outpatient clinic of a children's hospital; single centre [For 10 weeks]	Prevalence: 29 % (for condition; 34 respondents)	Proxy report used	Descriptive statistics (%); univariate analysis (frequency table)	AE: Harmful 3 % (1 user)	Limitations acknowledged: 1. Setting bias (nephrology clinic) 2. Short data collection period 3. Non-generalisability (local study) 4. Response bias (inaccuracies)
26. Shakeel et al (2007) [351] Conducted in the UK (SCOTLAND) [Profession of primary author - Medical doctor]	554 eligible paediatric subjects	English-literate parents or caregivers of children [0-16 years]	Cross sectional study design [Self-completion survey]	No mention of ethics committee approval; but informed consent obtained	A list of 49 CAM products or therapies was provided, along with space provided for entry of any other CAM type used	Perceived effectiveness; AE not studied	Nominal scale: 3 categories (Effective /Not effective /Unsure)	PE: 61 % (57 users)	Findings on outcomes validly summarised; but no conclusions made on the data [No recommendations made on UPES outcomes data]
	327 respondents [RR 59 %]	Convenience sampling (consecutive, eligible outpatients, and all elective admissions were recruited) [Sample size not justified]	No report of validation, pilot or previous use of CAM tool	Otolaryngology outpatient clinic and surgical ward of a secondary and tertiary care hospital providing health coverage for North-East of Scotland; single centre [For 3 months]	Prevalence: 23 % (ever used; 93 respondents); 20 % (12-month; 18 respondents)	Proxy report used	Descriptive statistics (%); outcomes data not statistically analysed	AE not studied	Limitations acknowledged: 1. Relatively high nonresponse rate (41 %; due to time pressure, and poor survey distribution) 2. Incomplete responses (due to self-completion study design; possible nonresponse bias) 3. Non-generalisability (possible confounding due to relative local affluence; ethnic variations) 4. Non collection of data on ethnicity
27. Huillet et al (2011) [376] Conducted in the USA [Profession of primary author - Medical doctor]	461 paediatric subjects	English-literate, primary caregivers of presenting children [Paediatric age range not specified]	Cross sectional study design [Self-completion survey]	No mention of ethics committee approval; but anonymous & informed consent obtained	A list of 25 categories of CAM therapies provided	Perceived helpfulness; perceived side effects	Ordinal scale: 4 categories (PE – Not /Somewhat /Moderate /Very helpful; AE – None /Mild /Moderate /Severe)	PE: Not fully/clearly reported: Product-type CAM therapies most commonly reported as "very helpful – Diet, 67 %; Melatonin, 57 %; Mega-vitamins, 50 % (No data for Moderate or Somewhat helpful; also the specific cohort of users referred to in each case was not specified)	Findings on outcomes validly summarised, with this conclusion: With the few noted side effects and parental impression of efficacy, it is likely that CAM use will continue [No clear recommendation made on UPES outcomes data]
	344 respondents	Convenience sampling	Developed survey was	2 general paediatric	Prevalence: 23 % (12-month; 63 of	Proxy report used	Descriptive statistics (%);	AE: 4 %	Limitations acknowledged: 1. Non-standardization of survey

	[RR 78 %] Also 255 additional survey data for children at home	(Consecutive, eligible subjects were recruited) [Sample size not justified]	piloted (among 10 parents) to ensure understandability	clinics located at a large military treatment facility; single centre [For 4 months]	278 respondents) {66 (19 %) of the recruited sample was incomplete, and so discarded.} 22 % (12-month; among 244 "additional" children) {11 of the 255 responses were incomplete, and so discarded}		outcomes data not statistically analysed	(the specific cohort of users referred to was not specified)	instrument 2. Non-generalisability (local study) 3. Broad definition of CAM – including faith healing (but not prayer), and dance and environmental therapies (although excluded in the final analysis to avoid confusion)
28. Losier et al (2005) [365] Conducted in Canada [Profession of primary author - Medical doctor]	800 paediatric subjects	Parents/ guardians of children at emergency department [aged 0-16 years]	Cross sectional study design [Self-completion survey]	Ethics committee approval; informed consent & anonymity	No CAM definition specifically reported; but questionnaire was reported to have been adapted from Fermandez et al, 1998, which provided a list of therapies	Perceived helpfulness; AE not studied	Type of outcomes measurement not described	<u>PE:</u> 91 % (63 of 69 users) (found CAM helpful or very helpful for child)	Findings on outcomes not summarised; nor were any conclusions made on UPES outcomes data [REC: Continuing education of parents and families is important]
	621 respondents [RR 78 %]	Convenience sampling (random families in waiting room) [Sample size not justified]	Adapted partly from an earlier tool used, piloted (in 20 families) and revised	Emergency department of health centre for women, children and families; single centre [For 8 months]	Prevalence: 13 % (ever used, 75)	Proxy report used	Descriptive statistics (%); outcomes data not statistically analysed	AE not studied	<u>Limitations acknowledged:</u> 1. Nonresponse bias (with respect to CAM use) 2. Non representative sample (low representation of rural population; large proportion of highly educated, high income, Caucasians)
29. Reznik et al (2002) [504] Conducted in the USA [Profession of primary author - Medical doctor]	200 eligible paediatric subjects, as identified from an earlier screening study	Adolescent high school students with asthma [aged 13-18 years]	Cross sectional study design [Self-completion survey]	Ethics committee approval only	Defined as "medical interventions not taught widely at US medical schools or not generally available in hospital, such as herbal use, chiropractic and massage therapy", with a list of common therapies for asthma	Perceived efficacy (relative to conventional treatment); AE not studied	Type of outcomes measurement not described	<u>PE:</u> <u>Satisfaction with CAM</u> 73 % (number of users not provided) <u>CAM as effective as conventional treatment</u> 59 % (number of users not provided) <u>Comparisons</u> Those who perceived CAM to be as effective as conventional treatment were	Findings on outcomes not summarised; nor were any conclusions made on UPES outcomes data [No recommendations made based on UPES outcomes data]

					provided; and the opportunity to include any therapies possibly omitted.			more likely to report that they would use CAM again (96 % vs. 22 %; p<0.001)	
	160 respondents [RR 80 %]	Convenience sampling (All available eligible subjects were surveyed) [Sample size not justified]	Survey was developed, piloted and then modified	An urban high school; single centre [For 1 month]	Prevalence: 80 % (12-month; 128 respondents)	Self-report used	Descriptive (%) and inferential (p value) statistics; bivariate analysis (Pearson's χ^2, or Fisher's exact test; significance level not stated)	AE not studied	Limitations acknowledged: 1. Use of self report by adolescents (information not verified; possible response bias) 2. Possible non-response bias (due to absence from study) 3. Possible confounders (socio-economic factors)
30. Zebracki et al (2007) [368] Conducted in the USA [Profession of primary author - Clinical psychologist]	39 eligible paediatric subjects	Parents of Latino children with juvenile idiopathic arthritis or arthralgia [aged 6-16 years]	Cross sectional study design [Self-completion survey]	Ethics committee approval; informed consent	CAM use defined as "utilizing at least one type of CAM in conjunction with conventional medical treatment"; but no specific CAM definition reported as provided	Perceived helpfulness; AE not studied	Ordinal scale: 3 categories (Very /Somewhat /Not helpful)	PE: Not clearly reported 80 % found it somewhat helpful (number of users not provided)	Findings on outcomes summarised with this conclusion: CAM was viewed by parents as somewhat helpful in minimizing symptoms and sequelae of JIA or arthralgia. [REC: Future research should assess reasons for nondisclosure of CAM use, and examine what CAM treatment factors differentially affect the child's medical and psychological status, and contribute to a positive outcome and optimal overall functioning]
	36 respondents [RR 92 %]	Convenience sampling (All eligible subjects) [Sample size not justified]	No report of validation, pilot or previous use of CAM tool	Rheumatology clinic of a tertiary care children's hospital; single centre [Study duration not stated]	Prevalence: 56 % (prevalence type unclear; number of respondents not provided)	Proxy report used	Descriptive statistics (%); outcomes data not statistically analysed	AE not studied	Limitations acknowledged: 1. Small sample size 2. Cross sectional study design 3. Reliance on parent-proxy report
31. Arykan et al (2008) [367] Conducted in Turkey [Profession of primary author – Nurse]	123 eligible paediatric subjects (7 of 130 subjects were ineligible)	Parents of diabetic children with type 1 diabetes [Paediatric age range not specified]	Cross sectional study design [Face to face interview]	Ethics committee approval; informed consent & confidentiality	CAM reported as defined to participants; but the specific definition not provided	Satisfaction; AE not studied	Type of outcomes measurement not described	PE: 54 % (28 users)	Findings on outcomes validly summarised with this conclusion: Several CAM practices and herbal remedies show potential promise for diabetes treatment [REC: ..further rigorous study is needed to establish safety, efficacy and mechanism of action]
	100 respondents	Convenience sampling	No report of validation,	Endocrine outpatient	Prevalence: 52 % (for condition; 52	Proxy report used	Descriptive statistics (%);	AE not studied	Limitations acknowledged: 1. Reliance on subjective report

	[RR 81 %]	(All available eligible subjects were surveyed) [Sample size not justified]	pilot or previous use of CAM tool	clinic of a large teaching hospital; single centre [For 12 months]	respondents)		outcomes data not statistically analysed		(non use of objective data to verify claimed beneficial effects) 2. PE may not be specific to CAM therapies 3. Non record of AEs
32. Al-Qudimat et al (2010) [355] Conducted in Jordan [Profession of primary author – Nurse]	84 eligible paediatric subjects	Parents of paediatric cancer patients [aged 0-18 years]	Cross sectional study design [Self-completion survey]	Ethics committee approval; informed consent	CAM reported as described to participants; but specific definition not provided	Perceived benefit /satisfaction; AE not studied	Ordinal scale: 4 categories (No benefits /Low benefits /Good benefits /Excellent benefit)	<u>PE:</u> 91 % (40 users): {Excellent benefit– 16 % (7 users); Good –46 % (20 users); Low -30 % (13 users)}	Findings on outcomes partially summarised (only the middle band reported); no conclusions drawn on the data obtained [REC: Potential drug-CAM interactions need to be discussed as well as potential benefits from CAM therapies….Potential interactions and benefits cannot be determined without adequate information on patient and parent CAM behaviour]
	69 respondents [RR 82 %]; but non-responders and responders with incomplete surveys were not distinguished	Convenience sampling (All eligible subjects were surveyed) [Sample size justified statistically]	Survey was developed and piloted (in 6 parents from the centre); then tested for content validity (a panel of experts); and reliability (Cronbach's alpha -0.79)	Outpatient department at a Paediatric cancer centre that treats 80 % of all paediatric cases in Jordan; single centre [For 9 months]	Prevalence: 65 % (for condition; 45 respondents)	Proxy report used	Descriptive statistics (%); outcomes data not statistically analysed	AE not studied	<u>Limitations acknowledged:</u> 1. Small sample size 2. Localized studied (one Middle Eastern country)
33. Neuhouser et al (2001) [353] Conducted in the USA [Profession of primary author – Dietician]	101 eligible paediatric subjects	English-speaking parents of living children with cancer Aged 0-18 years]	Cross sectional study design [Computer-assisted, telephone interview]	Ethics committee approval; informed consent	CAM defined using the 7 categories of alternative medicine described by the NCCAM collapsed into 3 sub-groups (with examples) for cognitive ease of participants	Perceived improvement; reported AEs	Ordinal scale: 4 categories (PE – Strongly agree to Strongly disagree; AE – Very mild to Very severe)	<u>PE:</u> Data presentation unclear About 60–90% of users reported improvements in health and well-being (for the whole range of CAM therapies studied) (number of users not provided)	Findings on outcomes validly summarised; but no conclusions drawn on the data obtained [REC: Further research is needed to clarify whether specific alternative treatments are associated with improved clinical outcome or enhanced quality of life among pediatric oncology patients. Clinicians should remain informed about therapies that may dhow harm or benefit, communicate with

									patients about various treatment options, and make referrals wherever appropriate]
	75 respondents [RR 74 %]	Simple Random [None provided]	No report of validation, pilot or previous use of CAM tool	Cancer Surveillance System for western Washington state; 13-county-wide, broad database [Study duration not stated]	Prevalence data unclear 73.3 % (12-month; 55 of 75 respondents); data on CAM use for condition unclear	Proxy report used	Descriptive statistics (%); outcomes data not statistically analysed	AE: Data unclear ["Very severe AE" reported by 2 participants; but the data was not presented.] Q: Were these the only AEs reported? What about the data?	Limitations acknowledged: 1. Small sample size 2. Possible non-response bias 3. Non-generalisability (limited to only living children with first primary cancers, and to Washington state) 4. Possible response bias 5. Possible overlaps in CAM classification
34. Andersen et al (2008) [360] Conducted in the USA [Profession of primary author – Medical doctor]	107 eligible paediatric subjects	Parents of children with autism spectrum disorders treated with melatonin [aged 2-18 years]	Case series [Chart review and parental sleep diaries]	Ethics committee approval only	CAM studied was melatonin, which had been prescribed by the paediatrician for sleep problems	Perceived improvement; reported AEs	Ordinal scale: 4 categories (Sleep no longer a problem /Improved sleep but with continued parental concern /Sleep continues to be a concern /Worsened sleep	PE: 85 % (91 users) {Sleep no longer a concern – 25 % (27 users(; Improved sleep with continued parental concern – 60 % (67 users)}	Findings on outcomes summarised with this conclusion: Melatonin may be a safe and effective treatment of insomnia for children with autism spectrum disorders [REC: Future prospective randomised, blinded placebo clinical trials appear warranted]
	107 participants [RR not applicable – not a primary study]	Convenience sampling (all eligible children) [Sample size not justified]	No report of validation, pilot or previous use of tool used to extract CAM data	Electronic medical records of a paediatrician [Study duration not stated]	Prevalence of CAM use not relevant as use of melatonin had been an inclusion criterion	Proxy report	Descriptive statistics (%); outcomes data not statistically analysed	AE: 3 % (3 users)	Limitations acknowledged: 1. Design bias (retrospective, non RCT) 2. Heterogeneity 3. Confounders (other medications, dose variability, etc.) 4. Small sample size 5. Subjective report bias
35. Rouster-Stevens et al (2008) [372] Conducted in the USA [Profession of primary author – Medical doctor]	76 eligible paediatric subjects	Parents of children with juvenile idiopathic arthritis (JIA) [aged 0-21 years]	Cross sectional study design [Postal survey -with monetary incentive]	Ethics committee approval; informed consent & anonymity	An extensive list of conventional and CAM therapies compiled from literature and local and state-wide experience of JIA management was provided	Perceived helpfulness; perceived side effects	Ratio scale: 4 levels from 0-3 (PE – Not /Somewhat /Moderately /Very helpful; AE – None /Mild /Moderate /Severe)	*PE for CAM therapies as a whole: Median (mean) rating 3 (2.5) There was no significant difference between the mean helpfulness ratings for conventional medications and CAM therapies {2.7 vs. 2.5 (p=0.29)}	Findings on outcomes summarised with this conclusion: Even though parents viewed some conventional medications as being more helpful for their children's JIA than some CAM therapies overall, the use of CAM was perceived as being similarly helpful as conventional medications. [REC: Future studies of CAM therapies, particularly those that parents feel are helpful and low in side effects, such as vitamin D, are

									patients about various treatment options, and make referrals wherever appropriate]
	75 respondents [RR 74 %]	Simple Random [None provided]	No report of validation, pilot or previous use of CAM tool	Cancer Surveillance System for western Washington state; 13-county-wide, broad database [Study duration not stated]	Prevalence data unclear 73.3 % (12-month; 55 of 75 respondents); data on CAM use for condition unclear	Proxy report used	Descriptive statistics (%); outcomes data not statistically analysed	AE: Data unclear ["Very severe AE" reported by 2 participants; but the data was not presented.] Q: Were these the only AEs reported? What about the data?	Limitations acknowledged: 1. Small sample size 2. Possible non-response bias 3. Non-generalisability (limited to only living children with first primary cancers, and to Washington state) 4. Possible response bias 5. Possible overlaps in CAM classification
34. Andersen et al (2008) [360] Conducted in the USA [Profession of primary author – Medical doctor]	107 eligible paediatric subjects	Parents of children with autism spectrum disorders treated with melatonin [aged 2-18 years]	Case series [Chart review and parental sleep diaries]	Ethics committee approval only	CAM studied was melatonin, which had been prescribed by the paediatrician for sleep problems	Perceived improvement; reported AEs	Ordinal scale: 4 categories (Sleep no longer a problem /Improved sleep but with continued parental concern /Sleep continues to be a concern /Worsened sleep	PE: 85 % (91 users) {Sleep no longer a concern – 25 % (27 users(; Improved sleep with continued parental concern – 60 % (67 users)}	Findings on outcomes summarised with this conclusion: Melatonin may be a safe and effective treatment of insomnia for children with autism spectrum disorders [REC: Future prospective randomised, blinded placebo clinical trials appear warranted]
	107 participants [RR not applicable – not a primary study]	Convenience sampling (all eligible children) [Sample size not justified]	No report of validation, pilot or previous use of tool used to extract CAM data	Electronic medical records of a paediatrician [Study duration not stated]	Prevalence of CAM use not relevant as use of melatonin had been an inclusion criterion	Proxy report	Descriptive statistics (%); outcomes data not statistically analysed	AE: 3 % (3 users)	Limitations acknowledged: 1. Design bias (retrospective, non RCT) 2. Heterogeneity 3. Confounders (other medications, dose variability, etc.) 4. Small sample size 5. Subjective report bias
35. Rouster-Stevens et al (2008) [372] Conducted in the USA [Profession of primary author – Medical doctor]	76 eligible paediatric subjects	Parents of children with juvenile idiopathic arthritis (JIA) [aged 0-21 years]	Cross sectional study design [Postal survey -with monetary incentive]	Ethics committee approval; informed consent & anonymity	An extensive list of conventional and CAM therapies compiled from literature and local and state-wide experience of JIA management was provided	Perceived helpfulness; perceived side effects	Ratio scale: 4 levels from 0-3 (PE – Not /Somewhat /Moderately /Very helpful; AE – None /Mild /Moderate /Severe)	*PE for CAM therapies as a whole: Median (mean) rating 3 (2.5) There was no significant difference between the mean helpfulness ratings for conventional medications and CAM therapies {2.7 vs. 2.5 (p=0.29)}	Findings on outcomes summarised with this conclusion: Even though parents viewed some conventional medications as being more helpful for their children's JIA than some CAM therapies overall, the use of CAM was perceived as being similarly helpful as conventional medications. [REC: Future studies of CAM therapies, particularly those that parents feel are helpful and low in side effects, such as vitamin D, are

									warranted]
	52 respondents [RR 68 %]	Convenience sampling (All eligible subjects) [Sample size not justified]	Developed CAM tool was piloted for clarity in two JIA adolescents not part of the sample. No revisions were required.	Patient medical records of a university children's hospital; local database [For 2 months]	Prevalence: 92 % (30-day; 48 respondents)	Joint report (Parents in consultation with their children)	Descriptive {median rating (mean)} and inferential (p values) statistics; univariate analysis (Wilcoxon signed-rank @ $p<0.05$)	<u>AE CAM therapies as a whole:</u> Median (mean) rating 0 (0.29) Mean perceived AE ratings for conventional medications was significantly higher than those for CAM therapies {1.0 vs. 0.29 ($p=0.002$)}	<u>Limitations acknowledged:</u> 1. Single centre study 2. Non-generalisability (geographic variations in CAM licensing and practice) 3. Too short a period surveyed for CAM use (last 30 days) 4. Non-insurance of joint report status of the outcomes reported 5. Anonymity (impossible to verify parental reports of medications used) 6. Possible (Type I) errors in statistical analyses due to small sample size
36. Simpson and Roman (2001) [348] Conducted in the UK [Profession of primary author – Medical doctor]	1134 children	Not specified (Parents/ guardians of?) Paediatric subjects [Aged up to-16 years]	Cross sectional study design [Postal survey]	Ethics committee approval only; but implied consent implied	CAM defined inclusively as "various therapies for which you see a therapist, such as a homeopath, and various self-treatments such as herbs, which you buy yourself."	Perceived helpfulness; AE not studied	Type of outcomes measurement not described	<u>PE:</u> 85 % (197 of 231 episodes of use)	Findings on outcomes not summarised; nor were any conclusions made on UPES outcomes data [No recommendations made based on UPES outcomes data]
	994 respondents [RR 79.7 %]	Simple random sampling [Sample size justified statistically]	CAM tool developed and piloted (n not stated).	Sample generated from a child health database; regional database [Study duration not stated]	Prevalence: 18 % (ever used, 162 respondents)	Type of report(er) not specified	Descriptive statistics (%); outcomes data not statistically analysed	AE not studied	<u>Limitations acknowledged:</u> 1. Possible confounding due to soci-economic factors
37. Bold and Leis (2001) [354] Conducted in Canada [Profession of primary author – Unclear]	48 eligible paediatric subjects	Parents of living children with cancer [0-14 years at time of diagnosis]	Cross sectional study design [Semi-structured telephone interviews]	No ethical considerations reported	Unconventional therapies were defined as those therapies, other than medical treatments that are considered standard in Saskatchewan, that patients	Satisfaction; problems	No rating scale used. Outcomes were rated qualitatively	<u>PE:</u> Reported by more than 80 % of users (described as: therapy had helped in some way; the provider was very good; and/or the child had been treated very well) (number of users not provided)	Findings on outcomes summarised with this conclusion: Parents who used unconventional therapies expressed satisfaction with them, and reported very few problems. In general parents described quite positive experiences in using unconventional therapies [REC: It is time to move beyond trying to understand why patients

					received specifically for their cancer and/or associated symptoms or conditions, regardless of type of provider				turn to unconventional therapies. Rather the health system needs to adapt to and support patients and families' needs to identify safe and potentially helpful therapies when they choose to do so. There is need for more research into the effectiveness of individual unconventional therapies using appropriate questions and methods. Evaluations must consider effectiveness in relation to users' expected outcomes]
	44 respondents [RR 92 %]	Convenience sampling (All eligible subjects) [A 2-year period was adjudged from the past annual entries as adequate in providing a sufficient number of subjects for descriptive and associational statistical analyses]	Interview schedule adapted from a previous cancer survey in adults; but no report of validation or pilot.	Province-wide mandatory and comprehensive cancer registry; state-wide database [Study duration not stated]	Prevalence: 36 % (for condition; 16 respondents)	Proxy report used	Descriptive statistics (%); outcomes data not statistically analysed	AE: Unsure -data unclear: "three quarters of parents reported no problems" – implying that about a quarter did?	No limitations acknowledged
38. Molassiotis and Cubbin (2004) [350] Conducted in the UK [Profession of primary author – Nurse]	96 eligible paediatric subjects	Parents of children with cancer receiving conventional treatment [aged 5-18 years]	Cross sectional study design [Postal survey]	Ethics committee approval; informed consent & confidentiality	CAM defined according to Ernst and Cassileth, 1998, p. 777: "diagnosis, treatment and/or prevention which complements mainstream medicine by contributing to a common whole, by	Perceived effectiveness /benefits; AE not studied	Interval scale and qualitative report: Helpfulness – 10-level scale, from 1 (not helpful at all) to 10 (very helpful); Benefits - qualitatively	*PE: No general rating for all CAM. Mean PE rating (SD) for specific CAMs: Multivitamins – 6.71 (1.7); Diet – 7.17 (0.98); Aromatherapy – 8 (1.46); Herbal medicine –1*; Homeopathy -1*;	Findings on outcomes validly summarised with this conclusion: Most parents who used some form of CAM for their children were satisfied with their chosen therapy in relation to the benefits it provided for their child. [REC: The fact that the use of CAM has been reported as having both positive and beneficial effects for children with cancer suggests that CAM use should perhaps be an

					satisfying a demand not met by orthodoxy, or by diversifying the conceptual frameworks of medicine"			Megavitamins -1*; Vegetable juices -10* (*SD not stated). <u>Correlations</u> A significant correlation was shown between using diets and the perception of improving the child's immune function (r_s =0.73, p<0.001) as well as with using multivitamins (r_s =0.68, p=0.004). <u>Perceived benefits:</u> Increased confidence (n=2); pain relief (n=6) and relaxation (n=5)	integral part of the treatment that children receive for their cancer]
	49 respondents [51 %]	Convenience sampling (All eligible subjects) [Sample size not justified]	Developed CAM tool was piloted in four parents who were not part of the final sample, and then revised	Patient database of the oncology unit of a hospital; local database [Study duration not stated]	Prevalence: 33 % (for condition; 16 respondents)	Proxy report used	Descriptive {mean ratings (SD)} and inferential (p values) statistics; bivariate analysis (Spearman's correlation; significance level not stated)	AE not studied	<u>Limitations acknowledged:</u> 1. Small sample size (difficult to generalise results) 2. Cross sectional study design (no time element considered) 3. Nonresponse bias (possibly skewed the results)
39. Christon et al (2010) [361] Conducted in the USA [Profession of primary author –– Clinical psychologist]	248 eligible parents (Number of paediatric subjects not stated)	Parents of children with autism spectrum disorders who had participated in a larger study [aged 21 months-21 years]	Data analysis of a sub-set of respondents to an online cross sectional survey [Secondary study]	Ethics committee approval; informed consent	A list of both conventional and CAM therapies (including biological and non-biological treatments) was provided to participants	Perceived improvement; outcome-related reason for stopping therapy; AE not studied	Ordinal scale: 5 categories (Much improvement to Much worse)	<u>PE (averaging across treatments):</u> 56 % (Much improvement -18 %; Some improvement -38 %) (number of users not provided) <u>Odds of "Improvement" rating:</u> The odds of parents rating the outcome of their use of various product-based CAM therapies as an improvement (much/somewhat) rather than as no improvement (no change/worse) were as follows: Animal therapy -1.8; Chelation -1.7; Secretin -0.4;	Findings on outcomes validly summarised; but the following ambivalent conclusion was reached: Parents vary considerably in their assessment of whether the CAM therapies actually helped their child: the most frequent reason for stopping a treatment was that, in the parents' view, it did not work. It is likely that some of the CAM treatments were helpful for some of the children, and that the treatments had no effect for some of the children; it is possible they harmed some children. Without valid assessment of efficacy, we do not know [REC: Clearly more methodologically sound research needs to be done on CAM

								Special diets -1.4; Special vitamins -3.2 Proportion of users that stopped therapy because it "did not work" (averaging across therapies): Stopped using CAM – 54 % of users; Stopped because CAM did not work – 27 % of users	treatments]
	248 respondents [RR not appropriate – not a primary study]	Convenience sampling (All eligible subjects) [Sample size not justified]	Online survey was developed using the Inquisite programme; but no report of validation or pilot	Database of participants in a larger online survey recruited through notices placed in parent newsletters by county-, state- and nation-wide autism organizations; broad database [Study duration not stated]	Prevalence: 71 % (ever used; 176 respondents) 51 % (current use; 127 respondents)	Proxy report used	Descriptive statistics (%, OR); univariate analysis (frequency table)	AE not studied	Limitations acknowledged: 1. Response bias (subjective and not clearly specific to specific therapies) 2. Non representative sample (required computer/online access, and membership of autism organization) 3. Outcomes ratings not validated
40. Ben Arush et al (2006) [378] Conducted in Israel [Profession of primary author – (Medical doctor]	Target sample size not stated	Adolescents and parents of children presenting for oncology treatment, hospitalization or follow-up [Paediatric age range not specified]	Cross sectional study design [Face-to-face interview]	Ethics committee approval; informed consent	CAM was defined as any practice not prescribed by a physician or not considered as a proven medical treatment. A list of CAM therapies was also provided	Perceived improvement; AE not studied	Type of outcomes measurement not described	PE: 69 % (42 users); for 63 % of 165 different treatments and remedies Specific benefits reported: General improvement in well-being – 70-85 % of treatments; Strengthening immune system – 68 % of treatments	Although no distinct summary statement was made on the outcomes findings reported, the following conclusion was reached: The optimal use of complementary therapies may improve quality of care, especially its impact on well-being [REC: Potential benefits and harms of CAM treatments have to be scientifically studied, verifying their impact on therapeutic trials]
	100 respondents [RR data not available]	Convenience sampling (All parents or adolescents	Developed CAM tool was piloted (in 10 patients) and then revised	Oncology department of children's hospital at a secondary and	Prevalence: 61 % (prevalence type unclear; 61 respondents)	Mixed report used: Adolescents - self-report; Children –	Descriptive statistics (%); outcomes data not statistically analysed	AE not studied	No limitations acknowledged

		who came on the specific interviewing days) [Sample size not justified]		tertiary referral centre for a multi-ethnic/cultural population in northern Israel; single centre [For 6 months]		parent-proxy report			
41. Sawni-Sikand et al (2002) [489] Conducted in the USA [Profession of primary author – (Medical doctor]	1045 paediatric subjects	Parents/caregivers of children presenting at practices [Paediatric age range not specified]	Cross sectional study design [Self-completion survey]	Ethics committee approval; informed consent & anonymity	CAM defined as any therapy for a medical illness that the child's regular doctor did not prescribe (excluding over-the-counter medications like multivitamins), with relevant examples	Perceived satisfaction – overall, and relative to conventional medicine; AE not studied	Type of outcomes measurement not described	PE: Overall Satisfaction - 55 % (number of users not provided); Relative to conventional medicine: 52 % reported that results were best when CAM is integrated with conventional medicine)	Findings on outcomes validly summarised; but no conclusions were drawn from them [No recommendations made on UPES outcomes data]
	Number of respondents not stated; but 1013 valid responses (67 %) were received [RR data not available]	Sampling method not described [Sample size not justified]	CAM tool adapted partly from tool used in an earlier study, and then piloted	3 Urban and 3 sub-urban general paediatric practices; multi-centre; multi-city [For 5 months]	Prevalence: Sub-urban practices: 12 % (prevalence type unclear; number of respondents not provided); Urban practices: 14 % (prevalence type unclear; number not stated)	Proxy report used	Descriptive statistics (%); outcomes data not statistically analysed	AE not studied	Limitations acknowledged: 1. Non-generalisability (regional differences in CAM use; clinical setting) 2. Social desirability bias 3. Non-validation of tool (reliability and validity)
42. Laengler et al (2008) [661] Conducted in Germany [Profession of primary author – (Medical doctor]	1595 eligible paediatric subjects	Parents of paediatric subjects with cancer registered in the German Childhood Cancer Registry [0-15 years]	Cross sectional study design [Postal survey]	Ethics committee approval; informed consent & anonymity	CAM defined as all the treatments not currently considered standard or largely accepted experimental methods. A "comprehensive" list of therapies was also provide	Perceived improvement; perceived AEs	Type of outcomes rating scales not described; perceived benefits reported qualitatively	PE: "Improvement" or "Marked improvement" was reported in over 50 % of the cases where the most popular CAM types (mainly CAM products) were used. Perceived Benefits: Reported by 91 % of users with positive expectations of CAM use, and 68 % of those	Findings on outcomes validly summarised; but no conclusions were drawn from them [No recommendations made on UPES outcomes data]

								with negative expectations. Most reported benefits for CAM products - 1. Strengthening of the immune system 2. Greater physical stability	
	Number of respondents not stated; but 1063 valid responses (67 %) were received [RR data not available]	Convenience sampling (All eligible subjects) [Sample size not justified]	CAM tool was previously piloted; but no report of validation	German Childhood Cancer Registry; broad database [8.5 months]	Prevalence: 35 % (for condition; 367 respondents)	Proxy report used	Descriptive statistics (%); outcomes data not statistically analysed	<u>AE</u>: 4 % (number of users not provided)	No limitations acknowledged
43. Gerasimidis et al (2008) [352] Conducted in the UK [SCOTLAND] [Profession of primary author – Clinical nutritionist]	104 of 135 eligible paediatric subjects	Guardians of paediatric patients with inflammatory bowel disease (IBD) [4.8-17.5 years]	Cross sectional study design [Self-completion survey]	Ethics committee approval; informed consent	CAM was defined as unconventional remedies and treatments that are not normally taught in the British medical schools as established approaches to IBD management; and that were not reimbursed by the NHS nor recommended by medical staff, excluding exercise and prayer. Multivitamins and dietary modifications were included only where they had been purchased over-the-counter without having been recommended by medical staff. A list	Perceived effectiveness; reported AEs	Type of outcomes measurement not described	<u>PE:</u> 48 % (16 users) <u>Association:</u> A PE rating of Effective was reported to be associated with the CAM type used: "CAM Therapist Users" were reported to be more (p=0.022) associated with an Effective rating for CAM "Self-prescribed CAM users: but data not presented.	Findings on outcomes validly summarised; but no conclusions drawn on UPES data [No recommendations made on UPES outcomes data]

					of grouped CAM therapies was also provided.				
	86 respondents [RR 83 %]	Sampling method not described [Sample size not justified]	Adapted from 2 previous questionnaires; checked for face validity, and then piloted in 10 IBD patients	Outpatient department of a regional IBD referral centre in an urban children's hospital; single centre [For 13 months]	Prevalence: 61 % (ever used -as from 3 months post diagnosis; 52 respondents) 37 % (current use; number of respondents not provided)	Proxy report used	Descriptive (%) and inferential (p values) statistics; bivariate analyses (OR @ 95 % CI)	AE: 1 patient (but % not provided; so data unclear). Q: Is this patient among the ever users or recent users of CAM?	No Limitation acknowledged
44. Rossi et al (2010) [358] Conducted in Italy [Profession of primary author – (Medical doctor]	337 paediatric patients	Paediatric patients with respiratory diseases [aged 0-14 years]	Prospective cohort study design [Routine medical consultation - Patient report of symptoms]	No mention of ethics committee approval; but informed consent obtained	Homeopathic therapies; no definition needed, as participants were patients presenting at homeopathic clinic [Single centre]	Outcome of therapy – degrees of improvement; AEs reported	Interval scale: 6 levels, numbered from -1 to 4 (Slight worsening /None /Slight improvement /Moderate improvement /Important improvement /Cured or Back to normal)	PE: Degree of Improvement- 96 % {Cured/Back to normal – 32 %; Important improvement – 36 %; Moderate improvement – 15 %; Slight improvement – 13 %} (number of users not provided) Regression – Outcome was significantly associated with type of diseases treated (p=0.005) {upper respiratory tract infection [77 % success; OR -4.2 (1.6-11.4)] > allergic rhinoconjuctivitis [63 % success; OR -1.2 (0.3-4.6) > lower respiratory tract infection [54 % success; OR -1.0 (C I not provided)]} and the duration of follow-up at which either an important improvement or a resolution was reported (p<0.001) {≥24 months [94 % success; OR -35.7 (8.5-150.0)] > 12-18 months [78 % success;	Findings on outcomes validly summarised with this conclusion: Our data evidence that nearly all patients with follow-up reported a positive outcome deriving from homeopathic treatment of respiratory diseases, with the probability of reporting at least an important improvement being highest for upper respiratory tract infections and the likelihood of success being higher in patients with follow-up of at least one year. These results tend to identify a positive therapeutic effect of homeopathy in the paediatric age. [REC: Homeopathic treatment should be encouraged, in particular for respiratory diseases, which are the most frequent in the paediatric phase of life]

								OR -6.3 (2.2-17.9)] > 6 months [50 % success; OR -1.2 (0.4-3.5)] > 2 months [38 % success; OR -1.0 (C I not provided)]}	
	168 patients returning for follow-up [RR 50 %]	Convenience sampling (Consecutive eligible subjects) [Sample size not justified]	Glasgow Homeopathic Hospital Outcome Score (GHHOS); a standard outcomes tool	Homeopathic clinic of a provincial hospital; single centre [For 10 years]	Prevalence of CAM use not relevant as use of homeopathy use had been an inclusion criterion	Report made by patient; but the specific report type (direct or proxy) not clearly stated	Descriptive (%) and inferential statistics (p value); Logistic multivariate analysis (Adjusted OR; 95 % C I)	AE: No negative effects reported	Limitations acknowledged: 1. Non-comparison of results with a control group on conventional treatment
Zuzak et al (2010) [369] Conducted in Switzerland [Profession of primary author – (Medical doctor]	Target sample size not stated	Adults – mainly parents-accompanying their children for clinic visits [Paediatric age range not specified]	Cross sectional study design [Self-completion survey]	Ethics committee approval; informed consent & anonymity	A list of CAM therapies was also provided	Experiences with CAM: frequency of perceived effect (CAM vs. conventional medicine, CM); comparative perceived effectiveness; AEs noticed (CAM vs. CM)	Ordinal scale: Frequency of benefit – 4 categories (Always /Sometimes /Rarely /Never); Comparative effectiveness – 3 categories (More /Equivalent /Less effective); Perceived AEs - 3 categories (Strong /Weak /No side effect)	PE: Frequency of perceived effect (CAM vs. CM)- Always – CAM -38 % (242 users) vs. CM -62 % (473 users); Sometimes – CAM -52 % (331 users) vs. CM -34 % (262 users); Rarely – CAM -3 % (19 users) vs. CM -1 % (11 users); Never – CAM -5% (33 users) vs. CM -2 % (14 users) Comparison of mean value of ratings (CAM vs. CM): 0.76 vs. 0.85 (p<0.001) Comparative effectiveness More effective – 49 % (370 users); Equivalent effect – 13 % (99 users); Less effective – 3 % (26 users)	Findings on outcomes validly summarised with this conclusion: Although CAM may be slightly less effective than CM, its good performance in some clinical situations and the superior tolerability leads to a high satisfaction of the users. Taken together, the data shows that for adults accompanying paediatric patients presenting to the emergency department, the strongest difference between CM therapies and CAM therapies concerned the tolerability of the two types of medical systems, with clearly more seldom and weaker side effects being experienced with CAM therapies. These observations seem to justify the recommendation of CAM therapies in certain situations, if accompanied by an individual assessment of the patient's risk situation by a medical doctor [No recommendations made on UPES outcomes data]
	Number of respondents not stated;	Sampling method not described	CAM tool was piloted (in 20 families) to	Urban paediatric emergency	Prevalence: 58 % (ever used; 665 respondents)	Proxy report used	Descriptive (%, mean ratings) and inferential (p	AE: AEs noticed CAM vs. CM CAM -7 % (47 users)	Limitations acknowledged: 1. Lack of clinical data 2. Exclusion of people not literate

	but 1143 (71 %) responses available for analysis [RR data not available]	[Sample size not justified]	ensure readability and question clarity; and then revised	department in a tertiary hospital; single centre [6 months]			value) statistics; univariate analysis (Mann-Whitney tests @ p<0.05)	{Strong -1.4 % (9 users), Weak -6 % (38 users), None -93 % (580 users)} CM -48 % (357 users) {Strong -10 % (73 users), Weak -38 % (284 users), None -52 % (381 users) <u>Comparison of mean value of ratings (CAM vs. CM):</u> 0.05 vs. 0.22 (p<0.001)	in German, English, French, or Italian 3. A wide definition of CAM 4. Use of a single centre 5. Use of collective expression – such as "all", "never", "sometimes", etc., without further numerical definition of what is meant
46. Keil et al (2008) [357] Conducted in Germany [Profession of primary author – (Medical doctor]	118 children (54 on homeopathy; 64 on conventional medicine, CM)	Patients with eczema and their parents [aged 0-16 years]	Prospective, comparative, cohort study design [Self-completion survey]	Ethics committee approval; informed consent	Homeopathy; but no definition necessary, as patients had already chosen to receive treatment at homeopathic clinics	Perceived improvement of symptom severity; perceived side effects In each case CAM vs. CM)	Ratio scale: Symptom severity – 11-point numerical rating scale, numbered from 0 (no symptoms) to 10 (worst symptoms)	<u>*PE:</u> <u>Mean improvement of symptoms</u> Symptoms improved gradually over time in both groups – CAM {[Baseline -3.7 (3.1-4.3); 6-month -3.3 (2.7-4.0); 12-month -2.7 (2.1-3.4)] p<0.001, unadjusted}; and CM {[Baseline -3.4 (2.8-3.9); 6-month -2.7 (2.1-3.3); 12-month -2.1 (1.5-2.7)] p<0.037, unadjusted}; but more severe cases tended to be found more often in the CAM group (p=0.077, unadjusted) than in the CM group (p<0.172, unadjusted). However, trends did not differ between the 2 groups (p=0.830, unadjusted; p=0.447, unadjusted) <u>Regression</u> Results displayed graphically	Findings on outcomes validly summarised with this conclusion: Comparing homeopathy with conventional treatments over a long period (12 months) in everyday practice, both therapy groups improved similarly regarding perception of eczema symptoms assessed by patients or parents. [REC: Further research is needed regarding the comparison of these therapy options for patients with eczema in relation to different study settings and patient populations as well as economic evaluations]
	Number of respondents not provided [RR for all 3 survey points (0, 6, 12 months)	No sampling carried out (Eligible subjects presenting at the selected study centres	Tool developed specifically for the study; but no report of pilot or validation	Homeopathic and conventional doctors' practices in urban and urban-rural	Prevalence of CAM use not relevant as use of homeopathy use had been an inclusion criterion	Mixed report used–Self report (mostly for children aged 8-16 years) or parent-proxy	Descriptive (mean ratings) and inferential statistics (95 % C I); univariate and logistic multivariate	<u>Mean AE rating scale (AE):</u> None reported for both groups	No limitations acknowledged

	-70 % for Homeopathy; and 75 % for CM]	were recruited) [Sample size not justified]		regions; multi-centre, multi-city [For 36 months]		or joint report (mostly for children aged 0-7 years)	analyses (@ p<0.05)		

Chapter 3

Yellow Card Reports Associated with Paediatric Use of Natural Health Products - An Exploratory Analysis

3.1 Introduction

The Yellow Card Scheme (YCS) is the main spontaneous adverse drug reaction (ADR) reporting scheme in the UK. Established in 1964 under the Committee on Safety of Drugs (CSD), and run since 2005 by the Commission on Human Medicines arm of the Medicines and Healthcare products Regulatory Agency (MHRA), the scheme collates reports made to it by healthcare professionals, patients and authorized bodies about suspected ADRs associated with the use of medicines, medical devices, biologicals, vaccines, blood products, or herbal or complementary products, whether self-medicated or prescribed. This includes suspected adverse drug reactions associated with misuse, overdose and medication errors, or from use of unlicensed and off-label medicines. A key finding of the SR reported in chapter two is the low report of adverse outcomes by CAM users participating in population studies reported in peer-reviewed journals. Possible reasons for this development could range from the failure of public health researchers to focus on and pick up such negative outcomes of CAM use; to social desirability bias among CAM users with regards to reporting negative outcomes from their elective therapies; to the actual relative scarcity of CAM-related ADRs among the population. This chapter seeks to explore the third possibility within the constraints and peculiarities of available data; while the other possibilities will be investigated in the following chapter. As efforts to obtain suitable data on CAMs from the Information Services Division of the Scottish NHS proved abortive, the data for this study will be the reports made on the UK's YCS from inception to July 2012. Also, as ethical considerations based on the provisions of the Data Protection Act of 1998 precluded

the isolation of Scotland-specific data; YCS reports for the whole of the UK will be used. Thus, the primary research question for this retrospective study can be summarised as: how common and serious are the suspected ADRs reported by the UK public for CAM products on the YCS, and what are the associated factors? While a general overview will be given on CAM-related ADRs among the UK population as a whole, these questions will be investigated in greater detail among paediatric subjects (children aged 0-17 years); while aspects of the data relating to younger children (subjects aged 0-11 years) and all adults (subjects aged over 17 years) will be presented, where necessary, for the purpose of comparison.

After a general overview of the theoretical bases for pharmacovigilance (PV) and the YCS with special focus on paediatric PV, this section will provide a historical overview of PV with emphasis on the YCS, and a summary of the distinctive features of the PV of CAM products. Thereafter a recap of previous research of the YCS data will be conducted to give the context of the current study. The methods and results of the YCS data analysis will then be reported in two distinct phases. Firstly, a general overview of the data will be provided by highlighting general distinctions between CAM and non-CAM reports, as well as those between adult and paediatric CAM reports. Then the specifics of paediatric CAM data will be investigated in greater detail by comparing the different constituent age-groups.

3.1.1 Pharmacovigilance and the Yellow Card Scheme –A Historical Perspective

To facilitate the understanding of the MHRA's YCS CAM data, it is helpful to have a historical overview of PV in general, and the YCS in particular. The first recorded PV historical milestone was a publication in The Lancet in 1893 reporting the findings of a commission on anaesthesia-related deaths which was set up following the death of a 15-year old girl in Northeast England from chloroform anaesthesia [525]. For a brief period following the incident, the commission had invited doctors in Britain and its colonies to report suspected anaesthesia-related deaths, thus becoming the fore-runner of the spontaneous reporting system for suspected ADRs [526]. This one-off event was followed sometime later by the opening of a register of suspected ADRs by the American Food and Drug Administration (FDA) following sudden deaths in 1937 associated with poisoning by an elixir of sulphanilamide [527]. However, in spite of these sporadic developments, the major historical event leading to the establishment of PV was the thalidomide tragedy in 1961. In the years following this incident, particularly between 1961 and 1965, many national centres monitoring suspected ADRs were established across the world. In the UK, the CSD was set up in 1963 to monitor new drugs and report on drug quality, efficacy, and safety [528]. Internationally, that same year, the World Health Assembly adopted resolution WHA 16.36 reaffirming the need to give more attention and surveillance to suspected ADRs. In 1968, the WHO launched the

Pilot Research Project for International Drug Monitoring, which subsequently developed into the Programme for International Drug Monitoring, coordinated since 1978 by the Uppsala Monitoring Centre (UMC) in Sweden [529]. The UMC now gathers suspected ADR reports (received since 1968) from over 100 WHO member countries into a global database of individual case safety reports (ICSRs) called VigiBase^{TM}. More recently in 2001, the European Medicines Agency (EMA) set up EudraVigilance as an international network tasked with gathering all reports of suspected ADRs for drugs authorized in the EU forwarded to it by regulatory agencies and by drug industries in the EU [530].

The UK's YCS is one of the oldest national spontaneous ADR reporting schemes. Although reports of a few suspected ADRs were received in 1963 following the establishment of the CSD, the YCS was established in 1964. Some key historical milestones have significantly affected suspected ADR reporting in the UK [531]. One of the most significant is the establishment of the Black Triangle Scheme in 1976, for newly introduced drugs or drug indications/routes of administration, which is still currently in use. Some other key milestones are: the establishment of regional monitoring centres in the 1980s; the inclusion of the Yellow Card in GP prescription pads and the BNF in 1986; the extension of the YCS reports to unlicensed herbal medicines in 1996 [532]; the broadening of ADR reporters to include pharmacists practising in hospitals (in 1997) and in the community (in 1999) [531]; the broadening of ADR reporters to include nurses, initially for vaccines only in 1999, and more broadly in October 2002 [533]; and finally, the national roll-out of patient-reporting in 2005 [186], and its formal launch in February 2008 [534]. The effects of these factors on the suspected ADRs reported for CAM products used in paediatric subjects will be investigated in this study. However, a broad overview of the trends in yellow card reporting shows that in the late 1970s and mid-1980s, and in the year 2000, ADR reporting increased significantly; while there was a general decrease in the early 1990s [531, 535, 536]. The current study will also verify whether the trends for ADR reporting for CAM products follow a similar pattern.

The chief limitation associated with spontaneous reporting schemes is a high degree of under-reporting [537]. Various factors have been identified for this development, ranging from physiological and pharmacological factors to factors related to professional ethics and public health in general to technological and educational factors [538, 539]. These factors have also been found to be relevant to ADR reporting in the YCS [540, 541]. While these factors have not nullified the utility of the YCS with respect to identifying specific important signals resulting in withdrawals of marketing authorisations or restricted prescribing conditions of several medicinal products since its inception [542, 543], they make it as unwise to draw specific conclusions about the UK population from the data as it would be to draw conclusions from a survey sample that is unrepresentative of its parent population [544]. Moreover, such data cannot be used to provide estimates of risk, as, apart from the fact that the true number of cases involved is often under-reported

reported, the denominator (i.e. all cases where the medicine was used within the period) is also not known [545, 546]. Additionally, the danger of basing important therapeutic and regulatory decisions on only one source of data has been highlighted [547]. Therefore, although every effort will be made in the current analysis to extract as much information as possible from the YCS data, the findings will be interpreted with caution with respect to the UK population.

3.1.2 Pharmacovigilance in children

ADRs are a significant problem among children in general [548, 549]. As such, while the report of suspected ADRs associated with all medicinal products is generally encouraged, special emphasis is placed on the report of all ADRs experienced by paediatric subjects. Up until October 2014, this was required in the UK in every instance, irrespective of the marketing status of the medicinal product concerned, or the perceived degree of seriousness of the suspected ADR [541]. Although the requirement in ADR reporting in children was restricted by the MHRA in October 2014 to ADRs that are serious, medically significant or life threatening/disabling, and all those occurring in Black Triangle drugs [550], the importance of PV in that demographic is still high [551]. Therefore, in the UK and many other countries, active (rather than passive) surveillance schemes have been set up for paediatric ADRs [552]. While there are several reasons for this, the British National Formulary for children (BNFC) summarizes them as being related essentially to specific physiological and pathological differences between children (particularly the very young) and adults; and the deficiency of drug-related data on, and appropriate drug formulations for, paediatric subjects (BNFC 2014). These points not only emphasize the need to improve the evaluation of paediatric drug safety, but also the importance of including age-specific and circumstantial data in such reports [553, 554]. Despite efforts to improve paediatric PV, the proportion of YCS reports for under-18-year-olds has remained low, contributing 4.4% all UK ADR reports received in 2011–2012 [539]. Whether CAM-related ADR reporting in children follows a similar trend remains to be seen; and is one of the objectives of the current study. It is also helpful to find out how such reports differ across paediatric age sub-categories. In view of this, in addition to comparing the CAM-related YCS data received for paediatric subjects (0-17 years) with those for the general adult population (< 17 years), this study will also consider the data with respect to the following age subcategories – infants (less than 2 years old); pre-school children (2-5 years); school-age children (6-11 years); and younger adolescents (12-17 years).

3.1.3 Pharmacovigilance of Complementary & Alternative Medicines

As CAM products differ from conventional medicines in various ways, the PV of CAM products presents distinctive challenges, an appreciation of which is helpful in understanding this aspect of the research. The first major challenge concerns the nature of the CAM products themselves;

while the other relates to the peculiarities in their use. As most CAM products are natural products that have been in use as food as well as home remedies for many centuries, and are thus associated with various cultural lifestyles, they are widely perceived as both effective and safe [31, 555]. Additionally, as they have not been subject to the same degree of regulation as conventional medicines, there have been fewer barriers and restrictions to their availability and use across the world [15, 556]. A major factor in this is that they are largely not available on many national health systems; and as such are often either self-prescribed by users based on their own (internet) search or experience, or used on the recommendation of family and friends [312, 557]. Additionally, they can be easily accessed from various outlets, nullifying the influence of gate-keepers associated with prescription medicines [101, 558]. In this last respect, the factors affecting CAM products are similar to, but not identical with, those affecting non-prescription conventional medicines [532, 559]. These factors negatively affect PV of CAM products, as users are less likely to attribute negative outcomes to them; and even when they do, most would be reluctant to report ADRs, as that would essentially amount to them reporting themselves [560, 561].

In addition to the above, there is also the issue of general confusion as to nomenclature [562]. Although this is more prevalent with herbal medicinal products [204], there is a general confusion as to where to draw the line between what can be normally called "food" and what actually is CAM [563]. The CAM subcategory of nutritional therapies or the product category of nutraceuticals makes this even more problematic [564, 565]. This factor affects such "special" foods as Mediterranean diets, which are cultural in certain parts of the world and yet are still CAM; as well as generally accepted foods like yogurts, which can also serve as CAM (probiotics). Also, many substances that are classified as dietary supplements, such as multivitamins, melatonin or ephedrine, are also used in conventional medicine [2]. Moreover, some dietary supplements are not used so much to manage or cure an ailment as to maintain general health and well-being –similar to a food item in a balanced diet [566]. To overcome the confusion in the definition of CAM, it has been proposed that attention should be focused on CAM users with respect to their purposes of use of CAM, rather than on the nature of the CAM products and practices themselves [567, 568]. From a PV point of view, however, this clarification is neither very helpful nor particularly important, as the focus of the database is on suspected ADRs and not indications. Indications would serve as a useful guide only where such specific details as would clarify the purpose of use of the natural product concerned are strictly reported, as has been recommended in the WHO guidelines on safety monitoring of herbal medicines in PV systems [569]. The extent to which these recommendations have been adhered to remains to be seen; and will be one of the objectives of the current analysis. For the purposes of clarity, however, CAM products will be taken in this chapter to refer to the natural health products (NHPs) reported in the YCS database, irrespective of their purpose of use. The NHPs to be studied will, therefore, include

vitamins and minerals; probiotics; amino acids and essential fatty acids; traditional and homeopathic medicines; synthetic duplicates of natural ingredients; various preparations of plants, algae, bacteria, fungi, nonhuman animal materials; and medicinal products containing extracts or isolates of plants, algae, bacteria, fungi, nonhuman animal materials as active ingredients [570] . These will be included in the current analysis whether they were used alone or in combination, or whether they were single or combination products [571].

Another key factor in the PV of CAM products is the fact they are frequently used in conjunction with conventional medicines, a practice further encouraged by the global trend towards integrative medicine [572, 573]. While the hazards of this practice have been particularly established with herbal medicines in terms of herb-drug interactions [574], the peculiarities associated with the general perception, understanding and use of CAM make it generally important for all CAM products [575]. It has been suggested that "adverse reactions apparently due to a conventional medicine, might in reality be due to a herbal medicine or a drug interaction between a herbal medicine and a conventional drug" leading to confusion in spontaneous reporting systems [576]. It is necessary to verify this suggestion based on the YCS data, and will be one of the objectives of the current study. Apart from being used along with conventional medicines, CAM products are also often used together, either separately as multiple products or as combination products, like poly-herbal formulations [577–579]. As poly-pharmacy has generally been associated with a higher risk of ADRs in conventional medicines [580], another objective of the current study is to understand the consequences of such combined use for CAM products with respect to adverse effects [573].

3.1.4 Summary of previous research on the Yellow Card Scheme

While substantial research has been carried out on ADRs in adults, little such work has been done for children, and much less for CAMs [204, 581]. Most previous studies either considered all reports received during a particular period [535, 582]; or focused on specific drugs or drug classes and/or health or physiological conditions [583–585]. Significantly, about the only YCS study that focused on CAM products [586] was based on the NIMH Yellow Cards, and not the whole YCS database. The paucity of reports on CAM-related ADRs is, however, not confined to the UK. However, although an analysis by [206] of 20 years of ADR reports to the WHO found "substantial evidence" that herbal medicines could cause serious ADRs; there is generally a lack of information regarding the rates of occurrence of ADRs with CAM products [587].

The situation of pharmacovigilance research is worse for paediatric subjects. Although a recent review of ADRs reported in children [588] indicated that the highest numbers of ADRs were reported in national ADR databases rather than in studies monitoring inpatients and outpatients, none of the eight database studies included in the review was carried out in the UK. Since a recent

global ADR report analysis at the Uppsala monitoring centre shows that the UK ranks second only to the US with respect to the total number of ADR reports received in both adults and children [589], the non-representation of the UK in the review highlights the scarcity of research on the YCS for paediatric subjects. While an overview of the literature in September, 2014 using Google Scholar yielded three papers analysing UK YCS reports for paediatric subjects, only one of them [590] covered all ADRs reported for paediatric subjects across the UK; with the other two focusing on either a region of the country [552] or a subset of paediatric ADRs –fatal ADRs [591]. Also, even the most comprehensive of the studies had a relatively short time span, focusing only on ADR reports submitted within the period 2000-2009. And most importantly, none of the studies focused on NHPs or CAMs. Thus, the relevance of the current study is not debatable.

3.1.5 Objectives of the current study

The aim of this study is to descriptively summarize the MHRA PV data for CAMs from the inception of the YCS to July 2012 in terms of patient demography, CAM product types, nature and clinical classification of reported events, and type of reporter involved. Data will be summarized in terms of:

(i) number of reports for individual products as well as CAM product types;

(ii) date of report (annually and in 10-year bands), and associated trends in ADR reports received;

(iii) patient characteristics (sex and age);

(iv) comparison of ADR reports (CAMs vs. non-CAMs; adults vs. paediatric subjects; and among paediatric sub-categories);

(v) effect of relevant public health legislations on ADR reporting (immediate and sustained effect);

(vi) reporter status;

(vii) MedDRA SOC distribution of paediatric ADRs;

(viii) reporter's opinion as to seriousness of the reaction (outcome and severity);

(ix) CAM classification of products associated with paediatric ADRs;

(x) ATC (level 1) classification of products associated with paediatric ADRs

(xi) indications/purposes of NHP use

(xii) most common ADRs (holistically, as well as for age & sex categories and CAM product types);

(xiii) serious, fatal and most common severe and unresolved ADRs (holistically, as well as for age & sex categories and CAM product types);

(xiv) reaction duration; and

(xv) richness of free text description of ADRs

The major research question that this study posed was: what is the number, frequency, and nature of the suspected ADRs reported on the YCS for children and adolescents aged up to 17 years with respect to CAMs, and how are these affected by:

1. patient demography (sex and age category);
2. public health legislations (UK and Europe); and
3. product type and mode of use (single, multiple or combined)?

3.2 Methods

3.2.1 Acquisition of YCS data and dataset description

An application for the release of Category II YCS data for CAMs was made to the Independent Scientific Advisory Committee for MHRA database research in July 2011. The application was considered on October 7, 2011, and approval was granted subject to a number of conditions with respect to computer security and data storage. After meeting the conditions, the data for reports on CAM products from 1963 to July 2012 was released in August 2012 as a pass-worded encrypted Excel file. The dataset provided contained 2167 data entries (in rows), with each entry providing a range of information in columns that can be generally grouped into five broad categories comprising a total of 31 specific items. The broad categories with their respective constituent items are:

(i) seven patient health data-related items:-"age", "age group", "sex", "medical history", "medical history comments", "case narrative" and "medical history";

(ii) eight reaction-related items:- "ADR number", "date received", "reaction + outcome", "reaction severity", "reaction start date", "reaction stop date", "treatment description" and "other drugs + indications";

(iii) five suspect drug-related items:- "suspect drug + indications", "route of administration", "additional dosage form information", "drug start date" and "drug end date";

(iv) three reporter-related items:- "qualification", "specialty" and "comment"; and

(v) eight Council for International Organisations of Medical Sciences (CIOMS)-related items:- "reporter serious", "any CIOMS serious", "congenital abnormality", "disability/incapacity", "hospitalization", "life-threatening", "other medically significant" and "patient died".

Additional data on the total number of reports received annually for the period of the review was obtained from the MHRA on July 11, 2013 and September 18, 2013 upon further requests. Copies of the application form and approval letters for data release are provided in Appendices (iii)-(vi); while a protocol drawn up to direct the database analysis is provided in Appendix (vii).

3.2.2 Data cleaning

To prepare the data for the current analysis, the data was cleaned in line with standard guidelines for database research [592, 593]. This was done in two main stages as follows:

3.2.2.1 Extraction of appropriate paediatric data

Firstly, specific data for paediatric subjects was extracted from the parent dataset. This was achieved essentially by filtering out entries for subjects aged > 17 years as well as those with no age-related details. As age-related details were recorded in the "age" and "age-group" columns of the dataset, specific data for paediatric subjects was extracted from the parent dataset using the filter criteria "< 18" (for age) and "infant", "child", and "adolescent" (for the "age group" category. To facilitate analysis, a single age-related data column was then created for the extracted paediatric dataset by ascribing fixed standard values for the four "age group" entries for which there were no corresponding "age" entries. As these entries were for "infant" (3 entries) and "child" (1 entry), the standard values "0.5 years" and "5 years" were arbitrarily selected and used for these specific entries, respectively. The "age group" column was thereafter deleted. Also, in order to focus on ADRs in children as autonomous beings, entries in which the route of administration was recorded as "transplacental" (3 entries) were excluded. Also, for the same reason, another entry for which the ADR reported was described as "congenital" was also removed.

3.2.2.2 Data organisation

3.2.2.2.1 Separation of merged items In addition to merging the age-related details into a single item, the data was further organised by unmerging the "reaction + outcome" and "suspect

drug + indications" items. Additional columns were created beside each of these items, and the contents of each column were copied into the adjoining new column. Then the contents of each cell were edited in such a way as to separate the combined entries.

3.2.2.2.2 Introduction of additional item columns To facilitate the study of the effect of CAM product type and mode of use on ADR number and outcome, as well as the richness of the narrative provided, seven additional columns were created at strategic points in the dataset. These enabled the generation of relevant additional information from the data. The columns were titled as follows: "Number of items used together"; "CAM product type"; "CAM product ATC (Anatomical, therapeutic and chemical classification) Code"; "ADR MedDRA SOC (System-organ class)"; "Number of ADRs reported"; "ADR duration"; and "Richness of narrative". CAM suspect drugs were grouped using a series of standard definitions and other distinctive criteria outlined in table 3.1 into one of seven CAM product categories in line with the study objectives.

TABLE 3.1: Classification scheme for suspect CAM products reported in the database

CAM product type	Standard definition (reference)	Distinctive criteria (reference)
Aromatherapy (Essential oils)	The use of concentrated essential oils extracted from herbs, flowers, and other plant parts to treat various diseases (Segen, 1998; Delgado, 2005)	Essential oil must act through its volatile aromatic effect (the sensual perception of the aroma) –not just a local action (Cooke and Ernst, 2000)
Dietary supplement	A product, other than tobacco, used in conjunction with a healthy diet and containing one or more of the following dietary ingredients: a vitamin, mineral, herb or other botanical, an amino acid, a dietary substance for use by man to supplement the diet by increasing the total daily intake, or a concentrate, metabolite, constituent, extract, or combinations of these ingredients. (Maughan et al, 2007)	These include vitamins, minerals, other nutrients, and botanical supplements, as well as ingredients and extracts of animal and plant origin (Cheema et al, 2001). The classification "Dietary supplement" was reserved for single products that are directly related to the diet, or combined products that are used regularly and/or for some specific "nontherapeutic" purpose (e. g.: weight loss, body-building, etc).
Herbal Remedy -classically herbal medicinal products	Medicinal products containing exclusively herbal drugs or herbal drug preparations as active substances (WHO, 1991; Silano et al, 2004)	This definition was restricted specifically to herbal medicines containing **1-3 herbs alone without any non-herbal products**
Herbal product	Medicinal combination products containing one or more herbs along with non-herbal substances **excluding** conventional medicines. (WHO, 2004; Sahoo et al, 2010)	The combination product must contain other substances apart from herbs, **but not conventional medicines**.
Herb-drug combination	Medicinal combination products containing one or more herbs along with one or more conventional medicines, with high probability of **herb-drug interaction** (Hu et al, 2005)	Here, the suspect drug **must contain one or more conventional medicines** apart from herbs –whether used conjunctively or in combination.
Homeopathic remedy	Products derived from natural substances of plant, mineral, or animal origin, and prepared by sequential dilution and succussion in a series of steps. (Khuda-Bukhsh, 2006)	Products are distinguished based on the "like cures like" homeopathic principle (Tedesco and Cicchetti, 2001)
Traditional Chinese medicines (TCM natural products)	Decoctions of mixtures of up to 20 herbs that are customized for each individual patient, thus with high potential for **herb-herb interaction** (Yuan and Lin, 2000; Yan et al, 2014)	Essentially combination herbal products of Chinese origin; but all poly herbal products (containing more than three herbs with no non-herbal components) are also placed in this category. (Viswanath et al, 2014)

Entries for products that could not be classified into any of these CAM product, types (2 entries) were excluded from further analysis. Product ATC codes for herbal medicinal products (HATC codes) were obtained from the Herbal ATC Index [594]; and the identified codes were further grouped at the anatomical and/or therapeutic levels (where possible) using the Guidelines for ATC Classification [595]. The ATC classification format used is outlined in table 3.2.

TABLE 3.2: Classification scheme for suspect CAM products reported in the database

Main groups	Anatomical classification (Level 1)	Range (Level 2)	Therapeutic classification (Level 2)
HA	Alimentary tract and metabolism	HA01-11; 13; 15; 16	Stomatological preparations; Drugs for acid-related disorders; Drugs for functional gastro-intestinal disorders; Anti-emetics and Anti-nauseants; Bile and liver therapy; Laxatives; Anti-diarrhoeals, intestinal anti-inflammatory/anti-infective agents; Anti-obesity preparations (excluding diet products); Digestives (including enzymes); Drugs used in diabetes; Vitamins; Tonics; Appetite stimulants; Other alimentary tract and metabolism products
HB	Blood and blood forming organs	HB05	Blood substitutes and perfusion products
HC	Cardiovascular system	HC01, 02, 04, 05, 10	Cardiac therapy; Anti-hypertensives; Peripheral vasodilators; Vaso-protectives; Serum lipid-reducing agents
HD	Dermatologicals	HD02-06; 08, 10, 11	Emollients and protective; Preparations for treatment of wounds and ulcers; Anti-pruritics (including anti-histamines, anaesthetics, etc.); Anti-psoriatics; Antibiotics and chemotherapeutics for dermatological use; Antisceptics anddisinfectants; Anti-acne preparations; Other dermatological preparations
HG	Genitourinary system and sex hormones	HG01-04	Gynaecological anti-infectives and antisceptics; Other gynaecologicals; Sex hormones and modulators of the genital system; Urologicals
HH	Systemic hormonal preparations excluding sex hormones	HH03	Thyroid therapy
HJ	Anti-infectives for systemic use	HJ01	Antibacterials for systemic use
HL	Antineoplastic and immuno-modulating agents	HL01, 03	Antineoplastic agents; Immunostimulants
HM	Musculoskeletal system	HM01-04	Anti-inflammatory & anti-rheumatic products; Topical products for joint & muscular pain; Muscle relaxants; Ant-gout preparations
HN	Nervous system	HN01; 02; 05-07	Anaesthetics; Analgesics; Psycholeptics; Psych-analeptics; Other nervous system drugs
HP	Anti-parasitic products	HP01-03	Anti-protozoals; Anthelmintics; Ectoparasites (Scarbicides, insecticides & repellents)
HR	Respiratory system	HR03, 05, 07	Drugs for obstructive airway disease; Cough and cold preparations; Other respiratory system products
HS	Sensory organs	HS01	Ophthalmologicals
HV	Various	HV03	All other therapeutic products

Where the specific indication of the suspect herbal remedy was not stated, the ATC code was determined from a consideration of a number of other factors -such as the subject age and/or sex, the products co-used with it (if a combination product or multiple product use), the dosage form, the subject's medical history, and/or the textual account of the event. Where no clear conclusion could be arrived at, it was categorized as "Unclear". For each herbal product or herb-drug combination, the HATC code for the herbal component was given. Where more than one herbal component with a related indication was involved, the Level 1 code was used; but where indications are unrelated, it was categorized as "Unclear". For poly-herbals with various unrelated ATC codes, the term "Various" was used. ATCs for homeopathic products were generally not

available (n. a.). The MedDRA primary SOCs were obtained from the Common Terminology Criteria for Adverse Events (CTCAE) version 4.0 [596]. ADRs were classified into SOCs based on the format outlined in table 3.3.

TABLE 3.3: Classification scheme for suspect CAM products reported in the database

	System-Organ Classes
1	SOC Blood and lymphatic system disorders
2	SOC Cardiac disorders
3	SOC Congenital, familial and genetic disorders
4	SOC Ear and labyrinth disorders
5	SOC Endocrine disorders
6	SOC Eye disorders
7	SOC Gastrointestinal disorders
8	SOC General disorders and administration site conditions
9	SOC Hepatobiliary disorders
10	SOC Immune system disorders
11	SOC Infections and infestations
12	SOC Injury, poisoning and procedural complications
13	SOC Investigations
14	SOC Metabolism and nutrition disorders
15	SOC Musculoskeletal and connective tissue disorders
16	SOC Neoplasms benign, malignant and unspecified (incl cysts and polyps)
17	SOC Nervous system disorders
18	SOC Pregnancy, puerperium and perinatal conditions
19	SOC Psychiatric disorders
20	SOC Renal and urinary disorders
21	SOC Reproductive system and breast disorders
22	SOC Respiratory, thoracic and mediastinal disorders
23	SOC Skin and subcutaneous tissue disorders
24	SOC Social circumstances
25	SOC Surgical and medical procedures
26	SOC Vascular disorders

Courtesy: MedDRA Introductory Guide Version 14.0 13, March 2011

The indications recorded for the suspect products were classified into various organ systems according to the general format for complete physical examination reports. The seriousness of the ADRs reported was determined solely from the description of the reporter based on the CIOMS criteria: no personal judgment was exercised. However, ADRs that could be interpreted as a cause/reason for, or an outcome of, the event –e.g. "aggression worsened"; "drug interaction"; *drug administration error"; "overdose"; etc. - were not included in the ADR count. Also, where an ADR was recorded multiple times for any given case report, only one such record was retained, and all other records for that specific case were deleted. In describing the ADR duration, "n. a." was used to indicate cases where there was absolutely no such record, or where the available record was incomplete –i. e. either the "Reaction start date" or "Reaction end date" was not available. On the other hand, "ERROR" was used to indicate cases where the START date reported was

after the END date, which is obviously an error. Similarly, the richness of each case narrative was categorised as "detailed" where the narrative described the details of the circumstances leading to the ADR or its management; or as "Additional information" where it provided further information on the ADR or suspect drug than were provided in earlier columns of the entry, but did not also describe the conditions surrounding the case. Case narratives not providing any further information on the ADR or suspect drug were classified as "Basic information"; while the category "No case narrative" was reserved for entries for which absolutely no narrative was recorded.

3.2.2.2.3 Additional categories introduced to facilitate data analysis Two additional reorganisations were carried out to facilitate data analysis of the original and derived data. The "Age" values were further broken into four paediatric subcategories (infants: < 2 years; pre-school children: 2-5 years; school-age children: 6-11 years; and younger adolescents: 12-17 years), with a fifth category (older adolescents: 18-21 years) added in order to facilitate the comparison of reports in children (0-11 years) and adolescents (12-21 years), where appropriate. Also, the ADR durations derived from the previous section were further grouped into six categories: Same day (0 days); Up to 3 days (1-3 days); About 1 week (4-8 days); Up to 2 weeks (9-15 days); Up to 1 month (16-31 days); and More than 1 month (> 31 days).

3.2.3 Data analysis

Data analysis was carried out using the Student Excel package of Microsoft Excel 2010©. Preliminary analysis was carried out on the original dataset, so as to provide an overview of the whole dataset with respect to age and sex distribution of case reports, trends in annual ADR reports for CAM and non-CAM suspect "drugs", as well as comparisons between adult and paediatric CAM reports. Population-based reporting ratios (PBRR), defined as the total number of ADR reports collected per year per million inhabitants, were determined for CAM versus non-CAM products according to the method of Srba et al [597]. Subsequent analyses were, however, focused on the age-filtered data set in line with the demographic focus of the study. Descriptive univariate and bivariate statistics (percentages, measures of central tendency, pictorial representations and cross-tabulations based on pivot tables), as well as frequentist inferential statistics (P value and confidence interval, C. I.) were determined in each case as appropriate. A significance level of $P \leq 0.05$ or 95% confidence interval was used for inference.

3.3 Results

The results of the detailed analysis of ADR reports in the yellow cards received are presented in tables 3.4 to 3.23 and figures 3.1 to 3.15. While a general summary of the findings will be presented in section 3.4.1 as part of the discussion of results, a brief running textual summary of the data presented in each table or figure will be provided along with their respective tables or figures all through the results section.

3.3.1 Overview and descriptive statistics for whole dataset

Tables 3.4 to 3.6 and figure 3.1 provide a demographic summary of the original YCS dataset, as well as the PBRRs for CAM and non-CAM suspect products.

A total of 2,167 individual case reports for CAMs were contained in the dataset for the period 1963 to July, 2012, amounting to 0.3% of all reports made to the database within the period. These case reports were for a range of subjects aged from birth to 96 years ($mean \pm SD = 43.65 \pm 20.89 years; median = 43 years; mode = 37 years$) , and amounted to a maximum PBRR of 1.193 reports per year per million (rym) UK inhabitants for CAMs as against 369.61 rym for non-CAMs. Less than 10% of the CAM-related reports (192 reports; corresponding to 0.03% of all ADR reports) concerned paediatric subjects aged under 18 years; with reports from middle-aged adults (aged 40-59 years) making up the highest proportion (one quarter) of the reports.

Although there were significantly more CAM-related reports for female subjects more than for male subjects in the whole dataset (63.5% vs. 33.4%; $p < 0.001$), this was only true for the adult population (> 17 years); as paediatric reports were uniformly distributed by gender (p=0.122). However, there were significantly more reports for female paediatric subjects aged 3 years old among ($P = 0.001$), just as there were for male subjects for infants in the first year of life ($p = 0.007$). The age ($\pm SD$) of the paediatric subjects for whom the mean CAM-related reports within the period was made was 6.59 ($\pm$5.49) years, with the highest number of single reports being made for children aged 3 years (19; 9.8%). However, when full age bands were considered, subjects in their first year of life (neonates and babies aged less than one year) accounted for the highest proportion of ADRs (38; 19.8%).

Although infant children aged under 2 years accounted for the highest proportion of paediatric reports (50; 26.1%), paediatric age categories did not differ significantly with respect to ADR reports (P=0.974). The converse was, however, the case among adult subjects ($p < 0.001$). Also, in about one fifth of the CAM-related ADR reports (442; 20.4%) there was no age-related data, thus invalidating the associated reports with respect to further detailed analysis. When the 1725 age-valid CAM-related ADR reports were categorised based on age groups and compared with

TABLE 3.4: Overview of the original MHRA data set by age and gender distribution over time

Age range (Age group/ sub-category)	Number of reports in period of report covered					Grand totals n (%)	X^2 test P value	Gender distribution n (%)			Binomial test P value[a]
	1963-1972	1973-1982	1983-1992	1993-2002	2003-2012			FEMALE	MALE	N/A	
<2 years (Infants)	-	9	17	8	16	**50, (26.0)[1] (2.3)[2]**		20, (40.0)[4]	29, (58.0)[4]	1, (2.0)[4]	**0.064**
(2-5 years (Preschool age)	1	5	16	12	14	**48, (25.0)[1] (2.2)[2]**	**0.989**	28, (58.3)[4]	19, (39.6)[4]	1, (2.1)[4]	**0.059**
6-11 years (School-age)	-	6	16	8	17	**47, (24.5)[1] (2.2)[2]**		27, (57.5)[4]	19, (40.4)[4]	1, (2.1)[4]	**0.090**
12-17 years (Young adolescents)	-	3	19	8	17	**47, (24.5)[1] (2.2)[2]**		27, (7.5)[4]	20, (42.6)[4]	**-**	**0.144**
All Paediatric subjects (0-17 years) n (%)	**1, (0.52)[1] (0.05)[2] [0.000][3]**	**23, (11.98)[1] (1.06)[2] [0.003][3]**	**68, (35.42)[1] (3.14)[2] [0.01][3]**	**36, (18.75)[1] (1.66)[2] [0.005][3]**	**64, (33.33)[1] (2.95)[2] [0.009][3]**	**192, (100)[1] (8.86)[2] [0.03][3]**	**-**	**102, (53.13)[4]**	**87, (45.31)[4]**	**3, (1.56)[4]**	**0.122**
18-25 years (Emerging adults)	-	10	47	29	50	136, - (6.3)[2]		97, (71.32)[4]	39, (28.68)[4]	-	**0.000**
26-39 years (Young adults)	6	36	109	37	36	424, - (19.6)[2]		296, (69.81)[4]	127, (29.95)[4]	1, (0.24)[4]	**0.000**
40-59 years (Middle-aged adults)	3	38	106	182	216	545, - (25.2)[2]	**0.000**	374, (68.62)[4]	166, (30.46)[4]	5, (0.92)[4]	**0.000**
60-74 years (Older adults)	2	14	59	90	144	309, - (14.3)[2]		192, (62.14)[4]	114, (36.89)[4]	3, (0.97)[4]	**0.000**
>74 years (The elderly)	1	13	16	32	57	119, - (5.5)[2]		70, (58.82)[4]	48, (40.34)[4]	1, (0.84)[4]	**0.004**
All adults (>17 years) n (%)	**12, - (0.55)[2] [0.002][3]**	**111, - (5.12)[2] [0.016][3]**	**337, - (15.55)[2] [0.048][3]**	**470, - (21.69)[2] [0.067][3]**	**603, - (27.83)[2] [0.086][3]**	**1533, - (70.7)[2] [0.219][3]**	**-**	**1029, (67.12)[4]**	**494 (32.22)[4]**	**10, (0.65)[4]**	**0.000**
Age not specified n (%)	96, - (4.43)[2]	87, - (4.01)[2]	148, - (6.83)[2]	43, - (1.98)[2]	68, - (3.14)[2]	442, - (20.40)[2]	-	244, (55.20)[4]	142, (32.13)[4]	56, (12.67)[4]	**0.000**
Grand total (CAM ADR reports) n (%)	**109, - (5.03)[2] [0.016][3]**	**221, - (10.20)[2] [0.032][3]**	**553, - (25.52)[2] [0.08][3]**	**549, - (25.33)[2] [0.079][3]**	**735, - (33.92)[2] [0.105][3]**	**2167, - (100.0)[2] [0.31][3]**	**-**	**1375, (63.45)[4]**	**723, (33.36)[4]**	**69, (3.18)[4]**	**0.000**
All Non CAM ADR reports n (%)	**27,093, - [3.87][3]**	**82,925, - [11.87][3]**	**163,604, - [23.42][3]**	**195,046, - [27.92][3]**	**227,803, - [32.61][3]**	**696,471 - [99.69][3]**	-	**-**	-	-	-
GRAND TOTAL (All ADR reports) n (%)	**27,202, - [3.89][3]**	**83,146, - [11.9][3]**	**164,157, - [23.5][3]**	**195,595, - [28.0][3]**	**228,538, - [32.71][3]**	**698,638, - [100][3]**	-	-	-	-	-
Descriptive statistics for all age-specific subjects for whom CAM-related ADR reports were made:											
Mean (SEM) ± SD: 43.65 (0.50) ± 20.89 years											
Median: 43 year olds											
Mode: 37 years											
Range: 96 years											

(%)[1]=Relative to grand total of paediatric subjects (192)

(%)[2]=Relative to grand total of CAM ADR reports (2167)

(%)[3]=Relative to grand total of all ADR reports (698,638)

(%)[6]=Relative to age group/sub-category grand total (various)

[a] –Excluding unknown sex

TABLE 3.5: Population-based reporting ratios (PBRRs) for CAM and non-CAM-related products

Period of report (in decades)	UK Population† (in millions)	CAM ADRs	PBRR	Non CAM ADRs	PBRR	All ADRs	PBRR
1963-1972	55.1	109	**1.98**	27,093	**491.71**	27,202	**493.68**
1973-1982	56.2	221	**3.93**	82,925	**1475.54**	83146	**1479.47**
1983-1992	56.9	553	**9.72**	163,604	**2875.9**	164157	**2885.01**
1993-2002	58.5	549	**9.39**	195,046	**3335.83**	195595	**3345.22**
2003-July 2012	61.6	735	**11.93**	227,803	**3698.1**	228538	**3710.03**
Total ADRs		2167		696,471		698,638	

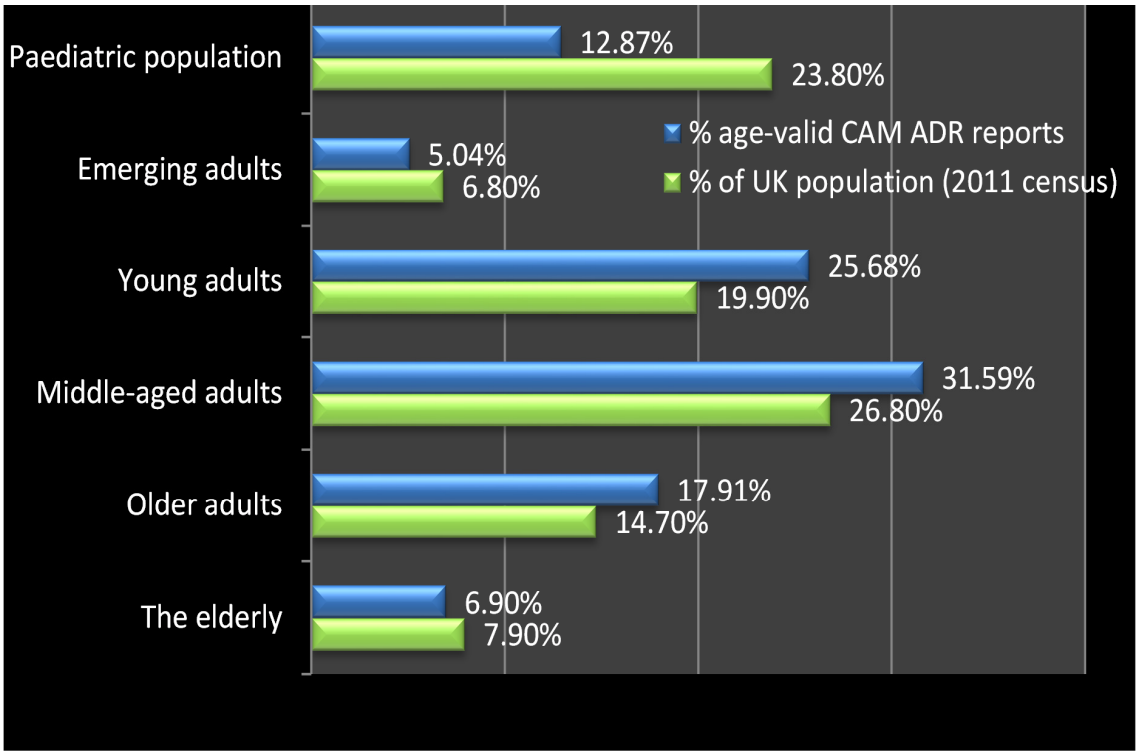


FIGURE 3.1: Comparative age group distribution of age-valid CAM-related ADR reports relative to the normal UK population

the normal UK population according to the 2011 census (figure 3.1), it was found that while the CAM-related ADR reports for most age groups generally aligned with expected proportions of the population, the reports for paediatric subjects were found to be much less than expected (12.3% vs. 23.8%; $p < 0.043$).

3.3.2 Comparison of trends of reports for CAMs and conventional medicines

Although CAMs contributed significantly less than one percent of all reports made to the database, the trends of ADR reporting for CAMs and conventional medicines were seen to be generally similar. However, while there was a general increase in the total number of ADR reports received over the period, the increase was not as proportional for CAM-related reports as they were for conventional medicines. This is clearly illustrated in the 10-year comparative trends displayed

TABLE 3.6: Age and sex distribution of individual paediatric reports

Age (year)	Total reports	Proportion by age (%)	Female	Male	N/A	Binomial test P value [a]
0	1	0.52		1		
0.01	1	0.52		1		
0.05	1	0.52	1			
0.08	1	0.52	1			
0.09	1	0.52		1		
0.2	9	4.69	2	7		
0.3	4	2.08	1	3		
0.4	2	1.04		2		
0.5	7	3.65	3	3	1	
0.6	2	1.04	2			
0.7	5	2.60	1	4		
0.8	2	1.04	1	1		
0.9	2	1.04	1	1		
<1	**38*†[1]**	**19.79***	**13***	**24***	**1***	**0.007**
1	10	5.21	6	4		
1.1	2	1.04	1	1		
1-<2	**12***	**6.25***	**7***	**5***		
2	8	4.17	3	4	1	
2.1	1	0.52	1			
2-<3	**9***	**4.69***	**4***	**4***	**1***	
3	**19†[2]**	**9.90**	**14**	**5**		**0.001**
4	10	5.21	7	3		
5	10	5.21	3	7		
6	9	4.69	4	5		
7	7	3.65	6	1		
8	7	3.65	6	1		
9	10	5.21	5	4	1	
10	6	3.13	2	4		
11	8	4.17	4	4		
12	9	4.69	6	3		
13	9	4.69	7	2		
14	3	1.56	2	1		
15	9	4.69	7	2		
16	9	4.69	3	6		
17	8	4.17	2	6		
Total	**192**	**100.00 %**	**102**	**87**	**3**	**0.122**
Proportion by gender			**53.13 %**	**45.31 %**	**1.56%**	
Descriptive statistics for paediatric subjects for whom CAM ADR reports were made:						
Mean age (SEM) ± SD:			**6.59 (0.40) ± 5.49 years**			
Median age:			**5 years**			
Mode (full years)[†1]:			**< 1 year olds**			
Mode (specific entries)[†2]:			**3 year olds**			
Range:			**17 years**			

*** -Full age subtotal;**

† -Highest number of reports for full age bands (1) or specific entries (2);

[a] –Excluding unknown sex

in figure 3.2, resulting in a plateau phase in the period between the 1980s and the 1990s. This difference was, however, not so obvious at a more detailed annual level.

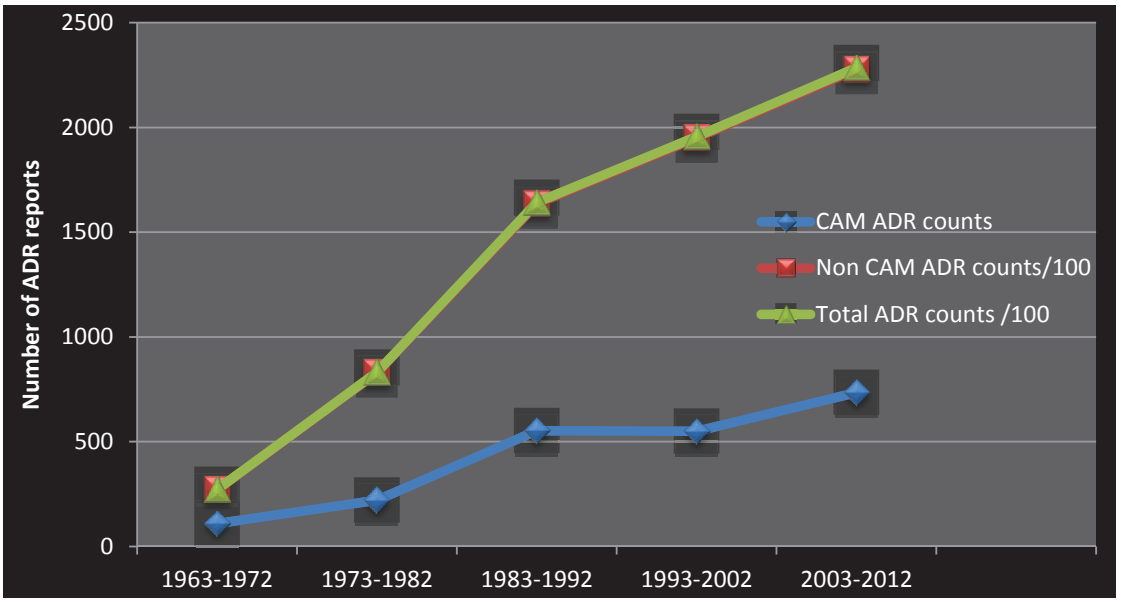


FIGURE 3.2: Comparative trends of 10-year reports for complementary and conventional medicines (1963-2012)

Figure 3.3 illustrates that annual ADR reports ranged in both cases from their lowest levels in the 1960s to a peak in the year 2000, with smaller spikes in the late 1970s and mid-1980s and a depression in the mid-1990s. Finally, the trends of annual reports increased equally in both cases between 2008 and 2012, albeit more consistently for conventional medicines than for CAMs. Unlike the sustained annual increase in the ADR reports for conventional medicines in the period from the mid-1980s to the early 1990s, the spike in CAM-related ADR reports in the mid-1980s was not sustained, leading to progressively less reports being received in that period, before the depression in the latter 1990s that was common to both categories. This obviously explains the absence of a plateau phase for reports associated with conventional medicines.

When the apparent effects of significant relevant public health policy milestones on annual ADR reports are considered (table 3.7), it is seen that the percentage change in total reports was generally greater for CAMs than for conventional medicines.

However, while this apparent advantage is possibly due the much smaller numbers of reports available for CAM products than for conventional products, it is also seen to be significantly more for immediate (1-year) than for sustained (2-year) changes in report totals, unlike the case for reports for conventional medicines. While many of the policies resulted in sustained increases in annual reports for conventional medicines, the only public health initiatives that resulted in continued increases in reports for both conventional medicines and CAM products are the introduction of the Black Triangle scheme in 1976 (from 34.8% to 141.8% for conventional

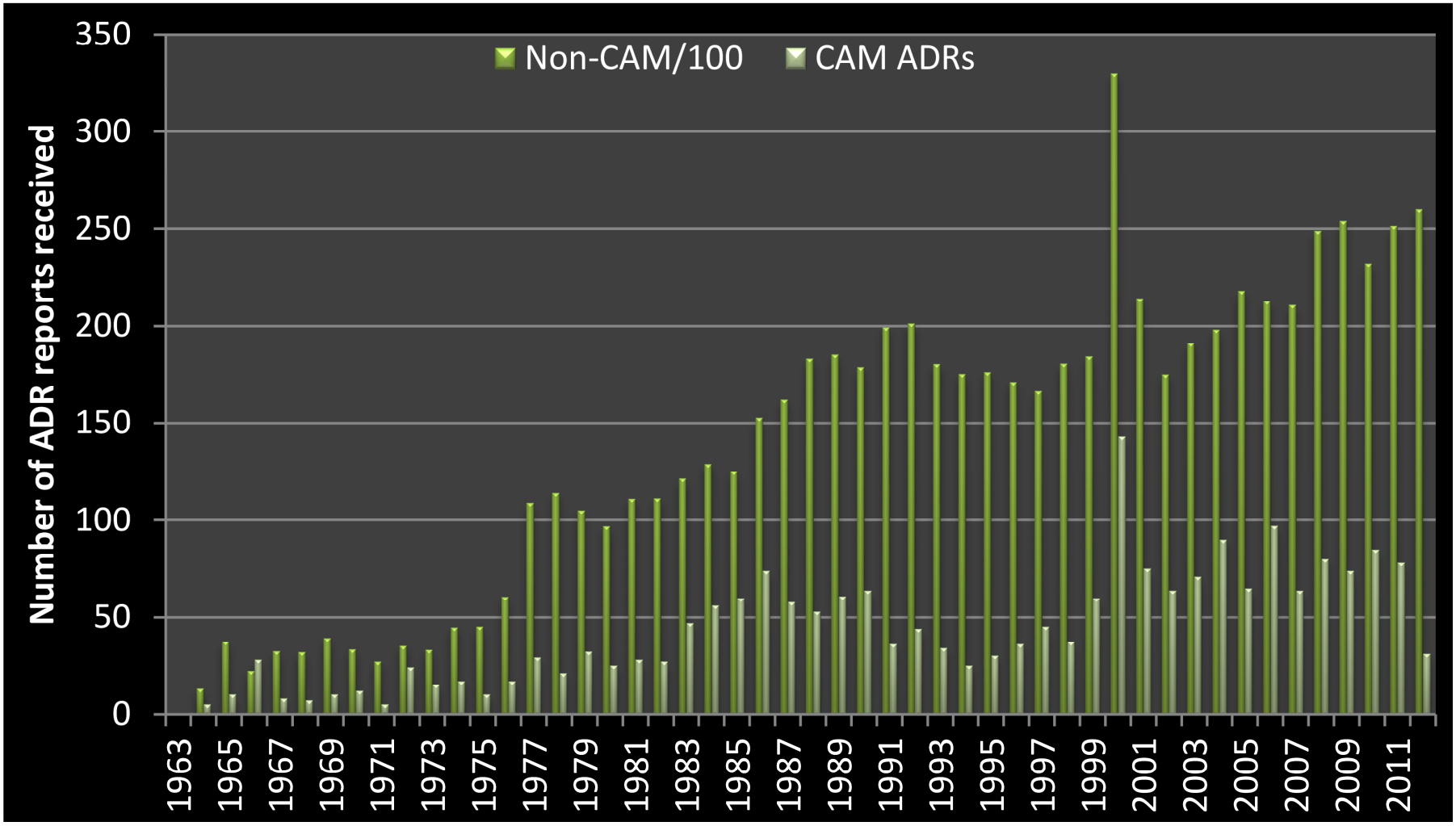


FIGURE 3.3: Comparative trends in annual ADR reports for complementary and conventional medicines (1963-2012)

TABLE 3.7: Effects of relevant significant public health policy changes on ADR reporting for complementary and conventional medicines (Immediate & Sustained Effect)

Significant Event	Date	Years compared	% Change in ADR Reports Received		Binomial test P(1)-P(2)		Years compared	% Change in ADR Reports Received		Binomial test P(1)-P(2)	
			Conventional	CAM	Estimate	P value		Conventional	CAM	Estimate	P value
Establishment of the Black Triangle Scheme	January, 1976	1975 & 1976	34.8 %	70.0 %	-0.35	0.015	1975 & 1977	141.8 %	190.0 %	-0.48	0.000
Inclusion of the Yellow Card in GP prescription pads and the BNF	May, 1986	1985 & 1986	21.2 %	23.3 %	-0.02	0.694	1985 & 1987	33.4 %	-3.3 %	0.36	0.000
Establishment of the NIMH* Yellow Card Scheme	January, 1994	1993 & 1994	-3.8 %	-26.5 %	-0.24	0.002	1993 & 1995	-2.3 %	--11.8 %	-0.09	0.086
Extension of Scheme to unlicensed herbal remedies	October, 1996	1996 & 1997	-2.8 %	25.0 %	-0.28	0.000	1996 & 1998	5.4 %	2.8 %	0.03	0.327
Extension of ADR reporting to community pharmacists	November, 1999	1999 & 2000	79.3 %	138.3 %	-0.59	0.000	1999 & 2001	16.0 %	25.0 %	-0.09	0.109
Extension of ADR reporting to Nurses, Midwives & Health visitors	October, 2002	2002 & 2003	9.1 %	10.9 %	-0.02	0.637	2002 & 2004	13.3 %	40.6 %	-0.37	0.000
Adoption of EMA directive 2004./24/ EC regulating herbal and homeopathic medicinal products	April, 2004	2003 & 2004	3.9 %	26.8 %	-0.23	0.000	2003 & 2005	13.8 %	-8.5 %	0.22	0.000
Extension of ADR reporting to patients	February, 2008	2007 & 2008	18.1 %	25.0 %	-0.07	0.204	2007 & 2009	20.2 %	15.6 %	0.05	0.319

*NIMH –National Institute of Medical Herbalists

medicines; and from 70.0% to 190.0% for CAMs); and the extension of ADR reporting to nurses, midwives & health visitors in October 2002 (from 9.1% to 13.3% for conventional medicines; and from 10.9% to 40.6% for CAMs). Judging solely from percentage changes in annual report totals, the public health policy that yielded the greatest immediate (same year) improvement in total annual ADR reports is the extension of reporting status to community pharmacists in 1999 (138.3% increase for CAMs vs. 79.3% increase for conventional medicines; $P < 0.001$). However, the policy that yielded the most sustained effect over a 2-year span is the introduction of the Black Triangle scheme in 1976 (190% increase for CAMs vs. 141% increase for conventional medicines; $P < 0.001$). Also, the only public health policy changes for which there was apparently no significant immediate difference in percentage change in annual reports between CAMs and onventional medicines were the inclusion of Yellow Cards in GP prescription pads and the BNF (23.3% vs. 21.2%; P=0.694), the extension of ADR reporting to nurses, midwives & health visitors (10.9% vs. 9.1%; P=0.637) and the extension of ADR reporting to patients (25% vs. 18.1; P=0.204). Strikingly, of the three CAM-related public health initiatives introduced within the period of analysis, the only one that did not yield any increase in CAM-related yellow card reports was the establishment of the National Institute of Medical Herbalists (NIMH) Yellow Card Scheme in January, 1994. However, while the other two CAM-related public health initiatives, the extension of the YCS to unlicensed herbal remedies in October, 1996, and the adoption of the European Medicines Agency directive 2004./24/ EC regulating herbal and homeopathic medicinal products use within the EU in April, 2004, were associated with higher increases in CAM-related ADR reports than for conventional medicines, these effects were not sustained beyond one year of their institution. A similar pattern was noted for the extension of ADR reporting to patients.

3.3.3 Comparison of trends in CAM-related ADR reports for adult and paediatric subjects

Figures 3.4 to 3.6 illustrate various comparisons of the trends in CAM-related ADR reporting among different age categories of paediatric subjects; as well as between adult and paediatric CAM ADR reports. Due to the much fewer number of CAM-related ADRs in the database, it was not possible to compare annual trends for paediatric data: therefore, only 10-year trends were compared.

Figure 3.4 shows that the plateau seen in CAM-related ADR reports is actually associated with reports for paediatric subjects rather than those for adults.

Figure 3.5 shows that, while it is not obvious which paediatric age category is most associated with the depression generally seen with paediatric subjects, it is least seen among preschool children. Additionally, figure 3.6 shows that the depression is not as much associated with younger (12-17 year olds) or older adolescents (18-21 year olds), as it is with children aged less than 12 years.

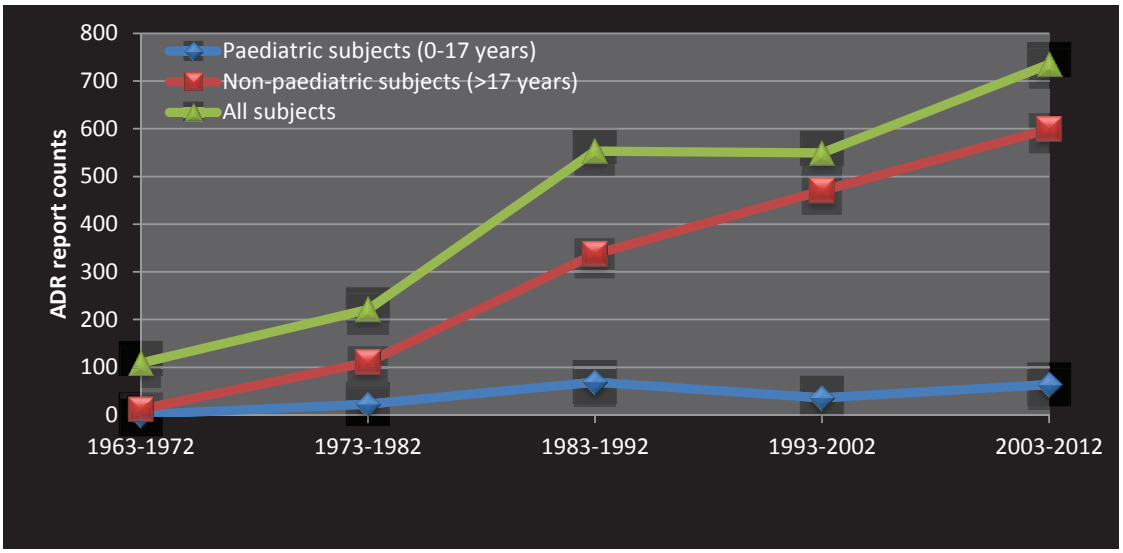


FIGURE 3.4: Comparative trends of 10-year CAM-related reports for adult and paediatric subjects (1963-2012)

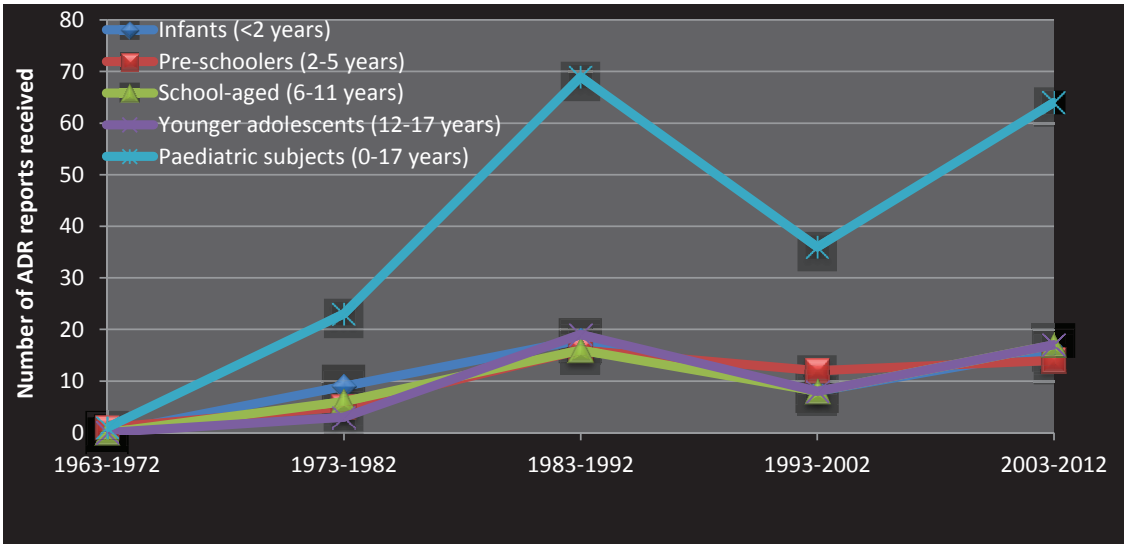


FIGURE 3.5: Comparative trends of 10-year CAM-related reports for among subcategories of paediatric subjects (1963-2012)

3.3.4 Comparison of reporter profile for adult and paediatric CAM-related ADRs

A comparison of adult and paediatric CAM-related ADR reports based on reporter profile shows that, while both categories follow a similar trend: Doctor> Other Health care professional (Other HCP)> Pharmacist > Patient > Nurse (table 3.8), only doctors (45.3% vs. 43.8%; p=0.683) and nurses (1.0% vs. 1.9%; p=0.569) contributed about the same proportions of the total reports for either category. Other HCPs contributed a significantly higher proportion of the reports for paediatric subjects than for adults (40.6% vs. 27.5%; $p < 0.001$); while pharmacists (9.7%

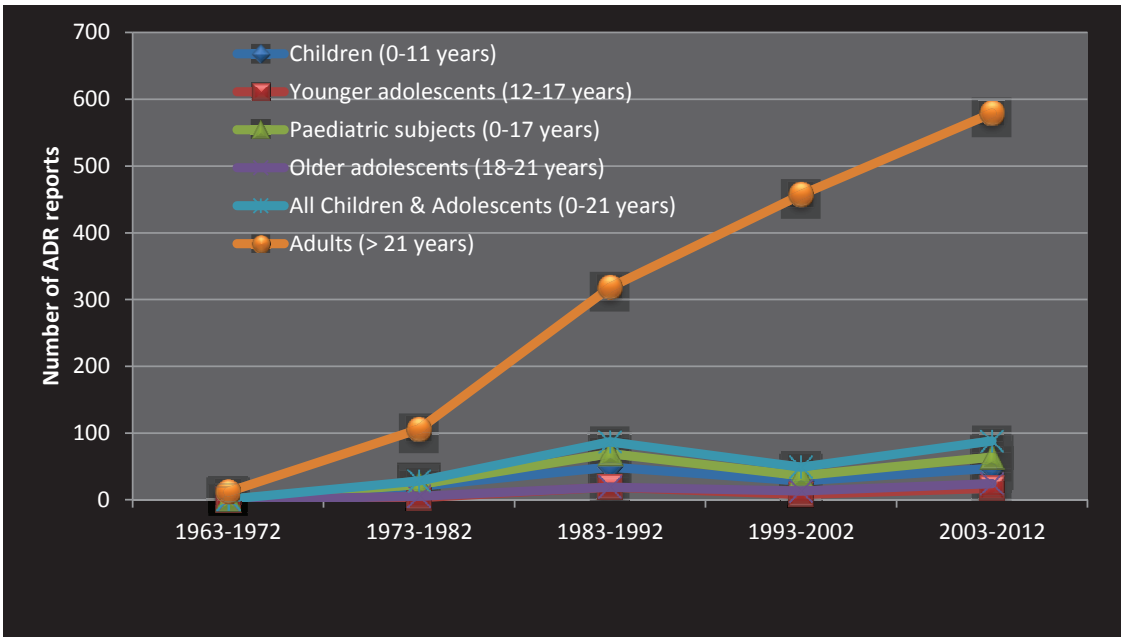


FIGURE 3.6: Comparative trends of 10-year CAM-related reports for children and adolescents aged up to 21 years (1963-2012)

vs. 16.2%; $p < 0.001$) and patients (3.7% vs. 10.1%; $p < 0.001$) contributed significantly lower proportions. When the ADR reporter type for specific age sub-categories were compared, however, it was found that while there were no significant differences ($p < 0.05$) among paediatric sub-categories in the number of CAM-related ADRs reported by doctors, other HCPs or pharmacists; the converse was the case among adult age categories for all ADR reporter types. Middle-aged and young adults were the subjects of most of the ADRs reported by doctors, other HCPs and patients; while young adults featured much less in the ADRs reported by pharmacists (19.7%) and nurses (10.3%). Notably, although only 31 age-specific CAM-related ADR reports (1.8%) were received from nurse reporters, subjects aged 60 years and over accounted for a high proportion of such reports both among the adult population (17; 58.6%) and the whole population (19; 61.3%).

3.3.5 Overview of paediatric ADRs

To specifically analyse ADRs associated with paediatric reports, the 2167 individual case safety report (ICSR) entries received from the MHRA were reduced to 186 paediatric ICSRs through a sequential screening process based on specified criteria (figure 3.6). Although the 186 paediatric entries included more reports for female than male subjects, there were no significant differences in the number of reports across paediatric age categories (p=0.991) or gender (p=0.059), nor were there any significant differences in their distribution among paediatric age categories for either sex (females, p= 0.674; males, p= 0.6). There were however two reports for subjects for

whom the gender was not specified. These 186 entries yielded 332 specific ADRs for paediatric subjects,171 (51.5%) of which were for female subjects (table 3.9).

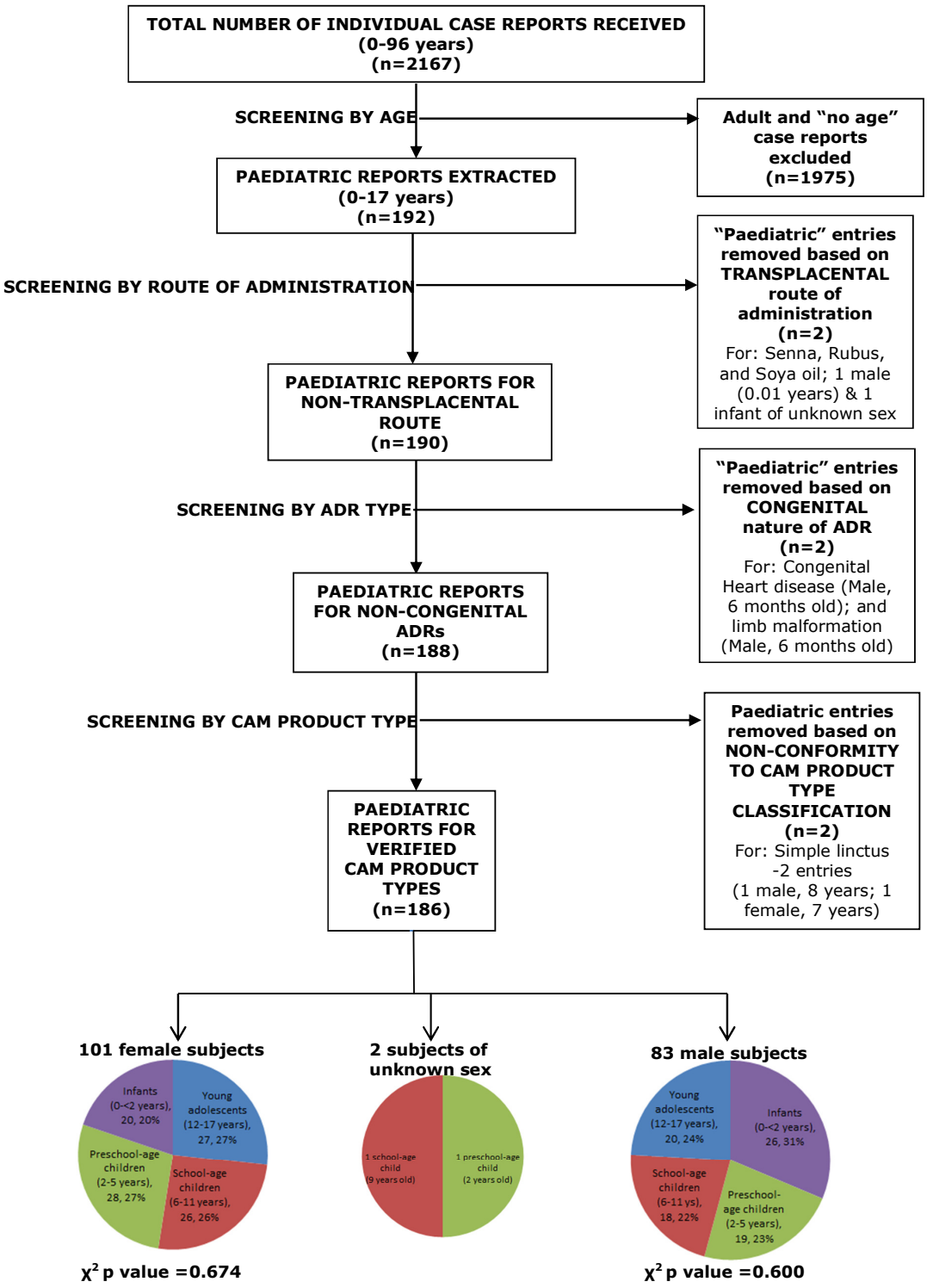


FIGURE 3.7: Sequential screening process for selection of paediatric data for analysis

TABLE 3.8: Comparison of adult and paediatric CAM-related ADR reporters

Type of Reporter	ADR report count by age categories n (% of grand total)												Binomial test P(Paed)-P(Adult)	
	PAEDIATRIC AGE CATEGORIES					ADULT AGE CATEGORIES								
	Infants (<2 yr)	Preschool children (2-5 yr)	School-age Children (6-11 yr)	Younger adolescents (12-17 yr)	Paediatric ADR Grand total	Emerging adults (18-25 yr)	Young adults (26-39 yr)	Middle-aged adults (40-59 yr)	Older adults (60-74 yr)	The elderly (>74 yr)	Adult ADR Grand total	All ADR Grand total	Estimate	P value
Doctor-reported	31, (16.15)	21, (10.94)	15, (7.81)	20, (10.42)	**87, (45.31)**	58, (3.78)	183, (11.94)	257, (16.76)	124, (8.09)	48, (3.13)	**670, (43.75)**	**756, (43.93)**	**0.016**	**0.683**
Pharmacist-reported	2, (1.04)	5, (2.60)	6, (3.13)	5, (2.60)	**18, (9.38)**	17, (1.11)	49, (3.20)	89, (5.81)	63, (4.11)	31, (2.02)	**249, (16.15)**	**265, (15.40)**	**-0.068**	**0.003**
Nurse-reported	-	-	2, (1.04)	-	**2, (1.04)**	1, (0.07)	3, (0.20)	8, (0.52)	11, (0.72)	6, (0.39)	**29, (1.90)**	**31, (1.80)**	**-0.009**	**0.569**
Other HCP-reported	14, (7.29)	22, (11.46)	23, (11.98)	19, (9.90)	**78, (40.63)**	47, (3.07)	134, (8.74)	135, (8.81)	79, (5.15)	26, (1.70)	**421, (27.53)**	**499, (28.99)**	**0.131**	**0.000**
Patient-reported	3, (1.56)	-	1, (0.52)	3, (1.56)	**7, (3.65)**	13, (0.85)	52, (3.39)	52, (3.39)	30, (1.96)	8, (0.52)	**155, (10.07)**	**161, (9.36)**	**-0.064**	**0.000**
Other sources	-	-	-	-	**-**		3, (0.20)	4, (0.26)	2, (0.13)		**9, (0.59)**	**9, (0.52)**	**-**	**-**
Grand total	**50, 26.04 %**	**48, 25.00 %**	**47, 24.48 %**	**47,, 24.48 %**	**192, 100 %**	**136, 8.87 %**	**424, 27.66 %**	**545, 35.55 %**	**309, 20.16 %**	**119, 7.76 %**	**1529, 100 %**	**1721, 100 %**		
Chi squared test (Variability of doctor-reported ADRs across paediatric age categories) P value =0.102														
Chi squared test (Variability of doctor-reported ADRs across adult age categories) P value =0.000														
Chi squared test (Variability of pharmacist-reported ADRs across paediatric age categories) P value =0.572														
Chi squared test (Variability of pharmacist-reported ADRs across adult age categories) P value =0.000														
Chi squared test (Variability of nurse-reported ADRs across age paediatric categories) –Insufficient data														
Chi squared test (Variability of nurse-reported ADRs across adult age categories) P value =0.029														
Chi squared test (Variability of other HCP-reported ADRs across age paediatric categories) P value =0.473														
Chi squared test (Variability of other HCP-reported ADRs across adult age categories) P value =0.000														
Chi squared test (Variability of patient-reported ADRs across age paediatric categories) –Insufficient data														
Chi squared test (Variability of patient-reported ADRs across adult age categories) P value =0.000														
Chi squared test (Variability of ADR reports from other sources across adult age categories) –Insufficient data														

†-Fisher's exact test

TABLE 3.9: Paediatric age group and gender distribution of subjects of CAM-related ADR reports

Paediatric age sub-categories	Number of ADRs reported, n (%) Female subjects	Male subjects	Unknown sex	Total (%)	Binomial test P value[a]	ODDs of ADR report among female subjects
Infants (<2 years)	**28, (40.0)**	**42, (60.0)**	**-**	**70, (21.08)**	**0.016**	**0.67**
Preschool Children (2-5 years)	**43, (51.2)**	**40, (47.6)**	1, **(1.2)**	**84, (25.30)**	**0.641**	**1.08**
School-age Children (6-11 years)	**50, (61.0)**	**31, (37.8)**	1, **(1.2)**	**82, (24.70)**	**0.002**	**1.61**
Younger Adolescents (12-17 years)	**50, (52.1)**	**46, (47.9)**	**-**	**96, (28.92)**	**0.563**	**1.09**
Grand total (%)	**171, (51.51)**	**159, (47.89)**	**2, (0.60)**	**332, (100)**	**0.350**	**1.08**
X^2 test for independence of ADR report on paediatric age categories: P value =0.251						
X^2 test for independence of ADR report on paediatric age category among female subjects: P value =0.056						
X^2 test for independence of ADR report on paediatric age category among male subjects: P value =0.386						

[a] –Excluding unknown sex

Although there was 1.08 times greater likelihood of ADRs reported being for female subjects than for male subjects, the odds of ADR report among female infants was 0.33 times less than for their male counterparts (p=0.016). However, there was a greater likelihood of the ADRs reported being for female subjects for all other paediatric age categories, resulting in higher female ADR counts for all such age categories. The paediatric age category associated with the highest odds of ADR report among female subjects, and the thus the greatest difference in the number of ADRs reported, was school-age children (p=0.002; odds =1.61).

In table 3.10, the 332 specific ADRs were categorised into their respective system-organ classes (SOCs), and were found to belong to 20 (76.9%) of the 26 SOCs in the MedDRA terminology. ADRs related to skin and subcutaneous disorders, SSD (86; 25.9%), nervous system disorders, NSD (47; 14.2%), gastrointestinal disorders, GID (42; 12.7%) and general disorders & administration site injuries, GDASI (38; 11.5%) accounted for the greatest proportions; while neoplasms (1; 0.3%), nutrition & metabolic disorders (2; 0.6%) and ear and labyrinth disorders (3; 0.9%) accounted for the least. Although, the total ADR counts were uniformly distributed across the paediatric age categories (P=0.251), they were significantly skewed ($P < 0.001$) across SOCs, with the SSD class accounting for over a quarter (86; 25.9%) of them. Also, all the four most commonly reported SOCs were uniformly distributed across paediatric age categories. In terms of gender, however, although only the SSD ($P < 0.001$) and the NSD (p=0.010) classes were not uniformly distributed among the sexes, the odds of report were higher among female subjects for the GDASI and SSD classes (1.38 and 1.97, respectively), and lower for the GID and NSD classes

TABLE 3.10: Age and gender distribution of paediatric CAM-related ADRs by System-Organ Classes

Adverse drug Reaction System-Organ Classes (ADR SOCs)	Infants (<2 yr)	Preschool-age children (2-5 yr)	School-age children (6-11 yr)	Younger adolescents (12-17 yr)	Grand total	X^2 test p value for age	GENDER SPREAD Female n (%)	GENDER SPREAD Male n (%)	Binomial test p value for gender	ODDs among FEMALE subjects (for Σn≥5)
	Number of ADRs, n (%)									
Blood & lymphatic System disorders	-	2	1	1	**4, (1.2)**	-	4	-	**-**	**-**
Cardiac disorders	1	-	-	3	**4, (1.2)**	-	1	3	**-**	**-**
Ear & labyrinth disorders	-	-	2	1	**3, (0.9)**	-	2	1	**-**	**-**
Eye disorders	2	2	1	2	**7, (2.1)**	-	4	3	**-**	**1.33**
Gastrointestinal disorders	6	11	8	17	**42, (12.7**	**0.087**	18, (42.9)	24, (57.1)	**0.186**	**0.75**
General disorders & Administration site injuries	8	8	12	10	**38, (11.5**	**0.674**	22, (57.9)	16, (42.1)	**0.163**	**1.38**
Immune system disorders	1	5	2	12	**20,* (6.0)**	-	8	11	**0.324**	**0.73**
Infections & Infestations	2	1	1	1	**5, (1.5)**	-	4	1	**-**	**4.00**
Injury, Poisoning & Procedural Complications	7	5	-	3	**15, (4.5)**	-	6	9	**0.439**	**0.67**
Investigations	2	-	1	1	**4, (1.2)**	-	2	2	**-**	**-**
Nutrition & Metabolic disorders	1	-	1	-	**2, (0.6)**	-	2	0	**-**	**-**
Musculoskeletal & Connective tissue Disorders	2	-	3	8	**13, (3.9)**	-	7	6	**0.264**	**1.17**
Neoplasms – benign, malignant or unspecified	-	-	1	-	**1, (0.3)**	-	0	1	**-**	**-**
Nervous system disorders	8	11	14	14	**47,* (14.2**	**0.550**	17, (37.0)	29, (63.0)	**0.010**	**0.59**
Psychiatric disorders	1	5	4	1	**11. (3.3)**	-	2	9	**-**	**0.22**
Renal & Urinary disorders	-	1	2	2	**5, (1.5)**	-	4	1	**-**	**4.00**
Reproductive system & Breast disorders	-	2	2	1	**5, (1.5)**	-	3	2	**-**	**1.50**
Respiratory, Thoracic & Mediastinal disorders	4	5	1	6	**16, (4.8)**	-	6	10	**0.144**	**0.60**
Skin & Subcutaneous disorders	25	25	25	11	**86, (25.9**	**0.077**	57, (66.3)	29, (33.7)	**0.000**	**1.97**
Vascular disorders	-	1	1	2	**4, (1.2)**	-	2	2	**-**	**1.00**
Total ADRs reported, (%)	**70, (21.08)**	**84, (25.30)**	**82, (24.70)**	**96, (28.92)**	**332, (100)**	**0.251**	**171, (51.51)**	**159, (47.89)**	**0.350**	**1.08**
X^2 test for independence of ADR report on ADR system organ class: P value <0.001										

*** -Includes subject of unknown sex**

TABLE 3.11: Age and sex distribution of skin and subcutaneous system-organ class ADRs

Specific reactions in the Skin & subcutaneous disorders MedDRA SOC	FEMALE SUBJECTS					MALE SUBJECTS					Grand Total	ODDs of ADR report among FEMALE subjects (for Σn≥5)
	Infants (<2 yr|	Preschool-age children (2-5 yr)	School-age children (6-11 yr)	Younger adolescents (12-17 yr)	All female subjects	Infants (<2 yr|	Preschool-age children (2-5 yr)	School-age children (6-11 yr)	Younger adolescents (12-17 yr)	All male subjects	Σn (%)	
Cyanosis	0	0				1				**1**	**1**	**-**
Eczema	2	1	2	1	**6**	2	2	1	1	**6**	**12**	**1.00**
Erythema	1	1	2	1	**5**	1	2			**3**	**8**	**1.67**
Hyperhidrosis	0	0	1		**1**						**1**	**-**
Petechiae	0	0	1		**1**						**1**	**-**
Photosensitivity reaction	0	0					1			**1**	**1**	**-**
Pruritus	0	3			**3**	1				**1**	**4**	**-**
Purpura	0	2			**2**	1				**1**	**3**	**-**
Rash % for sex; (% in SOC); (% of all ADRs)	9	10	10	8	**37, 64.9 % (43.0 %)**	5	2	6		**13, 44.8 % (15.1 %)**	**50, (58.1 %) (15.1 %)**	**2.85**
Skin exfoliation	0	0	1		**1**						**1**	**-**
Thermal burn	0	0	1		**1**	2	1			**3**	**4**	**-**
Grand total % by sex; (% in SOC); (% of all ADRs)	**12, 21.0 %**	**17, 29.8 %**	**18, 31.6 %**	**10, 17.5 %**	**57, 100 % (66.3 %)**	**13, 44.8 %**	**8, 27.6 %**	**7, 24.1 %**	**1, 3.5 %**	**29, 100 % (33.7 %)**	**86, (100 %) (25.9 %)**	**1.97**
X^2 test P value (all ADRs)			**P=0.37**					**P=0.018**				
X^2 test P value (rash)			**P=0.961**					**Insufficient data**				
Binomial test for independence of total skin and subcutaneous disorders ADR count on sex: P value <0.001												
Binomial test for rash P(Female)-P(Male): Estimate = 0.200847; P-Value = 0.073												

(0.75 and 0.59, respectively). Although ADRs belonging to the SSD class had the highest odds of report among female subjects (1.97) when the four most prevalent SOCs alone were considered, ADRs in the infections and infestations (I & I) and renal and urinary disorders (RUD) classes showed the highest odds of report among female subjects overall (4.00). These two classes, however, accounted for much fewer ADR reports than the SSD class (5 each; 1.5% vs. 86 ADRs; 25.9%).

Table 3.11 outlines the distribution of specific ADRs in the SSD class, indicating them to be predominantly associated with rash (50; 58.1%), which alone accounted for 15% of all CAM-related ADRs reported among children. Although this reaction was reported to about the same degree in each sex (64.9% vs. 44.8%; p=0.073), it was almost three times more likely to be reported among female subjects than among the males (odds =2.85), as well as more uniformly distributed across female paediatric age categories (p=0.961). Among male subjects, however, the 29 SSD ADRs reported were skewed (p=0.018) towards children aged up to 5 years (21 ADRs; 72.4%), particularly infants (13; 44.8%).

Table 3.12 outlines the distribution of specific ADRs in the NSD class. While no specific ADR predominated, the high proportions of ADRs related to cognitive impairment (15; 31.9%), hyperkinesia (13; 27.7%), and abnormal sensation (10; 21.3%) were obvious. Also, while abnormal sensation had the highest odds of being reported for female subjects, hyperkinesia had the least such likelihood, being very highly reported for male subjects (p=0.001). At the specific ADR level, convulsions were found to be the most recorded (6 reports), closely followed by burning sensation and dizziness (5 reports each). While convulsions were predominantly reported for male subjects; burning sensation was highly reported for female subjects. Although various specific ADRs were reported exclusively in subjects of certain specific paediatric age categories, on the whole ADRs in the NSD class were evenly spread across age categories for both sexes.

Table 3.13 outlines the 3 most commonly reported ADRs for male and female subjects per paediatric age category. In addition to underlining the high incidence of the report of rash among female subjects (37; 21.6%), it also highlights the co-dominance of NSD ADRs with SSD ADRs among male subjects (29 each; 18.2%). Also, while rash was shown to be the most predominant ADR reported for each age category among female subjects, the incidence of report of NSD ADRs among males generally increased with increasing age, albeit non significantly (p=0.565). The report of ADRs in the GID class among males also followed the same trend.

A classification of the ADRs reported based on the associated CAM product types in table 3.14 shows a highly non-uniform distribution ($P < 0.001$), with herb-drug combinations and herbal remedies together accounting for over half of the ADRs reported (192; 57.8%). Among specific CAM product types, there were significant differences in the distribution of reported ADRs

TABLE 3.12: Age and sex distribution of nervous system disorders ADRs

Specific reactions groups in the nervous system disorders MedDRA SOC	FEMALE SUBJECTS					MALE SUBJECTS					UNKNOWN SEX	Grand Total	Binomial test P value (gender spread)	ODDs of ADR report among FEMALE subjects (for Σn≥5)
	Infants (<2 yr|	Preschool-age children (2-5 yr)	School-age children (6-11 yr)	Younger adolescents (12-17 yr)	All female subjects n (%)	Infants (<2 yr|	Preschool-age children (2-5 yr)	School-age children (6-11 yr)	Younger adolescents (12-17 yr)	All male subjects	School-age child (6-11 yr)	Σn (%)		
Abnormal sensation	**1**	**1**	**3**	**2**	**7**	**2**	**-**	**-**	**1**	**3**	**-**	**10. (21.3)**	**0.179**	**2.33**
Burning sensation	1	1	2	-	**4**	1	-	-	-	**1**	-	**5**		**4.00**
Hyperaesthesia	-	-	1	-	**1**	-	-	-	-	**-**	-	**1**		
Hypoesthesia	-	-	-	2	**2**	-	-	-	-	**-**	-	**2**		
Paraesthesia	-	-	-	-	**-**	1	-	-	1	**2**	-	**2**		
Cognitive impairment	**-**	**1**	**3**	**1**	**5**	**1**	**3**	**2**	**3**	**9**	**1**	**15, (31.9)**	**0.115**	**0.56**
Disorientation	-	-	1	-	**1**		1		1	**2**	**1**	**3**		
Dissociation	-	-	-	-	**-**	1				**1**	-	**1**		
Dizziness	-	1	1	-	**2**			2	1	**3**	-	**5**		**0.67**
Hallucination	-	-	-	-	**-**				1	**1**	-	**1**		
Nightmare	-	-	-	-	**-**		1		-	**1**	-	**1**		
Syncope			1	1	**2**		1		-	**1**	-	**3**		
Hyperkinesia	**-**	**1**	**-**	**1**	**2**	**2**	**4**	**3**	**2**	**11**	**-**	**13, (27.7)**	**0.001**	**0.18**
Ataxia	-	-	-	-	**-**	**-**	2	-	-	**2**	-	**2**		
ADHD	-	-	-	-	**-**	**-**	1	-	-	**1**	-	**1**		
Convulsion	-	1			**1**	1	1	1	2	**5**	-	**6**		**0.2**
Psychomotor hyperactivity	-	-	-	-	**-**	-	-	2	-	**2**	-	**2**		
Status epilepticus	-	-	-	-	**-**	1	-	-	-	**1**	-	**1**		
Tremor	-	-	-	1	**1**	-	-	-	-	**-**	-	**1**		
Visual impairment	**-**	**-**	**-**	**-**	**-**	**-**	**1**	**1**	**1**	**3**	**-**	**3**	**-**	**-**
Diplopia	-	-	-	-	**-**	-	1	-	1	**2**	-	**2**		
Nystagmus	-	-	-	-	**-**	-	-	1	-	**1**	-	**1**		
Miscellaneous	**2**	**-**	**1**	**-**	**3**	**-**	**-**	**-**	**3**	**3**	**-**	**6**	**-**	**1.00**
Cerebral infarction	1	-	-	-	**1**	-	-	-	-	**-**	-	**1**		
Cranial nerve disorder	-	-	-	-	**-**	-	-	-	1	**1**	-	**1**		
Dependence	1	-	-	-	**1**	-	-	-	-	**-**	-	**1**		
Headache	-	-	1	-	**1**	-	-	-	1	**1**	-	**2**		
Neurological symptom	-	-	-	-	**-**	-	-	-	1	**1**	-	**1**		
Grand total	**3,**	**3,**	**7,**	**4,**	**17,**	**5,**	**8,**	**6,**	**10,**	**29,**	**1,**	**47,**	**0.010**	**0.58**
% of sex total	**17.7 %**	**17.7 %**	**41.2 %**	**23.5 %**	**100 %**	**17.2 %**	**27.6 %**	**20.7 %**	**34.5 %**	**100 %**				
% of grand total					**36.2 %**					**61.7 %**	**2.1 %**	**100 %**		
X^2 test P value (all ADRs)			**0.470**					**0.565**						

TABLE 3.13: The 3 most common ADRs reported per paediatric age sub-category distributed by sex†

Paediatric age category	FEMALES Major specific ADR or ADR SOC	n (% for category)	MALES Major specific ADR or ADR SOC	n (% for category)
Infants (<2 years)	Rash	9 (32.1)	Other skin & subcutaneous disorders (excluding rash)	8 (19.0)
	General disorders & administration site injuries	3 (10.7)	Injury, poisoning & procedural complications	6 (14.3)
	Nervous system disorders	3 (10.7)	Nervous system disorders	5 (11.9)
Category total (% for sex)	28 ADRs (16.4)		42 ADRs (26.4)	
Preschool-age children (2-5 years)	Rash	10 (23.3)	Skin & Subcutaneous disorders	8 (20.0)
	Other skin & subcutaneous disorders (excluding rash)	7 (16.3)	Nervous system disorders	8 (20.0)
	General disorders & administration site injuries	6 (14.0)	Gastrointestinal disorders	6 (15.0)
Category total (% for sex)	43 ADRs (25.2)		40 ADRs (25.2)	
School-age children (6-11 years)	Rash	10 (20.0)	Rash	6 (19.4)
	Other skin & subcutaneous disorders (excluding rash)	8 (16.0)	Nervous system disorders	6 (19.4)
	General disorders & administration Site Injuries	8 (16.0)	Gastrointestinal disorders	4 (12.9)
Category total (% for sex)	50 ADRs (29.2)		31 ADRs (19.5)	
Younger Adolescents (12-17 years)	Rash	8 (16.0)	Nervous system disorders	10 (21.8)
	Gastrointestinal disorders	8 (16.0)	Gastrointestinal disorders	9 (19.6)
	Immune system disorders	7 (14.0)	General disorders & administration site injuries	5 (10.9)
Category total (% for sex)	50 ADRs (29.2)		46 ADRs (28.9)	
Paediatric subjects (0-17 years)	Rash	37 (21.6)	Nervous system disorders	29 (18.2)
	General disorders & administration site injuries	22 (12.9)	Skin & Subcutaneous disorders	29 (18.2)
	Other skin & subcutaneous disorders (excluding rash)	20 (11.7)	Gastrointestinal disorders	24 (15.1)
Category total (% for sex)	171 ADRs (100)		159 ADRs (100)	
% in population	51.7 %†		48.3 %†	
X^2 test for independence of nervous system disorders ADRs on male paediatric age: P=0.565				

† -Excluding subjects of unknown sex

across paediatric age categories. While ADRs associated with aromatherapy products were predominant among infants (64.3%; $p < 0.001$), those associated with homeopathic products were predominant among younger adolescents (65.2%; $p < 0.001$), and those associated with dietary supplements were predominant among school-age children (51.9%; p=0.004). For ADRs associated with herbal remedies and herb-drug combinations, however, although they were uniformly distributed (p=0.163; p=0.961) among children aged over 2 years, they were much less associated with infants (p=0.002; p=0.031). A comparison of the various modes of herbal medicinal product use shows that the combined use of herbal medicines with conventional medicines, chemical

TABLE 3.14: Distribution of ADR reports based on the associated CAM product types

CAM product types (or specific modes of use)	Infants (<2 yr)	Preschool-age children (2-5 yr)	School-age children 6-11 yr)	Younger adolescents (12-17 yr)	Grand total n (%)	X^2 test p value (all ages)	X^2 test p value (age >2 yr)
Aromatherapy products (essential oils)	27	9	5	1	**42, (12.7)**	**0.000**	**0.041**
Dietary Supplements	8	3	14	2	**27, (8.1)**	**0.004**	**0.001**
Herbal Products	6	3	0	2	**11, (3.3)**	**-**	**-**
Herbal Remedies	7	30	23	17	**77, (23.2)**	**0.002**	**0.163**
Herb-Drug Combinations	15	34	34	32	**115, (34.6)**	**0.031**	**0.961**
Homeopathic Remedies	6	5	5	30	**46, (13.9)**	**0.000**	**0.000**
TCM/Poly-herbal formulations	1	0	1	12	**14, (4.2)**	**-**	**-**
TOTAL ADRs Reported (%)	**70, (21.08)**	**84, (25.30)**	**82, (24.70)**	**96, (28.92)**	**332, (100)**		
X^2 test for independence of ADR report on CAM types involved: P value <0.001							
Binomial test comparing ADR report based on the mode of herbal product use P(Herbal remedies)−P(Herb-drug combinations): Estimate = -0.114458; P-Value = 0.001							

products or more than two other herbal medicines resulted in more ADRs than the use of 1-3 herbs alone only when the additional agent was a conventional medicine. While herb- drug combinations were associated with a much higher proportion of ADRs than herbal remedies (34.6% vs. 23.2%; estimate = −0.114458; p =0.001); herbal products and poly-herbal formulations were associated with much fewer proportions (3.3% vs. 23.2%; estimate = −0.198795; $p < 0.001$; 4.2% vs. 23.2%; estimate = −0.189759; $p < 0.001$).

The level one ATC classification of the CAMs (table 3.15) shows a highly non-uniform distribution ($P < 0.001$), with CAMs in the alimentary system & metabolism class accounting for almost one third of the ADR reports and those in the genito-urinary system & sex hormones class accounting for only 1% of them. Among products in the 3 anatomical main groups whose ADR reports were associated with all paediatric age categories, only the ADRs reports for dermatological CAM products were uniformly distributed across age categories (p=0.238). While ADR reports for respiratory system CAM products were skewed ($p < 0.001$) towards infants; those for products in the alimentary system & metabolism class were skewed against them (P=0.012).

Figure 3.8 illustrates the indications recorded for the CAM products used in the 186 paediatric subjects for whom ADRs were reported, highlighting the high degree of non-inclusion of indications for the products used (83; 44.6%), as well as the high proportion of abdominal and rectal conditions among the indications that were reported (54; 52.4%). This indication was followed distantly by head, eye, ear, neck and throat conditions (16; 15.5%), skin conditions (11; 10.7%); and allergy (10 cases; 9.7%), respectively. A detailed analysis of the specific indications constituting the abdominal and rectal conditions associated with the ADRs in figure 3.9 indicates that

TABLE 3.15: Distribution of ADR reports based on the anatomical main group classification of associated CAM products

CAM product types (or specific modes of use)	Infants (<2 yr)	Preschool-age children (2-5 yr)	School-age children 6-11 yr)	Younger adolescents (12-17 yr)	Grand total n (%)	X^2 test p value (all ages)	X^2 test p value (age >2 yr)
Aromatherapy products (essential oils)	27	9	5	1	**42, (12.7)**	**0.000**	**0.041**
Dietary Supplements	8	3	14	2	**27, (8.1)**	**0.004**	**0.001**
Herbal Products	6	3	0	2	**11, (3.3)**	**-**	**-**
Herbal Remedies	7	30	23	17	**77, (23.2)**	**0.002**	**0.163**
Herb-Drug Combinations	15	34	34	32	**115, (34.6)**	**0.031**	**0.961**
Homeopathic Remedies	6	5	5	30	**46, (13.9)**	**0.000**	**0.000**
TCM/Poly-herbal formulations	1	0	1	12	**14, (4.2)**	**-**	**-**
TOTAL ADRs Reported (%)	**70, (21.08)**	**84, (25.30)**	**82, (24.70)**	**96, (28.92)**	**332, (100)**		
X^2 test for independence of ADR report on CAM types involved: P value <0.001							
Binomial test comparing ADR report based on the mode of herbal product use P(Herbal remedies)−P(Herb-drug combinations): Estimate = -0.114458; P-Value = 0.001							

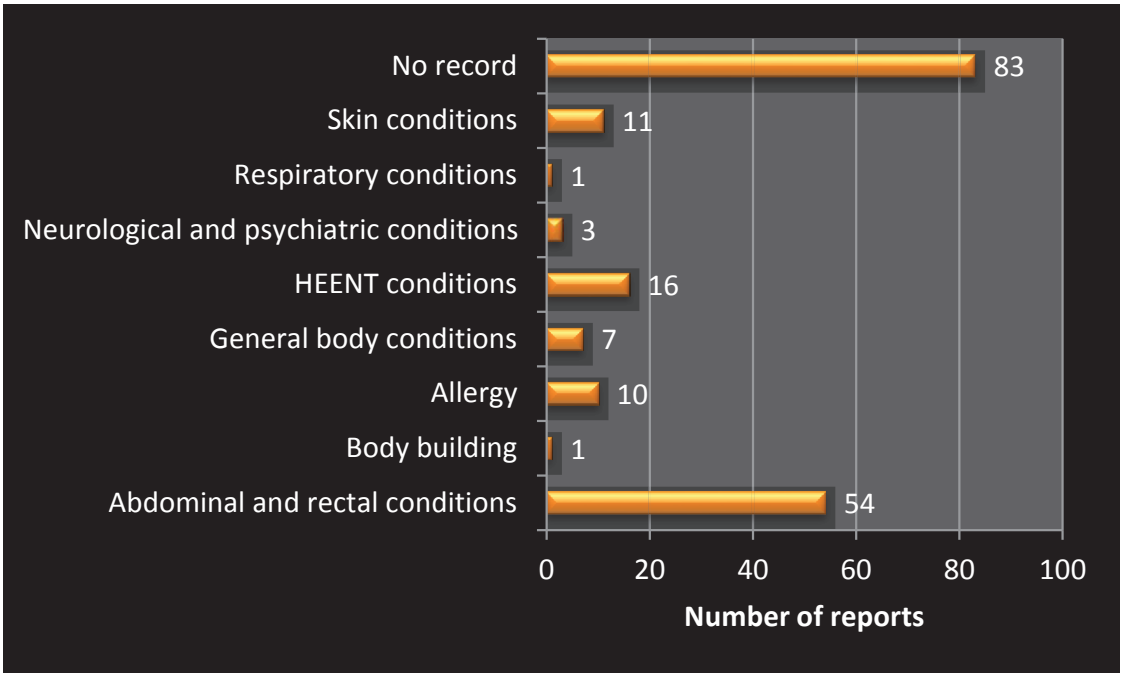


FIGURE 3.8: Indications provided for CAM products associated with ADRs in paediatric subjects

enterobiasis, the eradication of round worm infestation, accounted for over two thirds of them (41; 76.0%).

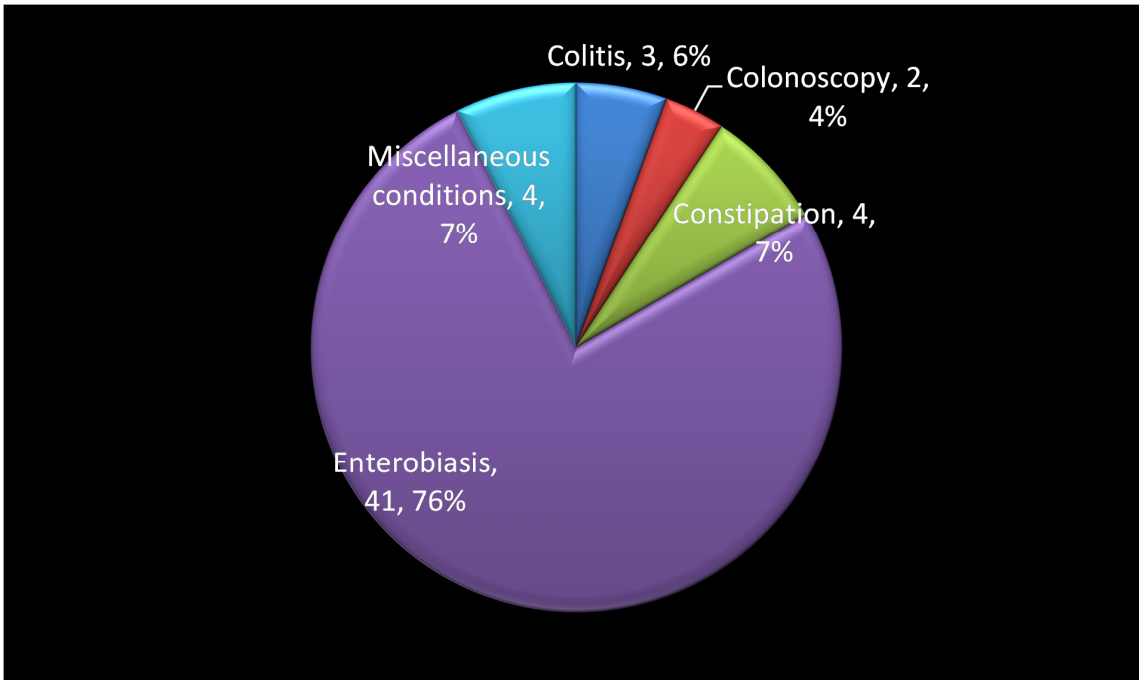


FIGURE 3.9: Details of abdominal and rectal conditions recorded as indications for CAM products associated with ADRs in paediatric subjects

Tables 3.16 and 3.17 outline the period taken for the ADRs reported to resolve as recorded in the database, and indicate that, although ADR duration was either not (validly) recorded for about 60% of the cases (190; 57.2%), in about 70% of the validly recorded cases, the ADRs reported resolved within the first 3 days of the report (97; 68.3%), with a third of them resolving on the very same day(47; 33.1%). When the SOC distribution of the ADRs reported was considered (table 3.15), the ADR durations of ADRs in the respective SOCs were found to follow the same general pattern as for the total ADRs reported, except for ADRs in the cardiac disorders; I & I; injury, poisoning & procedural complications (IPPC); neoplasms; and psychiatric disorders (PD) classes, for which most (or all) of the associated ADRs took more than 3 days to resolve. When the CAM product types associated with ADRs were considered (table 3.16), the ADR resolution periods for the various product types were also found to follow a similar pattern. Only the ADRs associated with dietary supplements and herbal products were found to have taken more than 3 days to resolve. Strikingly, there was no record for records involving poly-herbal preparations.

Figure 3.10 illustrates the richness of the narrative associated with CAM-related paediatric ADR report entries. Although a detailed case narrative was presented in about half of the cases reported (88; 47.3%), no narrative whatsoever was provided in a third of the cases (64; 34.4%), and some "additional information" in about one eighth of the cases (26; 14.0%). Most of the additional information provided was in terms of further details of the ADR reported, including

TABLE 3.16: Duration of CAM-related ADRs reported according to their respective system-organ classes

Adverse drug Reaction System-Organ Classes (ADR SOCs)	Reported period of ADR resolution						Reports with valid ADR duration data	Reports with missing or erroneous ADR duration data	All ADRs reported
	Same day	1-3 days	4-7 days	8-15 days	16-31 days	>31 days	n (%)	n (%)	n (%)
Blood & lymphatic System disorders	1		1				2, (50.0)	2, (50.0)	**4, (1.2)**
Cardiac disorders			1			1	2, (50.0)	2, (50.0)	**4, (1.2)**
Ear & labyrinth disorders		1	1				2, (66.7)	1, (33.3)	**3, (0.9)**
Eye disorders	1	1				1	3, (42.9)	4, (57.1)	**7, (2.1)**
Gastrointestinal disorders	6	10	2		1	3	22, (52.4)	20, (47.6)	**42, (12.7)**
General disorders & Administration site injuries	4	4	1			2	11, (28.9)	27, (71.1)	**38, (11.5)**
Immune system disorders	5	3				1	9, (45.0)	11, (55.0)	**20, (6.0)**
Infections & Infestations			1			1	2, (40.0)	3, (60.0)	**5, (1.5)**
Injury, Poisoning & Procedural Complications	1		1		1		3, (20.0)	12, (80.0)	**15, (4.5)**
Investigations		1	1				2, (50.0)	2, (50.0)	**4, (1.2)**
Nutrition & Metabolic disorders							0	2, (100)	**2, (0.6)**
Musculoskeletal & connective tissue Disorders	2	2		1			5, (38.5)	8, (61.5)	**13, (3.9)**
Neoplasms –benign, malignant or unspecified			1				1, (100)		**1, (0.3)**
Nervous system disorders	14	11	3	1	1	1	31, (66.0)	16, (34.0)	**47, (14.2)**
Psychiatric disorders	1		2	2			5, (45.5)	6, (54.6)	**11. (3.3)**
Renal & Urinary disorders							0	5, (100)	**5, (1.5)**
Reproductive system & Breast disorders		1					1, (20.0)	4, (80.0)	**5, (1.5)**
Respiratory, Thoracic & Mediastinal disorders	5	2					7, (43.8)	9, (56.3)	**16, (4.8)**
Skin & Subcutaneous disorders	7	14	8	4		1	34, (39.5)	52, (60.5)	**86, (25.9)**
Vascular disorders							0	4, (100)	**4, (1.2)**
TOTAL ADRs Reported (% of valid entries) (% of all entries)	**47, (33.1) (14.2)**	**50, (35.2) (15.1)**	**23, (16.2) (6.9)**	**8, (5.6) (2.4)**	**3, (2.1) (0.9)**	**11, (7.7) (3.3)**	**142, (100) (42.8)**	**190, - (57.2)**	**332, - (100)**

associated reactions and its onset and duration. Also included in some cases were further details of the suspect drug, including the specific brand, the person who prescribed or recommended it, its purpose of use, as well as any other co-administered agents. Finally, a few cases included suggestions of possible causes of the reaction, such as an overdose, a drug interaction, etc.

3.3.6 Severity and outcome of paediatric ADRs

Table 3.18 outlines the severity and outcomes of the ADRs reported according to their respective SOCs. While there was no report on the severity of about 92% of CAM-related ADRs reported for paediatric subjects, about 6% of them (19, 5.7%) were described as severe. Among the nine

TABLE 3.17: Duration of ADRs associated with various CAM product types

CAM product types (or specific modes of use)	Reported period of ADR resolution						Reports with valid ADR duration data	Reports with missing or erroneous ADR duration data	All ADRs reported
	Same day	1-3 days	4-7 days	8-15 days	16-31 days	>31 days	n (%)	n (%)	n (%)
Aromatherapy products	10	8	2	1	1		22, (15.5)	20, (10.5)	**42, (12.7)**
Dietary supplements		1		3	1		5, (3.5)	22, (11.6)	**27, (8.1)**
Herbal products		1	2				3, (2.1)	8, (4.2)	**11, (3.3)**
Herbal remedies	7	19	10		1	1	38, (26.7)	39, (20.5)	**77, (23.2)**
Herb-drug combinations	23	19	8	3		6	59, (41.5)	56, (29.5)	**115, (34.6)**
Homeopathic remedies	7	2	1	1		4	15, (10.6)	31, (16.3)	**46, (13.9)**
TCM/Poly-herbal formulations							0,	14, (7.4)	**14, (4.2)**
TOTAL ADRs reported	**47,**	**50,**	**23,**	**8,**	**3,**	**11,**	**142,**	**190,**	**332,**
(% of valid reports)	**(33.1)**	**(35.2)**	**(16.2)**	**(5.6)**	**(2.1)**	**(7.7)**	**(100)**	**-**	**-**
(% of all reports)	**(14.2)**	**(15.1)**	**(6.9)**	**(2.4)**	**(0.9)**	**(3.3)**	**(42.8)**	**(57.2)**	**(100)**

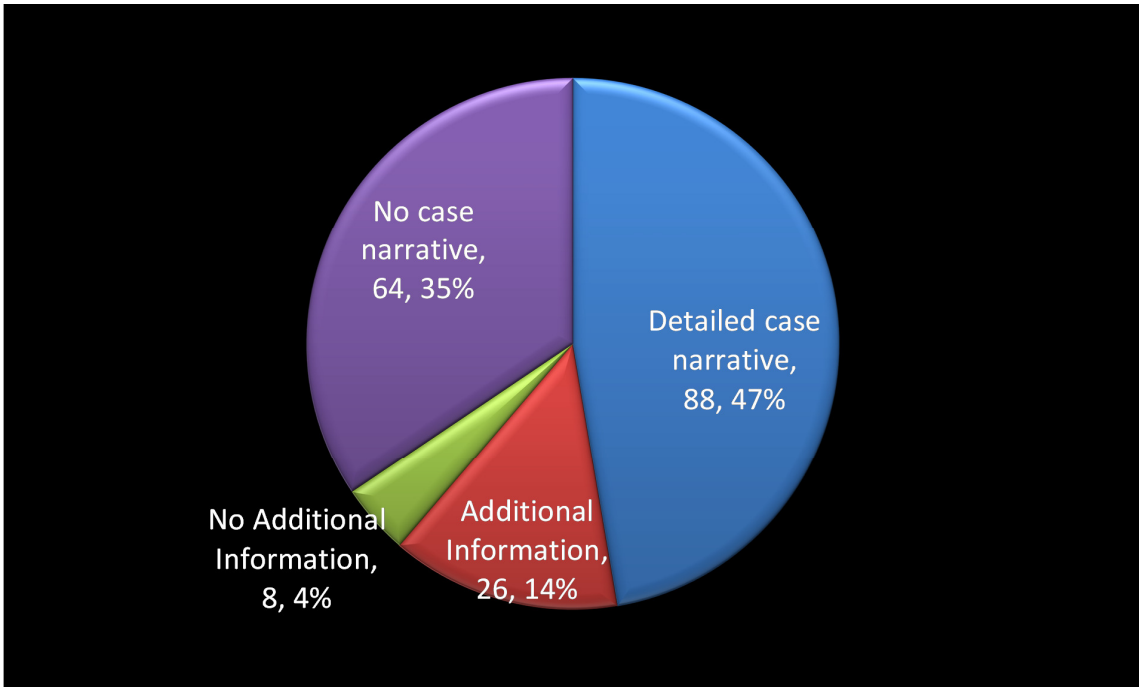


FIGURE 3.10: Richness of report narrative associated with paediatric case reports

SOCs which had at least 10 ADRs, the immune system disorders (ISD) class (2; 10.0%), GID class (4; 9.5%) and PD class (1; 9.1%) had the greatest prevalence of severe ADRs, and were followed distantly by other classes. The lowest incidences of severity were associated with the two SOCs with the highest ADRs representation (SSD class - 5; 5.8% and NSD class -1; 2.1%).

TABLE 3.18: Distribution of paediatric adverse drug reactions by severity and outcome

Adverse drug Reaction System-Organ Classes (ADR SOCs)	SEVERITY			Grand total n (100 %)	OUTCOME			
	Severe n (%)	Not severe	Not reported		Fatal n (%)	Not resolved n (%)	Resolving/ resolved n (%)	Not reported
Blood & lymphatic system disorders	1, (25.00)		3	**4**		1, (25.00)	2 (50.00)	1
Cardiac disorders			4	**4**		1, (25.00)	3, (75.00)	
Ear & labyrinth disorders			3	**3**			1, (33.33)	2
Eye disorders	1, (14,29)		6	**7**			6, (85.71)	1
Gastrointestinal disorders	4, (9.52)	2	36	**42**		3, (7.14)	35, (83.33)	4
General disorders & administration site injuries			38	**38**	1, (2.63)	6 (15.79)	25, (65.79)	6
Immune system disorders	2 (10.00)		18	**20**			17, (85.00)	3
Infections & infestations		1	4	**5**	1, (20.00)		2, (40.00)	2
Injury, poisoning & procedural complications	1, (6.67)		14	**15**	4 (26.67)	2 (13.33)	9 (60.00)	
Investigations			4	**4**			3, (75.00)	1
Nutrition & metabolic disorders	1, (50.0)		1	**2**				2
Musculoskeletal & connective tissue disorders			13	**13**		1 (7.69)	10 (76.92)	2
Neoplasms –benign, malignant or unspecified			1	**1**			1, (100)	
Nervous system disorders	1 (2.13)	3	43	**47**	1, (2.13)	1 (2.13)	40, (85.11)	5
Psychiatric disorders	1 (9.09)		10	**11**		3, (27.27)	8, (72.73)	
Renal & urinary disorders		1	4	**5**			5, (100)	
Reproductive system & Breast disorders	1 (20.00)		4	**5**		1, (20.00)	3, (60.00)	1
Respiratory, thoracic & mediastinal disorders	1 (6.25)		15	**16**			14, (87.50)	2
Skin & subcutaneous disorders	5, (5.81)	1	80	**86**		6, (6.98)	69 (80.23)	11
Vascular disorders			4	**4**			3, (75.00)	1
TOTAL ADRs Reported (% of grand total)	**19, (5.72)**	**8, (2.41)**	**305, (91.87)**	**332, (100)**	**7, (2.11)**	**25, (7.54)**	**256, (77.11)**	**44, (13.25)**

In terms of the outcomes of the ADRs reported, over 75% of the ADRs reported (256; 77.5%) were described as either resolving or fully resolved by the time of report, while only 2% of the ADRs (7; 2.1%) were described as fatal. The highest incidence of fatality was seen in ADRs in the IPPC class (4; 26.7%), while the lowest incidence was seen in ADRs in the NSD class (1; 2.1%). 25 ADRs (7.6%) were unresolved at the time of report; about half of which (12; 48.0%) were equally contributed by the SSD and GDASI classes. Among SOCs with 10 or more ADRs, the prevalence of non-resolved cases was highest for ADRs in the PD class (3; 27.3%); intermediate for those in

the GDASI class (6; 15.8%) and IPPC class (2; 13.3%); and (like for severity status) lowest in the NSD class (1; 2.1%). The degree of resolution of CAM-related ADRs seen was proportional to the number of ADRs contributed by each SOC, with the four most highly represented SOCs contributing about two thirds of resolved ADRs (169; 66.0%). At the individual SOC level, however, and among classes with at least 10 ADRs, the highest prevalence of resolution was seen with ADRs in the respiratory, thoracic & mediastinal disorders (RTMD) class (14; 87.5%). These were closely followed by ADRs in the NSD class (40; 85.1%), the ISD class (17; 85.0%), the GID class (35; 83.3%), and the SSD class (69; 80.2%); with the lowest prevalence being seen in the IPPC class (9; 60.0%).

Tables 3.19 to 3.21 classify the fatal and unresolved ADRs reported based on subject age category and sex, CAM product type, and specific CAM products, respectively. Table 3.19 shows that most of the seven fatalities reported occurred in infants (6; 85.7%), without gender disparity. Fat embolism was the most notable fatal ADR (4; 57.1%). Rash and device occlusion accounted for over half of the 13 unresolved ADRs reported for female subjects (7; 53.9%); while abnormal behaviour joined device occlusion in making up about 42% of male ADRs (5; 41.7%). Most of the unresolved ADRs in male subjects were reported among preschool-age children (9; 75.0%); while male infants were not at all associated with such ADRs. Although unresolved ADRs were more widely distributed among female age categories, about half of them (6; 46.2%) were reported for school-age children. Although there were no significant sex-related differences in the proportion of unresolved ADRs reported in the two sexes (P(female)-P(male) Estimate =0.04; p =0.777), unresolved ADRs were more frequently reported for female subjects (13; 52.0%), while the converse held for fatal ADRs (3; 42.9%).

The classification of fatal and unresolved ADRs based on CAM product types in table 3.20 implicates dietary supplements as the predominant culprits, accounting for (85.7%) of fatal ADRs and 32% of unresolved ADRs. Poly-herbal formulations and herbal products (i. e. products containing herbs along with non-herbal substances other than conventional medicines) were not at all associated with fatal and unresolved ADRs. Herbal remedies were most associated with unresolved ADR%s (12; 48.0%), closely followed by dietary supplements (8; 32.0%). The overview of the specific CAMs most associated with ADRs in table 3.21 indicates that while PRIPSEN®, a herb-drug combination of senna and piperazine, accounted for more than 25% of all ADRs reported, the herbal remedy, senna, topped the CAM product list for unresolved ADRs, and the dietary supplement, soybean oil, topped the list for CAMs associated with fatal outcomes. Although PRIPSEN® was highly associated with ADRs for every paediatric age category, KARVOL®, an aromatherapy product, was most associated with ADRs among infants by a wide margin. Several products were associated with severity in the different age categories, without any particular distinction.

TABLE 3.19: Age and sex distribution of fatal and unresolved ADRs reported for paediatric subjects

Specific ADR Or ADR System-organ class (SOC)	FEMALE SUBJECTS					MALE SUBJECTS					All paediatric subjects (<18 years)
	Infants (<2 years)	Preschool Children (2-5 years)	School age Children (6-11 years)	Younger Adolescents (12-17 years)	All female subjects	Infants (<2 years)	Preschool Children (2-5 years)	School age Children (6-11 years)	Younger Adolescents (12-17 years)	All male subjects	
FATAL ADRs											
General disorders & administration site injuries									1	**1**	**1, 14.3 %**
Pneumonia	1				1						**1**
Fat embolism	1				1	3				**3**	**4, 57.1 %**
Cerebral infarction	1				1						**1**
Grand total (FATAL ADRs)	**3, 100 %**				**3, 100 % 42.9 %**	**3, 75.0 %**			**1, 25 %**	**4. 100 % 57.1 %**	**7, 100 %**
UNRESOLVED ADRs											
Aplastic anaemia				1	**1, 7.7 %**						**1, 4.0 %**
Supraventricular tachycardia									1	**1**	**1**
Anal injury				1	**1**						**1**
Diarrhoea							1			**1**	**1**
Mouth ulceration				1	**1**						**1**
Application site reaction			1		**1**						**1**
Device occlusion	1	1	1		**3, 23.1 %**			2		**2**	**5, 20.0 %**
Blister							1			**1**	**1**
Chemical injury							1			**1**	**1**
Arthropathy			1		**1**						**1**
Attention-deficit hyperactivity							1			**1**	**1**
Abnormal behaviour							3			**3**	**3, 12.0 %**
Perineal pain							1			**1**	**1**
Erythema							1			**1**	**1**
Rash	2		2		**4, 30.8 %**						**4, 16.0 %**
Skin exfoliation			1		**1**						**1**
Grand Total	**3, 23.1 %**	**1, 7.7 %**	**6, 46.2 %**	**3, 23.1 %**	**13, 100 % 52.0 %**	**0, 0 %**	**9, 75.0 %**	**2, 16.7 %**	**1, 8.3 %**	**12, 100 % 48.0 %**	**25, 100 %**
Binomial test of gender for unresolved ADRs, P(female)-P(male): Estimate=0.04; P value =0.777											

TABLE 3.20: Classification of fatal and unresolved ADRs reported based on the associated CAM product type

Fatal ** and 5 most commonly reported unresolved suspected ADRs or SOCs per CAM Product Type [n, (%)]							
Aromatherapy products	**Dietary supplements**	**Herb-drug combinations**	**Herbal products**	**Herbal remedies**	**TCM/Poly-herbal formulations**	**Homeopathic remedies**	**TOTAL**
A total of 7 FATAL ADRs reported (2.1 %)							
1 fatal ADRs (14.3 %)	**6 fatal ADRs (85.7 %)**	**-**	**-**	**-**	**-**	**-**	**7 fatal ADRs (100 %)**
Pneumonia, [1, (100 %)]**	**Fat embolism**, [4, (66.7 %)]**						
	General disorders, [1, (16.7 %)]**						
	Cerebral infarction, [1, (16.7 %)]**						
A total of 25 suspected ADRs reported as UNRESOLVED (7.5 %) Where >5 unresolved ADR reports were received for any given CAM product type, the 5 most commonly reported are listed							
1 unresolved ADRs (4.0 %)	**8 unresolved ADRs (32.0 %)**	**1 unresolved ADR (4.0 %)**	**-**	**12 unresolved ADRs (48.0 %)**	**-**	**3 unresolved ADRs (12.0 %)**	**25 ADRs (100 %)**
Rash, [1, (100 %)]	**Device occlusion, [5, (62.5 %)]**	**Rash, [1, (100 %)]**		**Gastrointestinal disorders, [3, (25.0 %)]**		**Abnormal behaviour, [2, (66.7 %)]**	
	Arthropathy, [1, (12.5 %)]			**Skin & subcutaneous disorders [2, (16.7 %)]**		**Attention-deficit /Hyperactivity disorder [1, (33.3 %)]**	
	Rash, [1, (12.5 %)]			**Injury, poisoning & procedural complications, [2, (16.7 %)]**			
	Skin exfoliation [1, (12.5 %)]			**Blood & lymphatic system disorders [1, (8.3 %)]**			
				Application site reaction [1, (8.3 %)]			

TABLE 3.21: Specific CAM products most commonly associated with severe, unresolved and fatal ADRs among paediatric subjects

Age categories	Specific CAM products most associated with: All ADRs	Unresolved ADRs	Severe ADRs	Fatal ADRs
Infants (<2 years)	**KARVOL [15, 21.4 %];** **PRIPSEN [9, 12.9 %];** **Soya bean oil [8, 11.4 %]** (Total: 70 ADRs)	**ASHTON & PARSON'S TEETHING POWDER** (Matricaria) **[1, 33.3 %]**; **Eucalyptus, Menthol & Thymus combination [1, 33.3 %];** **Soya bean oil [1, 33.3 %]** (Total: 3 ADRs)	**KARVOL (1, 100 %)** (Total: 1 ADR)	**Soya bean oil** [5, 83.3 %]; **KARVOL** (1, 16.7 %) (Total: 6 ADRs)
Preschool-age children (2-5 years)	**PRIPSEN [30, 35.7 %];** **Senna [15, 17.9 %];** **Azadirachta, Lavandula angustifolia & Melaleuca combination [6, 7.1 %]** (Total: 84 ADRs)	**Senna [6, 60 %];** **Hyoscyamus niger [3, 30 %];** **Soya bean oil [1, 10 %]** (Total: 10 ADRs)	**CERUMOL [1, 20 %];** **Echinacea [1, 20 %];** **Hyoscyamus niger [1, 20 %];** (Total: 5 ADRs)	**None** (Total: 0 ADR)
School-age children (6-11 years)	**PRIPSEN [30, 35.7 %];** **BALNEUM bath oil [9, 11.0 %];** **EYE Q CHEWS [6, 7.3 %]** (Total: 82 ADRs)	**EYE Q CHEWS [3, 37.5 %];** **Soya bean oil [3, 37.5 %];** **BALNEUM bath oil [1, 12.5 %];** (Total: 8 ADRs)	**GOLDENSEAL COMPOUND [1, 50 %];** **Podophyllum & Salicylic acid combination [1, 50 %]** (Total: 2 ADRs)	**None** (Total: 0 ADR)
Younger adolescents (12-17 years)	**PRIPSEN [20, 20.8 %];** **Phleum pratens [12, 12.5 %];** **SWEAT SLEEPER [11, 11.5 %]** (Total: 96 ADRs)	**Echinacea [1, 25 %];** **Senna [1, 25 %];** **St. John's Wort [1, 25 %];** (Total: 4 ADRs)	**SWEAT SLEEPER [2, 33.3 %];** **Dactylis glomerata allergy combination [1, 16.7 %];** **Melaleuca [1, 16.7 %**] (Total: 6 ADRs)	**1-Androstenediol, Ephedra, Ephedrine, Methyl-testosterone, Naringin, Oxymetholone, Sida cordifolia, Testosterone combination [, 100 %]** (Total: 1 ADR)
All paediatric subjects (<18 years)	**PRIPSEN [89, 26.8 %];** **Senna [22, 6.6 %];** **KARVOL [21, 6.3 %]** (Total: 332 ADRs)	**Senna [7, 28.0 %];** **Soya bean oil [5, 20.0 %];** **EYE Q CHEWS [3, 12.0 %]** Total: 25 ADRs)	**Echinacea [2, 14.3 %];** **KARVOL [2, 14.3 %];** **SWEAT SLEEPER [2, 14.3 %]** (Total: 14 ADRs)	**Soya bean oil [5, 71.4 %];** **KARVOL [1, 14.3 %];** **1-Androstenediol, Ephedra, Ephedrine, Methyl-testosterone, etc combination [1, 14.3 %];** (Total: 7 ADRs)

Product proprietary (brand) names are CAPITALISED.

3.3.7 Seriousness of paediatric ADRs

Table 3.22 classifies paediatric ADR reports based on the reporter's perception of their seriousness. Of the 332 ADRs reported for paediatric subjects, about a third (100; 30.1%) was deemed serious by the reporter. An overview of the reporters involved outlined in figure 3.11 indicates that almost 60% were doctors (58; 58.0%), and one fifth were pharmacists (20; 20.0%); while about one tenth (9; 9.0%) of the serious ADRs were patient-reported. A classification of the serious ADRs reported based on the Council for International Organizations of Medical Sciences (CIOMS) ADR classification criteria is presented in figure 3.12. The findings show that, although only three serious ADRs (3.0%) resulted in the death of the subject, 23% resulted in hospitalisation; 10% was reported as life threatening; and 5% was considered disabling or incapacitating. However, about six in ten of them (59; 59.0%) were considered medically significant for reasons other than these. Understandably, the "congenital abnormalities" serious ADR marker was absent.

TABLE 3.22: Distribution of paediatric CAM-related adverse drug reactions based on reporter's opinion on their seriousness

Adverse drug Reaction System-Organ Classes (ADR SOCs)	Serious	Not serious	Not reported /Unknown	Grand total
Blood & lymphatic System disorders	1		3	**4**
Cardiac disorders	3	1		**4**
Ear & labyrinth disorders		1	2	**3**
Eye disorders	3		4	**7**
Gastrointestinal disorders	10	5	27	**42**
General disorders & Administration site injuries	16	5	17	**38**
Immune system disorders	8	1	11	**20**
Infections & Infestations		2	3	**5**
Injury, Poisoning & Procedural Complications	2	6	7	**15**
Investigations	1		3	**4**
Nutrition & Metabolic disorders	1	1		**2**
Musculoskeletal & Connective tissue Disorders	3	3	7	**13**
Neoplasms –benign, malignant or unspecified	1			**1**
Nervous system disorders	13	6	28	**47**
Psychiatric disorders	7	3	1	**11**
Renal & Urinary disorders	1	2	2	**5**
Reproductive system & Breast disorders	1	1	3	**5**
Respiratory, Thoracic & Mediastinal disorders	9	2	5	**16**
Skin & Subcutaneous disorders	19	15	52	**86**
Vascular disorders	1		3	**4**
TOTAL ADRs Reported (%)	**100, 30.12 %**	**54, 16.27 %**	**178, 53.61 %**	**332, 100 %**

The categorisation of the serious ADR report cases based on gender outlined in table 3.23 shows that, although much fewer serious ADRs were reported for female subjects than for males (38.0% vs. 60.0%; p=0.001), the greater proportion of these were in the SSD class (14; 36.8%) -predominantly rash (8; 57.1%); followed by ADRs in the GDASI class (7; 18.4%). The majority of the serious ADRs reported for male subjects were, however, spread out among five SOCs –the GDASI (9; 15.0%); GID (8; 13.3%); NSD (8; 13.3%); PD (7; 11.7%); and RTMD (7; 11.7%).

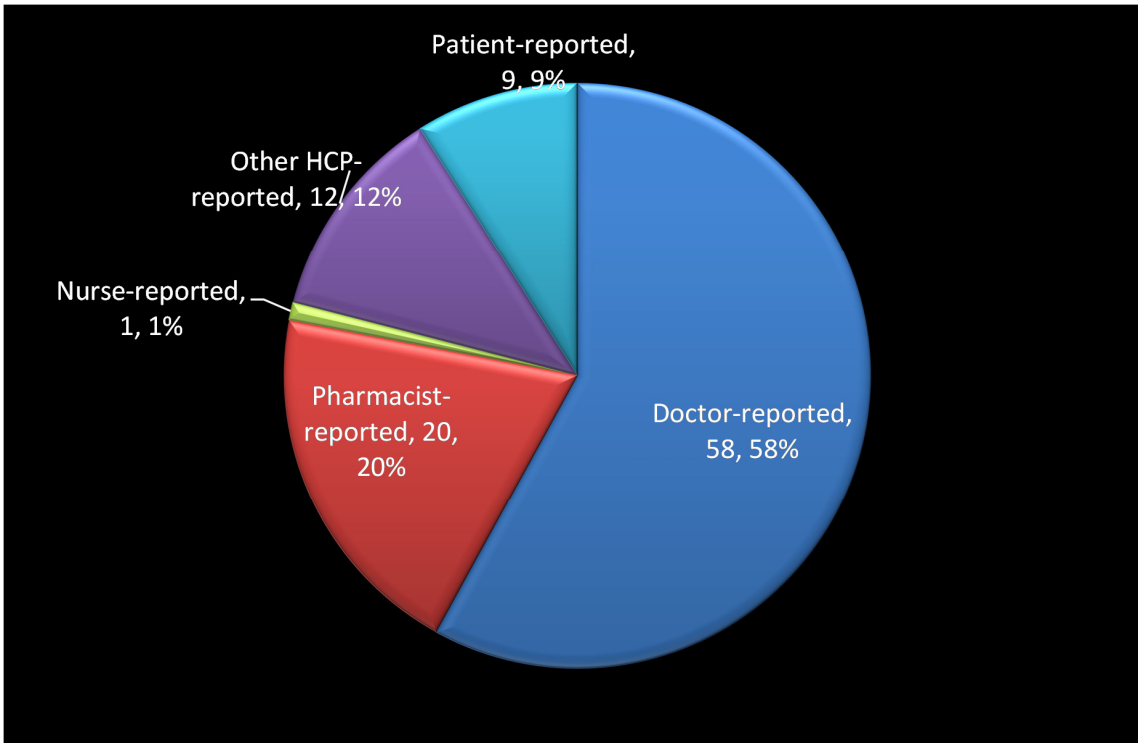
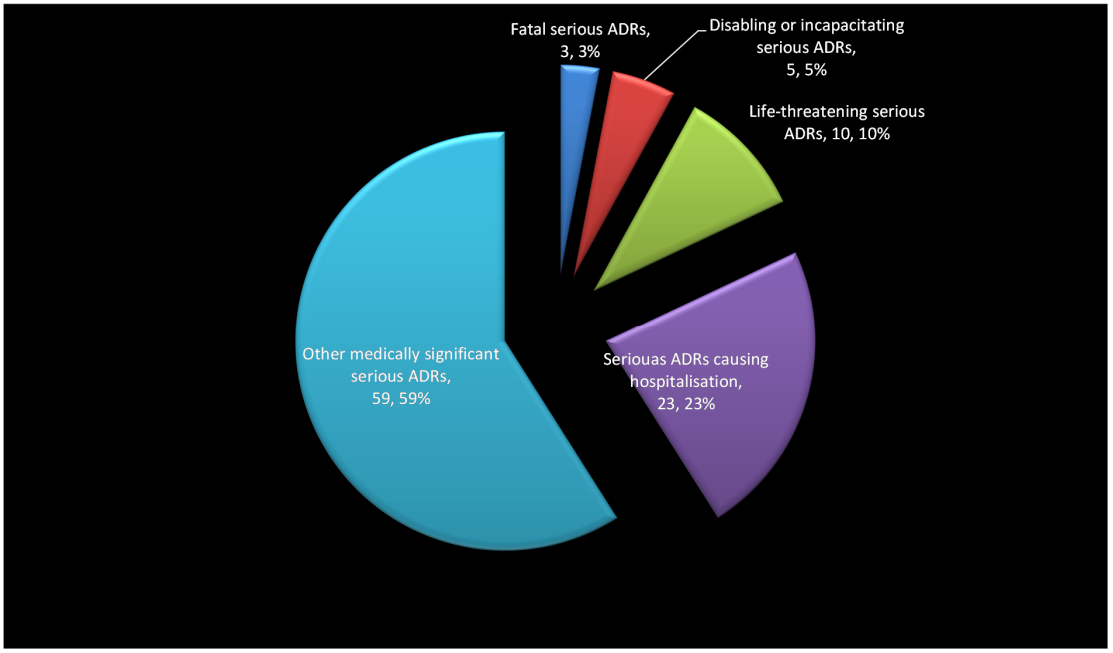


FIGURE 3.11: Reporter profile of serious ADRs



†The "congenital abnormalities" class of CIOMS serious ADRs was understandably not represented in the 100 ADRs considered serious by reporters

FIGURE 3.12: Classification of serious ADRs according to the available† CIOMS markers of seriousness

TABLE 3.23: Age group and sex distribution of serious adverse drug reactions

Serious Adverse drug Reactions System-Organ Classes (ADR SOCs)	FEMALE SUBJECTS					MALE SUBJECTS					UNKNOWN SEX		Grand total
	Infants (<2 years)	Preschool-age children (2-5 years)	School-age children (6-11 years)	Younger adolescents (12-17 years)	All female Subjects (0-17 years)	Infants (<2 years)	Preschool-age children (2-5 years)	School-age children (6-11 years)	Younger adolescents (12-17 years)	All male subjects (0-17 years)	Preschool-age children (2-5 years)	School-age children (6-11 years)	
Blood & lymphatic System disorders				1	**1**								**1**
Cardiac disorders									3	**3**			**3**
Eye disorders		1			**1**	1			1	**2**			**3**
Gastrointestinal disorders		1		1	**2**	3			5	**8**			**10**
General disorders & Administration site injuries	1	3	2	1	**7**	2		3	4	**9**			**16**
Immune system disorders				3	**3**		1		3	**4**	1		**8**
Injury, Poisoning & Procedural Complications				1	**1**	1				**1**			**2**
Investigations									1	**1**			**1**
Nutrition & Metabolic disorders	1				**1**								**1**
Musculoskeletal & Connective tissue Disorders				1	**1**				2	**2**			**3**
Neoplasms –benign, malignant or unspecified								1		**1**			**1**
Nervous system disorders	2		2		**4**		2	2	4	**8**		1	**13**
Psychiatric disorders							2	4	1	**7**			**7**
Renal & Urinary disorders									1	**1**			**1**
Reproductive system & Breast disorders				1	**1**		2						**1**
Respiratory, Thoracic & Mediastinal disorders	2				**2**	2		1	2	**7**			**9**
Skin & Subcutaneous disorders	4	2	5	3	**14**	4			1	**5**			**19**
Cyanosis						1				1			1
Eczema	1	1	1		2	1			1	2			4
Erythema	1		1		2	1				1			3
Purpura					1								1
Rash	2	1	2	3	8								8
Thermal burn			1		1	1				1			2
Vascular disorders									1	**1**			**1**
GRAND TOTAL	**10**	**7**	**9**	**12**	**38,** 38.0 %	**13**	**7**	**11**	**29**	**60,** 60.0 %	**1**	**1**	**100,** 100 %
X^2 test of independence of serious ADRs on paediatric age category	P=0.713					P=0.000							
Binomial test for independence of serious ADRs on gender: P value =0.001													

Among the paediatric age categories, the number of serious ADRs varied in both male and female subjects according to the following pattern: younger adolescents > infants > school age children > pre-school children. However, while serious ADRs among female subjects were uniformly distributed across the various age categories (P=0.713), they were significantly associated with adolescents aged 12-17 years (P=0.000) among male subjects.

Table 3.24 presents the categorisation of CAM product types according to their association with serious ADRs. Serious ADRs were found to be dependent on CAM product type (p=0.03), with herbal products accounting for only 4% of serious ADRs reported. Apart from aromatherapy products, which were highly associated with hospitalisation (11; 73.3%) and accounted for almost half of all hospitalised cases (47.8%), all other CAM product types were mainly associated with ADRs besides the major CIOMS markers of ADR seriousness -death, hospitalisation, threat to life, or disability/incapacity. Although dietary supplements were the product types associated with fatalities (3%); herb-drug combinations (5%) and homeopathic remedies (5%) were the only ones associated with life threatening serious ADRs. Herbal remedies, in addition to being the product type most associated with serious ADRs (22%), also accounted for four fifths (4; 80%) of the serious ADRs described as disabling or incapacitating by the reporter.

In terms of their potential for serious ADRs, while CAM products generally have less than 30% potential of generating serious ADRs in paediatric subjects (52 of 186 ADRs reported; 28.0%), the serious ADR potential was seen to be highest in dietary supplements (14 of 20 ADRs reported; 70.0%), and least in herb-drug combinations (8 of 59 ADRs reported; 13.6%). While the serious ADR potentials of other CAM product types were roughly situated around that for all CAMs in general, they ranged from as low as 23.9% for herbal remedies (11 of 46 episodes of use) to as high as 34.8% for homeopathic remedies (8 of 23 episodes of use).

3.3.8 Comparison of CAM products based on their mode of use

The results of the comparison of ADR reports for CAM products based on their mode of use, which was carried out in three phases, are illustrated in figures 3.13 to 3.15. In figure 3.13, the outcomes of suspect products were compared according to whether they had been used alone (as single products) or in combination (multiple products). In figure 3.14, the outcomes of specific ADRs associated with various modes of use of herbal medicinal products were compared. Figure 3.15, however, presents a holistic ADR profile comparison at the specific product level for senna, the CAM product with the highest number of reports in the database, based on the two most commonly reported formulations with which it was associated: as the herb-drug combination product, Pripsen®, or as the single herbal medicine, senna.

Figure 3.13 illustrates that, although many more ADR reports were associated with combination product use (115; 61.8%), in most of the cases, the ADRs reported were described as either

TABLE 3.24: Classification of CAM product types with respect to their association with serious ADRs

CAM product types	Serious ADRs causing hospitalisation	Life-threatening serious ADRs	Disabling or incapacitating serious ADRs	Fatal serious ADRs	Other medically significant serious ADRs	All serious ADRs	All ADR reports	Episodes of use associated with serious ADRs	Episodes of use associated with any ADRs	Serious ADR potential (%)
Aromatherapy products	11, 73.33 % 47.83 %				4, 26.67 % 6.78 %	15, 100 % 15.00 %	42, - 12.65 %	8	27	29.63 %
Dietary supplements	3, 16.67 % 13.04 %			3, 16.67 % 100 %	12, 66.67 % 20.34 %	18, 100 % 18.00 %	27, - 8.13 %	14	20	70.00 %
Herbal products	2, 50.00% 8.70 %				2, 50.00 % 3.39 %	4, 100 % 4.00 %	11, - 3.31 %	2	7	28.57 %
Herbal remedies	5, 22.73 % 21.74 %		4, 18.18 % 80.00 %		13, 59.09 % 22.03 %	22, 100 % 22.00 %	77, - 23.19 %	11	46	23.91 %
Herb-drug combinations		5, 39.46 % 50.00 %	1, 7.69 % 20.00 %		7, 53.85 % 11.86 %	13, 100 % 13.00 %	115, - 34.64 %	8	59	13.56 %
Homeopathic remedies	2, 11.76 % 8.70 %	5, 29.41 % 50.00 %			10, 58.82 % 16.94 %	17, 100 % 17.00 %	46, - 13.96 %	8	23	34.78 %
TCM/Poly-herbal formulations					11, 100 % 18.64 %	11, 100 % 11.00 %	14, - 4.22 %	1	4	25.00 %
Grand total %	**23, 100 %**	**10, 100 %**	**5, 100 %**	**3, 100 %**	**59, 100 %**	**100, 100 %**	**332, 100 %**	**52**	**186**	**27.96 %**
X^2 test for independence of serious ADRs on CAM product type: P value =0.03										

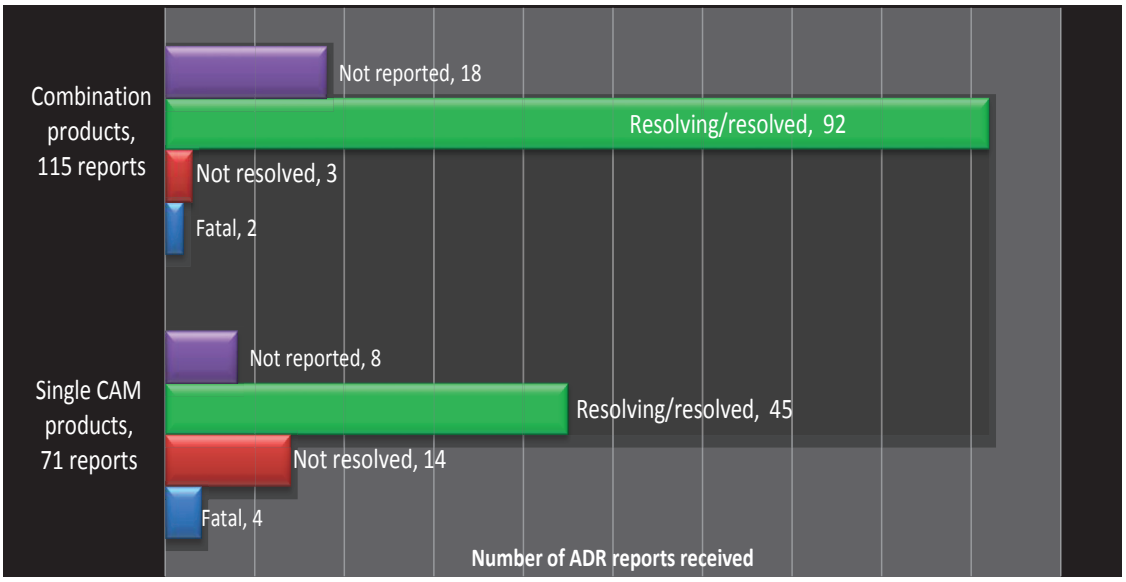


FIGURE 3.13: Comparison of outcomes associated with single and combination CAM product use

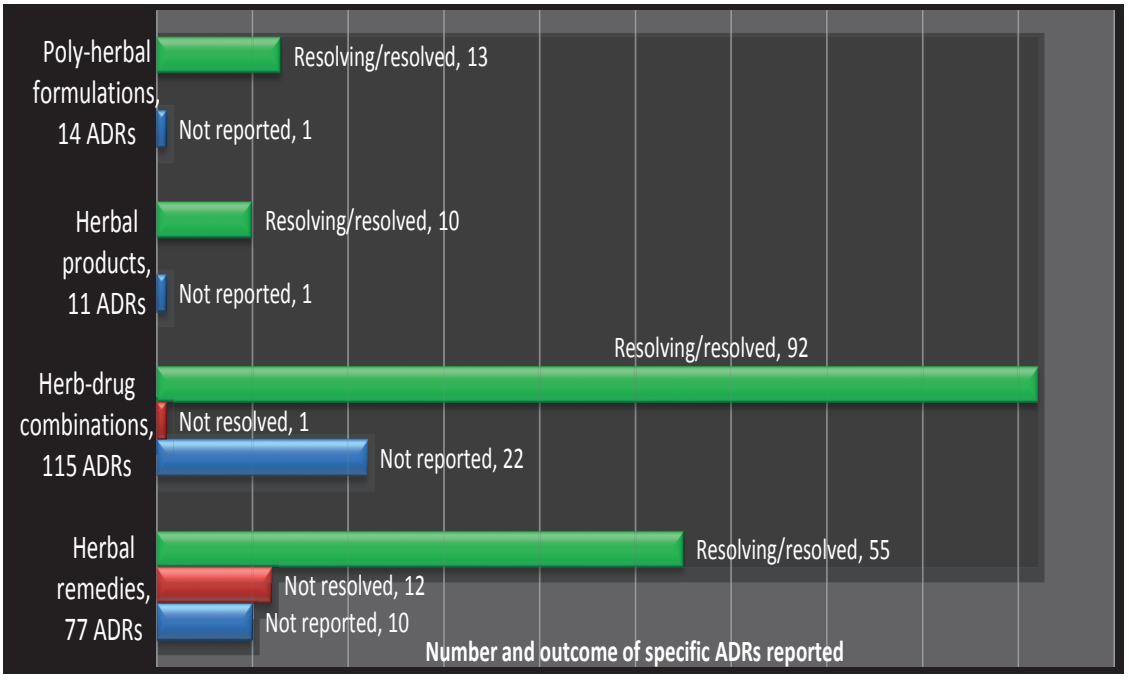


FIGURE 3.14: Comparison of outcomes of adverse drug reactions associated various modes of use of herbal medicinal products

resolving or fully resolved (92; 80.0%). This was much higher than the proportion of resolving or resolved ADRs associated with single CAM product use (45; 63.4%; P(Combination)-P(Single): p =0.015). Combination product use was also associated with much fewer unresolved ADR reports (3; 2.6% vs. 14; 31.1%; P(Combination)-P(Single): $p < 0.001$), and less fatality (2; 1.7% vs. 4; 5.6%; p =0.204).

This general pattern was also seen in figure 3.14 in which the outcomes of the specific ADRs resulting from herbal medicinal product use alone or in combination with various types of products were compared. For this analysis, the herbal medicinal products suspected in the ADR reports were compared in two ways: firstly, according to whether they were used as simple herbal preparations containing 1-3 herbs alone (herbal remedies), or as combinations of herbs with conventional drugs (herb-drug combinations); and secondly, according to whether they were used as preparations combining more than 3 herbs without any chemicals or conventional drugs (poly-herbal formulations) or as medicinal products combining herbs with chemical products besides conventional drugs (herbal products). In the first case, although herb-drug combinations were associated with significantly more ADRs than herbal remedies (34.6% vs. 23.2%; p=0.001), they also had a higher proportion of ADRs that were either resolving or fully resolved than herbal remedies did, although the difference was not significant (92; 80.0% vs. 55; 71.4%; p=0.178). Additionally, reports for herbal remedies were associated with a much higher proportion of unresolved ADRs than those for herb-drug combinations (12; 15.6% vs. 1; 0.9%; $p < 0.001$). In the second case, although poly-herbal preparations were associated with slightly more ADRs than herbal products, they also had a slightly higher proportion of ADRs that were either resolving or fully resolved (92.6% vs. 90.9%; p=0.860). However, none of the ADRs associated with either of these was unresolved at the time of report. Notably, fatal outcomes were not associated with any of the ADRs associated with herbal medicines irrespective of the mode of use.

In confirmation of the above pattern at the product level, figure 3.15 illustrates that, although Pripsen®, a combination product of senna and piperazine, was significantly associated with more ADRs than the single herbal medicine, senna, (26.8% vs. 6.6%; p=0.001), it also had a marginally higher proportion of ADRs that were either resolving or fully resolved at the time of report (73; 82.0% vs. 15; 68.2%; p=0.197). Additionally, reports for senna were associated with a much higher proportion of unresolved ADRs than those for Pripsen® (7; 31.8% vs. 1; 1.1%; $p < 0.001$). Finally, while there was no difference between the two products in terms of ADR severity (0; 0% vs. 1; 1.1%; p=1.000), senna was associated with a much higher proportion of serious ADRs when it was used alone (4; 18.2% vs. 0; 0%; p=0.001) than when it was used in combination with piperazine.

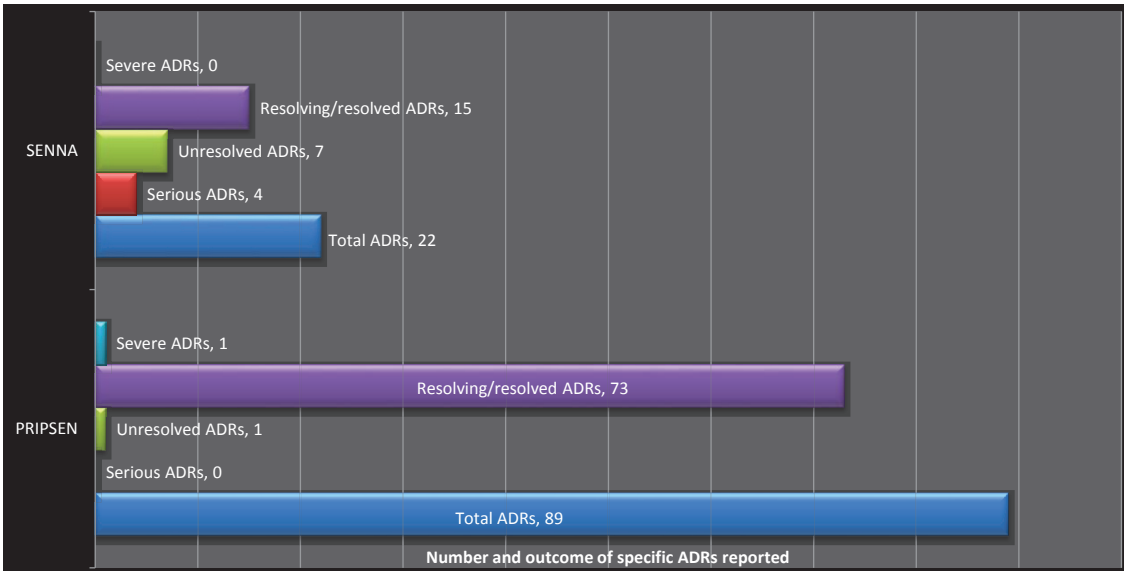


FIGURE 3.15: A holistic comparison of the ADR profiles of PRIPSEN® (Senna + Piperazine) and Senna herbal product

3.4 Discussion

3.4.1 Summary of findings

Generally, CAM products contributed a very insignificant proportion ($< 1\%$) of ADR reports in the YCS database within the (nearly) 50-year period studied, with an extremely low population-based reporting ratio for the UK population relative to conventional medicines. This was in spite of the various public health policy initiatives introduced within the period aimed at improving ADR reporting. Most of the policies were specifically targeted at improving ADR report for conventional medicines, and resulted in sustained increases in reports for conventional medicines from the mid-1980s to the early 1990s, as well as following the year 2004. However, hardly any of these policy changes yielded any sustained positive effect on the number of CAM-related YCS reports received, including the three that were targeted at promoting ADR reports for CAMs. As such, the sustained increases in YCS reports seen for conventional medicines could not be replicated for CAMs, resulting in much lower CAM-related reports. This tendency towards non-sustained increases in annual reports for CAMs was also found to be more greatly associated with paediatric reports than with adult reports; with paediatric subjects contributing less than 10% of the reports received. A major contributory factor is the high proportion (20.4%) of CAM-related ADR reports for which no age-related information was provided; which would have most likely included those for paediatric subjects. Also, at the reporter profile level, the much lower paediatric ADR reports can be explained by the fact that, while the extension of ADR reporting to community pharmacists in 1999 yielded the highest immediate improvement in CAM ADR reports in general, pharmacist reporters accounted for much fewer reports ($p=0.003$) among

paediatric subjects than they did among adults. This same argument can also be extended to the introduction of self-reporting of ADRs by patients; which, while contributing significantly to annual increases in CAM-related ADR reports generally, actually contributed much less ($p < 0.001$) to paediatric ADR reports.

On the whole, a combination of these factors resulted in paediatric subjects accounting for only 192 (8.6%) of the 2167 ADR reports received for CAM products in the period from the inception of the YCS until July, 2012. Upon data filtering based on specified criteria, the 192 reports yielded 186 valid paediatric ADR reports that profiled 332 specific paediatric ADRs, 30% of which were described as serious by the reporter based on the CIOMS markers of seriousness. Further analyses indicated rash and other skin and subcutaneous disorders as the most common ADRs. Also, because over 75% of the ADRs reported were either resolving or fully resolved at the time of report, and 6% were described as severe, about 70% of the reactions were brief, lasting 0-3 days, and 2% of them were fatal. Among the 100 serious ADRs, 23 resulted in hospitalisation, 10 were life-threatening, 5 were disabling or incapacitating, and 3 were fatal; while 59 were described as serious for other medically significant reasons.

Age and sex were also found to play significant roles in the distribution of CAM-related ADR reports. Although female subjects contributed a larger proportion of CAM-related ADR reports than males in both adults and children, the difference was significant only for adult subjects ($P < 0.001$). At the age group level, with the exception of the proportion of ADR reports for the paediatric age group which was much lower than the proportional representation of that demographic in the population (p=0.043), the proportions of ADR reports for the various age groups generally aligned with the corresponding proportions of the respective sectors in the UK population. However, while ADR reports were uniformly distributed among the four paediatric age categories (p=0.122), they varied widely among the age groups for the adult population ($p < 0.001$), with a significantly greater proportion of adult reports being received from middle-aged adults. Despite the uniform distribution of ADR reports among paediatric age categories, male subjects were found to have contributed a significantly higher proportion of ADR reports received for subjects in the first year of life (p=0.007); while the converse was the case for subjects aged 3 years (p=0.001). At the specific ADR level, female paediatric subjects contributed marginally more ADRs than males (51.5%). This is related to the fact that, while ADRs belonging to two of the four highly represented SOCs in the database, the SSD and GDASI classes, had higher odds of being reported for female subjects, those for the other two highly represented SOCs, the NSD and GID classes, had higher odds of report among male subjects. Also, among the two most highly represented SOCs, the much higher female proportion of the SSD class ADRs ($p < 0.001$) was almost totally offset by the much higher proportion of male NSD ADRs (p=0.010). While rash was found to be the predominant ADR in the SSD class, as well as across all SOCs represented, no specific ADR was seen to predominate among the ADRs in

the NSD. However, ADRs associated with cognitive impairment, hyperkinesia and abnormal sensation were found to be most reported. Although rash was reported in about two thirds of female subjects and almost half the male subjects, it was only significantly associated with male infants (p=0.018), However, while hyperkinesia-related ADRs, especially convulsions, were found to be very high reported for male subjects (p=0.001), it was not associated with any specific age category. While male subjects also accounted for a significantly greater proportion of serious ADRs for paediatric subjects (p=0.001), these ADRs were particularly associated with younger adolescents ($P < 0.001$).

Among the suspect CAM products reported in the database, products combining herbal medicines with conventional medicines (herb-drug combinations) were found to generate the most ADRs. Further analyses revealed these product types to be mainly associated with the alimentary system & metabolism anatomical main group, with Pripsen® being the product most frequently associated with ADRs (89 ADRs). This proprietary combination product of senna and piperazine is applied in the treatment of enterobiasis, which indication was found to be predominant among those reported for the CAM products in the database. Pripsen® was distantly followed by senna, a herbal laxative, (22 reports) and Karvol®, an aromatherapy combination product (of chlorbutol, levomenthol, pinus, terpineol and thymol) used for nasal decongestion (21 reports). Although herb-drug combinations were associated with the highest number of ADRs, they were least associated with serious ADRs. This was because most of the ADRs associated with them were found to be resolving or fully resolved at the point of report, with no serious ADRs and no fatalities. While no fatalities were also seen with all other modes of herbal medicinal product use reported, these other product types were all associated with lower degrees of ADR resolution and higher degrees of ADR non-resolution and seriousness. The same pattern was also seen with serious ADRs associated with CAM product types generally, an analysis of which showed dietary supplements and homeopathic remedies to have the highest serious ADR potentials, and herb-drug combinations to have the least. These findings suggest that the nature of the CAM product used is a far more critical factor with respect to its safety profile than its mode of use. The CAM product most associated with fatalities was soyabean oil (71%), and predominantly in infants.

On the whole, CAM-related ADRs reported for paediatric subjects in the YCS were relatively few, and of low severity (6%) and fatality (2%), with over 75% resolution rate, and mostly within the first 3 days of the report (68%). These generally positive outcomes were, however, complicated by their association with a high degree of incomplete or missing data. Although the case narratives provided in the reports added extra information to the basic ADR report data in 61% of the cases, there was still a high degree of non-report of key ADR criteria. For instance, there was 92% of missing data on ADR severity, about 60% of missing data on ADR duration, and 45% of missing data on indications or purpose of use.

3.4.2 Comparative analysis of results

This study found that less than 1% of all ADR reports in the YCS belonged to paediatric subjects < 18 years. A recent similar study based on the Uppsala Monitoring Centre database over a comparable period reported an incidence of 7.7% for children 0-17 years [589] for all medicines; while a slightly older study reported 9.8% paediatric reports for Spain [598]. A UK study of YCS reports from 2000 to 2009 reported 14.2% paediatric reports [590], about 70% of which was vaccine-related. A more recent MHRA analysis of the trends in ADR reports from 2008-2012 shows that 11% of the reports for the period related to paediatric subjects [582]. The much lower finding in the current study is attributable to the focus on CAMs. The low contribution of CAMs to paediatric ADRs in pharmacovigilance databases has been well noted. Zuzak et al reported a low frequency of 8.6% of toxic reactions for herbal and homeopathic remedies in a poison centre database in Switzerland, a country for which they described the use of CAM as "rather high" [369]. The much lower level found in the current study is attributable both to the country of study as well as the type of database used (poison centre). CAM use in the UK has been found to be generally low relative to other European countries [599]. A 17-year analysis of Yellow Card reports made to the NIMH database found only 60 reports for herbal remedies [586]. The findings also align with those of database studies in other parts of the world. An analysis of reports made to the Singapore pharmacovigilance database in the period 1998-2012 [600] reported an incidence of 3.8% for all CAM products, and 0.2% for CAMs among subjects aged 0-20 years. The very low population-based reporting ratio (PBRR) of 1.193 reports per year per million UK inhabitants (rym) found for all CAM-related ADRs in this study is supported by the finding of a high degree of non-report of ADRs among British CAM users [559]. The non-sustained improvement in ADR reports for CAM products noted in this analysis has also been reported for other PV efforts for such products [601]; and emphasizes the need for active PV initiatives for these products [602]. Recent SRs have highlighted the importance of using combined or multiple strategies to achieve this end [603, 604]. As international long-term data and experience have shown PBRR values greater than 300 rym to be reliable for signal detection [597], the much lower PBRR found for CAMs in this study indicates the difficulty of relying on the YCS data for signal detection for CAMs, as has been used in other national databases [605]. It has, however, been suggested that the few number of CAM-related ADRs in the YCS could make it relatively easy to identify adverse effects of concern by examining individual reports without waiting for statistical signal detection [602].

ADR reports from female subjects and middle-aged adults were found to make up the largest proportions of the CAM-related reports. This demographic pattern differs slightly from that seen for conventional medicines. While a higher association of the female sex with ADRs has been generally noted [584, 606, 607], a higher proportion of older adult-associated ADRs has been seen for conventional medicines [582, 606]. The over-representation of CAM-related ADR

reports for middle-aged adults and women found in the current study is, however, in line with the demographic pattern reported for CAM use [608]. This suggests that the incidence of CAM-related ADRs generally follows observed usage patterns for CAM. The over-representation of infant males in the ADR reports aligns with most ADR report studies for that age group [609–611]. Possible reasons for this finding could be related to those for the generally higher mortality seen for male infants [612].

The finding of skin rash (and other SSD ADRs) as the most common ADRs found for paediatric subjects, while already reported for CAMs [586, 613], is not in any way limited to them [403, 589, 614, 615]. This has been suggested to be due to higher skin sensitivity in children [589]. Nervous system-related ADRs have also been reported as very common [610]. The proportion of serious ADRs found in this study is similar to or less than the finding in many other paediatric studies [610, 611, 616, 617].

Because a high safety profile is usually attributed to homeopathic products due to their long-standing use and their use of ultra-dilutions of the "active" substances in the preparations [618–620], the finding of a relatively high serious ADR potential for homeopathic medicinal products in this study seems surprising. However, a recent SR of case reports and series has highlighted the potential of these products for sometimes serious ADRs [621]. Also, suggestions have been made as to the possible scientific bases for such untoward effects [622]. But objections have been raised as to the true homeopathic nature of some of the products implicated in such reports [623]. Also, some of the ADRs reported have been termed "homeopathic aggravations" that are ultimately helpful to the patient, rather than adverse effects [624, 625]. From a patient safety perspective, however, the findings of this study emphasize the need for more sensitive methods of detecting harmful substances where they exist in such products [626, 627]. They also stress the need for stricter regulation of the products, as well as more public education and reorientation as to the safety concerns associated with them [628, 629]. These policies are particularly important for Scotland in view of the high level of prescription of such products in Scottish GP practices, particularly for children [630].

The high association of herb-drug combinations with ADRs seen in this study emphasizes the importance of the contribution of herb-drug interactions to PV, as has been well noted in literature [574, 631]. The value of including detailed case narratives in ADR reports in improving the detection of such drug interactions has also been noted [632]. However, the finding in this study of higher incidences of non-resolved and serious ADRs associated with single CAM products, as well as herbal remedies, herbal products and poly-herbal formulations, suggests the greater relevance of CAM product regulation with respect to enhancing CAM safety [15, 573, 633]. Apart from ensuring proper and safe marketing strategies, consumer access and mode of use of these products [634], such oversight would also ensure the use of proper methods of preparation for specific product types, which has been recognised as another key safety concern [635].

Soybean oil, which has been in medical use since 1962 as a source of omega-3 and -6 fatty acids in parenteral nutrition [636], was the product most associated with fatal ADR reports in this analysis. Despite its many nutritional benefits and medicinal uses, it has been implicated in various adverse effects. While its topical use as an insect-repellent has been associated with aspiration pneumonia [637], its parenteral use, either as a nutritional supplement or as a component of the anaesthetic, propofol, has been associated with allergic reactions [638, 639], particularly in young children [640]. Its allergenic potential has also been emphasized in a Spanish enquiry into potential hypersensitivity due to food or food additive content of medicinal products [641]. Although the updated guidelines on reducing the risk of anaphylaxis during anesthesia published by the European Network for Drug Allergy (ENDA) in 2011 does not preclude its use in food allergy to egg or even soy products [642], there have been a number of reported cases of soybean oil-associated hypersensitivity reactions in children [643–645].

3.4.3 Limitations of the study

The chief limitation of high degree of under-reporting that is associated with spontaneous reporting schemes also applies to this study. Moreover, as the problem of high non-report of ADRs has been especially noted for CAMs [206, 559], it is likely that the ADR report pool used for this analysis is not representative of CAM-related ADRs in the UK population. More importantly, such under-reporting could have accounted for the relatively low proportion of ADR reports from such practice-based CAM products as homeopathic remedies and the essential oils used in aromatherapy. This is particularly relevant for homeopathic remedies, as some of the associated adverse outcomes might not have been reported due to their perception as "homeopathic aggravations". These points emphasize the need not only for active pharmacovigilance initiatives, but also for proper public enlightenment as to the importance of reporting every adverse outcome experienced irrespective of how it may be perceived. Also, the high degree of missing data found in the database, while not particularly specific for CAMs [589], none-the-less reduces the reliability of the findings of this study. Finally, just as some of the natural health products included in this analysis may not ultimately qualify to be classified as CAM, having now become fully integrated into conventional medicine, so also the framework used in classifying products into respective CAM types is far from fool-proof; as certain products may fall into more than one specific CAM type depending on the formulation.

3.5 Conclusion

3.5 Conclusion There is a very low frequency of ADR reports in the YCS for CAM products in general, and particularly in children aged < 18 years. This low frequency of reports is a

huge challenge for effective database-oriented pharmacovigilance of complementary medicines in the UK, particularly for paediatric subjects. It points to the need to apply more active pharmacovigilance approaches for CAM products, thus justifying the inclusion of a primary study of the outcomes of paediatric CAM use as the third aspect of this doctoral research, as will be reported in the next chapter of the thesis. Because of the limitation of high degree of under-reporting that is common with national PV databases, which was further complicated in the current study by the high non-report of adverse outcomes associated with CAMs, the findings of the next phase of the research are expected to help put into proper context the findings of the exploratory analysis of YCS data reported in this chapter. Based on the present findings, however, it can be surmised that CAM-related paediatric ADRs are few and short-lasting, and of low severity and fatality. Although the combined used of herbs with conventional medicines has been seen to be associated with high ADR reports, herbal remedies containing 1-3 herbs, homeopathic remedies and dietary supplements have been found to be much more associated with serious ADRs, with the dietary supplement, soybean oil, being most associated with fatal outcomes. This suggests that the type of CAM product used should be a far more important safety concern than the number or nature of the products used along with them. Thus, while the need to minimise herb-drug and herb-herb interactions cannot be ruled out, these findings emphasize the greater relevance of the proper regulation of CAM products, and justifies the stricter guidelines for CAM product registration introduced by the European Medicines Agency.

Chapter 4

The Use of Complementary & Alternative Medicine Among Children in Aberdeen -A Cross-Sectional Survey

4.1 Introduction

4.1.1 Background to the study

The findings of the systematic review reported in Chapter 2 highlight the paucity of paediatric CAM use research in the UK, and particularly in Scotland. This is probably related to the relatively lower prevalence of CAM use in the country relative to other economically advanced countries in Europe and North America [555]. Global prevalence has been reported to be about 20-40% among healthy children seen in outpatient paediatric clinics, and over 50% in children with chronic, recurrent and incurable conditions [482]. However, a recent SR of surveys (published between 2000 and September 2011) that estimated the prevalence of CAM use among UK paediatric patients reported an average one-year prevalence of 34% and an average lifetime prevalence of 42% [395]. These low prevalence values contrast markedly with data reported for other European countries (Germany, Switzerland, Denmark and Ireland) in another recent SR of studies published from 1945 to July, 2013 [646]. Strikingly, however, these UK data were drawn largely [395] or wholly [646] from England, with Scotland contributing only two studies in all, published in 2007 [351] and 2008 [352], respectively. Although another Scottish paediatric CAM use study was published recently that reported the use of CAM among cancer patients in Edinburgh [647],

the need for more paediatric CAM use studies in Scotland, especially in the general population, is clear. The importance of filling this gap is thus the main inspiration for the work reported in this chapter. However, as in previous chapters, the main objective of this facet of the research transcends merely obtaining an estimate of the prevalence of paediatric CAM use in Scotland. It extends to ascertaining the outcomes associated with such paediatric CAM use in terms of user-perceived effectiveness and safety; as well as investigating the attitudinal inclinations of the Scottish population towards such therapies and research on them.

As another finding of the SR reported in chapter 2 is the observed tendency for non-rigorous research, resulting in low methodological quality, this chapter will describe the special efforts taken in the design of this aspect of the research to overcome this limitation. While, due to the preliminary nature of paediatric CAM research in Scotland, and in view of the limitations of doctoral research, a cross-sectional design was chosen for the research, care was taken to ensure that it was analytical, and not merely descriptive. In addition to ensuring greater external validity and generalisability by employing multi-centre participant recruitment, the data collection instrument was validated (face and content validity) by pre-testing and cognitive interviewing of purposive samples of the target population in order to ensure the validity of the resulting findings. Also, inferential statistical analyses were conducted on the findings, including not only point and interval estimates for the population, but also bivariate logistic regression to identify potential predictors of CAM use and associated outcomes. Finally, effort was made to emphasize certain aspects of paediatric CAM use and its research that were considered particularly relevant to the main objectives of the current research, but had been overlooked or de-emphasized in previous studies. Chief among these aspects is the prevalence and nature of reported adverse effects associated with paediatric CAM use, which had been found (in the SR in chapter 2) to have been over-looked by more than 60% of included studies. The exploratory analysis of the MHRA YCS database presented in chapter 3 also pointed to a very low frequency of ADR reports for natural health products in general, and particularly in children aged < 18 years, suggesting that CAM-associated paediatric ADRs are few, and of low severity and fatality. The findings of these secondary studies emphasize the need for their verification in a suitable primary study, making this matter an important objective of the research reported in this chapter. Also, the SR in chapter 2 highlighted a tendency towards confirmation bias due to a low incidence (46%) of valid conclusions congruent with the outcomes reported by study participants, and its ethical implications, particularly in the current patient-centred healthcare dispensation. Effort was therefore made in the study herein reported to accord the opinions of the participants their due consideration so as to ensure a valid summary of the findings that would lead to equally valid conclusions and POEM-based recommendations. Another source of weakness observed among included studies in the SR is the high use of proxy report of outcomes. While, as a result of ethical factors, it was not possible to avoid this source of weakness by surveying paediatric subjects directly, the participants were encouraged to complete the relevant sections of the survey

in consultation with the children affected. Although it was hoped to result in a joint report of the outcomes of the CAM modalities used, it is not clear if this was actually achieved in all cases.

In all, this chapter reports the detailed procedures, findings, discussion and conclusions of a novel and up-to-date analytical cross-sectional survey of paediatric CAM use in the Aberdeen metropolitan area of North-east Scotland.

4.1.2 Survey setting

The survey was carried out within Aberdeen metropolitan area. This refers to Aberdeen city and the surrounding suburbs within its commuter belt to which it is related socio-economically. Although no clear-cut boundaries were set for the locus of the study, as Aberdeen is the main urban centre for NE Scotland geo-political region, the study participants were broadly drawn from across this region in the degree to which they relate with Aberdeen city. Geographically, the NE Scotland region ranges from Aberdeenshire East and Banffshire & Buchan coast on the north through Aberdeen metropolis and West Aberdeenshire to Angus and Dundee city on the south. The region accounts for 32 postcodes in the Scottish postcode division. Understandably, as the study was not intended as a survey of the entire North-east Scotland region, a greater part of participant recruitment was conducted within Aberdeen metropolis.

4.1.3 Specific aims and objectives

As detailed in chapter 1, the specific aims of this aspect of this research are summarised in the following research questions:

1. What is the nature and demography of the use and user-reported outcomes of paediatric CAM products and practices in the Aberdeen area with respect to user-perceived effectiveness and safety?
2. What implications do the findings have for research and/or health policy and planning in Scotland?

In order to properly answer these questions, the following specific objectives were identified:

1. to develop a suitable and validated user-reported outcomes measures instrument for the study;
2. to carry out a survey on paediatric CAM use in Aberdeen metropolitan area using the pre-tested instruments;

3. to carry out descriptive and inferential statistical, as well as regression, analyses of the data obtained in order to:

   (a.) determine the extent and nature of paediatric CAM use/non-use in the Aberdeen metropolitan area;

   (b.) determine the dependent and independent factors associated with paediatric CAM use/non-use in the target population;

   (c.) determine user-perceived effectiveness and safety outcomes of paediatric CAM use in the target groups, and their associated dependent and independent factors;

   (d.) identify the attitudes of the parents within the target area towards paediatric CAM use, and future research on it;

   (e.) generate data on paediatric CAM use in the target area that can be compared with that reported for similar population groups in other aspects of this research;

4. to draw out conclusions and recommendations from the findings of the study.

4.2 Methods

4.2.1 Research governance

To ensure that the study would be carried out to the highest ethical standards and in conformity with Robert Gordon University's research ethics committee, approval for the study was sought from the Robert Gordon University School of Pharmacy & Life Sciences Ethics committee. As the study was to be conducted in the general population, and would not involve any NHS patients, it was not considered necessary to seek approval from the North of Scotland Research Ethics Committee. As public schools/crèches and other establishments were to be used for participant recruitment, permission was also sought from the relevant officers in the Aberdeen City Council Education Board, as well as from the chief administrators of all establishments used for (participant recruitment for) the survey. Additionally, various specific measures were instituted in the course of questionnaire design and administration, as well as data entry and analysis, to respect the freewill and social desirability of the participants, and to protect, safeguard and preserve their respective identities.

4.2.2 Development and validation of survey instrument

From an overview of some of the paediatric CAM use studies identified in the course of the SR, a list of items was gathered to develop a questionnaire for the study. Additional items were

also included to the pool of items based on the peculiarities of the study setting, and the list was re-organised into a 10 paged, 46-item draft questionnaire divided into 3 sections (Appendix 4.1). Following internal review by members of the research team, the draft questionnaire was revised to yield an 8 paged, 32-item version. This was then used to develop a user-adaptive online questionnaire using the SNAP® survey software (Version 10). In order to make it user-adaptive, in addition to a survey feedback section, a number of mandatory routing questions were incorporated into the original list of questions, resulting in a total of 61 questions in all. The developed questionnaire was thereafter uploaded to the RGU web server, and a unique clickable link (http://www2.rgu.ac.uk/Pharmacy/survey/cam/pilot) was generated for it to facilitate online access by participants. The first version comprised five sections organised as follows:

(i) A cover page introducing the study to the potential participant, and defining CAM, with clickable links to lists of common CAM products and practices as a memory aid; and finally requesting the potential participant to opt (via their response to a screening question) whether or not to participate in the study (1 question);

(ii) Section 1 requesting information about the participant (9-11 demographic questions, depending on adaptation);

(iii) Section 2 requesting information on CAM use in own children, with clickable links to lists of common CAM products and practices as a memory aid (4-20 questions, depending on adaptation);

(iv) Section 3 requesting information on the participant's own use of CAM, and his/her general views on CAM use and research (9-13 questions depending on adaptation); and

(v) A Survey Feedback Questionnaire requesting specific feedback on the questionnaire as a whole, as well as the preferred mode of access to it (i. e. online vs. paper), and suggestions on specific sections of the questionnaire (8-16 questions depending on adaptation).

The uploaded questionnaire was thereafter validated by two sequential phases of focus group pre-tests, which were held in May and October 2013. After each phase, the questionnaire was revised in line with the feedback received, so as to improve the eventual outcome of the survey. The focus groups involved purposive samples of parents drawn from two separate settings within Aberdeen city centre; and were aimed at verifying the comprehensibility and acceptability of the questionnaire in a bid to ascertain its face and content validity. As explained in chapter 1, because the objective of the study was not to measure specific health status in patients with particular health conditions, detailed psychometric analysis was not required.

Although both focus groups sought to verify the quality of the questionnaire in the two aspects described above, the first was more elaborate, and focused much more on the comprehensibility

of the survey, while the second laid greater emphasis on its general acceptability by participants. Each focus group was preceded by online completion of the questionnaire by participants, after receiving the link to the survey from the student in an invitation mail. In the first case, although ten parents were mailed the online link to the survey and invited to take part in the focus group after completing the survey, two opted out of the survey through the screening question on the cover page. While the remaining eight went on to complete the survey, two of them finally opted out of participating in the focus group for reasons of convenience, leaving only six parents –two fathers and four mothers- to participate in the session. The questions asked during the focus group discussion sought to determine the initial impressions and opinions of the participants on each section of the questionnaire, as well as how each participant understood and then responded to the questions. In this sense, the focus group discussion was akin to a group cognitive interview aimed at identifying possible socio-cultural, linguistic or other related barriers to proper comprehension and completion of the survey by parents. Then suggestions were sought on how such could be overcome. The hour-long, audio-recorded session was facilitated by the student using a topic guide he developed specifically for the study (see Appendix viii). A member of the supervisory team was also in attendance, and acted as time keeper/recorder. Afterwards all factors highlighted were summarised by the student for discussion by the research team. The survey feedback questionnaire data generated by the eight pre-test survey participants were also summarised for consideration by the team. After due consideration, the points on which there was significant agreement were taken on board in the revision of the questionnaire ahead of the next phases of the research. The revised version was eleven questions shorter than the previous one. While it had a much briefer cover page that still contained the links to the list of examples of CAM types as well as the preliminary screening question giving participants an option on taking the survey, it had no survey feedback questionnaire at the end. Also while the previous questionnaire focused on school-aged children schooling solely within Aberdeen city, the revised version contained additional questions that would be relevant to parents with children of all age groups in Aberdeen and Aberdeenshire.

4.2.3 Pilot and secondary validation of survey instrument

A pilot study of the revised survey instrument was conducted in two schools (one primary and one secondary) located in one of the Aberdeen Northern suburbs between the months of June and September, 2013. Firstly, early in the month of June, a brief mail to parents containing the unique link to the revised survey (http://www2.rgu.ac.uk/Pharmacy/survey/cam/pilot2/index.htm) was sent to each school administrator for circulation to parents. Each was requested to inform the parents of the coming survey before circulation so as to avoid a perception of cold-calling; and also to utilise the very same mediums of communication they normally used. A reminder mail was also sent to each administrator for circulation a fortnight later. Following

a zero response from the parents in the schools by the end of the school session in the first week of July, further interactions were made with the school administrations with a view to understanding the possible causes. Although the feedback received indicated that a technical failure had complicated survey administration in one of the schools, the general suggestion was that the nonresponse was not unrelated to the general apathy to school-related activities among schoolchildren and their parents towards the end of a school year and the approaching summer vacation. The administrators, therefore, suggested that the pilot be repeated in August 2013, early in the coming school year.

The pilot survey was re-launched in the schools on August 22 (primary school) and 27 (secondary school) for a 4-week period, with reminder mails recirculated at fortnightly intervals. In the first case, the school administrator had the student's invitation mail containing the survey link posted on their school blog, preceded by a brief introduction from him. In the second case, the survey invitation mail was circulated to all parents through the contact e-mail addresses they provided the school. At the end of the survey period, only seven responses had been received –solely from the first school, and all within the first two days of the blog being initially uploaded. After a consideration of the very poor response by the research team, it was considered necessary to convene another focus group of parents of schoolchildren to re-evaluate the instrument with the specific objective of determining whether the presence or absence of any particular features in the instrument could have contributed to the poor showing observed. This led to the second validation phase of the instrument in October, 2013.

All the seven parents/guardians invited to participate in this second pre-test and focus group fully participated. Unlike the first focus group session, this session focused much more on validating the general acceptability and user-friendliness of the survey, especially in terms of identifying possible barriers to participant engagement. Moreover, since, unlike in the first session, all but one of the participants had used CAM for their children, the session was further used to explore whether any key issues generally considered important by CAM users had been overlooked in the instrument. Also revisited was the question of whether the online method of parental access to the survey was considered sufficient to achieve a sufficient reach of participants within the target area. Suggestions were also received on possible ways of improving the appeal of the questionnaire to participants as well as its reach. As in the first case, the focus group discussion was facilitated by the student using a topic guide also developed specifically for the study (Appendix ix); a member of the supervisory team was also in attendance. The session lasted 30 minutes.

Based on the inputs received, additional revisions were made to the questionnaire, and final preparations were made for launching the main survey. The major revisions effected on the previous version were the removal of the screening question at the bottom of the cover page, the inclusion of colourful pictures of people using various CAM products and practices at strategic parts of the survey, and ten additional questions. The new questions aimed to gather information

on the specific medium of online access to the survey and also relevant details of previous CAM use by parents of adult children. However, to cover all the possible hindrances to survey engagement, it was also agreed that a paper version of the questionnaire should be developed as an alternative access mode. While the two versions were essentially similar in content and general outlook, the paper version was significantly shorter than the online one (39 questions instead of 60 questions). However, this was mainly due to the absence of the mandatory routing or linked questions that were necessary in the online survey to make it user-adaptable to a more diverse parent group. Also, while both versions contained similar free-text tabular sections for entry of the specific CAM types used, the paper version also contained a much less detailed list of CAM types in a tick box format, rather than the links to the detailed list of common CAM types included in the online version. In addition, the paper version also contained a question aimed at finding out participant preference on mode of survey access (online vs. paper). A copy of the paper-based version is provided in Appendix x.

4.2.4 Main Survey

The main survey was conducted in two sequential phases over five months, between November 2013 and March 2014. A number of points were taken into consideration to determine the minimum sample size required for the study to be statistically representative of the child population in Aberdeen. According to the 2011 population census, the number of primary and secondary school children in Aberdeen City was 21, 204 (11, 955 primary and 9, 249 secondary). Also, according to the Infact® database of the Scottish Funding Council and the Higher Education Statistics Agency, the numbers of undergraduate students aged up to 18 years enrolled in the 2009/10 session in the three HEIs in Aberdeen were 11,420 (7,690 for Aberdeen College, 2,185 for Aberdeen University, and 1,545 for Robert Gordon University). These data were used to determine the minimum sample size required using the formula: n= $[Z^2 * P(1-P)]/D^2$ (21). For this study, the z statistic of the 95% confidence level chosen was 1.96; the prevalence level of CAM use, P, (or response distribution between paediatric CAM users and non-users) was assumed as 50% (or 0.5); and a ±5% (or 0.05) degree of precision (or margin of error), D, was allowed. Based on these assumptions, the minimum sample of children required for a statistically representative study of the Aberdeen area was calculated to be 378. Assuming one child per parent and a 30% response rate for the study, it was determined that at least 1,260 parents would need to be surveyed in order to be certain of recruiting the required minimum sample. As a dual approach was used for recruitment, this figure was shared equally between the two survey modes; leading to 600 copies of the paper-based questionnaire being produced for distribution. However, considering the low response rates often associated with web surveys (22-24), no restriction in the number of potential participants approached was set for the online survey.

The online survey was launched on November 1, 2013 and was live for the next two months. It was hosted on the RGU web server; and, in view of the poor response experienced following a localised distribution during the pilot phase, the web link generated for it (http://www.rgu.ac.uk/cam/parent) was distributed to the public through a variety of media outlets. These included: the RGU home page; mails to institutional e-mails of staff in Aberdeen College, Aberdeen University and RGU; a radio interview of the student about the study on the Aberdeen Radio Station Original 106 on November 12, 2013; NetMums NE Scotland (http://www.netmums.com/ne-scotland); its own Facebook page (https://www.facebook.com/groups/CAM.RGU/?fref=ts); twitter messages; the Aberdeen Facebook page with 21, 830 members as at November 13, 2013 (https://www.facebook.com/pages/Aberdeen/47236254126); a press release by the RGU Communications Unit resulting in news articles on local dailies across NE Scotland (the Aberdeen Evening Express of November 14, 2013; the Fraserburgh Herald and Inverurie Herald of November 16, 2013; and the Peterhead Buchan Observer of November 20, 2013); and finally a friends-of-friends mail approach through a network of friends of the student and members of the research team residing in different parts of Aberdeen. In each case, periodic reminders were provided where appropriate up until the end of December, 2013. All completed online surveys were transmitted via the internet to the student's e-mail box upon submission, enabling the tracking of submissions received over the survey period.

The paper-based survey was conducted between January 20, 2014 and March 28, 2014. A variety of locations within Aberdeen were used for recruitment. However, although participant recruitment was largely based in Aberdeen city, because participants were recruited from their places of work without prejudice to their area of residence, in addition to their children's schools/crèches, it was possible to reach a wider population residing beyond the city. For participant recruitment at work places, the student obtained permission to stand at specific locations within the premises, especially close to the entrances, and handed out questionnaires to consenting parents as they passed by. Participants had the option of completing and returning the questionnaire immediately on the spot, or doing so privately and returning it later completion via collection boxes left at designated points for that purpose. For participant recruitment through schools, the student provided the school administrators with as many copies of the questionnaire as they requested for, which they then handed out to their wards or their parents; and also collected them back after completion. In all eight different centres -three schools, three work places and two social centres- located in different parts of Aberdeen metropolis were surveyed.

4.2.5 Data entry, validation and analysis

At the end of the survey, data resulting from responses to the online survey were automatically imported via SNAP® into SPSS worksheets. After formatting the database to ensure compatibility

with the paper version, the student manually entered the responses from the paper-based survey in line with the pattern pre-set by SNAP®, resulting in a comprehensive database for the study. After data cleaning, the quality of data entry was validated by one of the supervisors through a quality control check on a sample of manually entered paper-based surveys. Afterwards, additional columns were inserted into the database to generate derived data from the dataset. These resulted in the generation of additional data such as geographical area, urban-rural classification, parental CAM use profile, parent-child CAM use similarity, and survey completion status among others. CAM use in children was measured in terms of lifetime (or ever) use and chronological use (Always/Current/Previous/Never); while personal CAM use by parents was measured solely as lifetime CAM use. Based on the outputs of frequency analyses and other descriptive statistical analyses of key variables in the data, further columns were inserted to further group key variables into dichotomous categories so as to enable bivariate correlation as well as binary logistic regression as appropriate. Although children of all ages were included in the study, the bulk of statistical analysis was focused on paediatric subjects. All analyses were carried out in IBM® SPSS Statistical package Version 21 or Minitab® 16, as appropriate. Inference was made at 95% confidence intervals, with significance level of $P \leq 0.05$.

4.3 Results

The results of the various steps taken in the instrument development and validation, main survey and survey data entry and analyses are presented in figures 4.1 to 4.13 and tables 4.1 to 4.19. While a general summary of the findings will be presented in section 4 as part of the discussion of results, a brief running textual summary of the data presented in each table or figure will be provided along with their respective tables or figures all through the results section.

4.3.1 Ethical Requirements

Approval for the study was obtained from the Robert Gordon University School of Pharmacy & Life Sciences Ethics committee (Appendix xi). Permission for the study was also obtained from the Head of Schools and Education Establishments at Aberdeen City Council, as well as from the chief administrator of each of the establishments in which (participant recruitment for) the survey was conducted. These included the administrative heads of Treehouse early care centre; Rocking horse nursery; the Public Relations, IT, and Communications departments for RGU, University of Aberdeen and North East Scotland College; Forehill school; Oldmachar Academy; the Junction church; and NetMums NE Scotland. In order to preserve and protect freewill in line with ethical requirements, each participant was provided with detailed information about the study before being invited to take part, such that participation implied informed

consent. Out of respect for the privacy of participants, not only was the survey administered anonymously, but also questions targeting specific personal information relating to social lifestyle and health condition were avoided. The standard operating procedures of the School of Pharmacy & Life Sciences for data collection were followed. Completed questionnaires were stored in locked cabinets upon return. The responses obtained were stored in SPSS file format in the student's password-protected university computer; and were processed and used only for the purposes of the study.

4.3.2 Development and validation of survey instrument

An overview of the outcomes of the questionnaire development and validation process is outlined in figure 4.1. The main areas of feedback received and taken on after the first and second pre-test focus group discussions are outlined in tables 4.1, 4.2 and 4.3, respectively; while a comparative summary of the online and paper versions of the questionnaire used for the main survey is presented in table 4.4.

Of the 23 comments/observations made during the first pre-test focus group discussion, only 5 (21.7%) were outrightly rejected, while the rest were accepted wholly or in part. The participants had the most agreement on the facts that the survey took an acceptable time to complete (100%); as well as in their preference for online mode (87.5%; 100%). While various aspects of the questionnaire had to be revised based on inputs from participants, the questions that generated the most comments, and thus required the most revision, were the compound grid format questions on specific CAM use and its associated outcomes. While the compound grid format was retained, both the introductory instructions and the layout were significantly reviewed resulting in no further complaints on it in the second focus group discussion. While the second focus group discussion re-emphasized the high acceptability of the online mode, it also highlighted the potential advantages of the traditional paper-based approach in certain settings, as well as the value of a multi-pronged, "all of the above" approach to participant recruitment in the online mode, with a view to including as many parents as possible who eventually came across it. Although the resulting paper version of the survey was considerably shorter than the online version, it covered an essentially similar ambit as its parent version. The sole differences between the two final versions used in the main survey were the absence in the paper version of the question on willingness of CAM users to participate in further CAM research, and the absence in the online version of the question on survey mode preference among participants in general.

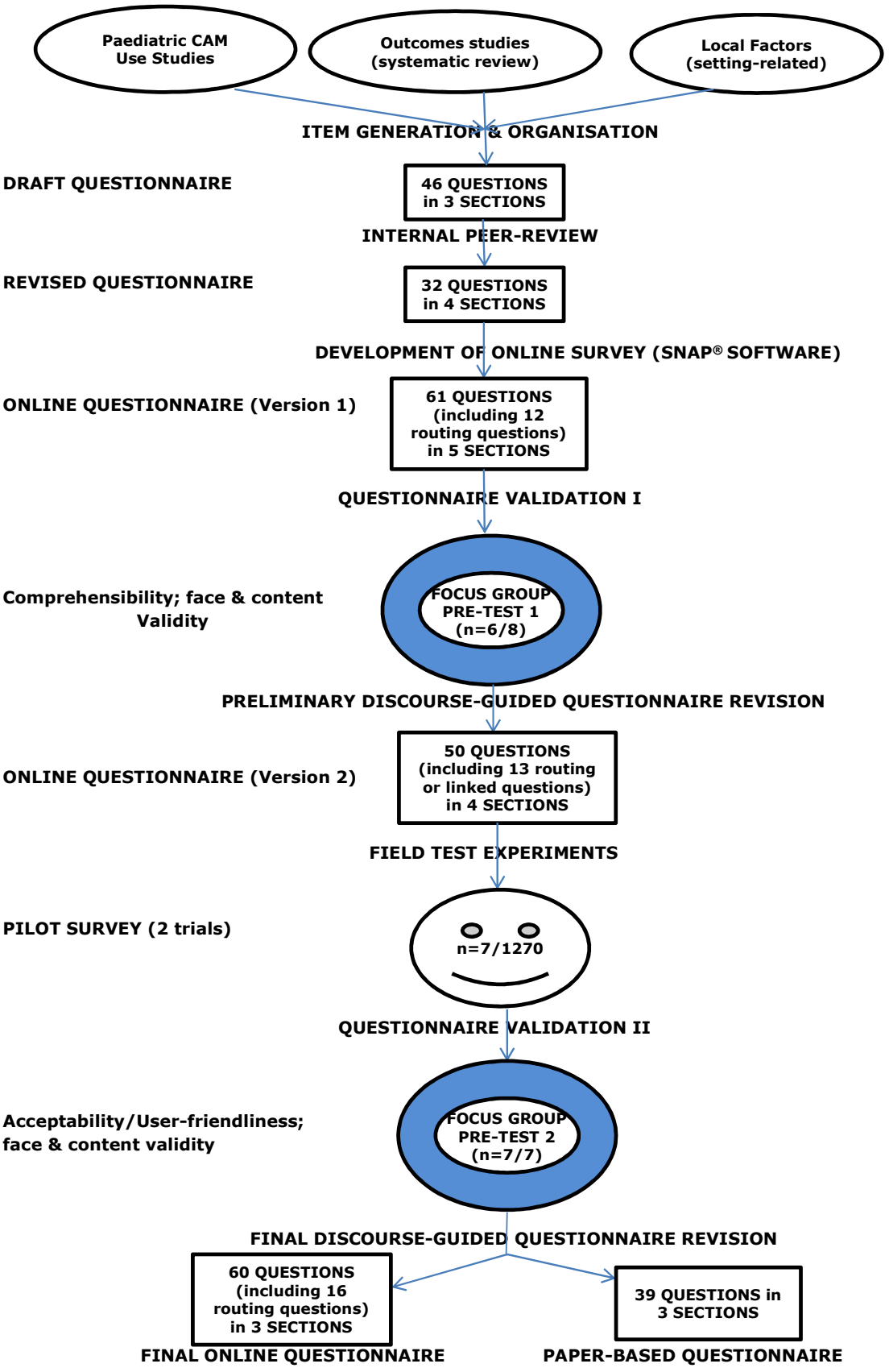


FIGURE 4.1: Survey development & validation process

TABLE 4.1: Summary of comments, proposals and decisions from first pre-test survey focus group discussion

Comment/Observation (Number of commentators; n/6)	Proposed solution	Decision taken
A. General impressions/Introductory (cover) letter		
1. A number of strange and difficult to pronounce terms –like "Anthroposorphic", "user-driven", "homeopathic medicines" (3/6)	Use words generally easy to understand; avoid jargon on cover page	Accepted
2. Pictures on the cover page –attractive (4/6)	Should be retained	Accepted
3. Too much text included; "too wordy" (3/6)	Reduce text; avoid using **bold** characters	Accepted: revised from a 356-word letter format to a 156-word free format
4. Links to the list of common CAM products and practices –helpful and informative (3/6)	Retain; but make headings more colourful	Accepted
5. 2 separate links to the lists for CAM types; also list for CAM products more detailed than that for CAM practices –a bit confusing (1/6)	Harmonize and merge into a single list	Rejected: list would be too long
6. Not be keen on completing it if seen for the first time among mails from child's school (2/6)	Avoid "cold-calling": send an introductory mail first	Accepted
7. Not be inclined to complete it if paper-based; prefer mail survey if introductory mail is short (1/6)	None made	Retain online mode
8. Online format preferred –much shorter, as user-adaptive (1/6)	Retain current mode	Accepted
9. Not interested in surveys generally (nor at all in CAM); so prefer online ones: easier to delete (1/6)	None made	Still retain online mode
10. General public apathy towards surveys (2/6)	Conduct survey in settings like CAM shops/centres, etc.	Rejected: would skew the findings
11. Using target survey area as just Aberdeen city is a bit too restrictive: 5/6 participants live in Aberdeenshire! (3/6)	None given	Broaden survey area to Aberdeen metropolitan area
B. SECTION ONE: Parent demographics		
1. Why ask about Marital status? (1/6)	Provide an opt out option –like: Prefer not to answer	Rejected; but make question non-mandatory
2. Confusion about some ethnic origin categories –like: White Scottish vs. Other White British vs. Other White –a bit confusing (2/6)	Use the standard categories used for ethnicity	Accepted; categories modified
3. Insufficient free text space provided to further describe "other White British" ethnic category (1/6)	Use "White British" only	Rejected: the "White Scottish" are chief target population
C. SECTION TWO: CAM use in children		
1. How "helpful and discomforting" CAM was? –a bit confusing; and question couldn't be skipped either –temptation to discontinue at that point (3/6)	Break into 2 separate questions to separate the "positive" effects of CAM from the "negative" ones	Instruction modified for clarity; but question format retained
2. Used "ifurther down in the past" –confusing; also that aspect was not rated (2/6)	Correct typo; modify expression and formatting	Accepted
3. Age by next birthday? –confusing (2/6)	"Age in years" or just "Age"	Accepted
4. Use of grid table format a bit confusing: did not know there were more than one questions to be answered (2/6)	None given	Instruction modified for clarity
5. Wrong sentence structure: "no more necessary to use CAM" (1/6)	Use correct structure	Accepted
D. SECTION THREE: Personal CAM use & attitudes towards CAM		
1. "CAM should be used in adults, but not in children"? –confusing, presumptuous, misleading (1/6)	Reword or ask as separate questions	Reworded to focus on children
2. "CAM should not be used together with conventional medicines" –confusing, as some could, while others wouldn't (1/6)	None given	All attitudinal questions to be prefaced by: "I think/believe"
3. "CAM can cause harmful side effects in children" –One's answer to that would depend on his background or knowledge level, wouldn't it? (1/6)	Include an "Don't know" or "Can't answer" option	"Don't know" option added
4. Personal lifetime use of CAM for parents versus only last 12 months as for children	Also request only 12-month CAM use for parents as well so as to generate comparable submissions	Rejected: the format is needed to answer research question

TABLE 4.2: Summary of responses from pre-test survey feedback questionnaire

Question	Responses (Frequency, %)	Details	Further explanations
1.Would you say the survey took you an acceptable time to complete	Yes (8, 100 %)		
2.About how long did it take you to complete the survey?	< 5 minutes (4, 50 %) 5-10 minutes (4, 50 %)		
3.Were there any questions you found in any way difficult to answer?	Yes (4, 50 %)	(i) Question on ethnicity	• Explanation required to proceed but could not explain as there was a text limit on the box provided
		(ii) Questions on CAM use and associated outcomes	• Knowing how many boxes needed to be ticked, and the line "how helpful and discomforting" confused me • Not sure if part of the question related to previous use of CAM • Q asks should CAM be used in children, but doesn't allow you to respond that CAM shouldn't be used
		(iii) Questions on sharing discomforting experiences related to CAM with others	• Not sure what this question was looking for
		(iv) Questions on personal views and opinions on CAM use in general	• Some errors in the text -still understandable - some ambiguous
	No (4, 50 %)	-	-
4.Were there any questions you found inappropriate or think to be unnecessary?	Yes (2, 25 %)	(i) Question on marital status	• I do not see how marital status is relevant to the study being undertaken
		(ii) Questions on CAM use and associated outcomes	• Don't think you need to ask is CAM more effective than conventional meds
	No (6, 75 %)	-	
5.Is there any other question or additional information you think should be added to the survey?	Yes (2, 25 %)	(i) Previous CAM use examples? Or do you just want to research the last 12 months?	
		(ii) What are the factors that influenced choice of CAMs in children? i.e. recommendation/effectiveness/	
	No (2, 25 %)	-	
	Don't know (4, 50 %)	-	
6.How user-friendly did you find the survey?	Very user friendly (7, 87.5 %)	-	
	Just OK (1. 12.5 %)	-	
7.Does it make a difference to you by which mode (either paper or on-line) this survey is presented to you for completion?	Yes, it does (7, 87.5 %)	Preference: Online mode (7, 100 %)	
	Not sure it does (1, 12.5 %)	-	
8.Do you have any comments to make on the questionnaire layout or structure -or any other aspect?	Yes (4, 50 %)	(i) 2 questions asked on the same line -shaded and unshaded boxes– think this could be better presented	
		(ii) Generally tidy up some minor text errors and review questions to remove ambiguity	
		(iii) My children don't attend school in Aberdeen	
		(iv) The question relating to children ages etc. is laid out poorly (insufficient space for full comment)	
	No (4, 50 %)	-	

TABLE 4.3: Summary of comments, proposals and decisions from second pre-test survey focus group discussion

	Comment/Observation (Number of commentators; n/7)	Proposed solution	Decision taken
1.	Official/institutional e-mails may not be a convenient medium of access to survey (3/7)	Consider using more direct routes like personal e-mails or institutional Blackboards (for students)	Accepted: an "all of the above" approach to be used; participant preference to be tested in main survey
2.	Online mode preferred over paper (7/7); but "paper version easier to distribute within enclosed settings like schools" (1/7)	Retain online mode; but don't rule out paper mode for enclosed settings	Paper mode to be considered for main survey
3.	Invitational e-mail title not really inviting enough, even for CAM enthusiasts (4/7); so high likelihood of immediately deleting mail without opening unless expecting it (1/7)	None made	Revise e-mail title; also, paper mode to be considered
4.	Local newspapers could be a good means of spreading survey information to older population (1/7)	None made	To be considered; survey to be broadened to cover older parents: enquire after previous use in adult children
5.	Survey posting on Facebook could help spread it quickly through "liking" (5/7)	None made	An "all of the above" approach to be used; participant preference to be tested in main survey
6.	Did not read the cover page –a bit bland, not really attention-grabbing (5/7)	Put in more pictures –especially of people using various CAM therapies	Accepted
7.	Links to list of CAM types not clicked (5/7)	Better to make the lists page compulsory	Accepted; but for the Paper-based version only
8.	Survey did not provide fresh information on CAM therapies (5/7) –except through lists of therapies (1/7)	None made	To be tested in main survey after inclusion of pictures of CAM types
9.	Lists contained too many therapies, so didn't really read through them all (2/7)	None made	A revised and much shorter list to be used in paper-based version
10.	Screening question on cover page requesting potential participants to opt to take survey would make it a lot easier to avoid taking survey –leading to further loss of potential participants (1/7)	Remove it; depend rather on the invite in the introductory mail containing link to survey	Accepted

TABLE 4.4: Comparative overview of the structural properties of the online and paper-based versions of the parent CAM questionnaires used for main survey

Section	Online version	Paper-based version
Cover page	Brief general definition of CAM followed by an invitation to "PLEASE CLICK HERE and HERE" for examples of CAM products and practices. This was prefaced by the information that CAM use in children is not required for participation in the study; and followed by a promise of a survey completion time of "about 5-10 minutes"	Same as for online version except in the absence of the invitation to "PLEASE CLICK HERE and HERE" for examples of CAM products and practices.
Section One	**13 questions in all:** A maximum of 12 questions on parent demographics, followed by one question on medium of online access to the survey	**16 questions in all:** 7 questions encompassing the 12 online questions on parent demographics, in addition to one question on geographical area of residence, another on survey mode preference, three on types of CAM modalities used in children, and four on child age, sex and lifetime or 12-month CAM use status.
Section two	**32 questions: CAM use in children** Four questions on child age, sex and lifetime or 12-month CAM use status; eight on the number, specifics and outcomes rating of child CAM use; six on knowledge of and continued/discontinued child CAM use; four on specific outcomes of child CAM use; three on helpful CAM recommendations and harmful CAM reporting; and seven on previous adult child CAM use and outcomes	**11 questions: Detailed information on CAM use in children.** Five questions on the specifics of CAM use in children (irrespective of age), as well as the timing (during or beyond the last 12 months) and outcomes rating for each therapy; two questions on knowledge of and continue/discontinued child CAM use; and four questions on helpful CAM recommendations and harmful CAM reporting
Section three	**15 questions:** Four questions on personal CAM use specifics and positive outcomes rating; 10 attitudinal questions on CAM use; and one final question on participation in further CAM study	**12 questions.** Two questions on personal CAM use specifics and positive outcomes rating; followed by 10 attitudinal questions on CAM use.
Total number of questions	A maximum of **60 questions** –including 16 routing questions	**39 questions**
Total number of questions for child CAM users	A maximum of **60 questions** in all (as above), depending on specific user features	**39 questions**
Total number of questions for child CAM non-users	A maximum of **29 questions**	**27 questions**

4.3.3 Participant recruitment

The results of participant recruitment for the study across the survey area via the online and paper-based approaches are outlined in tables 4.5 and 4.6. 550 of the 600 paper-based questionnaires produced were distributed to parents in different settings within Aberdeen city; and 152 completed questionnaires were returned. Eight of these were invalidated for not providing information on CAM use in children. While it was not possible to determine the exact number of parents reached through the online route, only 68 responses were received, all of which were usable. The combined 212 valid responses were widely distributed across the study area. 29 of the 32 postcode areas within the survey area were represented in the study, participants were understandably not uniformly distributed across the area either by postcode (X^2 = 572.825; df=28; p=0.000) or geographical area (X^2 = 108.095; df=8; p=0.000). In all 212 parents of 391 children were recruited, 149 (70.3%) of which were drawn from Aberdeen city and its northern and western suburbs; with participant recruitment decreasing as the distance from Aberdeen city increased.

The paper-based mode accounted for the bulk of recruitment, as only about one third of the participants (68 parents; 32.1%) were recruited by the online approach. However, while the proportions of participants recruited via the paper-based approach were significantly greater than those recruited via the online mode in many parts of Aberdeen city, the converse was the case as the distance from Aberdeen increased, albeit non-significantly.

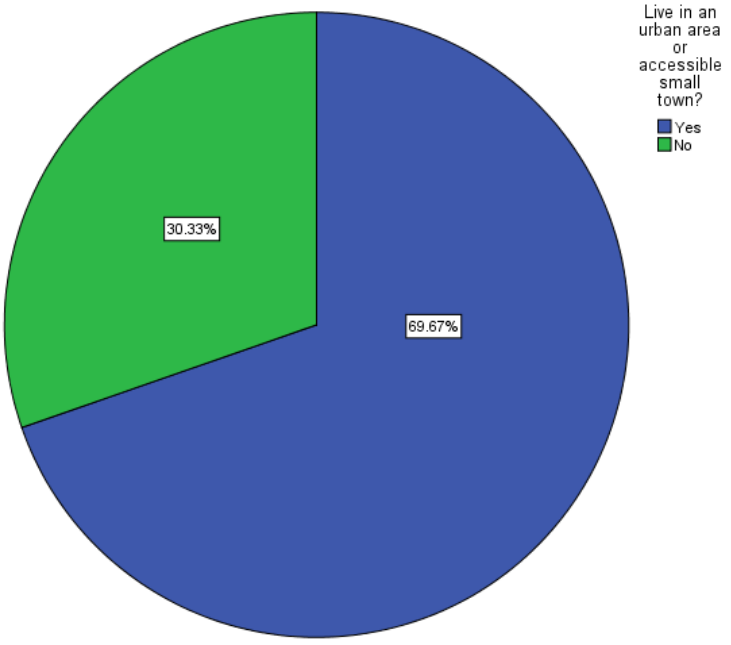


FIGURE 4.2: Distribution of study participants based on their residence in urban or rural areas

Figure 4.2 and table 4.6 show that, while almost 70% of the participants resided in urban areas or accessible small towns, this was significantly accounted for by the use of the paper-based approach

TABLE 4.5: Results of participant recruitment via online and paper-based surveys

Geographical Area	Specific towns/communities	POST CODE	%	Parents	Children	Mean	SEM	ONLINE MODE Parents	ONLINE MODE Children	ONLINE MODE Mean	ONLINE MODE SEM	PAPER-BASED MODE Parents	PAPER-BASED MODE Children	PAPER-BASED MODE Mean	PAPER-BASED MODE SEM	X^2 P value
ABERDEEN CITY CENTRE	Bridge of Dee area	AB10	6.1	13	24	1.85	.191	6	10	1.67	.211	7	14	2.00	.309	
	Bon accord crescent/Crown street; Torry	AB11	3.3	7	14	2.00	.309	4	8	2.00	.408	3	6	2.00	.577	
	George street, Foresterhill, Rosemount, Kittybrewster areas	AB25	7.1	15	25	1.67	.211	1	1	1.00	-	14	24	1.71	.221	
			16.5	**35**	**63**	**1.80**	**.128**	**11**	**19**	**1.73**	**.195**	**24**	**44**	**1.83**	**.167**	**.028**
NORTH ABERDEEN	Old Aberdeen, Woodside, Tillydrone, etc.	AB24	**6.6**	**14**	**28**	**2.00**	**.314**	**3**	**5**	**1.67**	**.333**	**11**	**23**	**2.09**	**.392**	**.033**
WEST ABERDEEN	Mastrick, Cornhill, Sheddocksley. etc.	AB16	**4.7**	**10**	**15**	**1.50**	**.167**	**4**	**5**	**1.25**	**.250**	**6**	**10**	**1.67**	**.211**	**.527**
ABERDEEN NORTHERN SUBURBS	Bridge of Don, Danestone, Grandholm, Persley, etc.	AB22	**30.7**	**65**	**107**	**1.65**	**.077**	**8**	**14**	**1.75**	**.366**	**57**	**93**	**1.63**	**.074**	**.000**
ABERDEEN WESTERN SUBURBS	Millitimber	AB13	1.9	4	10	2.50	.645	1	3	3.00	-	3	7	2.33	.882	
	Peterculter	AB14	0.9	2	3	1.50	.500	1	2	2.00	-	1	1	1.00	-	
	Bieldside, Cults, Craigiebuckler, Kingswells, Summerhill, etc.	AB15	9.0	19	31	1.63	.137	7	8	1.14	.143	12	23	1.92	.149	
			11.8	**25**	**44**	**1.76**	**.156**	**9**	**13**	**1.44**	**.242**	**16**	**31**	**1.94**	**.193**	**.162**
ABERDEEN-ABERDEENSHIRE	Altens/Cove area, Nigg, Portlethen, etc.	AB12	4.2	9	26	2.89	.588	3	9	3.00	1.00	6	17	2.83	.792	
	Blackburn, Bucksburn, Dyce, etc.	AB21	1.4	3	8	2.67	.333	2	5	2.50	.500	1	3	3.00	-	
	Balmedie, Potterton, Whitecairns, etc.	AB23	0.9	2	4	2.00	.000	-	-	-	-	2	4	2.00	.000	
			6.6	**14**	**38**	**2.71**	**.384**	**5**	**14**	**2.80**	**.583**	**9**	**24**	**2.67**	**.527**	**.285**
ABERDEENSHIRE EAST AND BANFFSHIRE & BUCHAN COAST	Ellon	AB41	1.4	3	5	1.67	.667	-	-	-	-	3	5	1.67	.667	
	Peterhead	AB42	0.9	2	4	2.00	.000	1	2	2.00	-	1	2	2.00	-	
	Fraserburgh	AB43	0.5	1	5	5.00	.	1	5	5.00	-	-	-	-	-	
	Banff	AB45	0.5	1	2	2.00	.	-	-	-	-	1	2	2.00	-	
	Inverurie	AB51	4.2	9	12	1.33	.167	6	8	1.33	.211	3	4	1.33	.333	
	Turriff	AB53	0.5	1	1	1.00	.	1	1	1.00	-	-	-	-	-	
			8.0	**17**	**29**	**1.71**	**.254**	**9**	**16**	**1.78**	**.434**	**8**	**13**	**1.63**	**.263**	**.808**
ABERDEENSHIRE WEST	Banchory	AB31	1.4	3	7	2.33	.333	3	7	2.33	.333	-	-	-	-	
	Westhill	AB32	1.4	3	8	2.67	.667	1	4	4.00	-	2	4	2.00	.00	
	Alford	AB33	0.9	2	6	3.00	.000	1	5	5.00	-	1	1	1.00	-	
	Aboyne	AB34	0.9	2	2	1.00	.000	2	2	1.00	-	-	-	-	-	
	Stonehaven	AB39	5.2	11	19	1.73	.195	7	11	1.57	.202	4	8	2.00	.408	
	Insch	AB52	0.5	1	2	2.00	.	-	-	-	-	1	2	2.00	-	
	Huntly	AB54	0.9	2	6	3.00	.000	1	3	3.00	-	1	3	3.00	-	
			11.3	**24**	**50**	**2.08**	**.208**	**15**	**32**	**2.13**	**.307**	**9**	**18**	**2.00**	**.236**	**.221**
ANGUS AND DUNDEE CITY	Laurencekirk	AB30	0.9	2	6	3.00	.000	1	3	3.00	-	1	3	3.00		
	Dundee, Perth & Kinross	DD2	0.5	1	2	2.00	.	-	-	-	-	1	2	2.00	-	
	Montrose	DD10	1.4	3	6	2.00	.000	3	6	2.00	.000	-	-	-	-	
	Arbroath	DD11	0.5	1	2	2.00	.	-	-	-	-	1	2	2.00	-	
			3.3	**7**	**16**	**2.29**	**.184**	**4**	**9**	**2.25**	**.250**	**3**	**7**	**2.33**	**.333**	**.705**
MISSING (Postcode data not provided)			**0.5**	**1**	**1**	**1.00**	**.000**	**-**	**-**	**-**	**-**	**1**	**1**	**1.00**	**-**	**-**
ABERDEEN METROPOLITAN AREA		x		**212**	**391**	**1.84**	**.061**	**68**	**127**	**1.87**	**.122**	**144**	**264**	**1.83**	**.070**	
		%	**100**					**32.1**	**32.5**			**67.9**	**67.5**			

TABLE 4.6: Participant distribution based on the Scottish 6 fold Urban-Rural classification profile

Scottish 6 fold Urban-Rural Classification	ONLINE				PAPER-BASED				X^2 test (Survey mode)
	Number of parents	Number of children	Mean	SEM	Number of parents	Number of children	Mean	SEM	
Large urban areas	31	57	1.84	.168	108	196	1.81	.083	X^2=42.655 df=1 P=0.000
Other urban areas	3	6	2.00	.000	1	2	2.00	-	-
Accessible small towns	1	3	3.00	-	3	7	2.33	.992	-
ALL URBAN AREAS (x; %[a,b])	**35; 23.8 %[a] 51.5 %[b]**	**66**	**1.89**	**.152**	**112; 76.2 %[a] 78.3 %[b]**	**205**	**1.83**	**.083**	**X^2= 40.33 df=1 p=0.000**
Accessible rural area	29	51	1.67	.183	29	53	1.88	.122	X^2=0.000 df=1 P=1.000
Remote small towns	-	-	-	-	-	-	-	-	-
Remote rural area	4	10	2.50	.957	2	5	2.50	.500	-
ALL RURAL AREAS (x; %[a,b])	**33; 51.6 %[a] 48.5 %[b]**	**61**	**1.85**	**.195**	**31; 48.4 %[a] 21.7 %[b]**	**58**	**1.87**	**.120**	**X^2= 0.063 df=1 P=0.803**
X^2 test (Urban-Rural)	**X^2=0.059 df=1 P=0.808**				**X^2=45.881 df=1 P=0.000**				

[a] = Percentage of recruitment by survey mode

[b]= Percentage of recruitment by Urban-Rural setting

(X^2 = 45.881; df=1; P=0.000), rather than the online one (X^2 = 0.059; df=1; P=0.808). Participant recruitment by the online mode was independent on the urban/rural setting of the survey area (X^2 = 0.059; df=1; p=0.808); just as the mode of survey used had no significant effect on participant recruitment in rural areas (X^2 = 0.063; df=1; P=0.803).

4.3.4 Participant demographics

The chief demographic features of the 212 parents who participated in the study are outlined in table 4.7. High proportions of them were Caucasian (84.4%), mothers or female guardians (73.6%), educated beyond secondary school level (85.3%), living largely in urban areas (69.7%), and currently married, cohabiting or in a civil partnership (87.2%), with mostly one to two children (86.3%). About 70% of the Caucasian population (corresponding to about 60% of the entire population) was White Scottish. More than half of the parents were aged 30-44 years (59.9%), and had children that were all aged less than 12 years (64.1%). However, they were uniformly distributed with respect to religious inclination (X^2 = 0.005; df=1; p=0.945). The parents provided information on 391 own children, 82.4% of which (322) were paediatric subjects aged up to 17 years. Only 23 parents (10.8%) had only adult children. Although there were virtually equal numbers of male and female paediatric subjects (X^2 = 0.304; df=1; P=0.435), the females were slight more numerous (52.2%) than males.

TABLE 4.7: Participant demographics

Demographic	Categories	Frequency	%	X^2 test
Parents		212	100	
Parental status	Father/Male guardian	56	26.4	X^2=47.170; df=1; P=0.000
	Mother/Female guardian	156	73.6	
Parent age (1 Missing)	16-29 years	23	10.9	X^2=151.597; df=4; P=0.000
	30-44 years	126	59.7	
	45-59 years	51	24.2	
	>60 years	11	5.2	
Marital status (1 Missing)	Married/Living with partner	184	87.2	X^2=116.920; df=1; P=0.000
	Single/Separated/Divorced/Widowed	27	12.8	
Ethnicity (1 Missing)	White Scottish	127	59.9	X^2=247.270; df=4; P=0.000
	Other White British or Other White	52	24.5	
	Black or Black British	21	9.9	
	Asian or Asian British	7	3.3	
	Mixed racial background/Other	4	1.9	
Level of educational (1 Missing)	Further or higher education	180	85.3	X^2=105.218; df=1; P=0.000
	Secondary education or below	31	14.7	
Locality of residence (1 Missing)	Urban areas	147	69.7	X^2=32.649; df=1; P=0.000
	Rural areas	64	38.3	
Religious inclination (1 Missing)	Religious	105	49.8	X^2=0.005; df=1; P=0.945
	No religious	106	50.2	
Self CAM use profile (2 Missing)	Ever used	141	67.5	X^2=135.3976; df=1; P=0.000
	Never used/Not sure	68	32.5	
Number of CAM modalities self-used	Sum	437		
	Mean (SD)	3.10 (2.33)		
Number of children per parent	1 or 2 children	183	86.3	X^2=111.868; df=1; P=0.000
	More than 2 children	29	13.7	
Child age categories	Aged <5 years	38	17.9	X^2=57.566; df=6; P=0.000
	Aged 5-11 years	63	29.7	
	Aged <12 years	35	16.5	
	Aged 12-17 years	14	6.6	
	Aged <17 years	24	11.3	
	Aged >17 years	23	10.8	
	Aged up to and above 17 years	15	7.1	
Children		391	100	
Number of children	Mean (SD)	1.84 (0.89)		
Age range	0-17 years	322	82.4	X^2=163.706; df=1; P=0.000
	>17 years	69	17.6	
Paediatric subject details				
Sex distribution	Females	168	52.2	X^2=0.304; df=1; P=0.435
	Males	154	47.8	
Age Descriptives (year)	Range	0.30-17.00		
	Mean (SD)	7.25 (4.47)		
	Median (IQR)	6.00 (4.00-11.00)		
	Mode	5.00		
Age group distribution	Infants (<2 years)	31	9.60	X^2=62.149; df=3; P=0.000
	Pre-schoolers (2-5 years)	103	32.00	
	School-age (6-11 years)	123	38.20	
	Adolescents (12-17 years)	65	20.20	

4.3.5 Extent and nature of paediatric CAM use

The extent and nature of paediatric CAM use in the survey setting is summarised in table 4.8. Two thirds of parents reported having ever used CAM in their children. 59.4% of these (corresponding to 40.1% of the whole sample) had always used CAM both in the past as well as within the last 12 months; 23.1% reported having used CAM only within the last 12 months; while only 17.5% (corresponding to just over 10% of the whole sample) reported having used it only in the past. Parents reported significant lifetime CAM use in all own children and across the main child age groups, as well as among paediatric subjects aged up to 17 years; but there was no significant difference ($X^2 = 0.014$; df=1; P=0.904) between the numbers of adult children who have ever or never used CAM. Although about two-thirds of both male and female paediatric subjects had ever used CAM, there was no difference in lifetime CAM use across the sexes. CAM was, however, reported to have used more in females than males. With respect to the chronology of CAM use, significantly more paediatric subjects were reported to have always used CAM, both in the past as well as within the last 12 months ($X^2 = 93.408$; df=1; p=0.000). While a similar pattern was observed among males and females separately, it was found to be independent on gender.

4.3.6 The dependent and independent factors associated with paediatric CAM use

The parent-related factors found to determine CAM use are outlined in table 4.9. Although significant differences were found between parent who had ever used CAM in their children (paediatric CAM users) and those who had never done so (paediatric CAM non-users) based on several categorical parental factors, only five of them were found to be significantly correlated with paediatric CAM use. These major determinants of paediatric CAM use included a parental age of 30-44 years ($X^2 = 0.231$; p=0.001); having a child aged either less than 12 years ($X^2 = 0.153$; p=0.026) or aged up to 17 years ($X^2 = 0.211$; p=0.002); having completed the paper-based survey ($X^2 = 0.321$; p=0.000); and having used CAM personally ($X^2 = 0.324$; p=0.000). Distinctively, the only parental factor for which there was a negative correlation with paediatric CAM use was religious inclination, although this was not significantly so ($X^2 = -0.094$; p=0.173).

Among the five factors found to determine paediatric CAM use, personal CAM use by parents was found to have the greatest likelihood of doing so [OR =4.235; 95% C I (2.274-7.887)], closely followed by completion of the paper-based survey rather than the online one [OR =4.177; 95% C I (2.251-7.751)]; while having a young child aged less than 12 years was found to have the lowest significant likelihood of doing so [OR =2.106; 95% C I (1.088-4.080)]. When these five major determinants were entered into a binary logistic regression model to determine the significance of their predictive abilities, the child age-related factors were found to be non-significant. When all

TABLE 4.8: Extent and nature of paediatric CAM use

CAM use status	Categories	Frequency	%	X^2 test	Mean (SD)
Parent level data on CAM use in children		**212**	**100**		
Lifetime CAM use in own children	Ever used	143	67.5	X^2=25.830; df=1; P=0.000	
	Never used/Uncertain	69	32.5		
Chronological CAM use in own children	Always used	85	59.4	X^2=44.531; df=3; P=0.000	
	Currently use	33	23.1		
	Previously used	25	17.5		
Number of different modalities used		**401**	-	**-**	**2.80 (2.04)**
Child level data on CAM use	-				
Number of Children (All parents)		**391**	**100**		**1.84 (0.89)**
(189 parents)	Paediatric subjects	322	82.4	X^2=163.71; df=1; P=0.000	1.70 (0.80)
(38 parents)	Adult children	69	17.6		1.82 (0.90)
Life-time CAM use					
In general	Ever used	247	63.2	X^2=27.133; df=1; P=0.000	
	Never used	144	36.8		
By current child age					
Across age groups	Ever used				
	0-17 years	213	86.2	X^2=129.72; df=1; P=0.000	
	>17 years	34	13.8		
	Never used	144			
	0-17 years	109	75.7	X^2=38.028; df=1; P=0.000	
	>17 years	35	24.3		
Within age groups	0-17 years	322			
	Ever used	213	66.1	X^2=33.590; df=1; P=0.000	
	Never used	109	33.9		
	>17 years	69			
	Ever used	34	49.3	X^2=0.014; df=1; P=0.904	
	Never used	35	50.7		
Parent-reported CAM use in paediatric subjects					
Life-time CAM use					
In general	Ever used	213	66.1	X^2=33.590; df=1; P=0.000	
	Never used/Uncertain	109	33.9		
By sex					
Across sexes	Ever used	213	66.1		
	Females	113	53.1	X^2=0.793; df=1; P=0.373	
	Males	100	46.9		
	Never used/Uncertain	109	33.9		
	Females	55	50.5	X^2=0.0092; df=1; P=0.924	
	Males	54	49.5		
Within sexes	Females	168	52.2		
	Ever used	113	67.3	X^2=20.024; df=1; P=0.000	
	Never used/Uncertain	55	32.7		
	Males	154	47.8		
	Ever used	100	64.9	X^2=13.740; df=1; P=0.000	
	Never used/Uncertain	54	35.1		
Chronology of paediatric CAM use					
In general	Always used	137	64.3	X^2=93.408; df=1; P=0.000	
	Currently use	45	21.1		
	Previously used	31	14.6		
By sex					
Across sexes	Always used	137	42.5		
	Females	75	54.7	X^2=1.234; df=1; P=0.267	
	Males	62	45.3		
	Currently use	45	14.0		
	Females	21	46.7	X^2=0.2000; df=1; P=0.655	
	Males	24	53.3		
	Previously used	31	9.6		
	Females	17	54.8	X^2=0.290; df=1; P=0.590	
	Males	14	45.2		
Within sexes	Females	113	53.1		
	Always used	75	66.4	X^2=55.712; df=1; P=0.000	
	Currently use	21	18.6		
	Previously used	17	15.0		
	Males	100	46.9		
	Always used	62	62.0	X^2=38.484; df=1; P=0.000	
	Currently use	24	24.0		
	Previously used	14	14.0		

TABLE 4.9: Dependent and independent factors of parental CAM use in own children (categorical variables)

Factor	Demographic categories (Possible factors)	Total	Ever used		Never used		X^2 test of independence		Correlation with paediatric CAM use		Odds of using CAM in children		Binary logistic regression	
			n	%	n	%	X^2	P value	r	P value	OR	95 % CI	Exp(B)	95 % CI
Parental status	Father/Male guardian	56	32	57.1	24	42.9	1.143	0.258						
	Mother/Female guardian	156	111	71.2	45	28.8	27.923	0.000*	0.132	0.055				
Parental age	Being aged 30-44 years	126	96	76.2	30	23.8	34.571	0.000*	0.231	0.001*	2.713	[1.501-4.902]	2.362*	[1.064-5.254]
	Any other age group	85	46	54.1	39	45.9	0.578	0.444						
Urbanity of residential area	Living in an urban/accessible small areas	147	104	70.7	43	29.3	25.313	0.000*	0.111	0.106				
	Living in a rural/remote areas	64	38	59.4	26	40.6	2.258	0.134						
Marital status	Married/Cohabiting/In civil Partnership	184	127	69.0	57	31.0	26.630	0.000*	0.096	0.165				
	Single/Separated/Divorced/Widowed	27	15	55.6	12	44.4	0.333	0.564						
Number of children	1 or 2 children	183	125	68.3	58	31.7	24.530	0.000*	0.046	0.508				
	3 or more children	29	18	62.1	11	37.9	1.690	0.194						
Child age category	Aged <5 years	38	25	65.8	13	34.2	3.789	0.052						
	Aged <12 years	35	25	71.4	10	28.6	6.249	0.011*	0.111	0.107				
	Aged <18 years	24	16	66.7	8	33.3	2.667	0.102						
	Aged >=18 years	15	11	73.3	4	26.7	1.087	0.109						
	Having a child aged <5 years old	80	57	71.3	23	28.7	14.450	0.000*	0.063	0.301				
	Having a child aged <12 years old	164	117	71.3	47	28.7	29.878	0.000*	0.153	0.026*	2.106	[1.088-4.080]	0.792	[0.357-2.439]
	Having a child aged <18 years old	189	134	70.9	55	29.1	33.021	0.000*	0.211	0.002*	3.790	[1.550-9.268]	2.298	[0.596-8.855]
	Having an adult child	38	20	52.6	18	47.4	0.105	0.746						
Child sex category	Only male children	65	45	69.2	20	30.8	9.615	0.002*						
	Only female children	73	51	69.9	22	30.1	11.521	0.001*						
	Both male and female children	51	38	74.5	13	25.5	12.255	0.000*						
	Having a male child	116	83	71.6	33	28.4	21.552	0.000*	0.018	0.805				
	Having a female child	124	89	71.8	35	28.2	23.518	0.000*	0.027	0.716				
Ethnicity	White Scottish	127	86	67.7	41	33.3	15.945	0.000*						
	White or Other White British	52	37	71.2	15	28.8	9.308	0.002*						
	Black or Black British	21	13	61.9	8	38.1	1.190	0.275						
	Asian or Asian British	7	3	42.9	4	57.1	0.143	1.000						
	Mixed racial background or Others	4	3	75.0	1	25.0	1.000	0.625						
	Being Caucasian	179	123	68.7	56	31.3	25.078	0.000*	0.071	0.302				
Highest educational qualification	Educated just to secondary level or less	31	19	61.3	12	38.7	1.581	0.209	-	-				
	Educated beyond secondary level	180	123	68.3	57	31.7	24.200	0.000*	0.053	0.442				
Religious inclination	Religious	105	66	62.9	39	37.1	6.943	0.008*	-0.094	0.173				
	Not religious/Uncertain	106	76	71.7	30	28.3	19.962	0.000*						
Survey mode	Online mode	68	31	45.6	37	54.4	0.529	0.467						
	Paper mode	144	112	77.8	32	22.2	44.444	0.000*	0.321	0.000*	4.177	[2.251-7.751]	4.682*	[2.237-9.802]
Personal CAM use	Ever used	141	110	78.0	31	22.0	44.262	0.000*	0.324	0.000*	4.235	[2.274-7.887]	6.680*	[3.172-14.067]
	Never used/Uncertain	68	31	45.6	37	54.4	0.529	0.467						

other factors are controlled for, parental self CAM use was found to be the strongest predictor of paediatric CAM use [OR =6.680; 95% CI (3.172-14.067)]. It was closely followed by completion of a paper-based survey [OR =4.682; 95% CI (2.237-9.802)]; while a parental age group of 30-44 years was found to be the least significant predictor [OR =2.362; 95% CI (1.064-5.254)]. The logistic regression model used was found to increase the ability of the null model to accurately predict paediatric CAM use from 67.3% to 78.4%, with a Hosmer-Lemeshow test indicating no significant differences between actual and predicted values (X^2 = 3.883; df=6; p=0.692).

More detailed analyses (table 4.10) revealed that level of personal CAM use by parents, as described by the mean number of CAM modalities they had used, was significantly (t=2.124; p=0.035) higher for the parents who also reported using CAM in own children (3.32 modalities/-parent) than in those who had not (2.32 modalities/parent). However, this significant difference was found to be only among the cohort of parents who have always used CAM in their children (3.61 modalities/parent); and not among those who either used CAM previously in their children, or have only just begun to do so within the last 12 months. When the relationship between the numbers of CAM modalities that had been used personally by parents and several continuous variables describing child CAM use by parents was determined (table 4.11), all the child CAM use variables were found to be significantly positively correlated with it except the mean numbers of adult children who had ever or never used CAM and that of the young children (paediatric subjects) who had never used CAM.

Linear regression models of the four significant correlates of level of personal parental CAM use showed that, while all four were significantly predicted, the number of different CAM modalities in children was the most significantly predicted (R^2 =0.4111; F=75.246; p=0.000); while the number of children aged up to 17 years who used CAM was the least (R^2=0.059; F=6.349; p=0.013). Specifically, the regression models imply that when all other factors are constant, we can be 95% confident that for every additional CAM used personally by parents, the number of their own young children aged up to 17 years that would use CAM would increase by 0.07 times; while the number of different modalities used in their children would increase by 0.56 times. Alternatively, while there is a 95% chance of 1.372 children in Aberdeen metropolitan area using CAM even when their parents have not done so, this number would increase by 0.05 times for every CAM modality used by their parents provided all other factors are unchanged. Similarly, while there is a 95% chance of 1.083 different CAM modalities to be used by young children in Aberdeen metropolitan area even when their parents had not used any, this number would increase by 0.56 times for every CAM modality their parents used, if all other factors are constant. This same analogy would apply for predicting the number of CAM modalities used by children either within the last 12 months or beyond that.

TABLE 4.10: Comparison of level of parental self CAM use with parental paediatric CAM use status

Level of parental Self CAM use	Paediatric CAM use status (2-way)	Number of parents	Number of CAM modalities	Mean	SD	t test for equality of means (Independent samples test) Equal variances assumed (Levene's test F=2.515; p=0.115) t	df	Sig. (2-tailed)	Mean difference	SEM (difference)	95 % CI of difference Lower	Upper
Number of CAM modalities used personally	Ever used	110	365	3.32	2.46	2.124*	139	0.035	0.996	0.469	0.089	1.922
	Never used	31	72	2.32	1.60							
	Total	141	437									

Level of parental Self CAM use	Paediatric CAM use status (4-way)	Number of parents	Number of CAM modalities	Mean	SD	Post Hoc multiple comparisons for One-way ANOVA test ANOVA test (2.660; p=0.051) I	J	Mean diff. (I-J)	SEM (difference)	Sig. (2-tailed)	95 % CI of difference Lower	Upper
Number of CAM modalities used personally	Always used	66	238	3.61	2.65	Always	-	-	-	-	-	-
	Currently used	25	79	3.16	2.50	-	Currently	0.446	0.539	0.409	-0.62	1.51
	Previously used	19	48	2.53	1.43	-	Previously	1.080	0.597	0.073	-0.10	2.26
	Never used	31	72	2.32	1.60	-	Never	1.283*	0.499	0.011	0.30	2.27
	Total	141	437									

TABLE 4.11: Relationship between degree of parental self CAM use and degree of paediatric CAM use by parents

Continuous CAM use variables	Number of parents	Sum	Mean	SD	Correlation		Linear regression						
							Model summary	ANOVA		Unstandardized coefficients			
										Gradient		Constant	
					r	P value	R square	F	Sig.	B	Std. Error	B	Std. Error
Number of CAM modalities used personally by parents	141	437	3.10	2.33	1.000	-	-	-	-	-	-	-	-
Number of children <=17 years who ever used CAM	134	213	1.59	0.70	0.243*	0.013	0.059	6.349*	0.013	0.070	0.028	1.372	0.114
Number of children <=17 years who never used CAM	68	109	1.60	0.92	-0.144	0.425	-	-	-	-	-	-	-
Number of children >18 years who ever used CAM	19	34	1.79	0.92	-0.006	0.982	-	-	-	-	-	-	-
Number of children >18 years who never used CAM	19	35	1.84	0.90	-0.383	0.275	-	-	-	-	-	-	-
Number of paediatric CAM modalities used within last 12 months	104	237	2.28	1.50	0.435*	0.000	0.189	20.102*	0.000	0.254	0.057	1.407	0.249
Number of paediatric CAM modalities used previously	88	188	2.14	1.37	0.412*	0.000	0.158	14.926*	0.000	0.234	0.060	1.365	0.264
Number of different CAM modalities ever used	143	401	2.80	2.04	0.641*	0.000	0.411	75.246*	0.000	0.560	0.065	1.083	0.267

4.3.7 The user-perceived effectiveness and safety outcomes of paediatric CAM use in the target groups, and their associated dependent and independent factors

The survey findings on the perceived effectiveness and safety outcomes of paediatric CAM use among parent users in the Aberdeen metropolitan area, as well as their determinants, are outlined in tables 4.12 to 4.19. While tables 4.12 and 4.13 provide an insight into the parental rating preferences observed during the study; tables 4.14 to 4.18 summarize the specific outcomes associated with the CAM products and practices at parent- and modality-levels; and table 4.19 outlines the factors that determine and/or predict user-perceived effectiveness.

Table 4.12 gives an overview of the use of CAM modalities in children as reported and assessed by their parents. Although the total number of CAM modalities self-used by parents was not significantly higher than that used for their children (t= -1.816; p=0.071), many more CAM practices were self-used by parents than for their children (t=-6.290; p=0.000). This was further emphasized by the fact that while there was no significant difference between the number of CAM products and practices self-used by parents (t=1.836; p=0.069), many more CAM products than CAM practices were used in children (t=6.496; p=0.000). With respect to child CAM use, although there was no significant difference between the number of CAM modalities that were used within or beyond the last 12 months (t=0.889; p=0.376), significantly more (t=4.780; p=0.000) novel CAM modalities were used (401 different modalities) than were reused by 52 parent cohorts (103 similar modalities; 25.7%). Similarly, while fewer CAM product and practice types were rated by participants in the paper-based than they had selected from the lists provided, the difference was significant only for CAM product types (t=2.224; p=0.028).

Table 4.13 gives a breakdown of the rating preferences of parents between CAM product and practice types, and further indicates that, although many more CAM products than CAM practices were used in children as compared to their parents, the proportion of products rated was similar for both parties (P(1) - P(2) =0.0922482; p=0.117). This was probably because the 20 parents (14.0%) who did not rate the CAM used by their children used many more product types than practice types (31 product types vs. 7 practice types).

The parent-level summary of the reported outcomes associated with CAM use outlined in table 4.14 indicates that of the 123 parents that rated the CAM they had ever used in their children, 102 (82.9%) perceived at least one of the modalities they had used helpful in their children, 74.5% of which number (76 parents) reported that at least one of such modalities had helped their children “a lot”.

Although the proportions of parents who perceived CAM use as “a lot helpful” were similar among child CAM users and self CAM users (74.5% vs. 73.1%; P(1) - P(2)= 0.0143288; p=0.805); the

TABLE 4.12: Number and rating of CAM modalities used

	CATEGORY ONE				CATEGORY TWO				Comparison	
	Number of parents	Sum	Mean	SD	Number of parents	Sum	Mean	SEM	t Statistic	P value
PARENTAL PAEDIATRIC CAM USE RATING vs. PARENTAL SELF CAM USE RATING										
	Different modalities ever used in children				**CAM modalities used personally by parents**					
Number of different CAM modalities used	143	401	2.80	2.04	141	437	3.10	2.33	-1.816	0.071
	Paediatric CAM use				**Self CAM use**					
Number of specific CAM products rated	107	241	2.25	1.33	106	256	2.42	1.81	-1.309	0.193
Number of specific CAM practices rated	52	74	1.42	0.78	84	176	2.10	1.34	-6.290*	0.000
	Specific CAM products rated				**Specific CAM practices rated**					
Paediatric CAM products vs. practices rated	107	241	2.25	1.33	52	74	1.42	0.78	6.496*	0.000
Self-used CAM products vs. practices rated	106	256	2.42	1.81	84	176	2.10	1.34	1.793	0.076
DETAILS OF PAEDIATRIC CAM USE & RATINGS										
	Within the last 12 months				**Beyond the last 12 months**					
Number of paediatric CAM modalities used	104	237	2.28	1.50	88	188	2.14	1.37	0.889	0.376
	Distinct modalities ever used currently or previously				**Modalities used previously as well as currently**					
Paediatric CAM modalities used distinctly or repeatedly	143	401	2.80	2.04	52	103	1.98	1.20	4.780*	0.000
	CAM product types selected				**CAM product types rated**					
Number of CAM product types selected/rated	104	250	2.40	1.35	82	173	2.11	1.08	2.224*	0.028
	CAM practice types selected				**CAM practice types rated**					
Number of CAM practice types selected/rated	63	91	1.44	0.84	40	57	0.75	0.118	0.137	0.892

TABLE 4.13: Parental CAM rating profiles for paediatric and self-used CAM

Product and practice types selected and rated for children				CAM rating profile		Paediatric CAM		Self-used CAM		Binomial test (2-P test)		
Product types		Practice types				Number of parents	%	Number of parents	%	P (1) - P (2)	z score	P value
Selected	Rated	Selected	Rated									
120	104	20	0	**Rated only products**		71	49.7	57	40.4	0.0922482	1.57	0.117
87	69	53	46	**Rated both products and practices**		36	25.2	50	35.5	-0.102862	-1.90	0.058
12	0	11	11	**Rated only practices**		16	11.2	34	24.1	-0.129247*	-2.90	0.004
31	0	7	0	**Did not rate any CAM used**		20	14.0	-				
250	**173**	**91**	**57**	**Total**		**143**		**141**				
				X^2 test	**Statistic**	52.608*		5.915				
					Degree of freedom	3		2				
					P value	0.000		0.052				

TABLE 4.14: Summary of user-perceived effectiveness and safety outcomes rating of parental paediatric and self CAM use

Aspect of CAM use assessed	Outcomes rating question	Number of respondents (parents)	Response distribution				X^2 test	
			Yes		No			
			n	%	n	%	Statistic	P value
For CAM modalities ever used in own children	Did you find any of the CAM you used for your child(ren) helpful	123	102	82.9	21	17.1	53.341*	0.000
	Did you find any of the CAM your child(ren) used A LOT helpful?	102	76	74.5	26	25.5	24.510*	0.000
	Did you find any of the CAM your child(ren) used not much or not at all helpful?	123	6	4.9	117	95.1	100.171*	0.000
	Were you unsure about the helpfulness of any of the CAM your child(ren) used?	123	60	48.8	63	51.2	0.073	0.787
	Did you experience any discomfort with any of the CAM your child(ren) used?	123	9	7.3	114	92.7	89.634*	0.000
	Did you experience a lot of discomfort with any of the CAM your child(ren) used?	9	2	22.2	7	77.8	2.778	0.096
For CAM modalities used in own children in the last 12 months	Did you find any of the CAM you used for your child(ren) helpful	104	84	80.8	20	19.2	39.385*	0.000
	Did you find any of the CAM your child(ren) used A LOT helpful?	84	65	77.4	19	22.6	25.190*	0.000
	Did you find any of the CAM your child(ren) used not much or not at all helpful?	104	3	2.9	101	97.1	92.346*	0.000
	Were you unsure about the helpfulness of any of the CAM your child(ren) used?	104	46	44.2	58	55.8	1.385	0.239
	Did you experience any discomfort with any of the CAM your child(ren) used?	104	5	4.8	99	95.2	84.962*	0.000
	Did you experience a lot of discomfort with any of the CAM your child(ren) used?	5	1	20.0	4	80.0	1.800	0.375
For CAM modalities used in own children beyond the llast 12 months	Did you find any of the CAM you used for your child(ren) helpful	88	70	79.5	18	20.5	30.727*	0.000
	Did you find any of the CAM your child(ren) used A LOT helpful?	70	52	74.3	18	25.7	16.514*	0.000
	Did you find any of the CAM your child(ren) used not much or not at all helpful?	88	4	4.5	84	95.5	72.727*	0.000
	Were you unsure about the helpfulness of any of the CAM your child(ren) used?	88	41	46.6	47	53.4	0.409	0.522
	Did you experience any discomfort with any of the CAM your child(ren) used?	88	5	5.7	83	94.3	69.136*	0.000
	Did you experience a lot of discomfort with any of the CAM your child(ren) used?	5	1	20.0	4	80.0	1.800	0.375
For CAM modalities ever used personally by parents themselves	Did you find any of the CAM you used for your child(ren) helpful	141	130	92.2	11	7.8	100.433*	0.000
	Did you find any of the CAM your child(ren) used A LOT helpful?	130	95	73.1	35	26.9	27.692*	0.000
	Did you find any of the CAM your child(ren) used not much or not at all helpful?	141	10	7.1	131	92.9	103.837*	0.000
	Were you unsure about the helpfulness of any of the CAM your child(ren) used?	141	37	26.2	104	73.8	31.837*	0.000

proportion who found at least one of the CAM modalities used to be helpful was significantly less for child CAM users than for self CAM users (82.9 vs. 92.2%; P(1) - P(2)= -0.0927175; p=0.023). Similarly, while equally small proportions of parents perceived their use of CAM for their children or for themselves as "not much" or "not at all" helpful (4.9% vs. 7.1%; P(1) – P(2) = -0.0221415; p=0.446); many more parents (P(1) - P(2) =0.225394; p=0.000) were unsure of the outcomes of the CAM they used for their children (60; 48.8%) than the CAM they self-used (37; 26.2%). Although adverse outcomes of CAM use (perceived discomfort) was not studied for self-used CAM modalities, only nine different parents (7.3%) reported any form of discomfort in their children following CAM use; two of whom (22.2%) described the adverse effect as extreme. These adverse outcomes were found to be uniformly distributed between parents who reported using CAM in their children within the last 12 months and those who had used it further down in the past.

With respect to the modality level outcomes of CAM use, the specific CAM modalities reported as having been used continuously (or re-used) over the years by the same parents, along with their user-perceived effectiveness (UPE) ratings, are listed in table 4.15; while the UPE ratings for the distinct modalities used in children are compared with self-used modalities in tables 4.16 and 4.17. The CAM modalities reported by parents as having caused "a little" or "a lot" of discomfort to their children, along with the specific discomforts reported, are outlined in table 4.18.

Among the modalities used consistently by parents listed in table 4.15, although parents rated 75% of product modalities and 95.66% of all practice modalities at least "a little" helpful to their children, they were unsure of the helpfulness of up to one third (33.75%) of the products. Although parents rated the helpfulness of both products and practices used in their children very highly, the parental UPE rating for the practices rated at least "a little" helpful was significantly higher than for products (95.7% vs. 65.0%; p=0.003)

Tables 4.16 and 4.17 show that parents perceive the CAM modalities they have used much more effective in themselves than in their children. However, in both child and adult CAM use, whether for all CAM modalities rated or only for the commonly used ones, CAM practices were associated with significantly higher UPE ratings than CAM products. There were only two instances where non-significant differences were observed: the mean % UPE ratings for commonly used CAM practices used in children relative to those used in their parents (-14.09%; t = -1.45; p = 0.167); and the % mean UPE ratings for the products used in children relative to the practices used in them (-10.3%; t = -0.92; p = 0.378). Generally, while the ratings for self-used modalities ranged from 79.3% in products to 93.2% for practices; they ranged from 67.3% to 82.5%, respectively, for paediatric CAM modalities. Also, while parents were uncertain about the effectiveness of a substantial number of modalities, only in relatively few instances was CAM rated as either "not much" or "not at all" helpful. There were only 6 such instances in child CAM use, 5 of which

TABLE 4.15: List and user-perceived effectiveness ratings for CAM modalities used both within the last 12 months as well as previously

CAM modality	Number of reports	UPE Ratings: A lot	A little	Not sure	Not much	Not at all	Prevalence (n=52)	% PE	Odds of a high PE rating
CAM Products									
Anthroposorphic medicine	1	1					1.9		
Arnica	4	2	1	1			7.7	75.0	1.00
Aromatherapy	3	2	1				5.8	100.0	2.00
Aveeno	1	1					1.9		
Bach flower remedy	1				1		1.9		
Balm	1	1					1.9		
Camomile	1		1				1.9		
Cod liver oil	2			2			3.9		
Echinacea	4	2		2			7.7	50.0	1.00
Garlic	1	1					1.9		
Ginger	1	1					1.9		
Herbal teas	1		1				1.9		
Herbal remedies	1	1					1.9		
Homeopathy	1		1				1.9		
Honey	2		1	1			3.9		
Lavendar oil	1	1					1.9		
Melatonin	1	1					1.9		
Multivitamins	16	6	1	9			30.8	43.8	0.60
Nettle soap	1			1			1.9		
Olbas oil	12	5	5	2			23.1	83.3	0.71
Omega 3	4	3		1			7.7	75.0	3.00
Organic foods	1	1					1.9		
Oscilococcinum	1	1					1.9		
Rescue® remedy	2	1	1				3.9		
Tea tree oil	2	1		1			3.9		
Teething remedy	1	1					1.9		
Thuja	1	1					1.9		
Traditional Chinese Medicine (TCM)	1	1					1.9		
Vitamin C	1			1			1.9		
Vitamin D	1			1			1.9		
Yogurt	9	2	2	5			17.3	44.4	0.29
Total ratings	80	37	15	27	1	0			
% of total product ratings	**100.0**	**46.25**	**18.75**	**33.75**	**1.25**	0.00			
Mean % PE for the products rated (with a prevalence of at least 5 %; x≥3 reports) =67.36 %									
CAM Practices									
Breathing exercises	3	3					5.8	100.0	∞
Chiropractic	1	1					1.9		
Cranio-sacral therapy	1	1					1.9		
Healing	5	5					9.6	100.0	∞
Massage	9	7	1	1			17.3	88.9	0.78
Reflexology	2	2					3.9		
Yoga	2	1	1				3.9		
Total ratings	23	20	2	1	0	0			
% of total practice ratings	**100.0**	**86.96**	**8.70**	**4.34**	0.00	0.00			
Mean % PE for the practices rated (with a prevalence of at least 5 %; x≥3 reports) =96.3 %									
Binomial test P(UPE Products)-P(UPE Practices): difference =-0.306522; p= 0.003									

TABLE 4.16: User-perceived effectiveness (UPE) ratings of CAM products in children and their parents

CAM Products	UPE rating (Child use)					Total	Prevalence	% PE (%)	Odds of rating "A lot"	UPE rating (Self use)					Total	Prevalence	% PE (%)	Odds of rating "A lot"	Odds of CAM use in children
	A lot	A little	Not sure	Not much	Not at all					A lot	A little	Not sure	Not much	Not at all					
African traditional medicines										1	1				2	1.89			
Agnus castus										1		1			2	1.89			
Aloe vera	2	1				3	2.80			4					4	3.77			
Anthroposorphic medicine	1					1	0.93			1					1	0.94			
Aptamil	1					1	0.93												
Arnica	3	3	2			8	7.48	75.0	0.6	1	5	1			7	6.60	85.7	0.17	1.14
Aromatherapy –non specific	3	2				5	4.67			4	3		1		8	7.55	87.5	1.00	0.625
Atkin's diet	-										2				2	1.89			
Aveeno	1					1	0.93												
Bach flower remedy	1			1		2	1.87			5	3	1			9	8.49	88.9	1.25	0.22
Balm	3					3	2.80			1					1	0.94			
Bilberry	1					1	0.93												
Bio propilis										1					1	0.94			
Calcium										1					1	0.94			
Camomile	1	1	1			3	2.80				1				1	0.94			
Chondroitin												1			1	0.94			
Cinnamon											1				1	0.94			
Clove oil										1					1	0.94			
Cod liver oil			2			2	1.87			1		4			5	4.67			
Colloidal silver											1				1	0.94			
Colocynthis		1				1	0.93												
Cranberry										1	1				2	1.89			
Dairy-free products			1			1	0.93												
Detox diet											1				1	0.94			
Dietary supplement	1			1		2	1.87			4	2				6	5.66	100.0	2.00	0.33
Echinacea	6	1	4			11	10.28	63.6	1.2	6	5	2			13	12.26	84.6	0.86	0.85
Essential oils										1					1	0.94			
Eucalyptus	1					1	0.93			1					1	0.94			
Evening primrose	1		1			2	1.87			4		2			6	5.66	66.7	2.00	0.33
Floradix® herbal remedy												1			1	0.94			
Folic acid										1		1			2	1.89			
Garlic	1					1	0.93			1					1	0.94			
Ginger	2					2	1.87			3					3	2.83			
Gingko biloba										1					1	0.94			
Ginseng										1		1			2	1.89			
Gluten-free diet										2	1				3	2.83			
Green tea				1		1	0.93												
Herbal tea	1	2	1			4	3.74			3	6	1		1	11	10.38	81.8	0.375	0.36
Herbal medicines	2					2	1.87			8	6	3	1	1	19	17.92	73.7	0.42	0.11

Home-made remedies		1				1	0.93			1					1	0.94				
Homeopathic remedy	1	2	2			5	4.67			5	2	1	1		9	8.49	77.8	1.25	0.56	
Honey	5	2	3			10	9.35	70.0	1.00	2	1	1			4	3.77			2.5	
Horsetail										1					1	0.94				
Iron supplements											1	1			2	1.89				
Jan de Vries supplements										1					1	1.94				
Lactose-free milk		1				1	0.93													
Lavendar oil	2	2				4	3.74			3	2	1			6	5.66	83.3	1.00	0.67	
Lemon/lime oil											4				4	3.77				
Macrobiotic diet										1					1	0.94				
Melatonin	1					1	0.93													
Milk thistle										1					1	0.94				
Multivitamins	17	5	28	1		51	47.66	43.1	0.5	8	6	8	1	1	24	22.64	58.3	0.50	2.125	
Nettle			1			1	0.93					1			1	0.94				
Olbas oil	15	14	4			33	30.84	87.9	0.83	11	5	1			17	16.04	94.1	1.83	1.94	
Omega 3	3	1	2			6	5.61	66.7	0.5	1	1	1			3	2.83			2.00	
Organic foods	1					1	0.93			1					1	0.94				
Oscilococcinum	1					1	0.93													
Pain relief										1					1	0.94				
Peppermint oil										1	1				2	1.89				
Raspberry										1					1	0.94				
Rescue remedy	1	1				2	1.87			1		1	1		3	2.83				
Rosemary		1				1	0.93				1				1	0.94				
Sleep remedy												1			1	0.94				
Special diet –non-specific										2					2	1.89				
St. John's wort											1			1	2	1.89				
Starflower oil										1	-				1	0.94				
Tea tree oil	2	2	1	1		6	5.61	66.7	0.50	2	5	1			8	7.55	87.5	0.33	0.75	
Teething remedy	3	2	1			6	5.61	83.3	0.50	-									∞	
Thuja	4		1			5	4.67			1					1	0.93				
Thyme oil	1					1	0.93			1					1	0.93				
Traditional Chinese medicines	3					3	2.80			4	1				5	4.67				
Vitamin C	1		3			4	3.74			2	2				4	3.77				
Vitamin D		2	2			4	3.74				1				1	0.94				
Vicks vapour rub	1	1				2	1.87				1				1	0.94				
White tea												1			1	0.94				
Yogurt	11	9	14			34	31.78	58.8	0.48	7	8	6			21	19.81	71.4	0.50	1.62	
Zinc											2	-			2	1.89	-	-	-	
Sum of UPE ratings	**105**	**57**	**74**	**5**	**-**	**241**			**0.77**	**119**	**84**	**44**	**5**	**4**	**256**			**0.87**	0.94	
% of total ratings	**43.6**	**23.7**	**30.7**	**2.0**	**0.00**	**100**				**46.5**	**32.8**	**17.2**	**2.0**	**1.5**	**100**					
Total number of users	107 parent users in own children									106 parent self-users										
Mean (SEM) % UPE RATING for products rated	68.1 (5.0) %									81.7 (2.9) %										
Statistical difference in UPE based on proportion of total ratings reported (child vs. parent)	-0.120770* (-0.198072, -0.0434667); z = -3.06 P = 0.002																			
Statistical difference in Mean % UPE RATING for commonly used products (child vs. parent)	-13.58%* (-24.81, -2.35); t= -2.52; p = 0.020																			

TABLE 4.17: User-perceived effectiveness (UPE) ratings of CAM practices in children and their parents

CAM Practices	UPE rating (Child use)					Total	Preva-lence	% PE (%)	Odds of rating "A lot"	UPE rating (Self use)					Total	Preva-lence	% PE (%)	Odds of rating "A lot"	Odds of CAM use in children
	A lot	A little	Not sure	Not much	Not at all					A lot	A little	Not sure	Not much	Not at all					
Acupuncture										13	7	4			24	28.57	83.3	1.18	0
Aerobics											1				1	0.12			
Alexander technique										1					1	0.12			
Breathing exercises	6	1				7	13.46	100.0	6.00	7	1				8	9.52	100.0	7.00	0.875
Chiropractic	1		2			3	5.77	33.3	0.50	8	4				12	14.29	100.0	2.00	0.25
Cranio-sacral therapy	1					1	1.92			1					1	0.12			
Cupping therapy										1					1	0.12			
Ear candling										1					1	0.12			
Guided imagery	1					1	1.92												
Healing	12					12	23.08	100.0	∞	10	1				11	13.10	100.0	10.00	1.09
Hypnotherapy			1			1	1.92	-	-	2				1	3	3.57			
Massage	20	7	7		1	35	67.31	77.14	1.33	25	11				36	42.86	100.0	2.27	0.97
Meditation										4	1				5	5.95	100.0	4.00	0
Mindfulness										1					1	0.12			
Music/dance therapy	1					1	1.92			3					3	3.57			
Naturopathy	1					1	1.92			2					2	2.38			
Osteopathy										10					10	11.90	100.0	∞	0
Pilates										4	1				5	5.95	100.0	4.00	0.00
Reflexology	3		2			5	9.62	60.0	1.50	12	4	4			20	23.81	80.0	1.50	0.25
Reiki	1					1	1.92			3	-	2			5	5.95	60.0	1.50	0.20
Relaxation therapy										1	1				2	2.38			
Shiatsu										1	1				2	2.38			
Special exercises										2					2	2.38			
Tai chi										1					1	0.12			
Thermotherapy										1					1	0.12			
Visualisation										1					1	0.12			
Yoga	5	1				6	11.54	100.0	5.00	12	4	1			17	20.24	94.12	2.40	0.35
Sum of UPE ratings	**52**	**9**	**12**	**-**	**1**	**74**			**2.36**	**127**	**37**	**11**	**-**	**1**	**176**			**2.59**	
% of total ratings	**70.3**	**12.2**	**16.2**	**-**	**1.3**	**100**				**72.2**	**21.0**	**6.25**		**0.56**	**100**				
Number of users	52 parent users in own children									84 parent self-users									
Mean % UPE RATING for practices rated	78.4 (11.0) %									92.5 (3.9) %									
Statistical difference in UPE based on proportion of total ratings reported (child vs. parent)	-0.107494* (-0.201856, -0.0131317); z = -2.23 p= 0.026																		
Statistical difference in Mean % UPE rating for commonly used practices (child vs. parent)	-14.09 % (-34.74, 6.57); t = -1.45; p = 0.167																		
COMPARISONS FOR RATINGS IN CHILD CAM USE																			
Statistical difference in UPE based on total ratings reported (products vs. practices)	-0.152125* (-0.257148, -0.0471024); z=-2.84; p= 0.005																		
Statistical difference in Mean % UPE rating for commonly used CAM (products vs. practices)	-10.3 % (-34.7, 14.2); t = -0.92; p = 0.378																		
COMPARISONS FOR RATINGS IN PARENT SELF CAM USE																			
Statistical difference in UPE based on total ratings reported (products vs. practices)	-0.138849* (-0.200899, -0.0767996); z=-4.39; p= 0.000																		
Statistical difference in Mean % UPE rating for commonly used CAM (products vs. practices)	-10.79 %* (-20.67, -0.89); t = -2.25; p = 0.034																		

were rated as "not much"; with the only one rated as "not at all" helpful being a CAM practice, massage, the most commonly used practice. Of the 10 modalities that parents rated poorly in terms of effectiveness, 4 were products (an unspecified herbal tea; an unspecified herbal medicine, multivitamins –the most commonly used product modality, and St. John's Wort, a medically recognised herb); and 1 practice modality, hypnotherapy. When the UPE ratings for the CAM modalities that were re-used or used consistently within and beyond the last 12 months (table 4.15) were compared with those of modalities that were used only at one point in time only, they were not found to be markedly higher, except for CAM practices.

Finally, table 4.18 shows the very low incidences of reported adverse events for CAM use in children. An adverse event incidence of just 3.81% was associated with overall CAM use in children, amounting to a 96.19% safety level for paediatric CAM use. Of the total of 12 adverse events reported, only 2 reports (0.63%) were described as causing a lot of discomfort. CAM safety was, however, not studied for self CAM use by parents.

Table 4.19 outlines the dependent and independent factors associated with parents finding paediatric CAM use helpful. Among the five parental factors upon which a positive perception of paediatric CAM use effectiveness was dependent, only two were associated with significant odds ratios –finding personal CAM use effective [OR (95% CI) =17.292 (3.011-99.305)] and the use of similar CAM type(s) in children [OR (95% CI) =3.327 (1.004-11.031). And of these two dependent factors, only finding personal CAM use effective was found to significantly predict perceived effectiveness outcomes for paediatric CAM use [Exp(B) (95% C) =9.301 (1.454-59.505)]. The results of the logistic regression indicate that a finding of a positive outcome for CAM use in parents would be associated with a 9-fold increased likelihood of a positive outcome report for CAM use in children when other factors are controlled for. The regression model used had a Hosmer and Lemeshow Chi square test of 0.863 (p=0.863), with a Cox and Snell R^2 value of 0.102; and improved the predictive power of the null from 81.8% to 84.1%.

4.3.8 Attitudes of the parents in Aberdeen metropolitan area towards paediatric CAM use and future research on it

The attitudes of parents within the Aberdeen metropolitan area towards paediatric CAM use and research are summarised in figures 4.3 to 4.13. The effect of CAM use status on parental attitudes was investigated by comparing the views of the 143 parents (67.5%) who had used CAM in their children to those of the 69 parents (32.5%) who had never done so on a set of ten questions. The investigation comprised six questions on the use of CAM in children generally; and two questions each on the effectiveness and safety outcomes of CAM use. As the questions were phrased in the first person singular, responding parents were able to own the responses they provided, rather than give general ones. The question that investigated participant disposition towards further

TABLE 4.18: CAM products and practices rated as having caused some degree of discomfort to children

Caused "a little" discomfort			Caused "a lot of" discomfort		
Modality (Discomfort reported)	**Number and frequency of report**	**Incidence**	**CAM Modality (with associated UPE level)**	**Frequency of report**	**Incidence**
CAM Practices					
Massage (Abdominal discomfort; Soreness)	2 reports (out of 35 episodes of use)	5.71 %			
Hot water massage (Scalding)	1 report (out of 1 episode of use)	Not determined			
Number of practices reported to have caused "a little discomfort"	**3 reports (out of 74 rated episodes of use)**	**4.05 %**	**Number of practices reported to have caused "a lot of discomfort"**	**0**	
CAM Products					
"Doctor's choice" (Allergy)	1 report (out of 1 episode of use)	Not determined	Homeopathic remedy (Skin reaction)	2 reports (out of 5 episodes of use)	40.0 %
Yogurt (Not stated/Unpleasant taste)	2 reports (out of 34 episodes of use)	5.88 %			
Thuja (Unpleasant taste)	1 report (out of 5 episodes of use)	20.0 %			
Homeopathic remedy (Unpleasant taste)	1 report (out of 5 episodes of use)	20.0 %			
Green tea (Unpleasant taste)	1 report (out of 1 episode of use)	Not determined			
Traditional Chinese medicine (Allergy)	1 report (out of 3 episodes of use)	33.3 %			
Number of products reported to have caused "a little discomfort"	**7 reports (out of 241 rated episodes of use)**	**2.90 %**	**Number of products reported to have caused "a lot of discomfort"**	**2 reports (out of 241 rated episodes of use)**	**0.83 %**
Total number of modalities associated with "a little discomfort"	**10 reports (out of 315 episodes of use)**	**3.17 %**	**Total number of modalities associated with "a lot of discomfort"**	**2 reports (out of 315 episodes of use)**	**0.63 %**
Percentage of adverse events reported among all rated episodes of CAM use			**12 adverse event reports out of 315 rated episodes of use (3.81 %)**		

TABLE 4.19: Dependent and independent factors of user-perceived effectiveness rating of paediatric CAM use

Factor	Total cases	Found CAM used in children helpful						Correlation with finding child CAM use helpful		Odds of finding child CAM use helpful		Binary logistic regression	
		Yes		No/ Not sure		Missing data							
		n	%	n	%	n	%	r	P value	OR	(95 % CI)	Exp(B)	(95 % CI)
Personal CAM use	141	85	60.3	17	12.1	39	27.7	0.042	0.646				
Finding personal CAM use helpful	130	83	63.8	12	8.2	35	26.9	0.399*	0.000	17.292*	(3.011-99.305)	9.301*	(1.454-59.505)
Use of similar CAM type in child	71	61	85.9	10	14.1	-	-	0.217*	0.042	3.327*	(1.004-11.031)	2.574	(0.705-9.401)
Having always used CAM in children	85	64	75.3	8	9.4	13	15.3	0.067	0.503				
Rating only CAM product use in children	71	54	76.1	17	23.9	-	-	0.046	0.643				
Continued use of a specific CAM in children	52	46	88.5	6	11.5	-	-	0.038	0.751				
Being a mother/female guardian	156	82	52.6	15	9.6	59	37.8	0.083	0.364				
Being aged 30-44 years	126	66	52.4	16	12.7	44	34.9	-0.087	0.340				
Living in an urban area/accessible small town	147	75	51.0	13	8.8	59	40.1	0.104	0.254				
Being in an on-going coupled relationship	184	89	48.4	19	10.3	76	41.3	-0.028	0.760				
Having a child aged <5 years	80	37	46.3	9	11.3	34	42.5	-0.051	0.574				
Having only children aged <5 years	40	18	45.0	5	12.5	17	42.5	-0.437*	0.000	0.686	(0.222-2.114)	-	-
Having a child aged <12 years	164	84	51.2	16	9.8	64	39.0	0.059	0.513				
Having only children aged <12 years	139	70	50.4	14	10.1	55	39.6	-0.202*	0.042	1.094	(0.403-2.970)	-	-
Having a child aged <18 years	189	85	50.3	20	10.6	74	39.2	-0.032	0.725				
Having only children aged <18 years	174	88	50.6	18	10.3	68	39.1	0.006	0.947				
Being Caucasian	179	83	46.4	21	11.7	75	41.9	-0.194*	0.032	0.000	-	-	-
Being educated beyond secondary level	180	92	51.1	28	10.0	70	38.9	0.055	0.547				
Being religious	105	61	48.6	8	7.6	46	43.8	0.090	0.324				
Completing a paper-based survey	144	77	53.5	16	11.1	51	35.4	-0.006	0.946				

paediatric CAM research was asked only to parents who had indicated in the online survey that they had ever used CAM for their children.

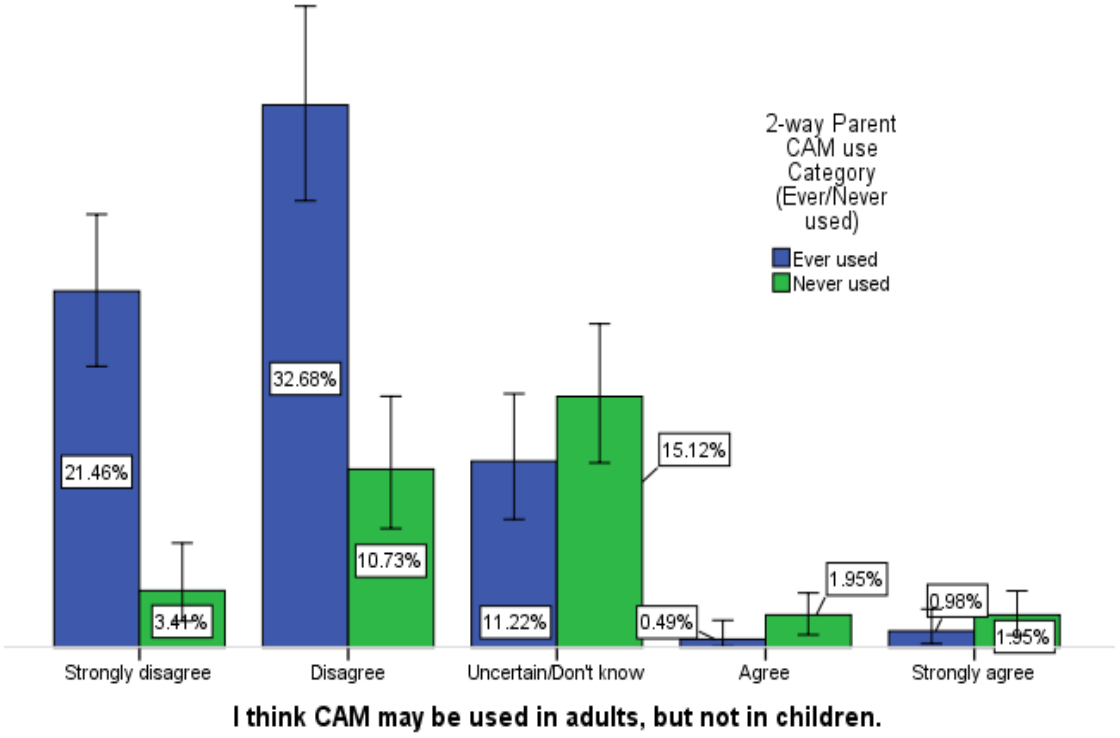


FIGURE 4.3: Parental attitudes towards CAM use in children

Figure 4.3 illustrates the attitudes of participants on the idea that CAM use should be avoided in children. The responses indicate that 140 parents (68.3 % of the 205 respondents), including 29 (42.03 %) of those who had never used CAM in their children, disagreed with the idea. About a quarter of the respondents, including statistically equal numbers of users and non-users, were however uncertain about it. Strangely, of the 11 parents (5.37%) who agreed with CAM use being avoided in children, 3 (1.47%) had used CAM in their children; with 2 of them having always used it for them. Closer investigation revealed that, while one of these three users had not rated the CAM their children had used, the other two had rated the CAM used as "a little helpful" with "no discomfort whatsoever" in three of the four reported instances of use (75%). The remaining case, the CAM practice massage, was rated "not sure" with "a little discomfort".

In line with this general trend in support of CAM use in children, the findings indicate that, while parents in the study area overwhelmingly (87.0%; 120 of 138 respondents) prefer to be allowed to make up their own minds on whether and what CAM they would use in their children (figure 4.4), four fifths of them (79.8%; 147 of 184 respondents) required more information on CAM to be able to do so (figure 4.5). In each of these instances, both users and non-users of CAM modalities in children supported the views.

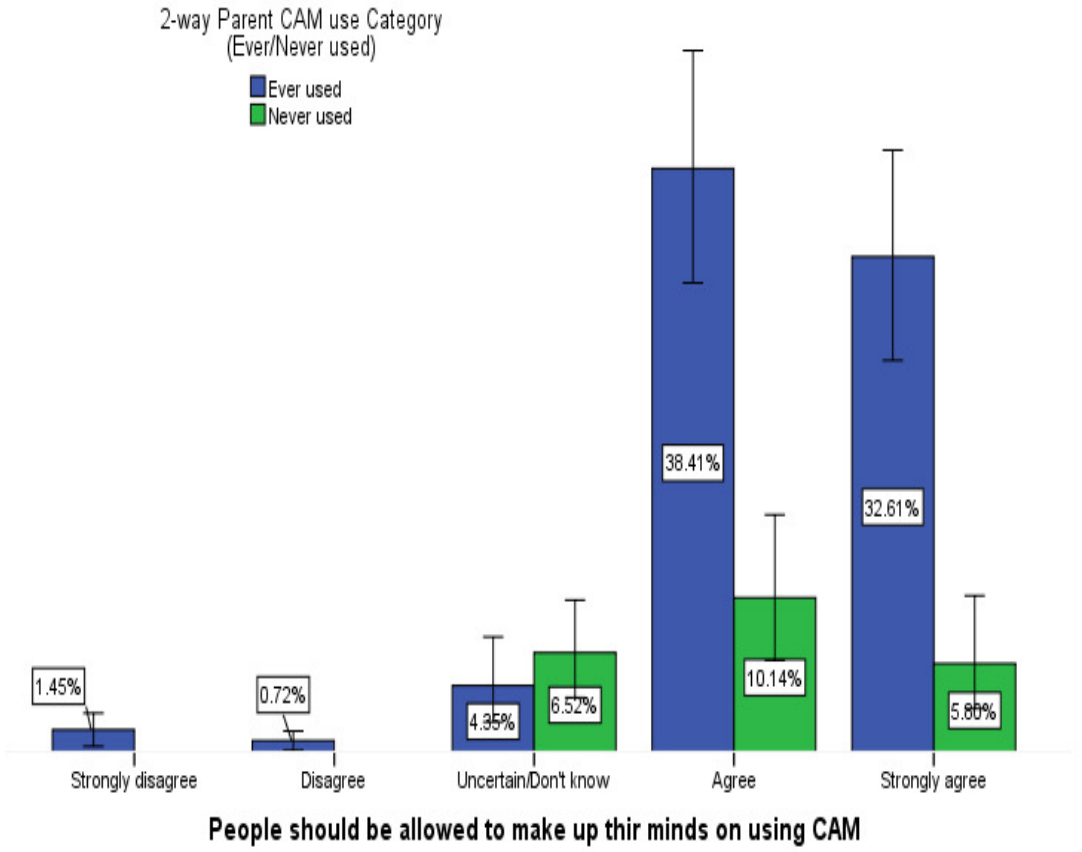


FIGURE 4.4: Parental attitudes on the idea that people should be allowed to make up their own minds about the choice to use CAM

In spite of the apparent preference among parents for CAM use in children to be a private affair, 74.2% of parents (156 of 206 respondents) agreed that parents should inform doctors of the use of CAM in their children (figure 4.6); and 63.1% (130 of 206 respondents) supported CAM being made readily available on the NHS (figure 4.7). However, while 47.1% (97 of 206 respondents) disagreed with the idea of avoiding the use of CAM along with prescribed conventional medicines, 31.1% (64 respondents, including 34 users) were uncertain about this.

Parental views on the outcomes associated with CAM use in children, illustrated in figures 4.9 to 4.12, indicate that, although nearly half of the respondents (46.4%; 95 of 205 respondents) believed certain health conditions in children were better managed with CAM than with conventional prescribed medicines (figure 4.9); 52.2% (107 of 205 respondents) were uncertain about CAM being more effective generally. Also, and notably, more parents disagreed (35.6%) than agreed (12.2%) with this idea; and most of those in opposition were CAM users (54 respondents; 74%). The same trend was seen among the majority who were uncertain on this matter, as about 60% (64 respondents; 59.8%) were CAM users. In all, 118 of the 137 CAM users (86.1%) who responded were either unsure about or totally against the idea that CAM is generally more effective than prescribed complementary medicines.

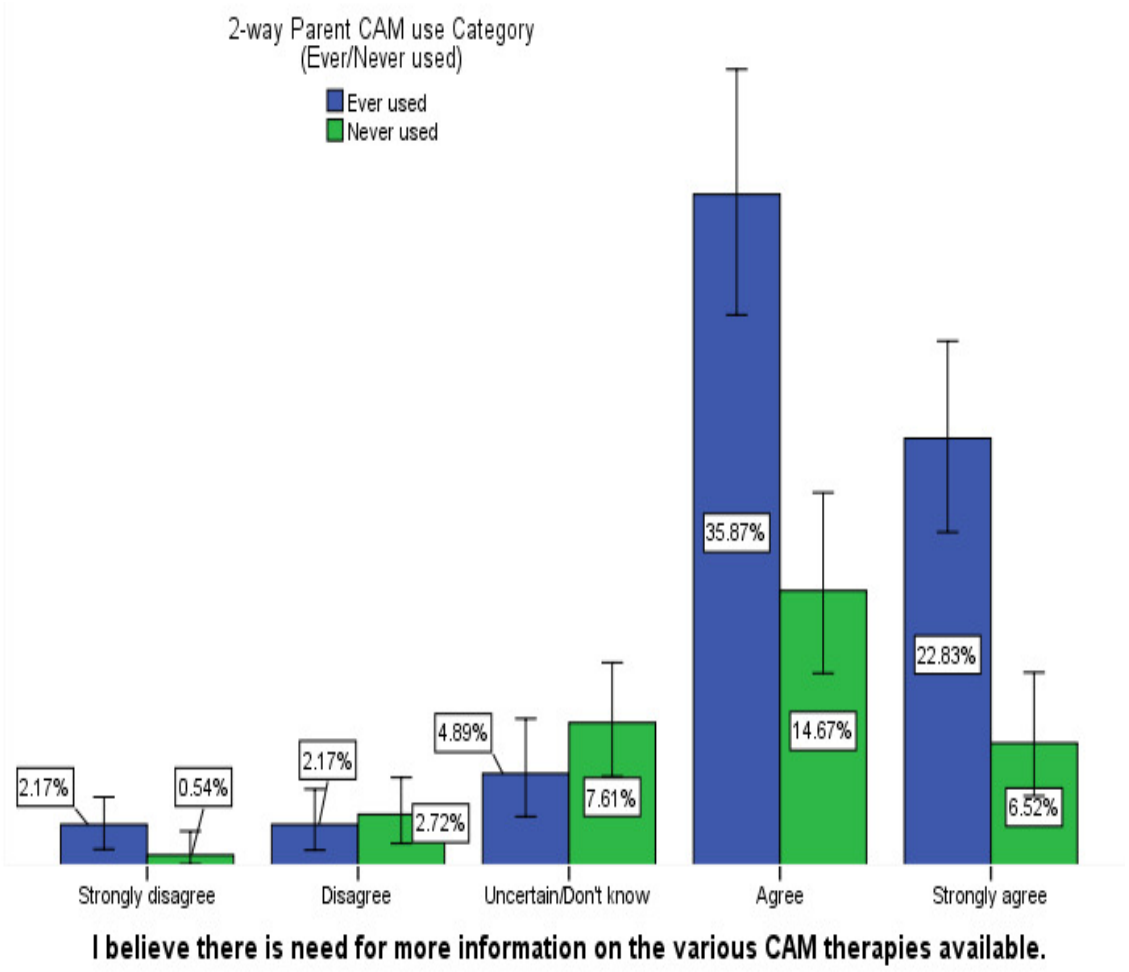


FIGURE 4.5: Parental attitudes on the need for more information on the various CAM modalities available

A similar trend was observed with respect to the safety outcomes associated with CAM use in children. While almost half of the parents (45.5%; 93 of 204 respondents) disagreed with the idea that CAM causes harmful side effects in children (figure 4.11); 44.4% of them (19 of 295 respondents) were not sure about CAM modalities being generally safer in children than prescribed conventional medicines (figure 4.12). However, unlike observed for perceived effectiveness, more people agreed (66; 32.2%) than disagreed (48; 23.4%) with the idea of CAM being safer than prescribed conventional medicines. But as seen earlier, a greater proportion of those who either totally disagreed with the idea (70.8%; 34 of 48 opposers) or were uncertain (59.3%; 54 of 91 respondents) were CAM users. In all, 64.2% of the CAM users that answered this question (88 of 137 CAM users) were either unsure of the idea of CAM being generally safer than prescribed conventional medicines or totally against it.

Finally, figure 4.13 illustrates the spread of opinions among the cohort of parents who were asked about their disposition towards participating in a further telephone interview study on CAM use in their children. Of the 16 participants of the online survey who had used CAM in their

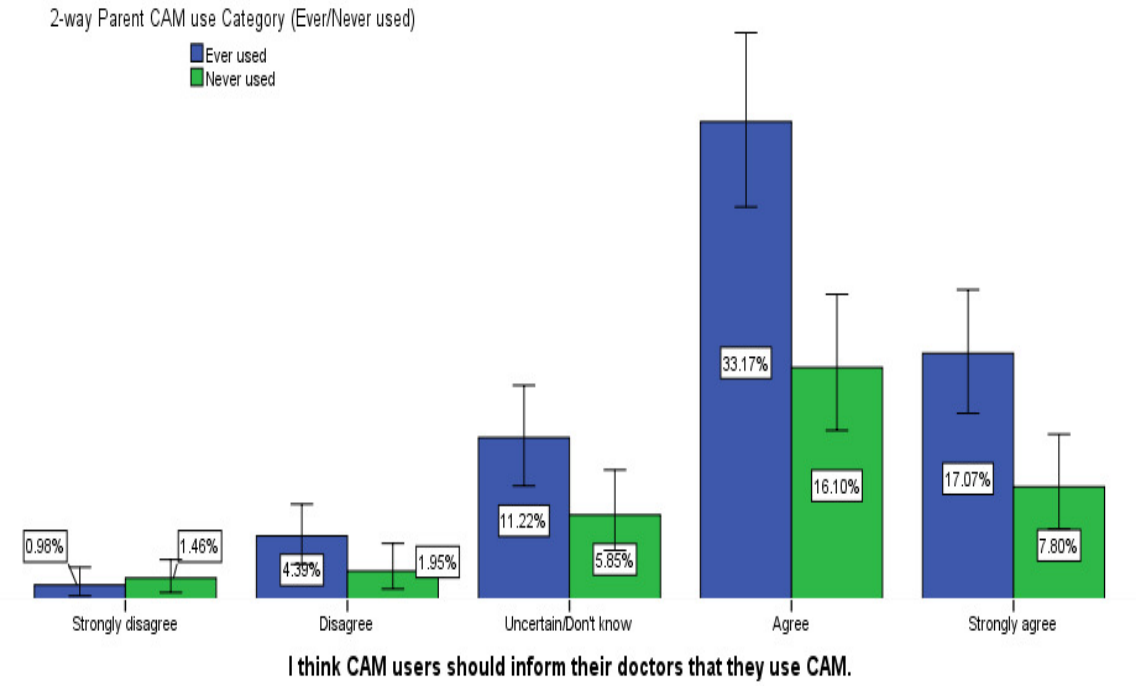


FIGURE 4.6: Parental attitude towards informing doctors of their use of CAM in their children

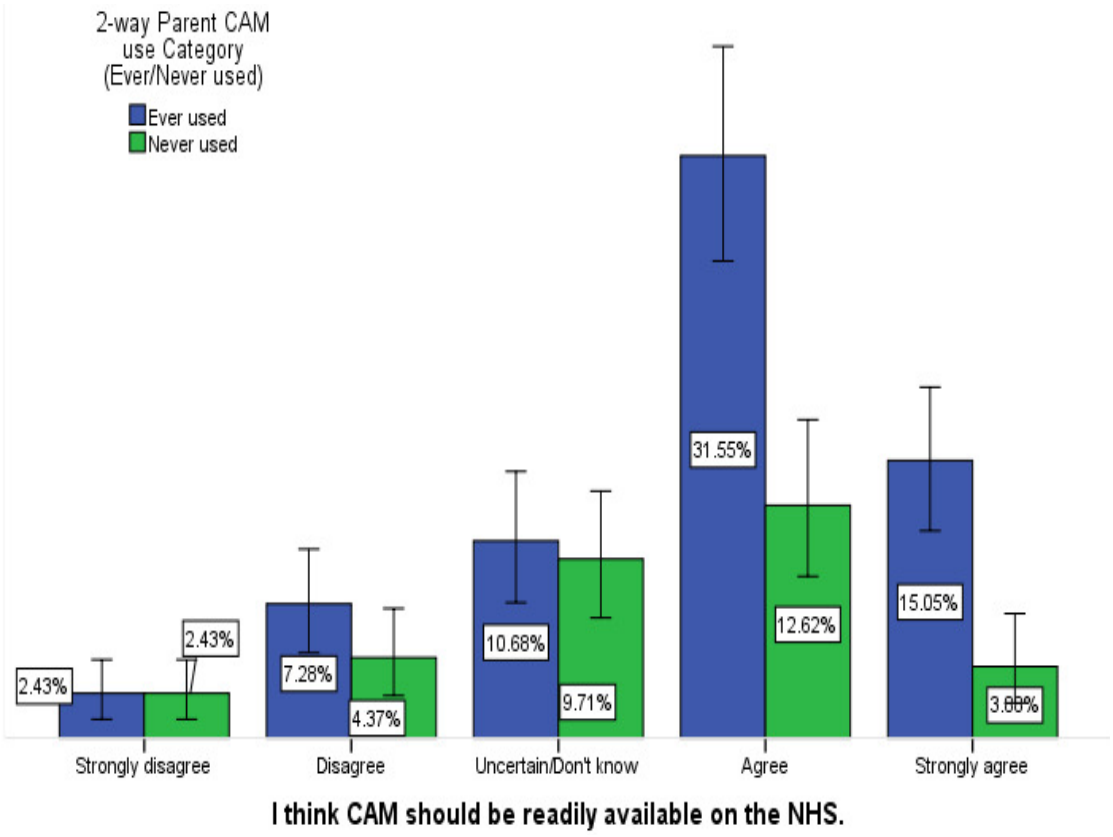


FIGURE 4.7: Parental attitudes on the ready availability of CAM on the NHS

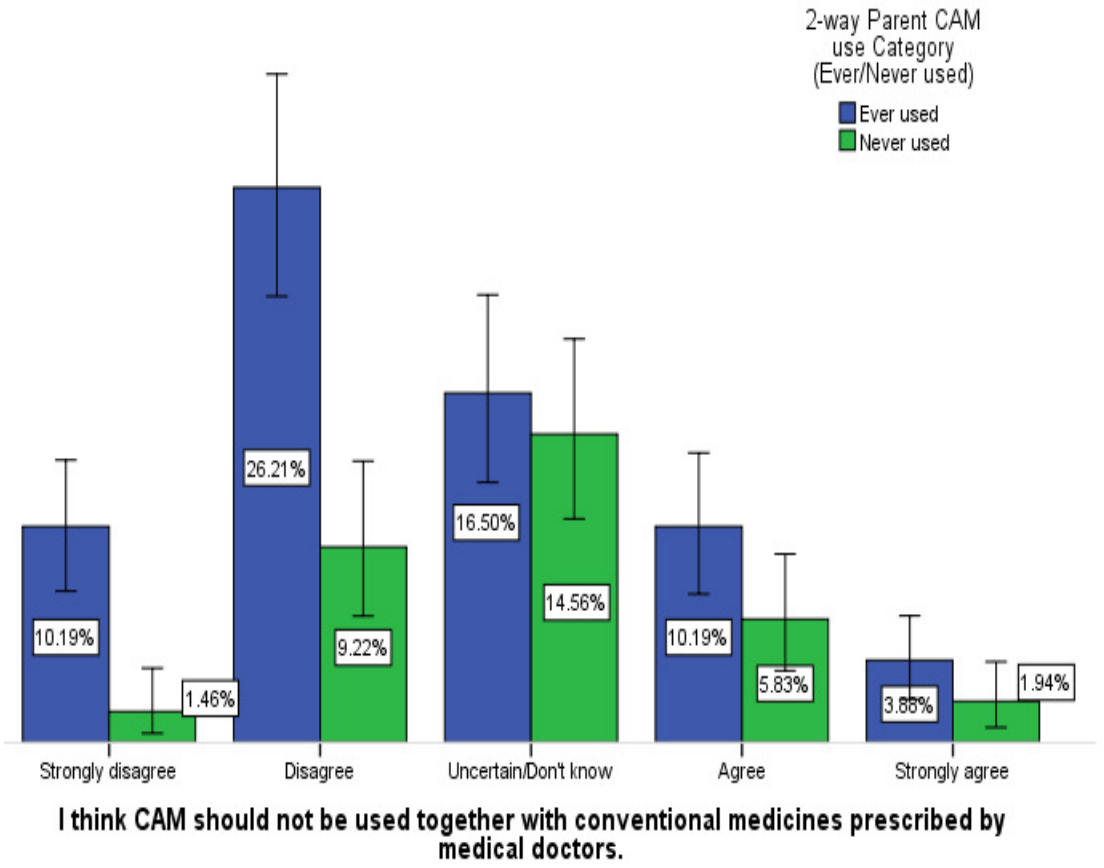


FIGURE 4.8: Parental attitudes on the idea that CAM should not be used along with conventional medicines in children

children, and thus qualified to be asked this question, close to two thirds (10; 62.5%) were willing to participate, while 3 participants (18.75%) each were either unwilling or yet to decide.

4.4 Discussion

4.4.1 Development and validation of survey instrument

The extensive process followed in the development and validation of the survey ensured that its content could not only be understood by the intended participants, but also was inclusive enough for a wide range of parents. Instrument validation is an important marker of study quality achieved by only 9 (20%) of the studies included in the SR reported in chapter 2. Although a non-statistical method was used to validate the questionnaire used in this study, qualitative methods like focus groups and cognitive interviews are recognised methods of questionnaire validation [80], even for health-related outcomes [648, 649]. Moreover, as the study was not designed to be longitudinal, and as such did not intend to measure change in health status, it was not specifically

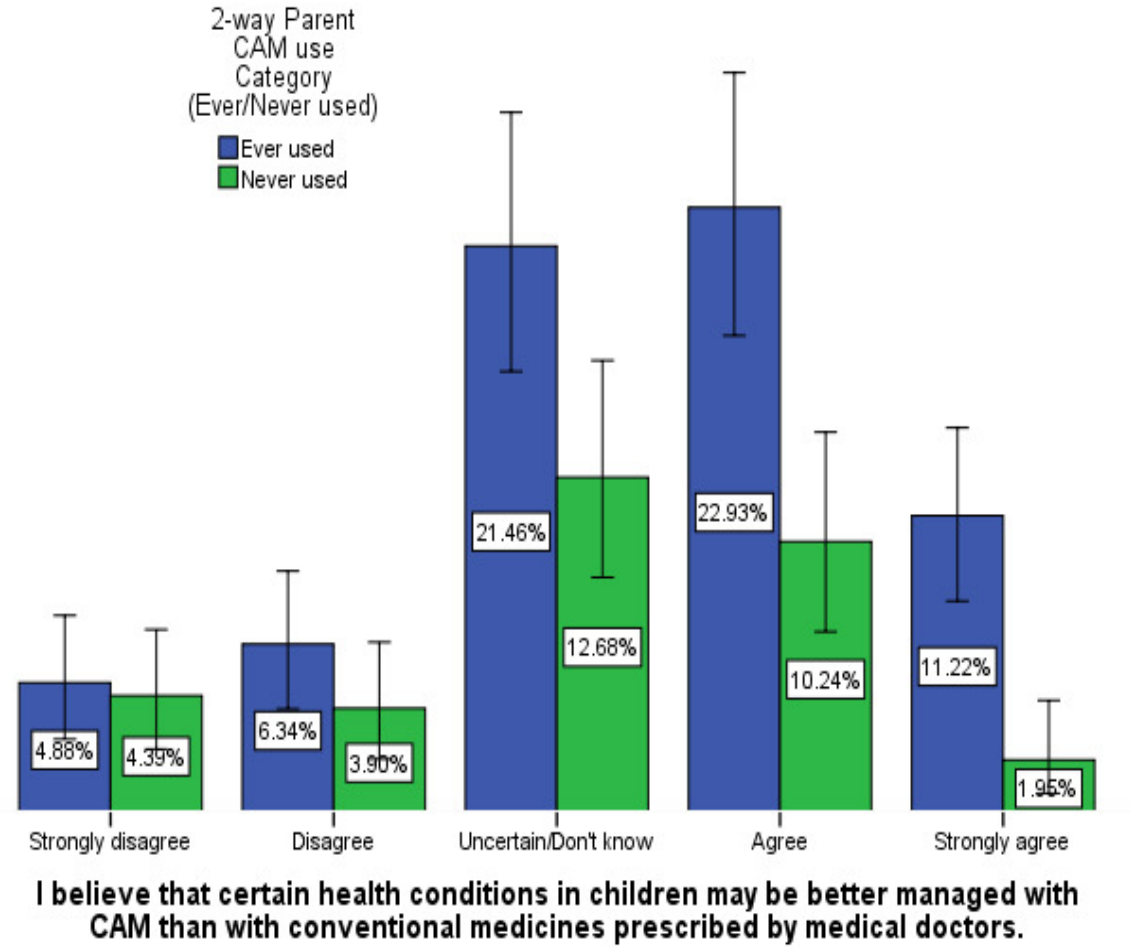


FIGURE 4.9: Parental attitudes towards preferential management of certain health conditions in children with CAM

necessary to further subject the instrument to detailed psychometric analyses to determine its reliability and sensitivity to change [79].

4.4.2 Participant recruitment

Although, no response rate (RR) could be calculated for the online aspect of the study, the 27.64% RR obtained for the paper-based version was much lower than the 60% generally accepted as the standard for paper-based surveys [329, 330]. However, this was similar to the RRs obtained in some of the papers included in the SR reported in chapter 2 [358, 373, 374, 492]. The most recent Scottish study on CAM use in children [647] had a RR of 44%, despite being specifically targeted at known children with cancer. In the light of these, the low RR obtained in this study is understandable. While the impact of response bias on the results of patient satisfaction surveys has been noted [650], it has also been established that low RRs do not automatically invalidate the findings of the survey studies with which they are associated [651]. Moreover, the poor showing in this singular respect was overcome in the study by achievement all the other indices of quality

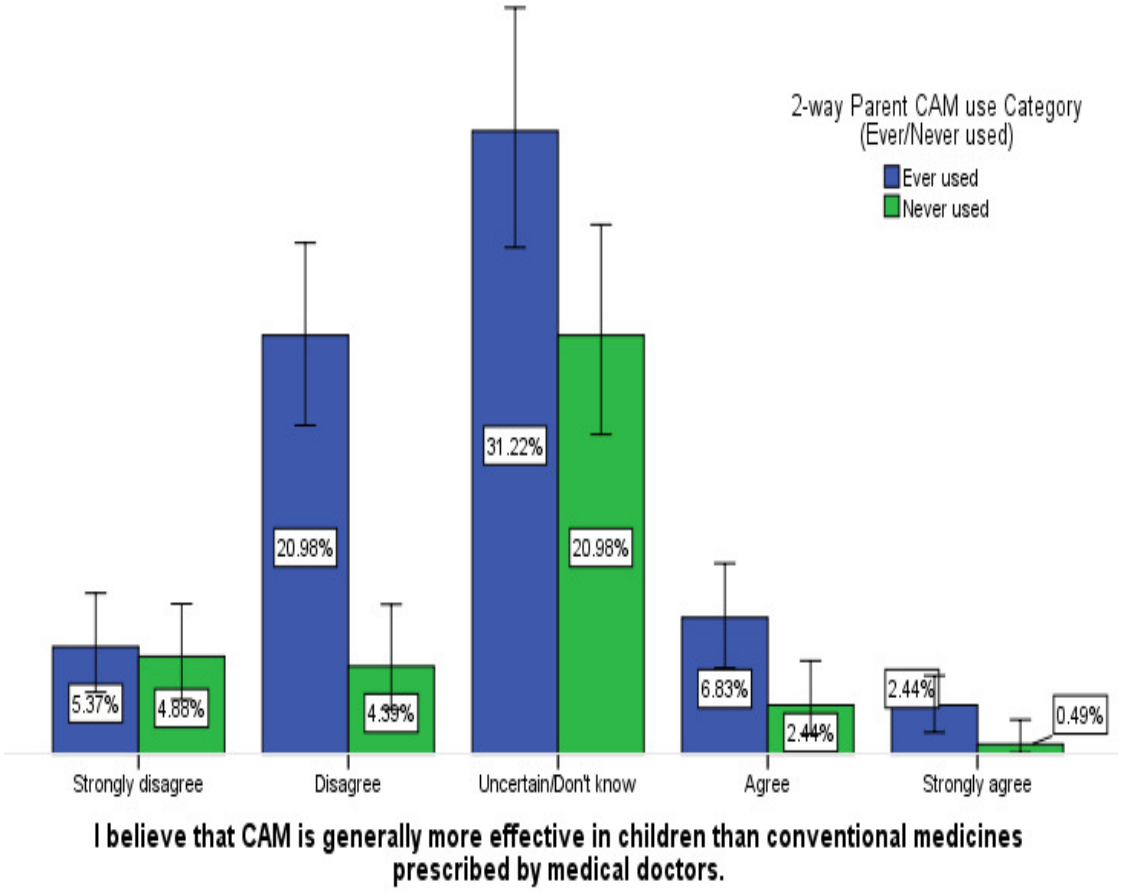


FIGURE 4.10: Parental attitudes on whether CAM modalities are generally more effective in children than conventional medicines

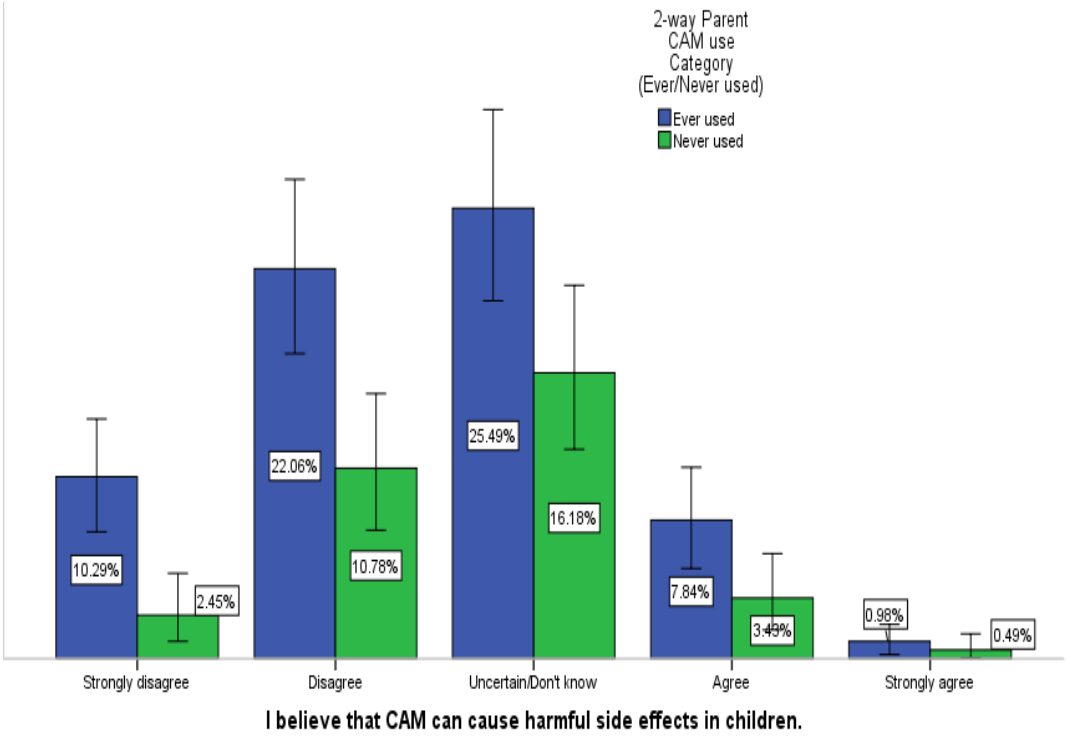


FIGURE 4.11: Parental attitudes on the potential of CAM to cause harmful side effects in children

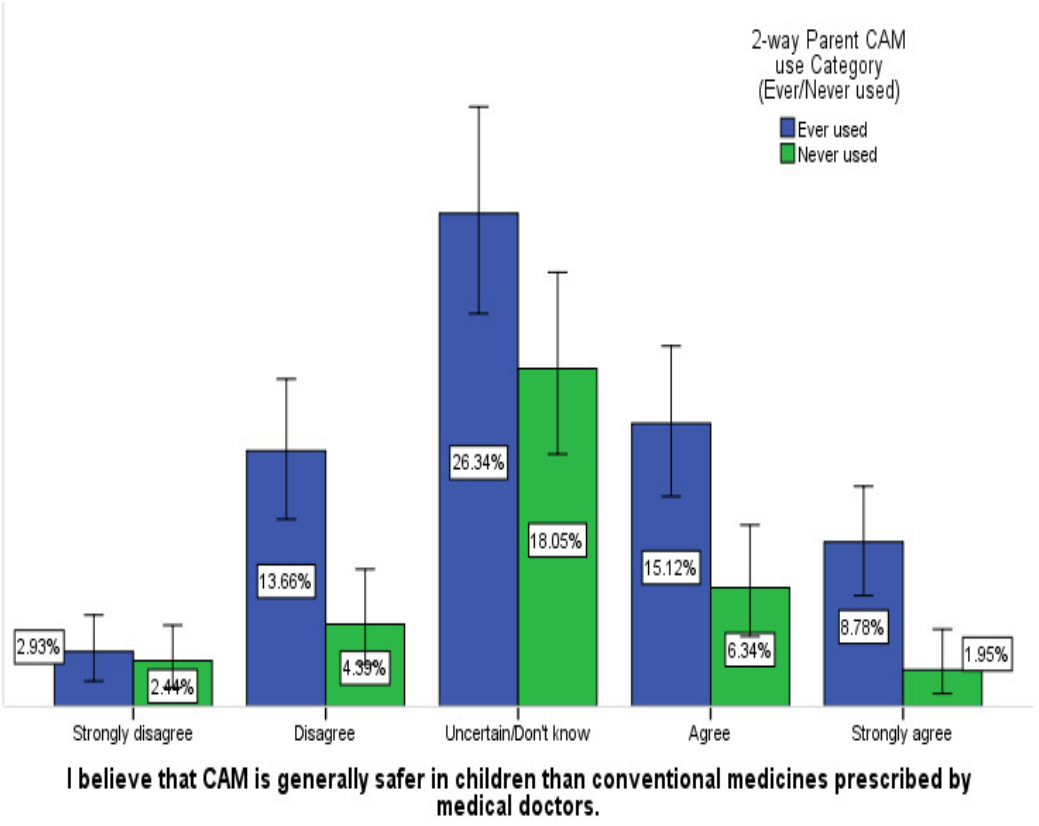


FIGURE 4.12: Parental attitudes on the greater safety of CAM use in children relative to conventional medicines

recruitment. Not only did the study achieve a sample size of > 300 children, it also surpassed the 378 children determined as the minimum sample required for statistical representativeness. In fact, this survey studied CAM use in the largest number of children amongst all the CAM surveys previously conducted in Scotland. The Scottish study with a sample size nearest to the one in the current study studied 327 children recruited from a hospital setting in Aberdeen [351]. Also, only one of the British paediatric CAM studies was able to recruit a larger number of children [348]. However, a similar study conducted in Finland in 2007 recruited 4,032 school children aged less than 12 years [652]. Also, of the eight studies in the SR reported in chapter 2 that obtained sample sizes of more than 600 children, only one was conducted in the UK. While the difficulty of recruiting paediatric subjects for research studies is generally acknowledged, the higher sample sizes recruited in studies conducted in other parts of the world suggest the relatively greater difficulty of conducting paediatric research in the UK.

Although, a large proportion of the respondents were eventually drawn from Aberdeen city's northern suburbs, this was not because efforts were not made to ensure uniform distribution of the study. The requirements of the use of multiple centres [331, 332]; a population-based approach [333, 334]; and a broad-based online sampling frame [653] were all met; which efforts were manifest in the spread of participants across 29 of the 32 postcode areas in the survey

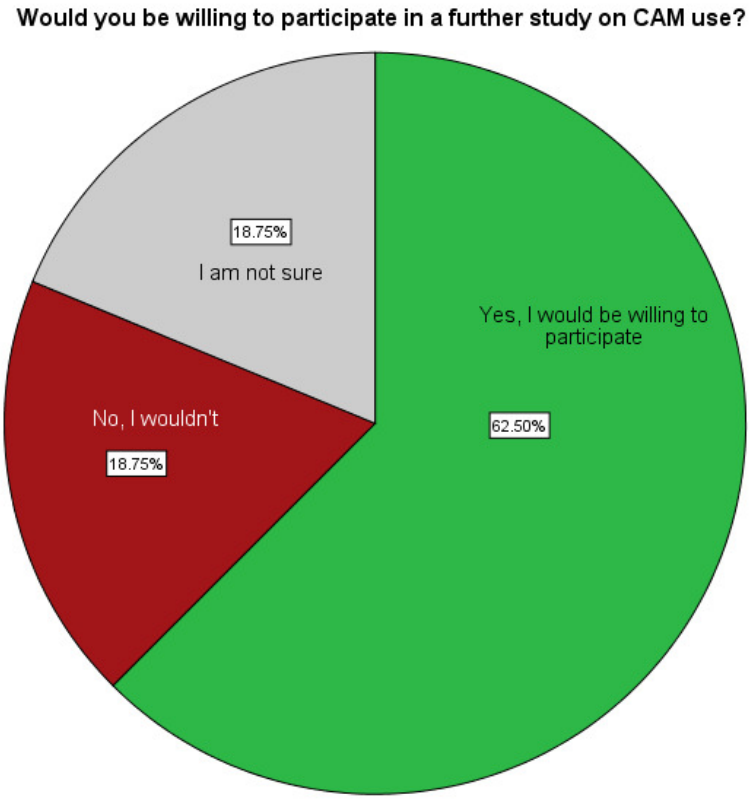


FIGURE 4.13: Disposition of parent CAM users towards participation in a further study on paediatric CAM use

area, and five of the six areas in the Scottish 6-fold urban-rural classification profile. Moreover, the key demographic features of the participants match those outlined for Aberdeen city and its shire in many respects [654]. These include features such as female young children being marginally more in number than males; a high proportion of "small family" households; a very low proportion of single parent households; a high population of people with post-secondary education qualification; and a relatively low proportion of those without formal qualifications, among others. The distribution of young children in different parts of the study area is also generally similar to available demographic data. Thus, while there is significant room for improvement in the area of participant recruitment, these facts indicate that the study and its findings can be considered generally representative of the target population.

4.4.3 Nature of paediatric CAM use and its correlates

67.5% of parents were found to have used CAM in their children at one point or the other; with the prevalence being 63.2% among children generally, and 66.1% for those aged up to 17 years. These prevalence values are much higher than the values indicated for UK children in general [395]; or even for children in Aberdeen [351]. One reason for this could be because the Aberdeen study focused only on product-based CAM modalities. Another Scottish study based in Glasgow

that included CAM practices along with products [352] found a prevalence level of 61% among children with inflammatory bowel disease. The most recent Scottish study based in Edinburgh [647] also studied both products and practices, and found a prevalence level of 55%. In the light of these data, the findings of this study indicate that paediatric CAM use is higher in Aberdeen area than other parts of Scotland, and the UK. This may not be unrelated to the relatively higher income status of Aberdeen city [655], a factor that has been associated with paediatric CAM use in other studies [220, 656].

Of the 213 children aged up to 17 years (66.1%) who had ever used CAM, 137 (64.3%) had always used it; while 45 (21.1%) and 31 (14.6%) either started using it within the last 12 months, or used it previously. The fact that much more of the children have always used CAM than have used it either in the past or only within the last 12 months indicates that paediatric CAM use is growing in Aberdeen metropolitan area as it is in other parts of the world, and particularly in Europe [599]. The last paediatric CAM use study conducted in Aberdeen 7 years ago [351] not only reported a much lower prevalence of 29% for CAM products, but also a 12-month prevalence of 20%, suggesting a declining level of use. While a longitudinal study is required to verify this finding, the findings of this study have high significance for healthcare policy and planning.

Paediatric CAM use was found in this study to be highly correlated with an age group of 30-44 years, Caucasian race, post-secondary education and parental self CAM use. These are all in line with the main demographic features associated with CAM use both in literature and also in the UK [608, 657]. Religiosity was however found not to be an important factor for CAM use in the study area, unlike reported for some other parts of the world [658, 659]. In line with other studies [370, 383], personal CAM use by parents was also found to be the strongest predictor of paediatric CAM use. This factor was also seen to be a predictor of consistent CAM use in children. This finding is significant given that, due to ethical reasons, many more CAM studies have been conducted in adults than in children. If these findings are verified in regression analyses in future paediatric CAM studies, it could reduce the necessity of conducting extensive paediatric CAM studies, given the huge challenges associated with them.

4.4.4 User-perceived effectiveness and safety outcomes of paediatric CAM use in the target groups

This study found a UPE of 68.1% and 78.4% for CAM products and practices, respectively. While these values are lower than the equivalent values for self-used CAM among parents, they are generally higher than the findings for most UK studies. Apart from Simpson and Roman [348] that reported a perceived effectiveness of 85% among therapies used, no other UK study reported a PE level as high as the current study. As the other Scottish study with a UPE level (61%) that is closest to this study was also carried out in Aberdeen [351], this finding may be

more indicative of parents in within the Aberdeen area. The finding is however lower than the 79% mean UPE rating reported by the studies in the SR of chapter 2. One reason for this could be the variety of measurement levels and format used for UPE measurement, varying from a simple "Yes/No" nominal rating scale to vastly varying levels of ordinal rating scales. The need for a more standardised method of rating UPE cannot therefore be over-emphasized.

This study also found a very low report of adverse events associated with CAM modalities (12 reports; 3.81%). This finding is very much in line with the finding among similar studies included in the SR; as well as the main outcome of the exploratory analysis of the YCS database reported in chapter 3. Of the 12 reports flagged up by respondents, only 2 were classified as having caused the users "a lot of discomfort". While these findings are further proof of the high degree of safety associated with CAM use, it is striking that homeopathic remedies are the most associated with the adverse events reported; and particularly with causing "a lot of discomfort". This finding, however, agrees with those of the exploratory analysis of the YCS data reported in chapter 3 of this thesis, which also highlighted the relatively high serious ADR potential of homeopathic medicinal products. Homeopathic products have severally been reported in literature as among the safest form of CAM [50, 157]; and have been promoted with the aim of avoiding the risk of drug interactions associated with herbal medicines [660]. Moreover, a study prescribing data in 323 medical practices in Scotland [630] found that "a substantial number of Scottish general practitioners prescribe homoeopathic and herbal remedies, with an approximate doubling in the number of children prescribed homoeopathic remedies". In the light of the findings from this study, there is great need for closer monitoring of homeopathic medicine use, particularly in children.

4.4.5 Limitations of the study

There are a number of limitations with this study. For one, there is still a lot of misunderstanding as to what really constitutes CAM. Many of the modalities listed as CAM are normally used by the participants without any intended health benefit. As such, although care was taken to define CAM to study participants, because the specific purposes for which the modalities they reported were used were not obtained, it is a bit difficult to verify that they were really used as CAM, and not just a food. A further qualitative study is needed to clarify this. Also, although a lot of effort was put into obtaining a truly representative sample, this could not really be achieved in the very sense of the word. A study with a stricter recruitment process is therefore needed. The many ethical challenges that hamper direct survey of children also came to play in this study. The need for direct reporting by the child users cannot be overstressed. As the current study was cross-sectional, it is limited in its deductive ability. A longitudinal study is therefore needed to verify most of the findings reported in this study, particular the high outcomes associated with the various CAM modalities.

4.5 Conclusion

The findings of this primary study provide clear evidence of a high prevalence of and significant satisfaction with CAM use by parents in their children within the Aberdeen metropolitan area. Also parental attitudes on CAM use in children have been shown to be generally positive; as they are most often shared by both those who have used CAM in their children and those who have not. This is an indication that paediatric CAM use is likely to increase with the passing years. This calls for significant attention from the government and other stake-holders in healthcare to ensure that this development is harnessed to the greatest advantage of the ordinary patient. One area of such emphasis would be to consider how best to meet the need expressed by a large proportion of our parent sample for more information on these therapies. Another is the consideration of recognising more of these modalities, especially the ones most highly perceived as effective by users, by bringing them into the NHS. Apart from meeting the needs of about two thirds of parents, it would also ensure that they are used more safely; and that any adverse events that arise are better managed.

Chapter 5

Comparative Summary of Research Findings

5.1 Triangulation of findings on UPES outcomes

The last three chapters reported the three broad research aspects of this doctoral research on the outcomes associated with paediatric CAM use. The current chapter aims to discuss the various strands of evidence obtained, to achieve a valid and concise summary of findings through triangulation.

Triangulation has been described as the use of more than one approach in the investigation of a research question in order to enhance confidence in the ensuing findings [661]. This may range from gathering data through the use of more than one method or sampling strategy; to the use of more than one researcher in gathering or interpreting data; to the application of more than one theoretical position in data interpretation [662]. However, while the term can be used to refer to all instances of multi-method research, it is more suited for those specific instances in which researchers seek to validate their findings by cross-checking them through another method [663, 664]. It is in this sense that triangulation is used in this chapter.

As stated in chapter one of this thesis, the aim of this doctoral research is to systematically determine the outcomes of CAM use in the general paediatric population of Aberdeen in north-east Scotland in terms of its user-perceived effectiveness and safety (UPES). As reported in the intervening chapters, this research has studied the UPES outcomes in the target population from various perspectives. Scope-wise, while the SR of relevant literature in the research area reported in chapter two served to set the broader context by identifying the global trends in that field of research; the database analysis reported in chapter three and the analytic cross-sectional study reported in chapter four served to verify those trends within the more specific contexts of the

UK (in general) and Aberdeen (in particular). With respect to methods, while the SR in chapter two and the database analysis in chapter three approached the study of the UPES outcomes from a secondary data perspective, the cross-sectional study reported in chapter four followed a primary study perspective. And finally, from a temporal perspective, while the research reported in chapters two and three approached the study retrospectively, that in chapter four focused on providing a snapshot of the current realities on the subject within the specific study area.

In terms of the paradigms that guided the various aspects of this research, while mainly positivist paradigms guided the research reported in chapters two and three; critical and subtle realist paradigms predominated in that reported in chapter four. Although the use of a mixture of research paradigms and methods can engender some tensions, because of the sequential application of the different paradigms in the course of this research, it was hoped that the resulting combination will be complementary rather than contradictory. Whether this was really achieved will be verified in the current chapter by seeking possible coherence in the various findings obtained from the preceding three strands of research. However, while a variety of issues were raised in the last three chapters of this thesis, the current chapter will focus on those relating to the UPES outcomes of paediatric CAM use.

5.2 Comparative summary of findings

5.2.1 High perceived effectiveness

A major finding of the SR reported in chapter two is the high report of positive outcomes by majorities of CAM users in primary research studies globally, with the notable exception of the UK studies. In that study, a positive outcome was described specifically as the report of perceived effectiveness (helpfulness, benefit, improvement, etc.) by more than 55% of CAM users surveyed or reported episodes of CAM use. While this finding was reported by 34 of the 46 studies included in the SR (74%), including 25 studies (54.3%) where it was so reported in $> 70\%$ of the subjects/episodes of use; the proportions of users reporting perceived effectiveness outcomes among the five UK studies included in the SR were not only relatively low, but also vastly different. Three of the five UK studies reported a UPE less than 50% [349, 350, 352]; and were among the five studies with the lowest UPE outcomes report of those included in the SR. Of the remaining two, while one of them, a hospital-based study conducted in Aberdeen, reported a UPE of 61% [351], the other, the oldest UK study, and the only population-based one, reported a UPE of 85% [348]. This observed marked departure of UK studies from the globally reported high positive outcomes of paediatric CAM use is confirmed by the findings of a recent SR of the prevalence of CAM use among paediatric patients in the UK, which reported an average PE of 48.3% (range 14-61%) for included studies [395].

At first glance, the findings of a UPE of 82.9% among users; and 74.9% among reported episodes of use of specific CAM therapies in the cross-sectional study reported in chapter four of this thesis seems to disagree with this trend. A second look, however, highlights a number of similarities, as well as suggests possible explanatory factors. Each of the two UK studies with high UPE reports was similar to the study reported in this thesis in either of two aspects –either in being conducted in the Aberdeen area or being population-based rather than hospital-based. While further research is required to verify this hypothesis, since these two factors are the most obvious features that distinguish these three studies from the other UK studies, there seems to be good justification to consider them relevant to the trends observed.

The effects of conducting CAM research in clinic-based settings, especially when they are conducted by medical professionals, are well noted in literature; and their possible contributions to the findings observed in the SR have already been discussed in section 2.4.5 (pp 49-50; paragraph 3). Primarily, they stem from social desirability bias; and may result in non-disclosure or over-enthusiasm by the patient participants, depending on their perception of the researcher's position on CAM use [356, 414, 665]. As such, they would be expected to limit the report of positive outcomes associated with CAM in research carried out in conventional medical centres; while overestimating those associated with research conducted in complementary health facilities. These trends have been discerned in the findings of the studies included in the SR, as earlier discussed (section 2.4.5). Also observed are the effects of use of non-clinic-based, population-based or postal research designs on the UPE reported. 10 of the studies included in the SR fell into this category; one of which [374] did not report a summary UPE rating for the therapies reported by participants. However, of the nine studies that did report summary data on UPE of the CAM modalities used, two thirds (7 studies; 78%) reported a UPE $> 60\%$ [348, 353, 354, 372, 375, 377, 504]; while only two studies reported a UPE $< 60\%$ [361, 666]. Similar trends have also been observed in adult population-based CAM studies [667–669]. These data highlight the intricate association between the setting and method of participant recruitment and the UPE outcomes reported; which explains the apparent disparity between the findings of the cross-sectional study reported in chapter four and those of the SR reported in chapter two.

Additionally, higher CAM use and UPE have been associated with affluent and educated communities [555, 670]. The status of Aberdeen as a relatively affluent city is well known in literature [671]. It has been recognised as fast out-pacing London's property boom, as average house prices are 120% higher than 10 years ago, representing the biggest regional percentage rise in the UK [672]. This relative affluence has been harnessed in comparative research designs that seek to investigate the role of affluence or urbanity in the research question [673, 674]. The high proportion of Aberdeen city residents in the cross-sectional study could therefore explain the much higher UPE outcomes found. Moreover, as the last study carried out in Aberdeen was conducted about 10 years ago, during the period of the economic recession; the vastly improved economic landscape

in Aberdeen within the period [672] can further explain the increased UPE outcomes reported in the present study. Thus, in view of these considerations, the findings of the cross-sectional survey arguably validate, rather than confound, those of the SR.

To further validate this opinion, the survey findings were mined for further evidence in this regard. Three specific aspects of the findings of the survey were considered. These included:

(i) the reasons for discontinuation of CAM use in children;

(ii) whether the main purposes for CAM use in children had actually been achieved; and,

(iii) the willingness of users to recommend CAM use to other parents

Of the 67 responses received from the 62 parents who provided insight as to why they had stopped using a CAM modality in their children, 40 (59.7%) stated that they had done so because their child's condition had improved; while only one parent (1.5%) stated that they had done so because their child's condition had not, leading them to try some other therapy. Of the 108 parents who responded to the question on whether they had achieved their main purposes for using CAM in the children, 99 (91.7%) stated that they had done so; 6 parents (5.6%) stated that they had not; while 3 parents (2.9%) were unsure. Finally, of the 114 parent users who responded to the question on recommending CAM to other parents, 107 (93.9%) stated that they would do so; while four (3.5%) responded negatively, and three (2.6%) were unsure. Taken together, these additional findings from the survey clearly highlight the high association of positive outcomes with CAM use in children, thus further strengthening the earlier findings on high perceived effectiveness.

These findings would, however, be strengthened by further studies on outcomes associated with the supervised use of CAM in clinic or hospital settings. While two of the studies included in the SR studied such outcomes, due to the fewness and non-conventional health care setting of such studies, the significant improvement in eczema [357] and respiratory diseases [358] reported by patients needs validation by studies carried out in conventional health care settings. As the survey findings also indicate that, of the 179 responses as to the source of recommendation of the CAM used in their children, 54 (30%) had specified various conventional health care practitioners, it implies that CAM is still very much used in conventional healthcare settings within Scotland, as Ross et al [630] reported a decade ago. The conventional health care professionals listed as sources of CAM recommendations included doctors (21 parents); pharmacists and nurses (17 parents); health visitors (15 parents); and psychologists (1 parent). It would be very helpful to determine through further research the outcomes of such instances of CAM use within conventional healthcare settings. In the absence of such further studies, however, it is safe to state that the findings of the cross-sectional study highly validate the high report of UPE found in the SR. This also implies that the perceptions of parents in the Aberdeen metropolitan area

on the effectiveness of paediatric CAM use are very much like those of parents in other parts of the world.

5.2.2 Low report of adverse outcomes

Another key finding of the SR is the low report of adverse outcomes by CAM users surveyed. While nine of the fourteen papers that provided clear numerical data on the adverse outcomes studied adverse outcomes (64%) reported them in $0-5\%$ of CAM users, and four of the remaining five studies reported them in $< 10\%$ of users, the majority of the studies included in the SR (27 of the 46 studies; 59%) showed no evidence of having investigated negative outcomes of CAM use in children. This observation questioned the validity of the low adverse outcomes found in the SR, as it made them no more representative of the studies included in the review. It was not obvious whether the non-mention of adverse outcomes in the majority of included studies was as a result of an omission or lack of research emphasis on the part of the researchers, or due to the actual absence of their report by users. It therefore became necessary to confirm the findings of the SR in this respect through other data sources.

The exploratory database analysis reported in chapter three provided a good opportunity to achieve this; even though, due to a couple of limitations, it was still not fool-proof. These limitations included the general non-representativeness that hampers pharmacovigilance efforts through national databases like the YCS due to under-reporting of ADRs. There was also the additional challenge of the relative difficulty in defining CAM, which made it difficult to clearly distinguish which particular products in the database were actually used as CAM. To avoid missing out on any reported incident of CAM use, a broad definition of "CAM product" was, therefore, adopted for the study; resulting in the analysis of ADR reports made for all natural health products on the YCS database. However, as the data analysed compassed a period of almost 50 years, from the inception of the database in 1963 to July, 2012, the analysis was expected to nonetheless provide a broad picture of the safety profile of the products in the UK population.

The findings of the analysis were found to align with the low level of ADR report suggested by the findings of the SR, as CAM-related ADRs reported for paediatric subjects in the YCS were relatively few; and predominantly skin rash. Of the 698, 638 ADRs reported on the database for the period, only 2,167 (0.3%) concerned a natural health product; with only 192 (0.03%) being reported for children aged up to 17 years. Although these 192 paediatric reports yielded a total of 332 specific ADRs, detailed analysis showed them to be of low severity (6%) and fatality (2%), with over 75% resolution rate, and mostly within the first 3 days of the report (68%). The significance of these findings was, however, questioned by their association with a high degree of

incomplete or missing data on both the severity of ADRs (92%) and their duration (60%). As a result, another source of validation was further necessitated.

In view of the above, the analytical cross-sectional study reported in chapter four was designed to focus, among other things, on elucidating the adverse outcomes associated with CAM use in children. This information was thus required of all who acknowledged any form of CAM use in their children. To improve the possibility of detecting such adverse outcomes with minimal guilt feelings on the part of users, adverse outcomes were described simply as "any discomfort"; and users were required to both rate the degree of such discomforts as well as specify what exactly they were. The findings indicated that only 9 of 123 parent users that answered that question (7.3%) reported either "a little" or "a lot" of discomfort following their children's use of CAM; with 97 parents (79%) stating that they had experienced "no discomfort whatsoever"; and 17 parents who had selected either "not sure" or "not much discomfort" (14%) not stating any specific adverse outcome upon further questioning. Of the 9 parents who indicated a positive degree of discomfort, only 2 parents (1.6%) described the discomfort as "a lot". Upon further enquiry, these nine parent users listed 11 specific discomforts, 8 (73%) of which were either allergy/skin reaction or unpleasant taste (4 reports each; 36%). Of the 14 responses received as to who they had informed of the discomforts they had experienced, 9 (64.3%) stated either nobody or other family members; and 3 (21.4%) mentioned a CAM therapist; while only 2 (14.3%) mentioned a doctor. Significantly, no parent mentioned having reported any of the discomforts experienced to the MHRA; thus validating the low proportion of report of patient-reported NHP-related ADRs observed in the exploratory analysis of the YCS data (7 reports; 3.7%).

These findings align with those of the YCS database analysis both in terms of the low frequency of adverse outcomes as well as their nature. They also indicate that the finding of low adverse outcomes reports seen in the SR was very much in order. Therefore, it is valid to state that CAM use in children within the Aberdeen metropolitan area is widely perceived as safe, just as it is in other parts of the world.

5.2.3 Safety concerns over homeopathic medicinal products

Homeopathic medicinal products have generally been accepted as safe [50, 157] -and essentially so for the very same reasons for which their effectiveness has long been contested –their relative lack of "biologically active substances" due to the use of ultra-high dilutions [619, 675]. Even when adverse outcomes have been associated with these products, such ADRs have been described as both rare and non-severe [624]. In the light of these opinions, the findings of different aspects of the current research on this subject are interesting.

The findings of the SR agree with the idea that homeopathic medicinal products are not really associated with adverse outcomes. While the two studies that focused solely on homeopathic

product use in children [357, 358] did not report any ADRs among users; the other study that focused on herbal and homeopathic medicinal product use [382] did not study adverse outcomes. The findings of the exploratory analysis of YCS database, however, seemed to differ markedly in this regard. While the 23 reported episodes of homeopathic product use in children in the database were associated with 46 ADRs, 13.9% of the 332 ADRs listed; they were also associated with 17 serious ADRs from 8 episodes of use. This resulted in a serious ADR potential of 34.8%. Also, although 10 of the 17 serious ADRs (59%) reported for such products were deemed serious for reasons other than for the main CIOMS markers of seriousness, and none of the ADRs was fatal; 5 of them (29.4%) were described as life-threatening, while the remaining 2 resulted in hospitalisation. Although homeopathic products were found to be very far behind dietary supplements in their serious ADR potential, in view of the general public opinion on the safety of these products, as well as the findings of the SR, these findings were still considered strange. It, therefore, became necessary to consider the findings of the cross-sectional survey in order to verify the validity of these findings.

The findings of the survey indicate that, not only was homeopathic product use among children in the Aberdeen area associated with adverse outcomes generally; it was also highly associated with "serious" ones. Based on the reports of parent users, homeopathic products accounted for four (44.4%) of the nine ADRs reported for CAM products. Also, these products alone accounted for the two "serious" ADRs reported, which had been described by users as having caused their children "a lot of discomfort". These findings therefore indicate that the implication of homeopathic products in serious ADRs in the exploratory analysis of the YCS is valid. They also suggest that the non-report of ADRs in the two studied that focused on such products in the SR could be another evidence in support of the tendency towards confirmation bias observed among authors in that review. On the other hand, it could also be that the ADRs reported were actually "homeopathic aggravations", rather than ADRs, as has been suggested by homeopaths [50, 676]. Stub et al [677] have proposed an adverse event duration of 14 days, as well as the absence of a feeling of well-being, as key criteria that distinguish ADRs from homeopathic aggravations. While information on the duration of the adverse outcomes reported was not obtained during the survey, the data available does indicate that the parents concerned did not find the implicated homeopathic products "a lot helpful". In addition, data from the YCS database analysis indicates that homeopathic products were generally associated with the longest ADR durations. Of the 15 ADRs for homeopathic products that had valid details on ADR duration, five (33%) were found to have lasted 14-72 days. Also, not only were three of the five ADRs considered serious by their reporters, but also they were not among the serious ADRs described as life-threatening or causing hospitalisation. While more specific data is needed for greater certainty, going by the criteria proposed by Stub et al, the additional details provided for the ADRs concerned do not really support their categorization as homeopathic aggravations. Whatever the case, however, as the consensus on reporting standards proposed as a supplement to the Consolidated Standards of Reporting

Trials (CONSORT) statement specifically for Reporting data on Homeopathic treatments (Red-Hot) requires that aggravations be included under adverse effects [678], such a distinction may not ultimately be particularly helpful.

Another caveat usually placed on adverse outcome reports associated with homeopathic products is the source of the product implicated; particularly in terms of whether or not it had been prescribed by a homeopath, and also the level of training and qualification of the homeopath prescriber [679, 680]. Such indirect, practitioner-associated factors, rather than those related to the medicine itself, have been proposed as the major source of risk associated with homeopathy [620, 681]. Although an enquiry was made as to the source of knowledge about the CAM used, the information provided was not product-specific. The parents concerned, however, did not include a homeopath, or any other CAM provider, among the sources they listed for the products implicated in the survey. Similarly, the source of the product used was generally not mentioned in the YCS database, except for a single case report in which the associated product was a pollen solution obtained from a homeopath. This product caused angioedema in a 5-year old male child; which resulted in emergency hospitalisation, but resolved fully within three days. In the absence of further details in this regard, however, nothing much can be made of this single isolated event. Thus, it is safe to conclude that there is insufficient evidence from the research reported in this thesis to rule out indirect or practitioner-related factors as causes of the ADRs observed.

The above mentioned limitations notwithstanding, an amalgamation of the findings of the YCS database analysis and the survey clearly raises serious concern about the safety of homeopathic products, as has also been emphasized in a recent SRs on the subject [621, 677]. This obviously calls for further investigation in view of the relatively high use of homeopathic products in the UK, not only within the four homeopathic hospitals, but also in different conventional health care settings [682]. This recommendation is particularly relevant for Scotland in view of the high level of prescription of such products in Scottish GP practices, particularly for children [630].

5.3 Conclusion

A triangulation of the findings of the three major aspects of this doctoral research indicates that the outcomes associated with CAM use among children in Aberdeen metropolitan area are similar to those reported for other parts of the world. There is a high perception of positive outcomes among parents for these therapies; and a low perception of negative outcomes. Specifically, paediatric CAM use in the area is associated with high user-perceived effectiveness and safety outcomes.

Chapter 6

Conclusions and Recommendations

6.1 Research overview

As outlined in chapter one of this report, this doctoral research aimed to answer the following research questions:

1. What is the strength and quality of published literature relating to user-reported effectiveness and safety outcomes of paediatric CAM product use in terms of methodologies, methods and models?
2. What are the key findings of published literature on impact of paediatric CAM product use in terms of user-reported effectiveness and safety outcomes?
3. What is the extent and nature of the pharmacovigilance data on paediatric CAM product use in the UK?
4. What is the nature and demography of the use and user-reported outcomes of paediatric CAM products and practices in the Aberdeen area of NE Scotland with respect to perceived effectiveness and safety?
5. What implications do the findings have for research and/or health policy and planning in Scotland?

This concluding chapter provides a summary of the answers obtained for these questions based on the findings of the research reported in the intervening chapters. The answers to the questions 1-4 are summarised in the next section; while their implications for health policy and planning in Scotland are outlined in the last section.

6.2 General conclusions

6.2.1 Conclusions from the systematic review

The SR of literature on user-perceived effectiveness and safety outcomes of paediatric CAM in the period between January 2000 and July 2011 identified 46 relevant studies, half of which were conducted in North America; five within the UK; and two in Scotland. These studies generally reported high degrees of positive outcomes, as well as a low degree of negative outcomes, by the majority of CAM users in the populations surveyed. Adverse outcomes were studied in less than half of included studies, indicating a lack of emphasis on such outcomes among paediatric subjects. These findings were, however, complicated by the generally low methodological quality of included studies; as only nine of the studies met 8 of the 12 standard quality indices by which the studies were assessed. This was mainly due to an observed tendency to non-rigorous research and confirmation bias among authors that manifested in various ways.

6.2.2 Conclusions from the Yellow Cards database analysis

Despite several public health policy initiatives to encourage ADR reporting, CAM product use in paediatric populations was found to contribute an insignificant proportion of ADR reports in the YCS database within the (nearly) 50-year period studied. The few CAM-related ADRs reported were of low severity and fatality; and with a high resolution rate. The reports, however, contained a high degree of incomplete or missing data. Among the CAM product types, although herb-drug combination products and herbal remedies accounted for the highest proportions of ADRs, and herbal products the least, nutritional supplement and homeopathic products were most associated with fatal and relatively high serious ADR potentials, respectively.

6.2.3 Conclusions from the cross-sectional survey of parents in the Aberdeen area

Paediatric CAM use was found to be both high and growing in the Aberdeen metropolitan area, as it is in other parts of the world; with a much higher use of product-based CAM than practice therapies among children. Trends in CAM use in the area were also found to generally align with those observed for CAM use in literature. Parents reported a much higher perception of the effectiveness of the therapies they used for their children than in most previous UK studies, with significantly better outcomes reported for practice therapies than products, except for the commonly used ones. Self CAM use among parents, as well as parental perception of helpfulness of the therapies self-used, were found to be the greatest determinants of paediatric CAM use and perceived effectiveness outcomes, respectively. Irrespective of their use of CAM for their children,

parents in the Aberdeen area indicated a general preference for a more informed choice of CAM therapies for use in their children along with conventional care; and all this within the supervised framework of doctors and the NHS. They also demonstrated high willingness to participate in future CAM research.

6.3 Implications of findings for health policy and planning

The findings of this study point to a number of recommendations for research as well as health policy and planning. A POEM-based, bottom-line summary will be provided at the end.

6.3.1 Recommendations for further work

(i.) The SR reported in this thesis covered the period between January 2000 and July 2011. It was also limited by language restriction to the English language. There is, therefore, need for an updated and more rigorous SR of the study area. Such further review should aim at verifying the findings of the review currently reported; especially with respect to the tendency to confirmation bias noted among authors.

(ii.) Future paediatric CAM studies need to ensure stricter adherence to procedural ethics, especially as stipulated in such standard reporting criteria as STROBE; so as to improve their overall methodological quality.

(iii.) The database analysis reported in chapter three covered a period up until July 2012. As the YCS officially marked its fiftieth year of formal establishment in 2014, a more up-to-date analysis is called for. Apart from ensuring that the analysis would contain annual data for full year periods, it would also provide a complete summary of the activities of the MHRA within its first 50 years.

(iv.) The survey reported in chapter four, although analytical, was nonetheless cross-sectional. The SR highlighted the paucity of longitudinal studies of CAM interventions, particularly in children. Such studies are particularly relevant for investigating effectiveness of interventions. Further studies should focus on such study designs. They would more clearly demonstrate whether the effectiveness outcomes reported by parents are sustained over a period.

(v.) In view of the few and non-specific responses to the enquiry about the details of the benefits reportedly associated with paediatric CAM use, there is need for in-depth qualitative studies to determine exactly what parents mean by stating that they perceive CAM to be helpful.

(vi.) The high degree of uncertainty among parents as to the outcomes associated with CAM product use in their children suggests that proxy report may not be as effective as one would desire. This is particularly emphasized by the significantly lower degree of uncertainty among parents of their own self-used CAM. Further studies on UPE should, therefore, emphasize direct reporting by the children in whom the CAM is used wherever possible.

(vii.) Considering the apparent non-emphasis on CAM safety investigation in previous paediatric CAM use studies, future studies need to strongly emphasize them. Also, in view of the extreme importance of patient safety, the outcomes found (or lack thereof) should also be reported, no matter how doubtful they may appear to the researchers.

(viii.) In view of the highlighted tendency towards confirmation bias among research authors on UPE of CAM interventions, authors of future studies on CAM use should ensure that the result summaries and conclusions they generate are strictly in line with the data their participants provided, irrespective of how implausible they may seem to the researchers themselves. This would ensure that the voices of participants are given their due place in research findings, particularly in the current patient-centred care era.

6.3.2 Recommendations for health policy and planning

(i.) In response to parental expression of their need for more information concerning CAM modalities, there is need for more open communication about CAM use in children. While the NHS website currently has a number of pages dedicated to CAM therapies, these appear to be mostly unknown to parents; and/or are probably not rich enough to properly inform them. Also, because the CAM-related information provided is usually science-based, rather than based on user outcomes, it tends to be generally more critical of CAM use; which could ultimately discourage parents. Therefore, in recognition of the broad acceptance of CAM among parents, the future CAM content of such websites need to be more inclusive of user outcomes; as well as more targeted to the needs of parents.

(ii.) The restrictions that currently hinder direct access to paediatric subjects for research in the UK should be reviewed in order to enable the voice of children to be heard in future research on paediatric health interventions. This is especially so for studies dealing with perceived outcomes.

(iii.) In view of the highlighted inefficiency of the various public health initiatives instituted over the years in improving ADR reporting for CAM products, there is need for more effective initiatives that are specifically targeted towards CAM products. One such policy that could prove helpful in this regard is the requirement of the placement of yellow cards as part of package inserts for such products. As parents indicated in the survey that they obtained

information about CAM mainly from the internet, and then the television, similar policy could target advertisements of CAM products in both print and electronic media, including parenting websites, requiring them to notify users of the possibility of adverse effects, and the need to report them where they occur.

(iv.) In view of the highlighted implication of homeopathic products in serious ADRs, as well as their reported high use in Scottish GP practices, there is great need for a Scottish agency specifically devoted to monitoring for NHP-related ADRs, especially for homeopathic products. While the function of gathering ADR-related data in the Scottish NHS is currently under the ambit of the ISD Scotland, the failure of several efforts by the supervisory team to obtain usable data on homeopathic products from this agency for analysis by the student suggests that more needs to be done to ensure that that aspect of ISD mission statement is fully realised for NHPs. Had such data been readily available, it would have helped bring the database analysis nearer home; as well as helped to further validate the findings of the UK-wide YCS analysis in this regard.

(v.) With high proportions of both parent-users and non-users of CAM calling for its integration in the NHS, stake-holders in the health industry need to commission more studies on CAM; so as to actively consider the modalities that qualify for such integration, and to encourage such. The establishment of a body similar to the US NCCIH that is specifically focused on CAM research with the goal of integration is highly recommended in this vein.

(vi.) Considering the desire of parents for more informed choice on their children's use of CAM within the context of a supervised health system, health professionals should realise that parents want to be more involved in their children's healthcare choices; and should collaborate with them to achieve the best outcomes.

6.3.3 Summative conclusion

This doctoral research deduced international perspectives on the UPES outcomes of paediatric CAMs from the findings of the maiden SR reported in chapter two. It highlighted that the high report of positive health outcomes and low report of adverse outcomes reported by CAM users in published studies were complicated by the generally low methodological quality of the studies. The premier analysis of the NHP-associated ADR reports made to the YCS that was reported in chapter three served to provide a British perspective of safety outcomes of CAM use in children; highlighting the fewness and low severity and fatality of the NHP-related ADRs reported. Finally, the local Scottish perspective provided by the first population-based Scottish study of paediatric CAM use reported in chapter four evidenced the high prevalence of and significant satisfaction with paediatric CAM use by parents in the Aberdeen area. The triangulation of the results from these three strands conducted in chapter five validated the common theme that CAM is used

widely among children, with high perceived effectiveness and safety outcomes. While various recommendations have been made in the preceding two sections of this chapter, this final section proposes to provide a POEM-based summary of the findings of this research on the outcomes of paediatric CAM use as reported by parents in the Aberdeen area of NE Scotland.

The findings reported in this thesis highlight that parents in Aberdeen are very much like their counterparts in other parts of the world as far as the use of CAM in their children and the associated outcomes are concerned. Not only do many more parents now use CAM in their children, but also many users and non-users acknowledge the importance of such use; implying a general trend towards increased paediatric CAM use in the future. Key evidence in this regard include not only the generally high perceived effectiveness of paediatric CAM use among parent users; but also the higher prevalence of self CAM use and its perceived effectiveness among parents generally. Also, as in other parts of the world, a high majority of parents in Aberdeen prefer to make up their own minds about CAM use in their children; but also express a need of suitable information to enable them do so effectively. As such, they do not mind discussing such CAM use with appropriately trained health care professionals; and would largely prefer the free availability of CAM on the NHS, so they can effectively use CAM along with prescribed conventional medicines. The bottom line therefore is that parents in Aberdeen, as with parents world-wide, highly desire to be involved in the health care decisions concerning their children; and consider the informed use of CAM in children a good opportunity to do so. The proper recognition and acceptance of this finding in future health care policy and planning will significantly improve child health and development in not only Aberdeen, but also the rest of Scotland.

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Appendix I

Systematic Review Protocol

This appendix contains the Protocol for the systematic review.

A PROTOCOL
FOR THE SYSTEMATIC REVIEW
OF THE TOPIC:
USER PERCEPTIONS OF THE EFFECTIVENESS & SAFETY OF PAEDIATRIC COMPLEMENTARY AND ALTERNATIVE MEDICINES

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CHAPTER ONE: BACKGROUND TO THE REVIEW

1.1 CAM: Definition and Classification

The World Health Organisation (WHO) views Complementary and Alternative Medicine (CAM) somewhat as a new improved version of Traditional Medicine (TM), in that it originated from it and shares many of its features, differing only in the context within which it is used. Therefore, while it defines TM as 'the sum total of knowledge, skills and practices based on the theories, beliefs and experiences indigenous to different cultures, whether explicable or not, used in the maintenance of health, as well as in prevention, diagnosis, improvement or treatment of physical and mental illnesses' (1), it defines CAM in the same document as 'a broad set of health care practices that are not part of a country's own tradition and are not integrated into the dominant health care system'. Because of the close association between the two terms, in its publications, the WHO prefers to use the term TM/CAM to either separate term. It, therefore, broadly categorizes TM/CAM into **Medication Therapies (MT)**— if they involve use of herbal medicines, animal parts and/or minerals — or **Non-Medication therapies (NMT**)— if they are carried out primarily without the use of medication, as in the case of acupuncture, manual therapies and spiritual therapies (2). Although not specifically so indicated by the WHO, MT can be extrapolated to include homeopathic medicines and essential oils. Although these products are utilized as part of some NMT, they still are essentially medication therapies in their own right. Described in this way, MT can be more correctly termed **Pharmaceutical-type CAM**, or simply **Complementary and Alternative Medicines (CAMs)** (3,4,5). As it would be practically impossible to systematically review all CAM types together -and considering the

pharmaceutical background of this research- the current review will be restricted to the CAMs.

The WHO's current goal is the integration of as many TM/CAM therapies as possible into national healthcare systems, in the bid to improve global health status and quality of life (2). While this has been greatly lauded by developing countries, in many developed countries –especially the UK and the USA – it has met with much conflict and opposition (6,6,7). In spite of this mixture of opinions, however, trends in CAM use have continued to rise world-wide (8,9,10,11,12,13,14,15). Similar trends have also been reported in paediatric populations (16,17,18,19,20,21,22,23,24,25,26,27,28).

1.2 CAMs: Popularity, Efficacy, and Safety

In virtually all surveys of CAM use world-wide, CAMs have consistently been found to be the most popular CAM type used –even among paediatric populations (18, 29, 30, 31, 32, 33, 34, 35, 36, 14, 37, 38, 39, 26, 40, 41, 42, 43). Apart from being the most popular form of CAM used world-wide, CAMs – with the notable exception of homeopathic products- also escape what can be rightly termed the bane of all CAM: the 'hocus pocus' label. Unlike most of the other CAM types, herbal products, dietary supplements and probiotics are largely evidence-based (44, 45, 46), with so many literature reports of experimental and quasi-experimental pre-clinical and clinical studies –including randomized controlled trials- validating their claims and affirming their efficacy (47, 48, 49, 50, 51, 52, 53, 54, 55). In spite of these advantages, however, CAMs – especially herbals- are plagued with the problems of large-scale adulteration (56, 57, 58, 59, 60, 61, 62, 63, 64), and a high tendency of often unfavourable

interactions with conventional drugs (65, 66, 67, 68, 69, 70, 71, 72, 73, 74). Homeopathic products, on the hand, in spite of numerous clinical trials in various health conditions, are still plagued with the problem of controversial efficacy (75, 76, 77, 6, 78, 79, 80). Given the popularity of these products, these drawbacks have grave implications for patient safety, and have raised concerns as to the over-all safety and effectiveness of these medicines. These concerns have been the subject of various studies (81, 82, 83, 84, 85, 86, 87, 88, 89, 90, 72), and have also been raised with respect to their use in paediatric subjects (91, 92, 93, 94, 95, 96, 97, 98,99).

1.3 Effectiveness of Health Interventions: Definition and Assessment

Historically, efficacy studies were the backbone of clinical research, being accepted as the gold standard for determining whether or not a treatment worked (100). From the turn of the century, however, there has been a shift of emphasis towards effectiveness studies. Effectiveness studies differ from efficacy studies in that they focus on real-world use of interventions as against an ideal-setting perspective.(101, 102, 103, 104, 105). In other words, efficacy studies are explanatory, whereas effectiveness studies are pragmatic (106, 107). Despite these distinctions, there is still sufficient confusion among researchers over the right terminology to warrant mislabelling of some 'effectiveness' studies as 'efficacy' studies, and vice versa. As a result, many systematic reviews of 'effectiveness' studies often mistakenly include studies that are actually 'efficacy' studies. To guard against this common error, Gartlehner and his colleagues at the RTI-International–University of North Carolina Evidence-based Practice Center, in a research carried out for the Agency of Healthcare Research and Quality of the United States' Department of Health and Human Services, have

identified six criteria by which effectiveness studies can be distinguished with high specificity and sensitivity from efficacy studies during systematic reviews (108).

The effectiveness of a health intervention can be assessed from two major perspectives –objectively: from the clinician's/experimenter's perspective **(clinical effectiveness, CE)**, or subjectively: from a patient's/consumer's perspective **(perceived effectiveness, PE)** (109, 110, 111). The **cost-effectiveness/cost-benefit** of the intervention can then be obtained by deducing the economic implications of achieving or improving the effectiveness data realized from these two perspectives relative to those for another intervention (112, 113, 114, 115). While CE focuses on the attainment of clinical/therapeutic outcomes/goals/end-points –and is best judged by carefully designed and well conducted pragmatic 'real world' randomized (controlled) trials. (116, 117, 118, 119, 120, 121), PE focuses on the attainment of humanistic outcomes through assessing the health-related quality of life (HRQoL) of the receiver, and is best assessed using observational studies – essentially cross-sectional surveys, cohort or case-control studies, and qualitative research (109, 122, 123, 124, 125, 126, 127, 128, 129, 130, 131, 132, 133, 134, 135, 136, 137, 138). With many CAMs having been reported to be efficacious in specific disease conditions, and the complications arising from their popularity, the importance of effectiveness studies in assessing their over-all usefulness cannot be overemphasized. This fact is even much more valid for homeopathic products, since effectiveness studies can help to settle the controversies generated by efficacy studies.

Although evidence obtained from well-conducted randomized controlled trials (RCTs) is generally accorded greater recognition and placed on a higher level in the popular hierarchies of evidence in the evaluation of healthcare interventions (139, 140, 141), studies have shown that observational studies are not particularly inferior to randomized trials (142, 143, 144), and are actually superior to them in studies where opinions, attitudes and perceptions about interventions are being investigated (145, 146, 111). As a result, these have increasingly been used in the study of the PE of CAM (147, 148, 149, 150, 151, 152, 153, 154, 155, 156, 157). Such studies have also been carried out in paediatric subjects (31, 158, 159, 160, 161, 162, 137), and these will be the focus of the present review.

1.4 Medication Safety –the CAMs Perspective

Despite the great advances in the field of surgery, and the persistent debates, the use of medications remains the most common intervention in allopathic medicine, being the preferred initial intervention in most health conditions, as well as an essential component of post-surgical management (163, 164, 165, 166, 167, 168). However, this popularity does not come without a price, as adverse drug events (ADEs) account for the greatest proportion of medical errors in both adults and children (169, 170, 171, 172, 173, 174, 175, 176, 177, 178, 179, 180). Consequently, medication safety has become a very important goal as far as patient safety is concerned (181, 182, 183, 184, 185, 186, 187). This is particularly so in unlicensed or 'off-label' medicine use –as is widespread in the treatment of paediatric subjects (188, 189, 190, 191, 192, 172, 193, 194, 195, 196, 197, 198, 199, 200, 201, 202, 203, 204, 205). As CAMs are the most popular CAM therapies used in both adults and children (see above), and are to

a large extent unlicensed as drugs by statutory regulatory agencies (206, 207, 208, 209, 3, 210), it is understandable that they will share the same safety concerns as orthodox medicines –if not (and very likely) much more.

Although the importance of reducing medication errors has been noted (171, 211, 212, 213, 214), the key factor in the achievement of medication safety is the early detection and subsequent prevention of ADEs (215, 216, 217, 218, 219, 220, 221, 222). In appraising the various methods that have been utilized in the detection of ADEs and measurement of medication safety in adults and children (173, 183, 223, 224, 225, 226),several studies have highlighted the importance of surveillance methods involving interaction with in patients and outpatients (227, 228, 229, 218, 230, 231, 232, 233). Apart from cases where diagnosis was required or where patient consciousness, judgement or communication was impaired (234, 235, 233), the ADE information realised from such interaction –essentially through patient interviews and surveys- was found to be not only in concord with that reported by clinicians, but also complementary to it (236, 237, 230, 231, 238). In addition to the improved generation of information about the experiences of past patients for the benefit of future patients in both hospital and community settings, potential advantages of such methods include earlier detection of ADEs, and additional toxicity data to compare with efficacy during regulatory review (239, 240, 241, 233).

Thus, in spite of initial criticism and scepticism (242, 243, 244, 245, 246, 247, 248, 249, 250, 251), the active role of 'users' or 'consumers' in the assessment of healthcare quality has become firmly established as a *sine qua non* in the achievement of not only individual patient medication safety, but also the HRQoL

of the entire populace (252-262). However, the general reluctance of patients and drug users to voluntarily report adverse drug events (247,249,263-267), greatly emphasizes the need for frequent, well-designed and innovative pharmacoepidemiological studies with a view to eliciting ADE reports (240,268-273). Such studies are particularly important in the area of CAMs if a significant degree of safety is to be achieved therein. Here, because their use is characterized by a high degree of self-medication as a result of strong cultural and familial sentiments (274-279), there is understandably a higher degree of under-reporting of adverse events (3,81,87,280-285).

1.5 Perceived Risk/Safety: Understanding the underlying motivations

With the trend towards 'switching' more and more prescription-only medications (POMs) to over-the-counter (OTC) medications (286-289), and the associated increase in self-medication with its many hazards (89,290-299), another important issue in the achievement of medication safety and the over-all HRQoL of the populace has become the perceived risk (or, conversely, perceived safety) of medication use among (especially) the lay public (300-312). Perceived risk (or, conversely, perceived safety) differs from actual risk (or, safety -as discussed in the previous section) in that it focuses, not particularly on specific adverse events experienced by patients/consumers, but rather on their feelings, attitudes, opinions, perceptions, and beliefs –even if not concrete- about the intervention (143,300,313-327). As such, psychological and sociological methodologies, rather than scientific methods, are employed in studying it (328-334), and these have been utilized in determining and understanding the motivations underlying the health and medication choices made by both

healthcare providers and the lay public, particularly in novel or fringe areas like CAM use (149,335-345).

Perceived safety/risk has been associated with various factors, including communication, age, gender, culture, experience and trust (346-351). Although it is understandably a greater underlying motivation for the use of self-prescribed medications, like OTC and complementary medicines (292,302,334,352-368), it has also been identified as an important factor in patient medication adherence (369-376).An understanding of the underlying motivations for unhealthy self-made choices offers the possibility of avenues through which the people concerned could be better informed as to the ways to better achieve their personal goals with better choices. This has been illustrated in several reports of –and arguments for- improvement of risk awareness of various interventions (and, thus, healthier choices) following suitably tailored patient-education and public health enlightenment initiatives (256,346,377-387). With the continued popularity of CAMs in spite of the reports of their safety risks (93,281,388-391), these efforts have also been directed at the improvement of CAM consumer risk awareness as a means of improving medication safety (150,392-399,399-408). Some of theses efforts have been targeted at paediatric subjects, and will be the subject of the current review.

CHAPTER TWO: REVIEW PROTOCOL

2.1 Systematic Reviews of Perceived Paediatric CAM Effectiveness and Safety: An Overview

Although there are quite a number of systematic reviews of the effectiveness and/or of safety paediatric CAM interventions in recent times (17,79,93,205,409-427), a scoping search with Google Scholar identified none that focused on user perceptions on paediatric CAM. The two closest hits –the reviews by Jackson et al (428) and Lorenc et al (429)- focused rather on the psychological models associated with the decision-making process used by parents in the choice of paediatric CAM, as have been highly researched recently in literature (353,430-437). In other words, they looked more at the '*hows*' of the choice of paediatric CAM use than on the '*whys*'. The other and more relevant study that focused on perceptions –that by Cuzzollin et al (438)- apart from focusing more on the relationship between the patients' mothers and paediatricians, rather than on the CAM interventions themselves, was just an overview of the literature, and not actually a systematic review. Moreover, considering the numerous recent articles on the subject discovered during the scoping search (439-446), it is obvious that it is quite dated. The need for a

fresh and systematic review of the subject cannot, therefore, be overemphasized. This current study aims at meeting that need.

2.2 Review Objectives

- To determine, outline and compare the strengths and weaknesses of all identified studies in peer-reviewed journals on paediatric CAM use in terms of methodological quality and consistency of findings (447).
- To summarize and discuss key findings of the studies identified;
- To identify gaps in the literature to inform further phases of the doctoral research;
- To inform the most appropriate methodological approaches in further research;
- To obtain standard reference data on the subject with which to compare the findings of the proposed research.

2.3 Inclusion criteria

- ***Populations***:

  - Specific CAM studies on subjects aged up to 21 years;

- ***Intervention***:

  Pharmaceutical-type CAM, i.e. CAMs, as earlier defined –specifically: herbal medicines, animal parts and/or minerals; homeopathic medicines, essential oils and dietary supplements/megavitamins - used alone or in combination with other forms of CAM/conventional medicine. Also Bach flower remedies and other such similar product-based CAM will also be included.

- ***Outcomes:***

  User views, opinions, attitudes and perceptions on effectiveness outcomes of CAM use; as well as any toxicity and adverse effects encountered during the intervention.

- ***Study design*****:** Surveys, and other observational studies –prospective or retrospective, quantitative or qualitative**.**

- ***Language:*** Although the importance of language non-restriction in systematic reviews of CAM use has been reported (448, 449), due to various limitations and logistic considerations, only articles published in English –or which include an abstract in English- will be selected for this study.

- ***Date limit:*** *Although focus on safety/risk perception of health interventions commenced in the early 1990s, and there has been no previous systematic review of the perceived outcomes of paediatric CAM use, since the systematic review of the prevalence of CAM use in children by Ernst in 1999 reported the perceived effectiveness outcomes of included papers, I propose that this current review covers articles published as from 2000 until July 2011.*

2.4 Exclusion criteria

- Perception studies that do not include research on paediatric subjects or their parents/guardians/carers, but are rather targeted **only** at health professionals or other non-user/consumers;

- Perception studies that do not focus on user perspectives on CAM use, but rather on the decision-making process involved.
- Studies on CAM use in general that do not focus on the specific, named CAMs that are the focus of the review.

2.5 Database Selection

A perusal of some of the systematic reviews of paediatric CAM use identified through the scoping search yielded a total of about 35 main databases utilized in the literature searches. Following a detailed descriptive analysis of the list, 13 databases were selected for the current review. These were selected not only on the basis of their specificity to CAM and their relevance to the major focus of the current review, but also on their general importance and acceptability among health researchers. The 13 databases thus selected are as follows:

1. Paediatric Complementary and Alternative Medicine (PedCAM)
2. NHS Evidence –Complementary and Alternative Medicine
3. PubMed
4. MEDLINE
5. Royal Council for Complementary Medicine)RCCM) Databases
6. Allied and Complementary Medicine Database (AMED)
7. EMBASE
8. CAB Global Health Dialog
9. Alt-Health Watch
10. Natural Medicines Comprehensive Database
11. Complementary and Alternative Library and Information Service (CAMLIS)

12. The Cumulative Index to Nursing and Allied Health Literature (CINAHL)
13. The International Pharmaceutical Abstracts (IPA)

Although no particular journals will be manually searched, all articles referred to in systematic review articles identified will be specifically looked up –if not already identified from the search of the databases already selected- and will be assessed for conformity with the stated inclusion and exclusion criteria. In addition, any outstanding paper/study noted/suspected by any member of the Team to have been missed out will be specifically searched for and tested for suitability using the inclusion and exclusion criteria. In either case, where any such study qualifies for inclusion following this specific search, the treason for its initial exclusion will be determined and reported appropriately. The references will be managed with the RefWorks software through the Robert Gordon University Library.

2.6 Search terms and search term combinations

The following words and phrases will be utilized in the search *with appropriate truncation or wild cards*. As such, although only singular forms of nouns are given, the search will be such as to also identify all the plural forms. Also, alternative spellings (for instance, paediatric vs. pediatric) will be accepted. These words/phrases are among those identified as relevant/key to the subject in the background to the review. The words/phrases are as follows:

- Adolescent
- Adverse/side effect
- Alternative Medicine

- Child(ren)
- Complementary Medicine
- Father
- Guardian
- Health-related Quality of Life (HRQOL)
- Holistic Health/Medicine
- Integrative Medicine
- Mother
- Nonconventional Medicine
- Opinion
- Outcomes
- P(a)ediatric
- Parent
- Patient-oriented
- Patient-led
- Perception
- Perspectives
- Perceived benefit
- Perceived effectiveness
- Perceived efficacy
- Perceived Safety
- Prevalence
- Traditional Medicine
- Unconventional Medicine
- Use

These words and phrases will be used in the following combinations in the ensuing search of the databases:

Combination 1

(Alternative Medicine **or** Complementary Medicines **or** Holistic Health **or** Holistic Medicine **or** Integrative Medicine **or** Nonconventional Medicine **or** Traditional Medicine **or** Unconventional Medicine)

AND

(Adolescent **or** Child(ren) **or** Father **or** Guardian **or** Mother **or** P(a)ediatric **or** P(a)ediatrics) **or** Patient-led **or** Patient-oriented **or** Parent)

AND

(Adverse effects **or** side effects **or** Perceived Benefit **or** Perceived Effectiveness **or** Perceived Efficacy **or** Perceived Safety **or** Opinions **or** Perspectives **or** Prevalence **or** Use)

Combination 2

(Bach flower remedies **or** Complementary medicines **or** Dietary supplements **or** Herbals **or** non-vitamin, non-mineral natural products **or** Homeopathy **or** Megavitamin therapy **or** Pharmaceutical-type CAMs **or** Traditional Chinese Medicine)

AND

(Adolescent **or** Child(ren) **or** Father **or** Guardian **or** Mother **or** P(a)ediatric **or** P(a)ediatrics) **or** Patient-led **or** Patient-oriented **or** Parent)

AND

(Adverse effects **or** side effects **or** Effectiveness **or** Opinions **or** Perceptions **or** Prevalence **or** Safety **or** Use)

2.7 Study selection and Data extraction

In all about 3-4 persons will be involved in the review, viz:

- ON will screen and select studies for relevance based on their titles.
- As a quality control measure, a random sample of 50 titles will be reviewed independently by DS/YK, according to stated criteria, and the two results will compared (with those obtained by ON) to ensure inter-rater reliability
- The very same process will be followed in order to identify relevant studies based on their abstracts.
- After removal of duplicates, ON will critically appraise the remaining papers, and systematically extract, and comparatively record in a clear tabular format, the basic characteristic features of the methodologies and findings/results of the studies.
- Similar quality control checks will be carried out separately by DS and YK for the whole papers, like those done for the titles and abstracts.
- DS and YK will cross-check the tabulated extracted information for reliability
- Any conflicts at each stage will be resolved in consultation with JM. Where there are unresolved conflicts, both views will be reported.

2.8 Assessment of Methodological Quality of Studies Identified

The studies selected for critical appraisal will be assessed for conformity with the standard guideline for each particular study -PRISMA and STROBE statements (452, 453) for systematic reviews/meta-analyses and observational studies respectively, and the CASP guidelines (454), for qualitative research reports. Reference will be made to other standard guidelines (455) whenever necessary.

2.9 Data synthesis and Strategy for dissemination of results

A combination of formats –narrative, quantitative and pictorial, as appropriate- will be used to present the data realized. As the intended audience includes other researchers, policy makers, and clinicians/healthcare providers, apart from the PhD thesis that is the ultimate purpose of this review, the results will also be disseminated through relevant peer-reviewed journals and conference papers/abstracts. Specific databases focused on either CAM –like the Paediatric Complementary and Alternative Medicine (PedCAM) and NHS–Complementary and Alternative Medicine databases, for instance- or systematic reviews –like the Centre for Reviews and Dissemination (CRD)- will be specially targeted.

2.10 Amendments to the protocol in the course of the review

As a quality check, before the commencement of the review, this protocol will undergo peer-review both internally among the Review Team, and externally by some key stake-holders from the intended audience. However, should the need arise, in the course of the review, to deviate from any of the strategies set out in this protocol, such amendment(s) will be discussed internally among the Review Team, and, where a consensus is reached, recorded as a separate document, with clear explanations as to the necessity that warranted it/them.

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Appendix II

Database Search Output

The following Appendix contains the database search output

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Wednesday, August 17, 2011 9:44:14 AM

#	Query	Limiters/Expanders	Last Run Via	Results
S41	S11 and S39	Search modes - Boolean/Phrase	Interface - EBSCOhost Search Screen - Advanced Search Database - MEDLINE;AMED - The Allied and Complementary Medicine Database;CAB Abstracts;CINAHL;International Pharmaceutical Abstracts	67
S40	S11 and S38	Search modes - Boolean/Phrase	Interface - EBSCOhost Search Screen - Advanced Search Database - MEDLINE;AMED - The Allied and Complementary Medicine Database;CAB Abstracts;CINAHL;International Pharmaceutical Abstracts	111
S39	(S12 or S13 or S14 or S15 or S16 or S17 or S18 or S19 or S20)	Search modes - Boolean/Phrase	Interface - EBSCOhost Search Screen - Advanced Search Database - MEDLINE;AMED - The Allied and Complementary Medicine Database;CAB Abstracts;CINAHL;International Pharmaceutical Abstracts	1367
S38	S13 or S21 or S22 or S23 or S24 or S25 or S26 or S27 or S28 or S29 or S30 or S31 or S32 or S33 or S34 or S35 or S36 or S37	Search modes - Boolean/Phrase	Interface - EBSCOhost Search Screen - Advanced Search Database - MEDLINE;AMED - The Allied and Complementary Medicine Database;CAB Abstracts;CINAHL;International Pharmaceutical Abstracts	2451
S37	TI ayurveda	Limiters - Published Date from: 19900101-20110731; Peer Reviewed;	Interface - EBSCOhost Search Screen - Advanced Search Database - MEDLINE;AMED -	24

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		English Language; Human; Publication Type: Journal Article; Languages: English; Document Type: Journal Article; Language: English; Publication Year from: 1990-2011; Publication Type: Journal Article; Language: English; English Language; Exclude MEDLINE records; Human; Publication Type: Journal Article; Language: English; Articles about Human Studies Search modes - Boolean/Phrase	The Allied and Complementary Medicine Database;CAB Abstracts;CINAHL;International Pharmaceutical Abstracts	
S36	TI 'ayurvedic Medicine*'	Limiters - Published Date from: 19900101-20110731; Peer Reviewed; English Language; Human; Publication Type: Journal Article; Languages: English; Document Type: Journal Article; Language: English; Publication Year from: 1990-2011; Publication Type: Journal Article; Language: English; English Language; Exclude MEDLINE records; Human; Publication Type: Journal Article;	Interface - EBSCOhost Search Screen - Advanced Search Database - MEDLINE;AMED - The Allied and Complementary Medicine Database;CAB Abstracts;CINAHL;International Pharmaceutical Abstracts	5

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		Language: English; Articles about Human Studies Search modes - Boolean/Phrase		
S35	TI 'Traditional Chinese Medicine*'	Limiters - Published Date from: 19900101-20110731; Peer Reviewed; English Language; Human; Publication Type: Journal Article; Languages: English; Document Type: Journal Article; Language: English; Publication Year from: 1990-2011; Publication Type: Journal Article; Language: English; English Language; Exclude MEDLINE records; Human; Publication Type: Journal Article; Language: English; Articles about Human Studies Search modes - Boolean/Phrase	Interface - EBSCOhost Search Screen - Advanced Search Database - MEDLINE;AMED - The Allied and Complementary Medicine Database;CAB Abstracts;CINAHL;International Pharmaceutical Abstracts	188
S34	TI CAMs	Limiters - Published Date from: 19900101-20110731; Peer Reviewed; English Language; Human; Publication Type: Journal Article; Languages: English; Document Type: Journal Article; Language: English;	Interface - EBSCOhost Search Screen - Advanced Search Database - MEDLINE;AMED - The Allied and Complementary Medicine Database;CAB Abstracts;CINAHL;International Pharmaceutical Abstracts	7

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		Publication Year from: 1990-2011; Publication Type: Journal Article; Language: English; English Language; Exclude MEDLINE records; Human; Publication Type: Journal Article; Language: English; Articles about Human Studies Search modes - Boolean/Phrase		
S33	TI pharmaceutical-type	Limiters - Published Date from: 19900101-20110731; Peer Reviewed; English Language; Human; Publication Type: Journal Article; Languages: English; Document Type: Journal Article; Language: English; Publication Year from: 1990-2011; Publication Type: Journal Article; Language: English; English Language; Exclude MEDLINE records; Human; Publication Type: Journal Article; Language: English; Articles about Human Studies Search modes - Boolean/Phrase	Interface - EBSCOhost Search Screen - Advanced Search Database - MEDLINE;AMED - The Allied and Complementary Medicine Database;CAB Abstracts;CINAHL;International Pharmaceutical Abstracts	0
S32	TI 'megavitamin	Limiters - Published	Interface - EBSCOhost	1

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	therapy'	Date from: 19900101-20110731; Peer Reviewed; English Language; Human; Publication Type: Journal Article; Languages: English; Document Type: Journal Article; Language: English; Publication Year from: 1990-2011; Publication Type: Journal Article; Language: English; English Language; Exclude MEDLINE records; Human; Publication Type: Journal Article; Language: English; Articles about Human Studies Search modes - Boolean/Phrase	Search Screen - Advanced Search Database - MEDLINE;AMED - The Allied and Complementary Medicine Database;CAB Abstracts;CINAHL;International Pharmaceutical Abstracts	
S31	TI 'mega-vitamin therapy'	Limiters - Published Date from: 19900101-20110731; Peer Reviewed; English Language; Human; Publication Type: Journal Article; Languages: English; Document Type: Journal Article; Language: English; Publication Year from: 1990-2011; Publication Type: Journal Article; Language: English; English Language; Exclude MEDLINE	Interface - EBSCOhost Search Screen - Advanced Search Database - MEDLINE;AMED - The Allied and Complementary Medicine Database;CAB Abstracts;CINAHL;International Pharmaceutical Abstracts	0

EBSCOhost: Print Search History Page 6 of 24

		records; Human; Publication Type: Journal Article; Language: English; Articles about Human Studies Search modes - Boolean/Phrase		
S30	TI mega-vitamin	Limiters - Published Date from: 19900101-20110731; Peer Reviewed; English Language; Human; Publication Type: Journal Article; Languages: English; Document Type: Journal Article; Language: English; Publication Year from: 1990-2011; Publication Type: Journal Article; Language: English; English Language; Exclude MEDLINE records; Human; Publication Type: Journal Article; Language: English; Articles about Human Studies Search modes - Boolean/Phrase	Interface - EBSCOhost Search Screen - Advanced Search Database - MEDLINE;AMED - The Allied and Complementary Medicine Database;CAB Abstracts;CINAHL;International Pharmaceutical Abstracts	0
S29	TI mega-vitamin*	Limiters - Published Date from: 19900101-20110731; Peer Reviewed; English Language; Human; Publication Type: Journal Article; Languages: English;	Interface - EBSCOhost Search Screen - Advanced Search Database - MEDLINE;AMED - The Allied and Complementary Medicine Database;CAB Abstracts;CINAHL;International Pharmaceutical Abstracts	0

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		Document Type: Journal Article; Language: English; Publication Year from: 1990-2011; Publication Type: Journal Article; Language: English; English Language; Exclude MEDLINE records; Human; Publication Type: Journal Article; Language: English; Articles about Human Studies Search modes - Boolean/Phrase		
S28	TI megavitamin*	Limiters - Published Date from: 19900101-20110731; Peer Reviewed; English Language; Human; Publication Type: Journal Article; Languages: English; Document Type: Journal Article; Language: English; Publication Year from: 1990-2011; Publication Type: Journal Article; Language: English; English Language; Exclude MEDLINE records; Human; Publication Type: Journal Article; Language: English; Articles about Human Studies Search modes -	Interface - EBSCOhost Search Screen - Advanced Search Database - MEDLINE;AMED - The Allied and Complementary Medicine Database;CAB Abstracts;CINAHL;International Pharmaceutical Abstracts	2

EBSCOhost: Print Search History Page 8 of 24

		Boolean/Phrase		
S27	TI homeopath*	Limiters - Published Date from: 19900101-20110731; Peer Reviewed; English Language; Human; Publication Type: Journal Article; Languages: English; Document Type: Journal Article; Language: English; Publication Year from: 1990-2011; Publication Type: Journal Article; Language: English; English Language; Exclude MEDLINE records; Human; Publication Type: Journal Article; Language: English; Articles about Human Studies Search modes - Boolean/Phrase	Interface - EBSCOhost Search Screen - Advanced Search Database - MEDLINE;AMED - The Allied and Complementary Medicine Database;CAB Abstracts;CINAHL;International Pharmaceutical Abstracts	188
S26	TI 'natural product*'	Limiters - Published Date from: 19900101-20110731; Peer Reviewed; English Language; Human; Publication Type: Journal Article; Languages: English; Document Type: Journal Article; Language: English; Publication Year from: 1990-2011; Publication Type: Journal Article;	Interface - EBSCOhost Search Screen - Advanced Search Database - MEDLINE;AMED - The Allied and Complementary Medicine Database;CAB Abstracts;CINAHL;International Pharmaceutical Abstracts	200

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		Language: English; English Language; Exclude MEDLINE records; Human; Publication Type: Journal Article; Language: English; Articles about Human Studies Search modes - Boolean/Phrase		
S25	TI 'herbal medicine*'	Limiters - Published Date from: 19900101-20110731; Peer Reviewed; English Language; Human; Publication Type: Journal Article; Languages: English; Document Type: Journal Article; Language: English; Publication Year from: 1990-2011; Publication Type: Journal Article; Language: English; English Language; Exclude MEDLINE records; Human; Publication Type: Journal Article; Language: English; Articles about Human Studies Search modes - Boolean/Phrase	Interface - EBSCOhost Search Screen - Advanced Search Database - MEDLINE;AMED - The Allied and Complementary Medicine Database;CAB Abstracts;CINAHL;International Pharmaceutical Abstracts	276
S24	TI 'herbal*'	Limiters - Published Date from: 19900101-20110731; Peer Reviewed; English Language;	Interface - EBSCOhost Search Screen - Advanced Search Database - MEDLINE;AMED - The Allied and Complementary	740

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		Human; Publication Type: Journal Article; Languages: English; Document Type: Journal Article; Language: English; Publication Year from: 1990-2011; Publication Type: Journal Article; Language: English; English Language; Exclude MEDLINE records; Human; Publication Type: Journal Article; Language: English; Articles about Human Studies Search modes - Boolean/Phrase	Medicine Database;CAB Abstracts;CINAHL;International Pharmaceutical Abstracts	
S23	TI 'dietary supplement*'	Limiters - Published Date from: 19900101-20110731; Peer Reviewed; English Language; Human; Publication Type: Journal Article; Languages: English; Document Type: Journal Article; Language: English; Publication Year from: 1990-2011; Publication Type: Journal Article; Language: English; English Language; Exclude MEDLINE records; Human; Publication Type: Journal Article; Language: English;	Interface - EBSCOhost Search Screen - Advanced Search Database - MEDLINE;AMED - The Allied and Complementary Medicine Database;CAB Abstracts;CINAHL;International Pharmaceutical Abstracts	368

EBSCOhost: Print Search History Page 11 of 24

		Articles about Human Studies Search modes - Boolean/Phrase		
S22	TI 'bach flower'	Limiters - Published Date from: 19900101-20110731; Peer Reviewed; English Language; Human; Publication Type: Journal Article; Languages: English; Document Type: Journal Article; Language: English; Publication Year from: 1990-2011; Publication Type: Journal Article; Language: English; English Language; Exclude MEDLINE records; Human; Publication Type: Journal Article; Language: English; Articles about Human Studies Search modes - Boolean/Phrase	Interface - EBSCOhost Search Screen - Advanced Search Database - MEDLINE;AMED - The Allied and Complementary Medicine Database;CAB Abstracts;CINAHL;International Pharmaceutical Abstracts	4
S21	TI 'bach flower remed*'	Limiters - Published Date from: 19900101-20110731; Peer Reviewed; English Language; Human; Publication Type: Journal Article; Languages: English; Document Type: Journal Article; Language: English; Publication Year	Interface - EBSCOhost Search Screen - Advanced Search Database - MEDLINE;AMED - The Allied and Complementary Medicine Database;CAB Abstracts;CINAHL;International Pharmaceutical Abstracts	2

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		from: 1990-2011; Publication Type: Journal Article; Language: English; English Language; Exclude MEDLINE records; Human; Publication Type: Journal Article; Language: English; Articles about Human Studies Search modes - Boolean/Phrase		
S20	TI 'non-conventional medicine*'	Limiters - Published Date from: 19900101-20110731; Peer Reviewed; English Language; Human; Publication Type: Journal Article; Languages: English; Document Type: Journal Article; Language: English; Publication Year from: 1990-2011; Publication Type: Journal Article; Language: English; English Language; Exclude MEDLINE records; Human; Publication Type: Journal Article; Language: English; Language: English; Articles about Human Studies Search modes - Boolean/Phrase	Interface - EBSCOhost Search Screen - Advanced Search Database - MEDLINE;AMED - The Allied and Complementary Medicine Database;CAB Abstracts;CINAHL;International Pharmaceutical Abstracts	0
S19	TI 'nonconventional	Limiters - Published	Interface - EBSCOhost	0

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	medicine*'	Date from: 19900101-20110731; Peer Reviewed; English Language; Human; Publication Type: Journal Article; Languages: English; Document Type: Journal Article; Language: English; Publication Year from: 1990-2011; Publication Type: Journal Article; Language: English; English Language; Exclude MEDLINE records; Human; Publication Type: Journal Article; Language: English; Language: English; Articles about Human Studies Search modes - Boolean/Phrase	Search Screen - Advanced Search Database - MEDLINE;AMED - The Allied and Complementary Medicine Database;CAB Abstracts;CINAHL;International Pharmaceutical Abstracts	
S18	TI 'traditional medicine*'	Limiters - Published Date from: 19900101-20110731; Peer Reviewed; English Language; Human; Publication Type: Journal Article; Languages: English; Document Type: Journal Article; Language: English; Publication Year from: 1990-2011; Publication Type: Journal Article; Language: English; English Language;	Interface - EBSCOhost Search Screen - Advanced Search Database - MEDLINE;AMED - The Allied and Complementary Medicine Database;CAB Abstracts;CINAHL;International Pharmaceutical Abstracts	331

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		Exclude MEDLINE records; Human; Publication Type: Journal Article; Language: English; Language: English; Articles about Human Studies Search modes - Boolean/Phrase		
S17	TI 'unconventional medicine*'	Limiters - Published Date from: 19900101-20110731; Peer Reviewed; English Language; Human; Publication Type: Journal Article; Languages: English; Document Type: Journal Article; Language: English; Publication Year from: 1990-2011; Publication Type: Journal Article; Language: English; English Language; Exclude MEDLINE records; Human; Publication Type: Journal Article; Language: English; Language: English; Articles about Human Studies Search modes - Boolean/Phrase	Interface - EBSCOhost Search Screen - Advanced Search Database - MEDLINE;AMED - The Allied and Complementary Medicine Database;CAB Abstracts;CINAHL;International Pharmaceutical Abstracts	11
S16	TI 'integrative medicine*'	Limiters - Published Date from: 19900101-20110731; Peer Reviewed; English Language;	Interface - EBSCOhost Search Screen - Advanced Search Database - MEDLINE;AMED - The Allied and Complementary	97

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		Human; Publication Type: Journal Article; Languages: English; Document Type: Journal Article; Language: English; Publication Year from: 1990-2011; Publication Type: Journal Article; Language: English; English Language; Exclude MEDLINE records; Human; Publication Type: Journal Article; Language: English; Language: English; Articles about Human Studies Search modes - Boolean/Phrase	Medicine Database;CAB Abstracts;CINAHL;International Pharmaceutical Abstracts	
S15	TI 'holistic medicine*'	Limiters - Published Date from: 19900101-20110731; Peer Reviewed; English Language; Human; Publication Type: Journal Article; Languages: English; Document Type: Journal Article; Language: English; Publication Year from: 1990-2011; Publication Type: Journal Article; Language: English; English Language; Exclude MEDLINE records; Human; Publication Type: Journal Article;	Interface - EBSCOhost Search Screen - Advanced Search Database - MEDLINE;AMED - The Allied and Complementary Medicine Database;CAB Abstracts;CINAHL;International Pharmaceutical Abstracts	9

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		Language: English; Language: English; Articles about Human Studies Search modes - Boolean/Phrase		
S14	TI 'holistic health'	Limiters - Published Date from: 19900101-20110731; Peer Reviewed; English Language; Human; Publication Type: Journal Article; Languages: English; Document Type: Journal Article; Language: English; Publication Year from: 1990-2011; Publication Type: Journal Article; Language: English; English Language; Exclude MEDLINE records; Human; Publication Type: Journal Article; Language: English; Language: English; Articles about Human Studies Search modes - Boolean/Phrase	Interface - EBSCOhost Search Screen - Advanced Search Database - MEDLINE;AMED - The Allied and Complementary Medicine Database;CAB Abstracts;CINAHL;International Pharmaceutical Abstracts	19
S13	TI 'complementary medicine*'	Limiters - Published Date from: 19900101-20110731; Peer Reviewed; English Language; Human; Publication Type: Journal Article; Languages: English; Document Type:	Interface - EBSCOhost Search Screen - Advanced Search Database - MEDLINE;AMED - The Allied and Complementary Medicine Database;CAB Abstracts;CINAHL;International Pharmaceutical Abstracts	771

		Journal Article; Language: English; Publication Year from: 1990-2011; Publication Type: Journal Article; Language: English; English Language; Exclude MEDLINE records; Human; Publication Type: Journal Article; Language: English; Language: English; Articles about Human Studies Search modes - Boolean/Phrase		
S12	TI 'alternative medicine*'	Limiters - Published Date from: 19900101-20110731; Peer Reviewed; English Language; Human; Publication Type: Journal Article; Languages: English; Document Type: Journal Article; Language: English; Publication Year from: 1990-2011; Publication Type: Journal Article; Language: English; English Language; Exclude MEDLINE records; Human; Publication Type: Journal Article; Language: English; Language: English; Articles about Human Studies	Interface - EBSCOhost Search Screen - Advanced Search Database - MEDLINE;AMED - The Allied and Complementary Medicine Database;CAB Abstracts;CINAHL;International Pharmaceutical Abstracts	784

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		Search modes - Boolean/Phrase		
S11	(S1 or S2 or S3 or S4 or S5 or S6 or S7 or S8 or S9 or S10)	Search modes - Boolean/Phrase	Interface - EBSCOhost Search Screen - Advanced Search Database - MEDLINE;AMED - The Allied and Complementary Medicine Database;CAB Abstracts;CINAHL;International Pharmaceutical Abstracts	101950
S10	TI parent	Limiters - Published Date from: 19900101-20110731; Peer Reviewed; English Language; Human; Publication Type: Journal Article; Languages: English; Document Type: Journal Article; Language: English; Publication Year from: 1990-2011; Publication Type: Journal Article; Language: English; English Language; Exclude MEDLINE records; Human; Publication Type: Journal Article; Language: English; Language: English; Articles about Human Studies Search modes - Boolean/Phrase	Interface - EBSCOhost Search Screen - Advanced Search Database - MEDLINE;AMED - The Allied and Complementary Medicine Database;CAB Abstracts;CINAHL;International Pharmaceutical Abstracts	1637
S9	TI 'patient-oriented'	Limiters - Published Date from: 19900101-20110731; Peer Reviewed; English Language;	Interface - EBSCOhost Search Screen - Advanced Search Database - MEDLINE;AMED - The Allied and Complementary	40

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		Human; Publication Type: Journal Article; Languages: English; Document Type: Journal Article; Language: English; Publication Year from: 1990-2011; Publication Type: Journal Article; Language: English; English Language; Exclude MEDLINE records; Human; Publication Type: Journal Article; Language: English; Language: English; Articles about Human Studies Search modes - Boolean/Phrase	Medicine Database;CAB Abstracts;CINAHL;International Pharmaceutical Abstracts	
S8	TI 'patient-led'	Limiters - Published Date from: 19900101-20110731; Peer Reviewed; English Language; Human; Publication Type: Journal Article; Languages: English; Document Type: Journal Article; Language: English; Publication Year from: 1990-2011; Publication Type: Journal Article; Language: English; English Language; Exclude MEDLINE records; Human; Publication Type: Journal Article;	Interface - EBSCOhost Search Screen - Advanced Search Database - MEDLINE;AMED - The Allied and Complementary Medicine Database;CAB Abstracts;CINAHL;International Pharmaceutical Abstracts	14

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		Language: English; Language: English; Articles about Human Studies Search modes - Boolean/Phrase		
S7	TI pediatric*	Limiters - Published Date from: 19900101-20110731; Peer Reviewed; English Language; Human; Publication Type: Journal Article; Languages: English; Document Type: Journal Article; Language: English; Publication Year from: 1990-2011; Publication Type: Journal Article; Language: English; English Language; Exclude MEDLINE records; Human; Publication Type: Journal Article; Language: English; Language: English; Articles about Human Studies Search modes - Boolean/Phrase	Interface - EBSCOhost Search Screen - Advanced Search Database - MEDLINE;AMED - The Allied and Complementary Medicine Database;CAB Abstracts;CINAHL;International Pharmaceutical Abstracts	9605
S6	TI paediatric*	Limiters - Published Date from: 19900101-20110731; Peer Reviewed; English Language; Human; Publication Type: Journal Article; Languages: English; Document Type:	Interface - EBSCOhost Search Screen - Advanced Search Database - MEDLINE;AMED - The Allied and Complementary Medicine Database;CAB Abstracts;CINAHL;International Pharmaceutical Abstracts	3540

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		Journal Article; Language: English; Publication Year from: 1990-2011; Publication Type: Journal Article; Language: English; English Language; Exclude MEDLINE records; Human; Publication Type: Journal Article; Language: English; Language: English; Articles about Human Studies Search modes - Boolean/Phrase		
S5	TI mother*	Limiters - Published Date from: 19900101-20110731; Peer Reviewed; English Language; Human; Publication Type: Journal Article; Languages: English; Document Type: Journal Article; Language: English; Publication Year from: 1990-2011; Publication Type: Journal Article; Language: English; English Language; Exclude MEDLINE records; Human; Publication Type: Journal Article; Language: English; Language: English; Articles about Human Studies	Interface - EBSCOhost Search Screen - Advanced Search Database - MEDLINE;AMED - The Allied and Complementary Medicine Database;CAB Abstracts;CINAHL;International Pharmaceutical Abstracts	4610

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		Search modes - Boolean/Phrase		
S4	TI guardian*	Limiters - Published Date from: 19900101-20110731; Peer Reviewed; English Language; Human; Publication Type: Journal Article; Languages: English; Document Type: Journal Article; Language: English; Publication Year from: 1990-2011; Publication Type: Journal Article; Language: English; English Language; Exclude MEDLINE records; Human; Publication Type: Journal Article; Language: English; Language: English; Articles about Human Studies Search modes - Boolean/Phrase	Interface - EBSCOhost Search Screen - Advanced Search Database - MEDLINE;AMED - The Allied and Complementary Medicine Database;CAB Abstracts;CINAHL;International Pharmaceutical Abstracts	98
S3	TI father*	Limiters - Published Date from: 19900101-20110731; Peer Reviewed; English Language; Human; Publication Type: Journal Article; Languages: English; Document Type: Journal Article; Language: English; Publication Year from: 1990-2011;	Interface - EBSCOhost Search Screen - Advanced Search Database - MEDLINE;AMED - The Allied and Complementary Medicine Database;CAB Abstracts;CINAHL;International Pharmaceutical Abstracts	860

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		Publication Type: Journal Article; Language: English; English Language; Exclude MEDLINE records; Human; Publication Type: Journal Article; Language: English; Language: English; Articles about Human Studies Search modes - Boolean/Phrase		
S2	TI child*	Limiters - Published Date from: 19900101-20110731; Peer Reviewed; English Language; Human; Publication Type: Journal Article; Languages: English; Document Type: Journal Article; Language: English; Publication Year from: 1990-2011; Publication Type: Journal Article; Language: English; English Language; Exclude MEDLINE records; Human; Publication Type: Journal Article; Language: English; Language: English; Articles about Human Studies Search modes - Boolean/Phrase	Interface - EBSCOhost Search Screen - Advanced Search Database - MEDLINE;AMED - The Allied and Complementary Medicine Database;CAB Abstracts;CINAHL;International Pharmaceutical Abstracts	73945
S1	TI adolescent*	Limiters - Published	Interface - EBSCOhost	15672

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	Date from: 19900101-20110731; Peer Reviewed; English Language; Human; Publication Type: Journal Article; Languages: English; Document Type: Journal Article; Language: English; Publication Year from: 1990-2011; Publication Type: Journal Article; Language: English; English Language; Exclude MEDLINE records; Human; Publication Type: Journal Article; Language: English; Language: English; Articles about Human Studies Search modes - Boolean/Phrase	Search Screen - Advanced Search Database - MEDLINE;AMED - The Allied and Complementary Medicine Database;CAB Abstracts;CINAHL;International Pharmaceutical Abstracts

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#	Query	Limiters/Expanders	Last Run Via	Results
S38	S35 and S36	Search modes - Boolean/Phrase	Interface - EBSCOhost Search Screen - Advanced Search Database - MEDLINE;AMED - The Allied and Complementary Medicine Database;CAB Abstracts;CINAHL;International Pharmaceutical Abstracts	2232
S37	S34 and S36	Search modes - Boolean/Phrase	Interface - EBSCOhost Search Screen - Advanced Search Database - MEDLINE;AMED - The Allied and Complementary Medicine Database;CAB Abstracts;CINAHL;International Pharmaceutical Abstracts	685
S36	S23 or S24 or S25 or S26 or S27 or S28 or S29 or S30 or S31 or S32 or S33	Search modes - Boolean/Phrase	Interface - EBSCOhost Search Screen - Advanced Search Database - MEDLINE;AMED - The Allied and Complementary Medicine Database;CAB Abstracts;CINAHL;International Pharmaceutical Abstracts	400715
S35	S2 or S10 or S11 or S12 or S13 or S14 or S15 or S16 or S17 or S18 or S19 or S20 or S21 or S22	Search modes - Boolean/Phrase	Interface - EBSCOhost Search Screen - Advanced Search Database - MEDLINE;AMED - The Allied and Complementary Medicine Database;CAB Abstracts;CINAHL;International Pharmaceutical Abstracts	10384
S34	S1 or S2 or S3 or S4 or S5 or S6 or S7 or S8 or S9	Search modes - Boolean/Phrase	Interface - EBSCOhost Search Screen - Advanced Search Database - MEDLINE;AMED -	4208

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			The Allied and Complementary Medicine Database;CAB Abstracts;CINAHL;International Pharmaceutical Abstracts	
S33	patient-oriented	Limiters - Published Date from: 19900101-20110731; Peer Reviewed; English Language; Human; Publication Type: Journal Article; Languages: English; Document Type: Journal Article; Language: English; Publication Year from: 1990-2011; Publication Type: Journal Article; Language: English; English Language; Exclude MEDLINE records; Human; Language: English; Language: English; Articles about Human Studies Search modes - Boolean/Phrase	Interface - EBSCOhost Search Screen - Advanced Search Database - MEDLINE;AMED - The Allied and Complementary Medicine Database;CAB Abstracts;CINAHL;International Pharmaceutical Abstracts	279
S32	patient-directed	Limiters - Published Date from: 19900101-20110731; Peer Reviewed; English Language; Human; Publication Type: Journal Article; Languages: English; Document Type: Journal Article; Language: English; Publication Year from: 1990-2011;	Interface - EBSCOhost Search Screen - Advanced Search Database - MEDLINE;AMED - The Allied and Complementary Medicine Database;CAB Abstracts;CINAHL;International Pharmaceutical Abstracts	33

		Publication Type: Journal Article; Language: English; English Language; Exclude MEDLINE records; Human; Language: English; Language: English; Articles about Human Studies Search modes - Boolean/Phrase		
S31	patient-led	Limiters - Published Date from: 19900101-20110731; Peer Reviewed; English Language; Human; Publication Type: Journal Article; Languages: English; Document Type: Journal Article; Language: English; Publication Year from: 1990-2011; Publication Type: Journal Article; Language: English; English Language; Exclude MEDLINE records; Human; Language: English; Language: English; Articles about Human Studies Search modes - Boolean/Phrase	Interface - EBSCOhost Search Screen - Advanced Search Database - MEDLINE;AMED - The Allied and Complementary Medicine Database;CAB Abstracts;CINAHL;International Pharmaceutical Abstracts	64
S30	pediatric*	Limiters - Published Date from: 19900101-20110731; Peer Reviewed; English Language;	Interface - EBSCOhost Search Screen - Advanced Search Database - MEDLINE;AMED - The Allied and Complementary	63813

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		Human; Publication Type: Journal Article; Languages: English; Document Type: Journal Article; Language: English; Publication Year from: 1990-2011; Publication Type: Journal Article; Language: English; English Language; Exclude MEDLINE records; Human; Language: English; Language: English; Articles about Human Studies Search modes - Boolean/Phrase	Medicine Database;CAB Abstracts;CINAHL;International Pharmaceutical Abstracts	
S29	paediatric*	Limiters - Published Date from: 19900101-20110731; Peer Reviewed; English Language; Human; Publication Type: Journal Article; Languages: English; Document Type: Journal Article; Language: English; Publication Year from: 1990-2011; Publication Type: Journal Article; Language: English; English Language; Exclude MEDLINE records; Human; Language: English; Language: English; Articles about Human Studies	Interface - EBSCOhost Search Screen - Advanced Search Database - MEDLINE;AMED - The Allied and Complementary Medicine Database;CAB Abstracts;CINAHL;International Pharmaceutical Abstracts	22847

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		Search modes - Boolean/Phrase		
S28	guardian*	Limiters - Published Date from: 19900101-20110731; Peer Reviewed; English Language; Human; Publication Type: Journal Article; Languages: English; Document Type: Journal Article; Language: English; Publication Year from: 1990-2011; Publication Type: Journal Article; Language: English; English Language; Exclude MEDLINE records; Human; Language: English; Language: English; Articles about Human Studies Search modes - Boolean/Phrase	Interface - EBSCOhost Search Screen - Advanced Search Database - MEDLINE;AMED - The Allied and Complementary Medicine Database;CAB Abstracts;CINAHL;International Pharmaceutical Abstracts	983
S27	parent*	Limiters - Published Date from: 19900101-20110731; Peer Reviewed; English Language; Human; Publication Type: Journal Article; Languages: English; Document Type: Journal Article; Language: English; Publication Year from: 1990-2011; Publication Type: Journal Article;	Interface - EBSCOhost Search Screen - Advanced Search Database - MEDLINE;AMED - The Allied and Complementary Medicine Database;CAB Abstracts;CINAHL;International Pharmaceutical Abstracts	45095

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		Language: English; English Language; Exclude MEDLINE records; Human; Language: English; Language: English; Articles about Human Studies Search modes - Boolean/Phrase		
S26	mother*	Limiters - Published Date from: 19900101-20110731; Peer Reviewed; English Language; Human; Publication Type: Journal Article; Languages: English; Document Type: Journal Article; Language: English; Publication Year from: 1990-2011; Publication Type: Journal Article; Language: English; English Language; Exclude MEDLINE records; Human; Language: English; Language: English; Articles about Human Studies Search modes - Boolean/Phrase	Interface - EBSCOhost Search Screen - Advanced Search Database - MEDLINE;AMED - The Allied and Complementary Medicine Database;CAB Abstracts;CINAHL;International Pharmaceutical Abstracts	25887
S25	father*	Limiters - Published Date from: 19900101-20110731; Peer Reviewed; English Language; Human; Publication Type: Journal Article;	Interface - EBSCOhost Search Screen - Advanced Search Database - MEDLINE;AMED - The Allied and Complementary Medicine Database;CAB Abstracts;CINAHL;International	6013

		Languages: English; Document Type: Journal Article; Language: English; Publication Year from: 1990-2011; Publication Type: Journal Article; Language: English; English Language; Exclude MEDLINE records; Human; Language: English; Language: English; Articles about Human Studies Search modes - Boolean/Phrase	Pharmaceutical Abstracts	
S24	child*	Limiters - Published Date from: 19900101-20110731; Peer Reviewed; English Language; Human; Publication Type: Journal Article; Languages: English; Document Type: Journal Article; Language: English; Publication Year from: 1990-2011; Publication Type: Journal Article; Language: English; English Language; Exclude MEDLINE records; Human; Language: English; Language: English; Articles about Human Studies Search modes - Boolean/Phrase	Interface - EBSCOhost Search Screen - Advanced Search Database - MEDLINE;AMED - The Allied and Complementary Medicine Database;CAB Abstracts;CINAHL;International Pharmaceutical Abstracts	255662

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S23	adolescent*	Limiters - Published Date from: 19900101-20110731; Peer Reviewed; English Language; Human; Publication Type: Journal Article; Languages: English; Document Type: Journal Article; Language: English; Publication Year from: 1990-2011; Publication Type: Journal Article; Language: English; English Language; Exclude MEDLINE records; Human; Language: English; Language: English; Articles about Human Studies Search modes - Boolean/Phrase	Interface - EBSCOhost Search Screen - Advanced Search Database - MEDLINE;AMED - The Allied and Complementary Medicine Database;CAB Abstracts;CINAHL;International Pharmaceutical Abstracts	214496
S22	traditional chinese medicine*	Limiters - Published Date from: 19900101-20110731; Peer Reviewed; English Language; Human; Publication Type: Journal Article; Languages: English; Document Type: Journal Article; Language: English; Publication Year from: 1990-2011; Publication Type: Journal Article; Language: English; English Language; Exclude MEDLINE	Interface - EBSCOhost Search Screen - Advanced Search Database - MEDLINE;AMED - The Allied and Complementary Medicine Database;CAB Abstracts;CINAHL;International Pharmaceutical Abstracts	815

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		records; Human; Language: English; Language: English; Articles about Human Studies Search modes - Boolean/Phrase		
S21	mega-vitamin therapy	Limiters - Published Date from: 19900101-20110731; Peer Reviewed; English Language; Human; Publication Type: Journal Article; Languages: English; Document Type: Journal Article; Language: English; Publication Year from: 1990-2011; Publication Type: Journal Article; Language: English; English Language; Exclude MEDLINE records; Human; Publication Type: Journal Article; Language: English; Language: English; Articles about Human Studies Search modes - SmartText Searching	Interface - EBSCOhost Search Screen - Advanced Search Database - MEDLINE;AMED - The Allied and Complementary Medicine Database;CAB Abstracts;CINAHL;International Pharmaceutical Abstracts	100
S20	mega-vitamin therapy	Limiters - Published Date from: 19900101-20110731; Peer Reviewed; English Language; Human; Publication Type: Journal Article; Languages: English;	Interface - EBSCOhost Search Screen - Advanced Search Database - MEDLINE;AMED - The Allied and Complementary Medicine Database;CAB Abstracts;CINAHL;International Pharmaceutical Abstracts	0

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		Document Type: Journal Article; Language: English; Publication Year from: 1990-2011; Publication Type: Journal Article; Language: English; English Language; Exclude MEDLINE records; Human; Publication Type: Journal Article; Language: English; Language: English; Articles about Human Studies Search modes - Boolean/Phrase		
S19	megavitamin therapy	Limiters - Published Date from: 19900101-20110731; Peer Reviewed; English Language; Human; Publication Type: Journal Article; Languages: English; Document Type: Journal Article; Language: English; Publication Year from: 1990-2011; Publication Type: Journal Article; Language: English; English Language; Exclude MEDLINE records; Human; Publication Type: Journal Article; Language: English; Language: English; Articles about Human	Interface - EBSCOhost Search Screen - Advanced Search Database - MEDLINE;AMED - The Allied and Complementary Medicine Database;CAB Abstracts;CINAHL;International Pharmaceutical Abstracts	2

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		Studies Search modes - Boolean/Phrase		
S18	mega-vitamin*	Limiters - Published Date from: 19900101-20110731; Peer Reviewed; English Language; Human; Publication Type: Journal Article; Languages: English; Document Type: Journal Article; Language: English; Publication Year from: 1990-2011; Publication Type: Journal Article; Language: English; English Language; Exclude MEDLINE records; Human; Language: English; Language: English; Articles about Human Studies Search modes - Boolean/Phrase	Interface - EBSCOhost Search Screen - Advanced Search Database - MEDLINE;AMED - The Allied and Complementary Medicine Database;CAB Abstracts;CINAHL;International Pharmaceutical Abstracts	2
S17	megavitamin*	Limiters - Published Date from: 19900101-20110731; Peer Reviewed; English Language; Human; Publication Type: Journal Article; Languages: English; Document Type: Journal Article; Language: English; Publication Year from: 1990-2011; Publication Type:	Interface - EBSCOhost Search Screen - Advanced Search Database - MEDLINE;AMED - The Allied and Complementary Medicine Database;CAB Abstracts;CINAHL;International Pharmaceutical Abstracts	15

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		Journal Article; Language: English; English Language; Exclude MEDLINE records; Human; Language: English; Language: English; Articles about Human Studies Search modes - Boolean/Phrase		
S16	homoeopath*	Limiters - Published Date from: 19900101-20110731; Peer Reviewed; English Language; Human; Publication Type: Journal Article; Languages: English; Document Type: Journal Article; Language: English; Publication Year from: 1990-2011; Publication Type: Journal Article; Language: English; English Language; Exclude MEDLINE records; Human; Language: English; Language: English; Articles about Human Studies Search modes - Boolean/Phrase	Interface - EBSCOhost Search Screen - Advanced Search Database - MEDLINE;AMED - The Allied and Complementary Medicine Database;CAB Abstracts;CINAHL;International Pharmaceutical Abstracts	132
S15	homeopath*	Limiters - Published Date from: 19900101-20110731; Peer Reviewed; English Language; Human; Publication	Interface - EBSCOhost Search Screen - Advanced Search Database - MEDLINE;AMED - The Allied and Complementary Medicine Database;CAB	570

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		Type: Journal Article; Languages: English; Document Type: Journal Article; Language: English; Publication Year from: 1990-2011; Publication Type: Journal Article; Language: English; English Language; Exclude MEDLINE records; Human; Language: English; Language: English; Articles about Human Studies Search modes - Boolean/Phrase	Abstracts;CINAHL;International Pharmaceutical Abstracts	
S14	natural product*	Limiters - Published Date from: 19900101-20110731; Peer Reviewed; English Language; Human; Publication Type: Journal Article; Languages: English; Document Type: Journal Article; Language: English; Publication Year from: 1990-2011; Publication Type: Journal Article; Language: English; English Language; Exclude MEDLINE records; Human; Language: English; Language: English; Articles about Human Studies Search modes -	Interface - EBSCOhost Search Screen - Advanced Search Database - MEDLINE;AMED - The Allied and Complementary Medicine Database;CAB Abstracts;CINAHL;International Pharmaceutical Abstracts	1118

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		Boolean/Phrase		
S13	herbal*	Limiters - Published Date from: 19900101-20110731; Peer Reviewed; English Language; Human; Publication Type: Journal Article; Languages: English; Document Type: Journal Article; Language: English; Publication Year from: 1990-2011; Publication Type: Journal Article; Language: English; English Language; Exclude MEDLINE records; Human; Language: English; Language: English; Articles about Human Studies Search modes - Boolean/Phrase	Interface - EBSCOhost Search Screen - Advanced Search Database - MEDLINE;AMED - The Allied and Complementary Medicine Database;CAB Abstracts;CINAHL;International Pharmaceutical Abstracts	3003
S12	dietary supplement*	Limiters - Published Date from: 19900101-20110731; Peer Reviewed; English Language; Human; Publication Type: Journal Article; Languages: English; Document Type: Journal Article; Language: English; Publication Year from: 1990-2011; Publication Type: Journal Article; Language: English;	Interface - EBSCOhost Search Screen - Advanced Search Database - MEDLINE;AMED - The Allied and Complementary Medicine Database;CAB Abstracts;CINAHL;International Pharmaceutical Abstracts	4431

		English Language; Exclude MEDLINE records; Human; Language: English; Language: English; Articles about Human Studies Search modes - Boolean/Phrase		
S11	bach flower	Limiters - Published Date from: 19900101-20110731; Peer Reviewed; English Language; Human; Publication Type: Journal Article; Languages: English; Document Type: Journal Article; Language: English; Publication Year from: 1990-2011; Publication Type: Journal Article; Language: English; English Language; Exclude MEDLINE records; Human; Language: English; Language: English; Articles about Human Studies Search modes - Boolean/Phrase	Interface - EBSCOhost Search Screen - Advanced Search Database - MEDLINE;AMED - The Allied and Complementary Medicine Database;CAB Abstracts;CINAHL;International Pharmaceutical Abstracts	5
S10	bach flower remed*	Limiters - Published Date from: 19900101-20110731; Peer Reviewed; English Language; Human; Publication Type: Journal Article; Languages: English;	Interface - EBSCOhost Search Screen - Advanced Search Database - MEDLINE;AMED - The Allied and Complementary Medicine Database;CAB Abstracts;CINAHL;International Pharmaceutical Abstracts	2

		Document Type: Journal Article; Language: English; Publication Year from: 1990-2011; Publication Type: Journal Article; Language: English; English Language; Exclude MEDLINE records; Human; Language: English; Language: English; Articles about Human Studies Search modes - Boolean/Phrase		
S9	unconventional medicine*	Limiters - Published Date from: 19900101-20110731; Peer Reviewed; English Language; Human; Publication Type: Journal Article; Languages: English; Document Type: Journal Article; Language: English; Publication Year from: 1990-2011; Publication Type: Journal Article; Language: English; English Language; Exclude MEDLINE records; Human; Language: English; Language: English; Articles about Human Studies Search modes - Boolean/Phrase	Interface - EBSCOhost Search Screen - Advanced Search Database - MEDLINE;AMED - The Allied and Complementary Medicine Database;CAB Abstracts;CINAHL;International Pharmaceutical Abstracts	20

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S8	traditional medicine*	Limiters - Published Date from: 19900101-20110731; Peer Reviewed; English Language; Human; Publication Type: Journal Article; Languages: English; Document Type: Journal Article; Language: English; Publication Year from: 1990-2011; Publication Type: Journal Article; Language: English; English Language; Exclude MEDLINE records; Human; Language: English; Language: English; Articles about Human Studies Search modes - Boolean/Phrase	Interface - EBSCOhost Search Screen - Advanced Search Database - MEDLINE;AMED - The Allied and Complementary Medicine Database;CAB Abstracts;CINAHL;International Pharmaceutical Abstracts	1484
S7	nonconventional medicine*	Limiters - Published Date from: 19900101-20110731; Peer Reviewed; English Language; Human; Publication Type: Journal Article; Languages: English; Document Type: Journal Article; Language: English; Publication Year from: 1990-2011; Publication Type: Journal Article; Language: English; English Language; Exclude MEDLINE	Interface - EBSCOhost Search Screen - Advanced Search Database - MEDLINE;AMED - The Allied and Complementary Medicine Database;CAB Abstracts;CINAHL;International Pharmaceutical Abstracts	1

		records; Human; Language: English; Language: English; Articles about Human Studies Search modes - Boolean/Phrase		
S6	non-conventional medicine*	Limiters - Published Date from: 19900101-20110731; Peer Reviewed; English Language; Human; Publication Type: Journal Article; Languages: English; Document Type: Journal Article; Language: English; Publication Year from: 1990-2011; Publication Type: Journal Article; Language: English; English Language; Exclude MEDLINE records; Human; Language: English; Language: English; Articles about Human Studies Search modes - Boolean/Phrase	Interface - EBSCOhost Search Screen - Advanced Search Database - MEDLINE;AMED - The Allied and Complementary Medicine Database;CAB Abstracts;CINAHL;International Pharmaceutical Abstracts	2
S5	integrative medicine*	Limiters - Published Date from: 19900101-20110731; Peer Reviewed; English Language; Human; Publication Type: Journal Article; Languages: English; Document Type: Journal Article;	Interface - EBSCOhost Search Screen - Advanced Search Database - MEDLINE;AMED - The Allied and Complementary Medicine Database;CAB Abstracts;CINAHL;International Pharmaceutical Abstracts	467

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		Language: English; Publication Year from: 1990-2011; Publication Type: Journal Article; Language: English; English Language; Exclude MEDLINE records; Human; Language: English; Language: English; Articles about Human Studies Search modes - Boolean/Phrase		
S4	holistic medicine*	Limiters - Published Date from: 19900101-20110731; Peer Reviewed; English Language; Human; Publication Type: Journal Article; Languages: English; Document Type: Journal Article; Language: English; Publication Year from: 1990-2011; Publication Type: Journal Article; Language: English; English Language; Exclude MEDLINE records; Human; Language: English; Language: English; Articles about Human Studies Search modes - Boolean/Phrase	Interface - EBSCOhost Search Screen - Advanced Search Database - MEDLINE;AMED - The Allied and Complementary Medicine Database;CAB Abstracts;CINAHL;International Pharmaceutical Abstracts	26
S3	holistic health	Limiters - Published Date from:	Interface - EBSCOhost Search Screen - Advanced	662

		19900101-20110731; Peer Reviewed; English Language; Human; Publication Type: Journal Article; Languages: English; Document Type: Journal Article; Language: English; Publication Year from: 1990-2011; Publication Type: Journal Article; Language: English; English Language; Exclude MEDLINE records; Human; Language: English; Language: English; Articles about Human Studies Search modes - Boolean/Phrase	Search Database - MEDLINE;AMED - The Allied and Complementary Medicine Database;CAB Abstracts;CINAHL;International Pharmaceutical Abstracts	
S2	complementary medicine*	Limiters - Published Date from: 19900101-20110731; Peer Reviewed; English Language; Human; Publication Type: Journal Article; Languages: English; Document Type: Journal Article; Language: English; Publication Year from: 1990-2011; Publication Type: Journal Article; Language: English; English Language; Exclude MEDLINE records; Human; Language: English;	Interface - EBSCOhost Search Screen - Advanced Search Database - MEDLINE;AMED - The Allied and Complementary Medicine Database;CAB Abstracts;CINAHL;International Pharmaceutical Abstracts	1588

		Language: English; Articles about Human Studies Search modes - Boolean/Phrase		
S1	Alternative medicine*	Limiters - Published Date from: 19900101-20110731; Peer Reviewed; English Language; Human; Publication Type: Journal Article; Languages: English; Document Type: Journal Article; Language: English; Publication Year from: 1990-2011; Publication Type: Journal Article; Language: English; English Language; Exclude MEDLINE records; Human; Language: English; Language: English; Articles about Human Studies Search modes - Boolean/Phrase	Interface - EBSCOhost Search Screen - Advanced Search Database - MEDLINE;AMED - The Allied and Complementary Medicine Database;CAB Abstracts;CINAHL;International Pharmaceutical Abstracts	1497

Appendix III

Yellow Card Scheme Application Form

The following appendix contains the Yellow Card Scheme Application Form

Guidance Notes and Application Form for Access to Yellow Card and Adverse Drug Reactions On line Information Tracking (ADROIT) Data

Access to Yellow Card and ADROIT Data Guidance Notes

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Access to Yellow Card and ADROIT Data Guidance Notes

1. INTRODUCTION

The Medicines and Healthcare products Regulatory Agency (MHRA), an executive agency of the Department of Health, protects and promotes public health and patient safety by ensuring that medicines, healthcare products and medical equipment meet appropriate standards of safety, quality, performance and effectiveness, and are used safely. The Agency operates post-marketing surveillance systems for reporting, investigating and monitoring adverse reactions to medicines and adverse incidents involving medical devices to safeguard public health.

The safety of medicines is monitored using the Yellow Card Scheme[1] which has been in existence since 1964. The Yellow Card database (Adverse Drug Reactions On line Information Tracking (ADROIT) database) contains over half a million reports of adverse drug reactions (ADRs) experienced by patients. Each report details an ADR or ADRs that the reporter suspects may be associated with the patient's use of a medicine or drug and the data are coded according to the internationally accepted Medical Dictionary for Regulatory Activities (MedDRA)[2]. The Yellow Card Scheme is voluntary for healthcare professionals and there are specific reporting requirements for the pharmaceutical industry. Patient reporting is being incorporated within the Scheme through ongoing initiatives but these data are currently held separately on the MHRA's database.

The 2004 Independent Review of Access to the Yellow Card Scheme[3] recognised the research potential of the Yellow Card/ADROIT database, as one of the largest single compendiums of suspected adverse drug reactions in Europe. Following the Review the systems described in this guidance document have been developed to ensure that (any) information included in the database that is subject to release on request under the Freedom of Information Act[4] (FOIA) will be readily available while at the same time protecting the confidentiality of individuals and their personal data as the Data Protection Act[5] (DPA) requires.

2. GENERAL PRINCIPLES

The MHRA welcomes the interest that other organisations and individuals have expressed in researching the Yellow Card database in the interests of patients and for public health benefit. The Agency is conscious of the duty of confidentiality to patients and reporters that is required by the DPA. Research on confidential data is

[1] Further information about the Yellow Card Scheme can be found on the MHRA website at www.yellowcard.gov.uk
[2] http://www.meddramsso.com/
[3] Report of an Independent Review of Access to the Yellow Card Scheme, TSO, London 2004
[4] http://www.hmso.gov.uk/acts/acts2000/20000036.htm
[5] http://www.hmso.gov.uk/acts/acts1998/19980029.htm

nevertheless lawful when it is undertaken with the consent of the subjects involved and in accordance with ethical and scientific principles.

The MHRA's purpose in opening the database is to maximise the accumulated value of the database for the benefit of patients and public health. This guidance summarises the arrangements the Agency has set up to enable any organisation or individual/applicant to access the Yellow Card database in order to carry out independent research or investigations. Any UK or non-UK resident, may apply for access to Yellow Card and ADROIT data and there are no restrictions in respect of the scientific experience or qualifications of any applicant. If you require any assistance completing this form or are unsure which parts to fill in, please contact the MHRA. Contact details are provided on page 6.

However, in providing access the MHRA needs to be assured of the appropriateness and quality of the research and the scientific integrity of proposals. Applicants are therefore required to accept the following principles:

1. The proposal must be of potential scientific value and/or have significant public health implications. The research methods must be described in the proposal so that their scientific merit and feasibility can be independently reviewed and evaluated.

2. Any potential benefits and risks for patients during the course of the research process and/or anticipated as a consequence of the research should be set out in the proposal.

3. Data from the Yellow Card Scheme that is subject to the Data Protection Act, such as individual personal data, must not be provided to third parties without the approval of the Independent Scientific Advisory Committee for MHRA database research (ISAC) and the consent of the reporter and patient.

4. The research must be conducted only by the principal applicant and co-applicants named in the application.

5. Any change or amendment to the research plan or methodology must be notified in writing to the MHRA for approval and should the principal applicant and/or co-applicants change during the course of the study the MHRA must be notified.

6. Any information which identifies a patient and/or reporter that is made available to a principal applicant will be released on a confidential basis. The applicant must ensure appropriate safeguards are in place to restrict further access only to those named in the research application.

7. Applicants are obliged to follow the general principles of the Human Rights Act 1998[6], the Data Protection Act 1998[7] and the principles set out for research by the Department of Health[8].

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[6] http://www.hmso.gov.uk/acts/acts1998/19980042.htm
[7] http://www.hmso.gov.uk/acts/acts1998/19980029.htm
[8]http://www.dh.gov.uk/PolicyAndGuidance/ResearchAndDevelopment/ResearchAndDevelopmentAZ/ResearchGovernance/ResearchGovernanceArticle/fs/en?CONTENT_ID=4002130&chk=pebh9u

2.1 Confidentiality of Yellow Cards

Since September 2000 all patient identifiers have been removed from the Yellow Card in line with the Data Protection Act (DPA) 1998 and the General Medical Council (GMC) guidelines on confidentiality (General Medical Council, 2000)[9]. Prior to this date, to identify duplicate reports reporters were asked to enter the patient's name and date of birth on the Yellow Card. The inclusion of identifying details also facilitated the follow-up of reports when additional data were requested.

In accordance with the legal requirements of the DPA, the MHRA has subsequently updated the Yellow Card and ADROIT database to remove all patient identifiers; and the MHRA will not release any information that could identify the person who submitted a Yellow Card, (the reporter), or the patient without the consent of the person(s) concerned.

2.2 Responsibilities of applicants provided with Yellow Card data

The principal applicant has responsibility for ensuring that any research using Yellow Card data has been clearly defined within their application and that these comply with the general principles as defined in this guidance document (listed above) and the undertakings provided on the application form (Annex A). The principal applicant must ensure that the data are held securely and used solely for the defined intended purpose.

3. APPLICATION FORM COMPLETION NOTES

When applying for access to Yellow Card and ADROIT data (Category II[10]) all applicants must complete the application form at Annex A and confirm that they have read and accept the undertakings on the application form and these guidance notes. The undertakings require that applicants do not disclose the data to persons not named on the application form or use the data for purposes not described in the research proposal. All data released by the MHRA for research is subject to the condition that the principal applicant must inform the MHRA of any issues effecting the safety of a medicine, whether licensed or unlicensed, that are identified during the research and submit all resulting publications to the Agency four calendar weeks prior to publication (see Section I).

Details of the proposed use of the data and statistical analyses should be provided. If approval has been given by a NHS research ethics committee prior to the application this should be mentioned and the ethics committee and its reference number specified[11]. Applicants should be aware that prior approval by an ethics committee does not predetermine approval by the ISAC. All relevant agreements with other academic, commercial or other organisations should be disclosed. If it is anticipated

[9] The GMC Guidelines were updated in April 2004 'Confidentiality: Protecting and Providing Information'. http//www.gmc-uk.org/standards/secret.htm

[10] Definitions of data categories are provided in section 3.1

[11] In most cases it is unlikely that ethical approval will have been obtained prior to scientific scrutiny by the ISAC.

that the research may have a patentable or commercially exploitable outcome this should also be recorded as the MHRA reserves the right to a share in any commercially exploitable outcome.

The application form at Annex A may be used for requests for Category Ib data releasable under FOIA. For such applications completion of only the first third of the application form is requested (as detailed on the form).

All applications should be submitted to the MHRA at the following address:

The Pharmacovigilance Group
Post Licensing Division
MHRA
Market Towers
1 Nine Elms Lane
London
SW8 5NQ

E-mail:
pharmacovigilance@mhra.gsi.gov.uk

3.1 Guidance for completing the application form[12]

Section A - REFERENCE NUMBER

Please leave this section blank. The reference number will be supplied by the MHRA.

Section B - PERSONAL DETAILS

The principal applicant and all co-applicants should provide their contact details within this section.

Section C - TITLE AND SUMMARY OF THE PROPOSAL

The applicant should set out the title of the proposal, the name and address of the Department / Institution / place at which the research will be conducted and the proposed start date.

In addition applicants should provide a short summary of their proposal including the key goals and set out the relevance of the research to future patient care and/or public health.

Section D – USE OF OTHER DATABASES

[12] Further information can be obtained from MHRA, contact details provided in Section 5.

The combination of Yellow Card data with other databases may have the potential to identify patients and/or reporters. All applicants must state whether they intend to use the Yellow Card and ADROIT data in combination with another database or any other data sources.

Section E - CATEGORY Ib YELLOW CARD DATA FIELDS &
Section F - DETAILS OF PROPOSAL

As with all other information held by the MHRA, release of Yellow Card data is subject to the Data Protection Act (DPA) 1998 and the Freedom of Information Act (FOIA) 2000. Some information is already routinely published or provided on request. Applicants should therefore consult the MHRA website[13] before developing details of the proposal and deciding on the range of data to be requested. See also Section J regarding the charges payable to the MHRA for release of certain data.

Data Protection Act (DPA)

The DPA[14] is primarily concerned with requests from individuals to know what personal information about them is held by, in this case, the MHRA (this is known as a subject access request). The DPA applies to data from which it is possible to identify a living individual. Subject to certain exemptions, it prohibits disclosure, without consent, of any personal information that identifies a living person. In certain cases this may apply to release of specific non-personal ADR data from a Yellow Card that may indirectly identify a reporter or a patient or in cases where only a limited number of cases exist.

Requests from individuals to find out whether the Agency holds information on them (subject access requests) will continue to be considered under the terms of the DPA and will not be subject to consideration by the ISAC.

The DPA principles are set out at Annex B.

Freedom of Information Act (FOIA)

The purpose of the FOIA[15] is to "make provision for the disclosure of information held by public authorities". The FOIA creates a statutory right of access to recorded information held by public authorities but the Act also provides exemptions from the duty to disclose the information, and imposes a requirement on public authorities to adopt and maintain a publication scheme. Certain FOIA exemptions are "absolute" while others are "qualified". A full list of the FOIA exemptions is provided at Annex C. If a researcher seeks information about patients, he is seeking third party information and such requests will be considered under the FOIA but are also subject to DPA principles. Exemptions that may preclude the disclosure of certain types of Yellow Card data include *Personal Information* (absolute exemption 40), *Information Intended For Future Publication* (qualified exemption 22) and *Investigations And Proceedings Conducted by Public Authorities* (qualified exemption 30).

[13] Go to www.yellowcard.gov.uk and select "download ADR listings"
[14] http://www.hmso.gov.uk/acts/acts1998/19980029.htm
[15] http://www.hmso.gov.uk/acts/acts2000/20000036.htm

The FOIA relates only to information that a public body, in this context the MHRA, holds at the time the request is made. The following paragraphs outline what information is already held by the Agency and is therefore subject to the FOIA. They also outline circumstances where the Agency will seek to obtain information that it does not hold in order to enable proposals recommended by the ISAC.

Categories of Yellow Card Data

In considering requests for Yellow Card and ADROIT data these can be divided into Category I requests that are releasable under the FOIA and not prohibited from release by DPA and Category II requests that are subject to FOIA exemptions and the restrictions of the DPA. In the latter case these data could not be released without scientific and ethical consideration of whether it would be appropriate for the reporter and patient to be approached to provide consent for use of their data.

Category Ia Data

Anonymised aggregated adverse drug reaction (ADR) data that do not identify the patient or reporter are known as Category Ia data, and are proactively provided on the MHRA website in the format of Drug Analysis Prints (DAPs) which are regularly updated[16]. Guidance on their interpretation is also available on the same website. Requests for these data are freely available under FOIA and are included in the Agency's FOIA Publication Scheme. Therefore, all anonymised Category Ia data will be available from the MHRA upon request on the same basis as other FOI requests that the Agency receives[17].

Category Ib Data

There are further data that can be provided from individual Yellow Cards that exclude any information that identifies a reporter and/or patient or provides any opportunity for the recipient to contact or identify the reporter and/or patient. Release of these data, known as Category Ib data, may include the age categories of the patients; the proportion of males and/or females who experienced the reaction; the drug or drugs involved; the dose and duration of drug therapy; the route of drug administration and the suspected adverse drug reaction(s) that the patient experienced (a full list of these Category Ib fields is provided at Annex D). These data are generally releasable under the FOIA, without consideration by the ISAC, although provision of these data will depend on the number of cases held by the Agency. In this context, among other Government departments, the Office of National Statistics (ONS) will only release information when at least five cases are included in any data subsets[18]. The ISAC has adopted the same policy to prevent identification of patients and/or reporters. Requests for data that have less than five cases in any one cell will be aggregated with adjacent cells prior to release. Any aggregation will be clearly marked when the data are provided.

[16] Go to www.yellowcard.gov.uk and select "download ADR listings"
[17] Go to http://www.mhra.gov.uk and select "About us", then "FOI"
[18] The ONS is in the process of a disclosure review of health statistics. When this is finalised the ISAC may follow a similar approach to release of subsets of data.

The MHRA will not charge for release of Category Ib data unless the time taken to edit or redact the data requested exceeds 24 working hours in which case the Agency will levy a fee in line with the Agency's charging policy for FOIA requests[19], (Section J).

Category II Data

Certain data contained on the ADROIT database may indirectly identify either the reporter or the patient. These data fields may, for example, include patient unique details in the narrative text provided by the reporter, the patient's medical history, dates of drug administration and reaction and specific test results relevant to the suspected adverse reaction, that might enable the patient to be identified. Requests for reporter and patient details or for data that may identify the reporter or patient are considered as Category II data. Release of these data is subject to the terms of the FOIA and the DPA. Exemption *40: Personal Information* of the FOIA and the DPA invoke certain restrictions on disclosure for these data that the Agency already holds that would identify individuals.

All Category II data requests will be reviewed by the ISAC. In certain cases ethical approval may also be required. Requests for data that relate to a small number of ADR cases may also identify the reporter or patient and these requests will have to be considered by the Committee. In addition, any requests for actual images of Yellow Cards or for large subsets of these data would be referred to the Committee.

The Independent Review proposed arrangements that would satisfy legal and ethical requirements for studies that might be undertaken that would involve direct access to confidential personal data on patients and/or might also involve direct access by the researcher to patients. A number of safeguards have been established to ensure that release of these data would follow scientific and ethical approval and that reporter and patient consent would be obtained prior to release of any of their identifiable data. These include requests in which the reporter would need to be approached in the first instance so that the reporter could decide whether the patient should be asked for his/her consent. This would be necessary for a genetic research study to investigate whether certain patients are predisposed to specific ADR(s) or when a researcher requested access to the entire database to develop signal detection methodologies. Under such circumstances, these applications will require ethical approval from a Research Ethics Committee (REC) through the Central Office for Research Ethics Committees (COREC[20]) system.

Following both scientific and ethical approval the MHRA will be responsible for contacting the reporter to ask if he/she is prepared to assist the applicant with the study. That responsibility will not be delegated outside the Agency under any circumstances. If appropriate, the reporter should also be told to ask the patient if they are willing to be contacted by a researcher in the context of a particular study. Consent from both the reporter and the patient must be obtained before their contact details are disclosed to the researcher. The MHRA will require a short summary of the

[19]Go to http://www.mhra.gov.uk and select "About us", then "FOI"
[20] http://www.corec.org.uk/

research proposal in layman's terms for the reporters to give to patients when informing them of the proposed research and possible implications.

It will be the responsibility of the reporter to decide in each case whether a patient should be asked to participate. The MHRA will allow a time period of two months for the reporter to respond before sending a reminder letter to the reporter. If no response is received within a month of sending the reminder the Agency will not pursue the request further. In writing to the reporter the MHRA will endorse participation for those studies approved by the Committee and REC but will not further influence their decisions. Once responses are available from reporters the MHRA will inform the researcher of the proportion of patients who have agreed to assist.

Data of deceased patients and reporters

As a general policy[21] the ONS treats the deceased the same as the living as they consider that there remains a duty of confidence owed to the deceased, even though the DPA refers to living individuals and does not extend to the deceased. The Committee supports this view and for this reason, all requests for release of data from deceased patients will be considered under the same conditions as the living. If a patient has deceased the reporter as a matter of courtesy should consider whether to contact the next of kin if he intends to disclose details of the patient for research.

When a reporter who has submitted a Yellow Card has died the decision on whether to contact the patient for consent would be referred by the MHRA to the reporter's NHS (or private) successor in-post.

Section G - RELEVANT APPLICATIONS AND PUBLICATIONS

Applicants should include details of all their previous or ongoing research that utilised Yellow Card and/or ADROIT data.

Section H - SECURITY & CONFIDENTIALITY

The ISAC and the MHRA consider that confidentiality of Yellow Card data is paramount. For this reason any release of data that is subject to the DPA must be subject to stringent conditions.

Applicants must confirm that they will guarantee the ongoing confidentiality of the data by abiding by the principles in the DPA (Annex B) and specify where any data released to them for research will be held and what security measures will be in place to prevent disclosure to third parties.

Section I - PUBLICATION

[21] The ONS is also reviewing its policy in relation to the deceased.

The MHRA encourages publication of research using the Yellow Card database. However, applicants must state on the application if they intend to publish or place the results of the research in the public domain.

The Agency requires that all publications or other data based on research using Yellow Card and ADROIT data are submitted at least four calendar weeks in advance of any public release of research findings. This requirement is not to impose a delay on publication but is necessary to enable the MHRA to fulfil its statutory responsibilities and arrange any necessary regulatory action required in the light of the research findings. Any regulatory action would be timed to coincide with publication. The Agency may also offer comments on the proposed publication but the principal applicant will not be obliged to accept these. However, in situations in which the MHRA has concerns about the implications of the research and the applicant does not acknowledge these the Agency reserves the right to comment independently.

A separate pre-publication notification must be submitted to the ISAC for every publication based on released Yellow Card / ADROIT data.

Section J - FINANCE

Category Ia Data

The MHRA as a Trading Fund, is required, under the terms of its Trading Fund Order, to cover its costs. No charge will be made for Category Ia anonymised aggregated ADR data, in the format of DAPs, as these are already provided free of charge on request as part of the MHRA's publication scheme.

Category Ib Data

The Agency will not normally charge for release of specific case details known as Category Ib data (Annex D) unless the time taken to edit or redact the data requested exceeds 24 working hours in which case the Agency will levy a fee in line with Agency's charges for FOIA requests[22].

Category II Data

In the long term a scale of three levels of fees proportionate to work incurred may be applied for release of Category II data in order to be cost-neutral to the Agency. The intended fee structures will reflect those situations where the Agency holds the requested data (but needs to remove personal identifiers) and those where the Agency will need to obtain the necessary information that it does not already hold. In the interim when information is already held by the Agency, the MHRA will levy an initial fee of £50 per application before the ISAC reviews an application for Category II data. This fee should be submitted at the time of application.

The Agency will then charge a fee based on £25 per Agency personnel per hour of work. This will enable requests for case details over and above those listed in Annex D to be provided the most economical to the applicant while the costs for research

[22] Go to http://www.mhra.gov.uk and select "About us", then "FOI"

which requires the Agency to contact the reporter and through them the patient will be proportionate to the amount of work required. In the latter case, additional costs including payment of reporters and patients for their time and inconvenience will have to be borne by the applicant. All fees are non-refundable to applicants even if the response from reporters (and patients) is poor.

Additional fees for pre-1991 data

Prior to introduction of the ADROIT database in 1991 the MHRA held Yellow Card data on the Norsk database, the original computer system on which the Product Licence Database was stored. When Norsk data were transposed onto the ADROIT database only basic details from each ADR report were added to the new database, such as the name of the drug, the reaction and the outcome of the reaction. For applicants who request pre-1991 Yellow Card data an additional charge may be incurred for the time required for Agency staff to retrieve additional data from old ADR case reports not currently held on ADROIT if more than the basic details are required the level of which will be discussed with the Agency.

Section K - CURRICULUM VITAE OF APPLICANT(S)

All applicants (the principal and all co-applicants) should enclose an abridged curriculum vitae with each application. A summary of relevant qualifications and career(s) to date and if applicable a list of not more than ten relevant publications should be provided.

Section L - SUPPLEMENTARY INFORMATION

For audit purposes, applicants are requested to provide details of the source from which they learnt about this application process for access to the Yellow Card database.

4. REVIEW PROCESS

4.1 Review process of applications

Upon receipt of an application a validation check will be made. If further information is required before the application can be processed, the principle applicant will be contacted before the application is accepted. Once an application has been logged the principal applicant will receive an acknowledgement for the application in the form of a letter or e-mail depending on the mode of submission. A reference number for the application will then be provided along with the intended date of review by the ISAC.

4.2 Outcome of the review process

The principal applicant will be informed of the outcome of their application following review by the ISAC. Where the application has been approved by the Committee the principle applicant will receive the requested data from MHRA staff within a defined timeframe. If an application is refused the applicant will be informed of the reasons

and have an opportunity to appeal (section 4.3) or re-submit an amended application to the Committee.

4.3 Appeal mechanism

If the MHRA accepts the advice of ISAC to turn down an application for data, the unsuccessful applicant will be sent a letter setting out the reasons why. The applicant will be told that he/she has 28 days from the date of the letter to make representations, and that these should be made in writing to the YellowCard ISAC Secretary as appropriate. The applicant will be informed that once this 28 day period has expired, he/she will have to make a fresh application. If an appeal is to be carried out then the Licensing Authority will appoint a person or persons to undertake a review of the documentation. A letter will be sent to the applicant with the outcome of the appeal. The decision of the Licensing Authority will be final.

5. CONTACT FOR FURTHER INFORMATION

Write to:

The Pharmacovigilance Group
Post Licensing Division
MHRA
Market Towers
1 Nine Elms Lane
London
SW8 5NQ

E-mail:
pharmacovigilance@mhra.gsi.gov.uk

Tel: 020 7084 2788

Glossary

Adverse Drug Reaction (ADR)
A reaction which is harmful and unintended and which occurs at a dose normally used for the prophylaxis, diagnosis or treatment of disease or the modification of physiological function.

Adverse Drug Reactions On line Information Tracking (ADROIT)
The MHRA's computer system for storage and analysis of UK and foreign adverse drug reaction (ADR) data.

Co-applicant
A co-applicant is a researcher who will have significant intellectual input into, and part responsibility for, the research if the application is successful.

Committee on Safety of Medicines (CSM)
The CSM was one of the independent advisory committees established under the Medicines Act (Section 4) which advises the UK Licensing Authority on the quality, efficacy and safety of medicines in order to ensure that appropriate public health standards are met and maintained. In November 2005 the CSM was replaced by the new Commission on Human Medicines (CHM).

Medical Dictionary for Regulatory Activities (MedDRA)
The internationally accepted medical terminology for use in drug regulation. Developed under the auspices of the ICH and based on MEDDRA (Medical Dictionary for Drug Regulatory Affairs) which was in turn based on the MHRA's medical dictionary.

Medicines Act
The Medicines Act was given Royal Assent in October 1968. It provided for a comprehensive system of licensing affecting manufacture, sale, supply and importation of medicinal products into the UK. Medicines regulation in the UK is now governed by a combination of powers under the Act on EU law.

Medicines and Healthcare products Regulatory Agency (MHRA)
On 1 April 2003, the Medicines and Healthcare products Regulatory Agency (MHRA) replaced the Medical Devices Agency (MDA) and the Medicines Control Agency (MCA). The MHRA is an Executive Agency of the Department of Health with Trading Fund status. The MHRA is committed to safeguarding public health by ensuring that medicines, healthcare products and medical equipment meet appropriate standards of safety, quality, performance and effectiveness, and are used safely.

Norsk Database
The original computer system on which the Product Licence Database was stored.

Pharmacovigilance
Pharmacovigilance is the process of (a) monitoring medicines as used in everyday practice to identify previously unrecognised or changes in the patterns of their adverse effects; (b) assessing the risks and benefits of medicines in order to determine what action, if any, is necessary to improve their safe use; (c) providing information to users to optimise safe and effective use of medicines; (d) monitoring the impact of any action taken.

Principal applicant

A principal applicant is the lead researcher who has the main intellectual input into, and responsibility for the research if the application is successful. This is the individual with whom the MHRA will correspond about the application.

Public domain
Information that is openly available to everyone and not subject to copyright protection.

Redaction
The careful editing of a document to remove confidential information.

Reporter
Reporters of adverse drug reactions via the Yellow Card Scheme are health care professionals (e.g. doctors, dentists, coroners, pharmacists, nurses, radiographers and optometrists). The Yellow Card Scheme is voluntary for health care professionals and they also report indirectly to us via the pharmaceutical industry. Patient reporting is being incorporated within the Scheme through ongoing initiatives but these data are currently held separately on the MHRA's database.

Side effect
A consequence other than the one for which an agent or measure is used.

Signal detection
A signal can be defined as reported information on a possible causal relation between an adverse event and a medicine, the relation being previously unknown or poorly documented. The Yellow Card Scheme can be used to detect signals that require further pharmacovigilance investigation.

Trading Fund
A Trading Fund is a financing framework for Government operations, covering operating costs and receipts, capital expenditure, borrowing and net cash flow, which gives an agency greater freedom to manage its financial affairs than if its costs are met by its parent Department.

UK Licensing Authority
UK Government Ministers of Health and Agriculture.

List of abbreviations

ADROIT	Adverse Drug Reactions On-line Information Tracking
ADR	Adverse drug reaction
COREC	Central Office for Research Ethics Committees
CSM	Committee on Safety of Medicines
DAP	Drug Analysis Print
DPA	Data Protection Act 1998
FOIA	Freedom of Information Act 2000
GMC	General Medical Council
REC	Research Ethics Committee
MCA	Medicines Control Agency
MDA	Medical Devices Agency
MedDRA	Medical Dictionary for Regulatory Activities
MHRA	Medicines and Healthcare products Regulatory Agency
ONS	Office of National Statistics

Annex A

ACCESS TO YELLOW CARD & ADROIT DATA APPLICATION FORM

Applicants requesting Category Ib Yellow Card data (Annex D) should only complete sections A, B, C, D and E of this form. Those requesting Category II data must complete all sections of the application form (except section E) and provide the undertakings below.

Undertakings by the MHRA in relation to information provided by applicants

The information submitted on this form will be considered by the ISAC established by the Medicines and Healthcare products Regulatory Agency (MHRA) to advise on applications for access to Yellow Card data. Any personal data provided in an application will be used only for statistical analysis, management, planning and in the provision of services by the MHRA. In accordance with the Data Protection Act 1998, the ISAC and the MHRA will respect the confidentiality of all personal information, but reserve the right to publish in an anonymous and unidentifiable form summary data about applications received (via the Internet or in its annual report) for reference and audit purposes.

Undertakings by the applicant(s) in relation to information provided by the MHRA

1. I confirm that I have read and understood the Data Protection Statement and the Access to Yellow Card Data Guidance Notes.
2. I agree to use the data only for the intended purpose for which access was granted.
3. I will submit in writing any change to the research plan or any amendment to the principal applicant and/or co-applicants to the ISAC for approval.
4. I will ensure that the data are stored in a confidential manner and that the data or analyses of the data are not released to third parties without consent from the ISAC.
5. I will inform the MHRA of any new drug safety issues identified at the time of recognition.
6. I agree to submit any draft publications from use of these data to the MHRA for comments four calendar weeks prior to publication.
7. To the best of my knowledge the information provided in this application is accurate and comprehensive.

Signature of principal applicant: _____ Date: _____

Signature of co-applicant: _____ Date: _____

Signature of co-applicant: _____ Date: _____

Signature of co-applicant: _____ Date: _____

Section A - REFERENCE NUMBER[23] _____

Section B - PERSONAL DETAILS

B.1 Principal applicant

Title (Prof/Dr/Mr/Mrs/Miss/Ms/other please detail): Professor

Full name: Derek Stewart

Place of work: Robert Gordon University

Job title and organisation: Professor of Pharmacy Practice

Address: School of Pharmacy & Life Sciences, Robert Gordon University

City: Aberdeen

Zip / Postcode: AB10 1FR

Country: UK

Telephone: 01224 262432

Fax: 01224 262555

E-mail: d.stewart@rgu.ac.uk

B.2 Co-applicant

Title (Prof/Dr/Mr/Mrs/Miss/Ms/other please detail): Dr

Full name: James McLay

Place of work: University of Aberdeen

Job title and organisation: Senior Lecturer

Address: Institute of Medical Sciences

City: Aberdeen

Zip / Postcode: AB25 2ZD

Country: UK

Telephone: 01224 552463

Fax: 01224

E-mail: j.mclay@rgu.ac.uk

[23] The reference number will be provided by the Committee on Yellow Card Data secretariat on receipt of a valid application. The applicant is not required to complete this section.

B.3 Co-applicant

Title (Prof/Dr/Mr/Mrs/Miss/Ms/other please detail): Dr

Full name: Yash Kumarasamy

Place of work: Robert Gordon University

Job Title and organisation: Lecturer in Clinical Pharmacy

Address: School of Pharmacy & Life Sciences, Robert Gordon University

City: Aberdeen

Zip / Postcode: AB10 1FR

Country: UK

Telephone: 01224 262595

Fax: 01224 262555

E-mail: y.kumarasamy@rgu.ac.uk

B.4 Co-applicant

Title (Prof/Dr/Mr/Mrs/Miss/Ms/other please detail): Mr

Full name: Okechukwu Obisike Ndu

Place of work: Robert Gordon University

Job title and organisation: PhD student

Address: School of Pharmacy & Life Sciences, Robert Gordon University

City: Aberdeen

Zip / Postcode: AB10 1FR

Country: UK

Telephone: 01224 262432

Fax: 01224 262555

E-mail: o.o.ndu@rgu.ac.uk

Section C - TITLE AND SUMMARY OF THE PROPOSAL

C.1 Title of proposal for use of Yellow Card data

A review of Yellow Card reports on complementary and alternative medicines (CAMs)

C.2 Summary of proposal including key goals
(not more than 500 words)

The World Health Organisation (WHO) defines complementary and alternative medicines (CAMs) as 'a broad set of health care practices that are not part of a country's own tradition and are not integrated into the dominant health care system', categorising these as 'medication therapies' and 'non-medication therapies'. While the use of 'medication therapies' (e.g. herbal products, homeopathic products, vitamins and minerals, essential oils) is increasing globally, there are few reports which focus on safety.

The aim of this research is to analyse reports of suspected ADRs from the UK Yellow Card Scheme (YCS) related to 'medication therapies' classified as CAMs. Data will be analysed in terms of

- the number of reports for individual products
- completeness of the reports
- patient characteristics (sex and age)
- reporter status (patient reports v healthcare professional reports)
- date of report
- the opinion of the reporter to the seriousness of the reaction
- free text description of the reaction, richness of descriptions
- MedDRA coded reaction terms
- reaction start and end date
- onset of reaction time
- reaction duration
- reaction outcome
- recovery time
- any specific treatment given
- reaction severity
- any sequelae
- name of product as reported
- prescribing indications
- dose
- dosage form and strength
- route
- patient medical and drug history
- information on the parent where relevant
- details of any death reported.

Please note that there is no intention to contact the patient/reporter/healthcare professional.

Analysis will be descriptive in terms of

- characteristics of those experiencing ADRs
- reactions
- products
- outcomes.

C.3 Name and address of Department / Institution / place at which the research / analysis will be conducted

School of Pharmacy & Life Sciences, Robert Gordon University

C.4 Proposed start date 1 December 2011

Duration if known 9 months

Section D – USE OF OTHER DATABASES

D.1 Are you intending to use the Yellow Card data in combination with another database or other data sources[24] (local, national, international or personal data archive)? No

If yes, please specify

Section E – CATEGORY Ib YELLOW CARD DATA FIELDS

This section is not required for applications for Category II data.

E.1 Please tick the following data fields that you require and provide details:

	Yes	No	Details
Patient age categories			
Patient gender			
Suspect drug(s)			
Dose of suspect drug			
Route of administration			
Duration of treatment			
Suspected adverse drug reaction(s)			

*Category I data case details listed above are releasable under the Freedom of Information Act (FOIA) without consideration by the ISAC. These are known as Category Ib data. Provision of these data will depend on the number of cases held by the Agency. The MHRA will not release any data subset in which there are five or fewer cases per cell. This is necessary to prevent identification of patients and/or reporters. Where there are less than five cases per cell the data will be aggregated with adjacent cells. Any aggregation will be clearly marked on the dataset.

[24] For example GP, hospital, Health board, death, employee records

APPLICANTS FOR CATEGORY II DATA MUST COMPLETE ALL THE SECTIONS THAT FOLLOW

Please remember your obligations under the DPA once you begin to process personal data. These are set out at Annex B.

Section F - DETAILS OF PROPOSAL

F.1 What category of data request are you requesting?
(refer to guidance notes for definitions of data categories)

Category II

F.2 Would your research involve contacting the reporter and/or patient via the MHRA? No
If yes, please justify why you are requesting data that include information related to individuals.

F.3 Do you consider that the exemptions under FOIA are applicable to the release of the data you are requesting? Yes

F.4 Please provide a short description of the proposed research methodology including design of the study, data management and data analyses. This section must be in language that is comprehensible to a non-specialist reader. (not more than 500 words)

Analysis of data will be undertaken by a PhD student at the School of Pharmacy & Life Sciences under the supervision of Professor Derek Stewart (principal supervisor), Dr James McLay and Dr Yash Kumarasamy. DS, JM and YK have expertise in pharmacovigilance research. Prior to undertaking analysis, logical checks on the data (outliers, missing data etc) will be performed and any anomalies clarified by contacting MHRA. Data will be imported into a bespoke SPSS database (SPSS Cary, NC, USA, version 17). Analysis will largely be descriptive (frequencies, means, medians etc) and univariate to explore any associations between independent variables (age etc) and outcomes (ADRs). A report of findings will be submitted to MHRA and for publication.

F.5 Please describe the statistical methods you plan to use in the analysis of the data.

Analysis will largely be descriptive (frequencies, means, medians etc) and univariate to explore any associations between independent variables (age etc) and outcomes (ADRs).

F.6 Have you received ethical approval for your request? No
If yes, please provide a copy of the ethics committee's approval and its reference number.

F.7 Is the proposal subject to any agreements with any academic, commercial or other organisations? No
If yes, give details

F.8 Is the proposal likely to lead to any patentable or commercially exploitable results? No
If yes, give details

F.9 Do you consider that the consequences of your research may have implications for public health? No
If yes, give details

Section G - RELEVANT APPLICATIONS AND PUBLICATIONS

G.1 Have you used Yellow Card data previously? No
If yes, give details (include relevant publications)

G.2 Is this application a resubmission of a previous application? No
If yes, give details of how this application differs from the original application

G.3 Have you previously submitted other applications to the ISAC or its predecessor, the Interim Committee on Yellow Card Data? No
If yes, give details

Section H – SECURITY & CONFIDENTIALITY

H.1 Please confirm that you will abide by the principles of the DPA 1998 as detailed in the guidance notes Yes

H.2 Where will the Yellow Card hard copy and consequential working papers and manuscripts be held? Where computer or electronic data systems will be used please give details.

Hard copies and working papers will be held in locked cupboards within the School of Pharmacy & Life Sciences at Robert Gordon University. Only the PhD student and supervisors will have access. Electronic data will be stored on one password protected PC within the university.

H.3 What security arrangements will be made to prevent unauthorised access to the Yellow Card data when held on a university or research network and/or a personal laptop or other computer?

All documents (SPSS database, SPSS outputs, draft and final reports will be stored on password protected computers). Only the PhD student and supervisors will have access.

H.4 Please provide details of data security policies that will apply to all individuals and organisations named in this application who will have access to the data.

We will strictly adhere to the data protection policies of Robert Gordon University, available at http://www4.rgu.ac.uk/dp/general/page.cfm?pge=45483

At Robert Gordon University we abide by the eight principles put in place by the Data Protection Act 1998. Data must be:
1. fairly and lawfully processed;
2. processed for limited purposes;
3. adequate, relevant and not excessive;
4. accurate;
5. not kept for longer than is necessary;
6. processed in line with your rights;
7. secure; and,
8. not transferred to countries without adequate protection.

By law, Robert Gordon University (a "Data Controller") must keep to these principles in its processing of personal data.

We will also adhere to all RGU research governance policies, available at http://www4.rgu.ac.uk/files/Research%20Governance%20Policy%20%2814%20Oct%202010%291.pdf

I have also attached a copy of the School of Pharmacy & Life Sciences Research Governance Standard Operating Procedure.

H.5 What measures will be put in place to ensure that the data are not disclosed to third parties not named in the research application?

Third parties will have no access to the data (all password protected).

H.6 How long do you intend to retain the Yellow Card Data?
If longer than 12 months please provide justification

Until five years following completion and award of the PhD.

H.7 What method of data destruction will be employed when the research use of the Yellow Card data has been completed?

Professor Stewart will ensure that all data will be deleted from password protected computers.

Section I - PUBLICATION

I.1 Are you intending to publish or place the results of your proposal in the public domain? Yes
If yes, please specify

Results will be presented in a PhD thesis at Robert Gordon University. In addition, we intend to submit findings to appropriate peer reviewed journals such as ‘Drug Safety’.

I.2 Please confirm that you will submit any draft publications to the MHRA for any necessary regulatory action at least four calendar weeks prior to publication Yes

Section J - FINANCE

Fees are detailed in the guidance notes.

Please indicate to whom the MHRA should send invoices

Professor Derek Stewart
Professor of Pharmacy Practice
School of Pharmacy & Life Sciences
Robert Gordon University
Aberdeen
Scotland
AB10 1FR

Section K - CURRICULUM VITAE OF APPLICANT(S)

K.1 All applicants (including principal and co-applicants) who will have access to any Yellow Card data must provide up-to-date curriculum vitae with each application.

K.2 Summary of relevant qualifications and career(s) to date, if applicable (not more than 200 words)

Professor Derek Stewart
Professor of Pharmacy Practice
School of Pharmacy & Life Sciences
Robert Gordon University
Aberdeen
Scotland
AB10 1FR

PgCert (Tertiary Learning Teaching Methods), BSc (Pharmacy, 1st), MSc (Clinical Pharmacology), PhD.
Member of the Royal Pharmaceutical Society, Scottish Pharmacy Board and British Pharmacological Society prescribing sub-committee. Executive editor of the British Journal of Clinical Pharmacology and the editorial panel of International Journal of Clinical Pharmacy.

Dr James McLay
Senior Lecturer Medicine and Therapeutics
Aberdeen Medical and Dental School
University of Aberdeen
BPharm, MBChB, PhD, FRCP

Executive member of the British Pharmacological Society. Executive Editor of the British Journal of Clinical Pharmacology. Chair of the British Hypertension Society Educational Committee. Chair of the Specialist Advisory Committee for Clinical Pharmacology and Therapeutics.

Dr Yash Kumarasamy
Lecturer in Clinical Pharmacy
School of Pharmacy & Life Sciences
Robert Gordon University
Aberdeen
Scotland
AB10 1FR

PgCert (Higher Education Learning and Teaching), MBBS, MSc (Clinical Pharmacology), PhD. FHEA, MRSC
A clinical pharmacologist with an interest in public health and epidemiology.

Okechuukwn Obisike Ndu
PhD student
School of Pharmacy & Life Sciences
Robert Gordon University
Aberdeen
Scotland
AB10 1FR

K.3 List up to ten relevant publications

Tobaiqy M, **Stewart D**, Helms P, Williams J, Crum J, Steer C, **McLay J**. Parental reporting of adverse drug reactions associated with attention-deficit hyperactivity disorder (ADHD) medications in children attending specialist paediatric clinics in the UK. Drug Safety 2011;34(3):211-219. 0114-5916/11/0003-0211/$49.95/0

Tobaiqy M, **Stewart D**, Helms PJ, Bond C, Lee AJ, Bateman N, McCaig D, **McLay JS**. A pilot study to evaluate a community pharmacy-based monitoring system to identify adverse drug reactions associated with paediatric medicines use. European Journal of Clinical Pharmacology 2010;66:627-632. 10.1007/s00228-101-0790-9

Tobaiqy M, **Stewart D**, Helms PJ, Bond CM, Lee AJ**, McLay JS**. Views of parents and pharmacists following participation in a paediatric pharmacovigilance study. Pharmacy World & Science 2010;32:334-338. 10.1007/s11096-010-9374-0

Stewart D, Helms P, McCaig D, Bond C, **McLay J**. Monitoring adverse drug reactions in children using community pharmacies: a pilot study. British Journal of Clinical Pharmacology 2005; 59: 677-683.

Elkout H, **McLay JS**, Simpson CR, Helms, PJ. Use and safety of long-acting $_2$-agonists for pediatric asthma. Pediatric Health. 2010; 4, Issue 3:295-310.

Elkout H, **McLay J.S**, Simpson C.R, Helms, P.J A retrospective observational study comparing rescue medication use in children on combined versus separate long-acting β-agonists and corticosteroids. Archive Dis Childhood. 2010; 95, Issue 10: 2010, 817-821.

Naina Mohamed, I., Helms, P.J., Simpson, C.R., Milne, R.M., **McLay, J.S**. Using primary care prescribing databases for pharmacovigilance. BJCP. 2011; 71, Issue 2; 244-249

Naina Mohamed, I., Helms, P.J., Simpson, C.R., Milne, R.M., **McLay, J.S.** Using routinely collected prescribing data to determine drug persistence for the purposes of pharmacovigilance. J Clin Pharmacol. 2011; 51:279-284

Elkout H, Simpson CR, Helms PJ, **McLay JS.** Changes in primary care prescribing patterns for paediatric asthma: A prescribing database analysis. Archives Dis Childhood. 2011. Accepted for publication.

Karzouini A Mohammed, B.S, Cameron, GA., Helms, PJ, **McLay JS** Paracetamol prescribing in primary care: Too little and too much? BJCP. 2011. Accepted for publication.

Section L - SUPPLEMENTARY INFORMATION

L.1 Where did you learn about this application process?

Internet _____

L.2 If you have any comments on this application form, please provide feedback below:

Annex B

The Data Protection Act 1998 Principles (Schedule 1)[25]

1. Personal data shall be processed fairly and lawfully and, in particular, shall not be processed unless (a) at least one of the conditions in Schedule 2 is met, and (b) in the case of sensitive personal data, at least one of the conditions in Schedule 3 is also met.

2. Personal data shall be obtained only for one or more specified and lawful purposes, and shall not be further processed in any manner incompatible with that purpose or those purposes.

3. Personal data shall be adequate, relevant and not excessive in relation to the purpose or purposes for which they are processed.

4. Personal data shall be accurate and, where necessary, kept up to date.

5. Personal data processed for any purpose or purposes shall not be kept for longer than is necessary for that purpose or those purposes.

6. Personal data shall be processed in accordance with the rights of data subjects under this Act.

7. Appropriate technical and organisational measures shall be taken against unauthorised or unlawful processing of personal data and against accidental loss or destruction of, or damage to, personal data.

8. Personal data shall not be transferred to a country or territory outside the European Economic Area unless that country or territory ensures an adequate level of protection for the rights and freedoms of data subjects in relation to the processing of personal data.

[25] http://www.hmso.gov.uk/acts/acts1998/80029--l.htm#sch1

Annex C

The Freedom of Information Act 2000 (FOIA) Exemptions

Absolute exemptions

Section 21 - Information accessible to applicant by other means.

Section 23 - Information supplied by, or relating to, bodies dealing with security matters.

Section 32 - Court records, etc.

Section 34 - Parliamentary privilege.

Section 40 - Personal information.

Section 41 - Information provided in confidence.

Section 44 - Prohibitions on disclosure.

Qualified exemptions

Section 22 - Information intended for future publication.

Section 24 - National security.

Section 26 – Defence

Section 27 - International relations.

Section 28 - Relations within the United Kingdom.

Section 29 - The economy.

Section 30 - Investigations and proceedings conducted by public authorities.

Section 31 - Law enforcement.

Section 33 - Audit functions.

Section 35 - Formulation of government policy, etc.

Section 36 - Prejudice to effective conduct of public affairs.

Section 37 - Communications with Her Majesty, etc. and Honours.

Section 38 - Health and safety.

Section 39 - Environmental information.

Section 42 - Legal professional privilege.

Section 43 - Commercial interests.

Annex D

Category I releasable data fields (Category Ib data)

Category I data case details listed below are releasable under the Freedom of Information Act (FOIA) without consideration by the ISAC. These are known as Category Ib data. Provision of these data will depend on the number of cases held by the Agency. The MHRA will not release any data subset in which there are five or fewer cases per cell. This is necessary to prevent identification of patients and/or reporters. Where there are less than five cases per cell the data will be aggregated with adjacent cells. Any aggregation will be clearly marked on the dataset.

Patient age categories (<18, 18-24, 25-34, 35-44, 45-54, 55-64, 65-74, 75-84, >85 years)
Patient gender (number of female and male patients)
Suspect drug(s)
Dose of suspect drug
Route of administration
Duration of treatment
Suspected adverse drug reaction(s)

Appendix IV

Approval Letter 1

The following appendix contains the approval Letter 1

Safeguarding public health

MHRA

Prof Derek Stewart
School of Pharmacy & Life Sciences,
Robert Gordon University
Aberdeen
AB10 1FR

19/10/2011

Our Ref: AYCD030

Dear Prof Stewart

Application: A review of Yellow Card reports on Complementary and Alternative Medicines (CAM).

The Independent Scientific Advisory Committee (ISAC) for MHRA database research considered the above application on 7th October 2011. The Committee considered that your application was an appropriate use of Yellow Card data and that the proposed methodology is appropriate for the objectives of the study. The Committee advised that the application should be granted provided you comply with the following conditions:

- The applicants should be asked to update their proposal for computer security, rather than password protected these should be encrypted.
- In addition, as your proposal will involve the release of Category II data, I should remind you of the undertakings you agreed to when you completed the application form. These are included at Annex A.
- You must abide by the *Guidelines for Safe Disposal of Electronic Yellow Card Data for External Users* included at Annex B.
- Please note the enclosed information at Annex C on the National Research Register (NRR). We strongly recommend that you register with the NRR.

The MHRA has accepted the advice of the ISAC. If you are willing to accept the above conditions, please let me know as soon as possible and no later than 28 days after the date of service of this letter.

Yours sincerely,

Ms Sharon Suri

Yellow card Secretary to the ISAC

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Annex A

Undertakings by the applicant(s) in relation to information provided by the MHRA

1. I confirm that I have read and understood the Data Protection Statement and the Access to Yellow Card Data Guidance Notes.

2. I agree to use the data only for the intended purpose for which access was granted.

3. I will submit in writing any change to the research plan or any amendment to the principal applicant and/or co-applicants to the ISAC for approval.

4. I will ensure that the data are stored in a confidential manner and that the data or analyses of the data are not released to third parties without consent from the ISAC.

5. I will inform the MHRA of any new drug safety issues identified at the time of recognition.

6. I agree to submit any draft publications from use of these data to the MHRA for comments four calendar weeks prior to publication.

7. To the best of my knowledge the information provided in this application is accurate and comprehensive.

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Annex B

Guidelines for Safe Disposal of Electronic Yellow Card Data for External Users

1. Scope

This guideline provides a brief on general procedures for the safe disposal of externally held paper and electronic[1] Yellow Card data for applicants requesting access to Yellow Card data for scientific research.

2. Introduction

The MHRA and most other modern organisations are increasingly dependent on computer systems. Substantial costs may be incurred if a system, or the information it contains, is lost, damaged, destroyed or if information is obtained by those not entitled to it. Large amounts of valuable information can be easily stored on external computers and portable computing devices, such as laptops, notebooks, smart phones and Personal Digital Assistants (PDA). It is therefore paramount to ensure data is protected by both minimising the amount of information stored and adequately safeguarding it.
The Data Protection Act 1998 (DPA) applies to personal data. Its purpose is to ensure that such data are processed fairly and lawfully and in particular that personal data is not disclosed to third parties unlawfully. The DPA covers computer records, discs, CDs, USB memory sticks and information held in paper files (e.g. index cards, filing systems etc).

The seventh data protection principle requires data controllers to ensure that appropriate security measures are in place to prevent the unauthorised or unlawful processing of personal data and against accidental loss or destruction of, or damage to, personal data. When the processing of personal data is carried out by a data processor on behalf of the data controller, the contract for that processing must require the data processor to comply with obligations equivalent to those imposed on the data controller by the seventh principle. Whether the measures in place are appropriate will depend upon whether they provide a level of security appropriate to the harm which might result from a breach of security and the nature of the data to be protected, as well as taking into account the state of technological development and the cost of implementing the measures.

3. Background

The MHRA operates post-marketing surveillance systems for reporting, investigating and monitoring adverse reactions to medicines and adverse incidents involving medical devices to safeguard public health. The safety of medicines is monitored using the Yellow Card Scheme which has been in existence since 1964.

The Independent Scientific Advisory Committee for MHRA database research (ISAC) and the MHRA consider that confidentiality of Yellow Card data is paramount. For this reason such data is provided to third parties on the following stringent conditions.

1 Data/Bits & bytes, stored on a digital storage device, e.g. hard disk, flash memory key, CD-ROM etc

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4. Data Use

4.1 Desktop Computers

If you use a desktop Personal Computer (PC) you must:

• Have adequate security in place at all times when you are not using it, i.e. lock the office when no one is there;
• Ensure that your computer receives regular Operating System security patches, firewall and anti-virus updates;
• Be familiar with your computer's connection capabilities. If it has network/telephone access, be sure to know how you can securely connect to an authorised network or the Internet. Be sure to disconnect any network/telephone connections and to turn it off when not in use;
• You must understand the level of data you are using. Never store or process information with protective markings unless authorised to do so and in a secure environment;
• Be aware of your surroundings and of the opportunity for un-authorised people looking 'over your shoulder.'

The items above are not exhaustive and provide general pointers to make you aware of the types of issues involved. It is always important to 'err, on the side of caution'.

4.2 Portable computers

Due to risk of theft, portable computers (including PDAs, laptops etc) **must not** be used to store identifiable Yellow Card data. Data must be stored at all times in the location you have told the MHRA.

4.3 Encrypting data for transmission

Recipients of Yellow Card data can only send data to third parties with permission of the MHRA, for example if an applicant has obtained data through an ISAC application and these data need to be shared electronically with a co-applicant.

Many software applications[2] are available that can encrypt files (of any size) to increase protection against unauthorised disclosure. These files can then be copied onto removable storage media (such as CD) for safer transportation and can also be sent as attachments via standard email. The current (2006)
US government approved encryption standard (and adopted in the UK) is the 'Rijndael - Advanced Encryption Standard' (AES).

AES is currently the most secure encryption standard available and is recommended for the encryption of identifiable Yellow Card data, if for any reason a researcher needs to send identifiable Yellow Card data by email to another colleague.

2 Dedicated 3rd party specialist applications are available. Also many leading compression applications have the facility to encrypt (& compress) data e.g. WinZip (v9 & above) or WinRar.(v3.6 & above)

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4.4 How to comply with the Advanced Encryption Standard when encrypting Yellow Card data for transportation

If sending data as outlined in 4.3, a few options are available:

4.4.1 Winzip
WinZip(v10) can encrypt data using the approved AES encryption algorithm. The European Medicines Agency (EMEA) has selected this method for the safe dispatch of information to its delegates and other Agencies.

4.4.2 Secure Email delivery Service
Another method is the use of a secure email delivery service. Encrypting an entire email message (including attachments) prevents 'outsiders' from reading it when it is in transit. There are two options:

1. Configure an email client (e.g. Outlook) to digitally encrypt and sign documents prior to transmission. This method requires the recipient's email application to be configured to successfully accept and decode the encrypted email.

2. The use of a secure web-based email delivery service, such as the popular Hushmail (hushmail.com) or Voltage mail (vsn.voltage.com/index.htm). The registered user would build the message on-line via the web interface and add any attachments before sending the email to the recipient. The recipient would not have to be a registered user to receive the email. However, he/she would have to register to send encrypted email via the service.

5. Data Removal Guidelines

You must be cautious of the fact that in the event your computer is sold or stolen, the data can potentially be accessed by unscrupulous people.

It is a professional and moral obligation to protect (in accordance with the DPA) sensitive Yellow Card data which is no longer required, from unnecessary disclosure. When required, data stored on a computer must be carefully disposed of in an efficient and cost-effective manner. The data owner must be certain that Yellow Card data which is no longer required is obliterated.

Proper organisation of research data on large storage devices is important as this will allow you to safely locate and clear the data, minimising the risk of accidental erasure. Ideally, Yellow Card data should be stored under a main folder. In order to manage large amounts of data, other folders should be created, these folders should be created in a hierarchy structure. This will make the task of shredding individual or even large chunks of data files easier and safer.

6. Hard Disk File Shredding
Proper organisation of research data on large storage devices is important as this will allow you to safely locate and clear the data, minimising the risk of accidental erasure. Ideally, research data should be stored under a main folder. In order to manage large amounts of data, other folders should be created, these folders should be created in a hierarchy structure. This will make the task of shredding individual or even large chunks of data files easier and safer.

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6.1 Removal Methods for NHS/DH

The NHS/DH computer system is part of a secure 'restricted' network (this is the minimum classification level for the NHS), so Yellow Card data stored on NHS computers can be deleted in the normal way, in accordance with the organisation's IT policies. The NHS routinely adopts special procedures when computers needs to be removed for disposal or a hard disk upgrade is required. If machines are reused internally they are simply rebuilt/re-imaged, if they are leaving the NHS then they are completely wiped clean using an accredited software application or degaussed for extra security. This echoes the Department of Health's (DH's) policy for erasing/discarding computers.

6.2 Removal Methods for non-NHS/DH organisations

6.2.1 Best Practice

When handling sensitive data, the following recommended options provide a safer and more secure data disposal environment.
The 'best practice' method would be a combination approach which includes:
• The creation of a formal computer data disposal document (like this one) explaining the process.

• The use of data wiping software or 'File Shredding' software

➢Where the user does not have a separate drive solely for working with Yellow Card data, File Shredding is the recommended option. File shredding is a technique used to wipe individual folders or files residing on hard disks but can also be used on other removable read/write media. The software will typically run a routine that deletes the chosen files/folders and then overwrites the areas of the hard drive with repeated patterns of random characters. The more "passes" made by the overwriting routine, the harder it becomes to recover the original information.
Recommended File Shredding software is Blancco's File Shredder[3]

➢Where the user has a separate drive letter (i.e. another partition) allocated for working with Yellow Card data, an option is to 'wipe' that drive partition using the recommended software. The partition will be completely wiped, overwritten many times (US Dept of Defence (DoD) standard) and may require the standard re-formatting. This method is ideal and will satisfy all critical concerns about possible recovery of sensitive data. However, this option requires additional technical knowledge.
Recommended software - the Government's, Communications Electronic Security Group(CESG) approved: *OnTrack's 'Data Erasure v2' Pro OR the Blancco Pro application.*[4]

• Use of data encryption software to maintain good security in the event the PC equipment is stolen and/or any unauthorised recovery of deleted data is performed

➢The whole system can be easily and transparently encrypted. Usually one additional password is required at boot up (to allow access) and the system can be used normally
Recommended Encryption software - Becrypt Disk Protect[5]

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6.2.2. Hard Disk Disposal/Re-use
When disposing hard disks containing Yellow Card data the MHRA recommends

- **The government (CESG) approved *OnTrack's 'Data Erasure v2' Pro OR the Blancco PRO application*[6]**

Please note that when wiping Yellow Card data from your storage media, the software must comply with the 'Gutmann' and US DoD. Of these, the Gutmann standard is most secure – use for personalised/identifiable medical data or documents classified as 'Confidential' or above, for other cases the US DoD standard is suitable. If you wish to use a different software package please contact the MHRA to see if it is suitable.
Be sure to understand all the places where data duplication may be located. Data residing on removable storage media (including for backup purposes) such as, CD/DVD's, USB Flash memory devices, floppy disks etc. need to be completely erased using the appropriate disk wiping software. If appropriate, the medium should be destroyed by physically breaking or shredding, this procedure is also known as purging.

6.2.3. Physical destruction/purging

Shredding
This is the most popular method of destroying paper or even CDs and floppy disks, etc. Shredders preferably the 'cross-cut' variety, come in a variety of sizes and capacities for office environments. For larger volumes, hiring the services of specialist vendors for disposal of information may be required.
Some vendors will bring equipment to your facility and shred documents on site. If records are to be shredded on the vendor's premises, certified shredding is required.

Purging
Whilst shredding works for paper and CDs, disposal of stronger rigid materials such as hard disks, digital tapes or optical disks require degaussing, pulverisation, drilling, melting/incineration (tasks usually outsourced). Sanding off the physical recording surface is another option.

MHRA/IMD

November 2006

3 Blancco - http://www.blancco.com/main.site?action=siteupdate/view&id=21
4 OnTrack - http://www.ontrack.co.uk/dataeraser/
5Becrypt Disk Protect - http://www.becrypt.com/our_products/disk_protect.php
6 Data Eraser - http://www.ontrack.co.uk/dataeraser/

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Annex C

National Research Register

The National Research Register (NRR) is a register of ongoing and recently completed projects funded by, or of interest to, the UK National Health Service.

*ISAC **strongly** recommends that UK researchers using Yellow Card data consider registering as NRR data providers, in order that others engaged in research within the UK can be made aware of current works.*

*Registration with the NRR is **entirely voluntary** and will not replace information on ISAC approved protocols published in summary minutes or in the ISAC Annual Report*

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Appendix V

Approval Letter 2

The following appendix contains the approval Letter 2

Professor Alison Strath
School of Pharmacy and Liife Sciences
Robert Gordon University
Schoolhill, Aberdeen
AB10 1FR

a.strath@rgu.ac.uk

MHRA
151 Buckingham Palace Road
Victoria
London SW1W 9SZ
United Kingdom
www.mhra.gov.uk

11/07/2013

Dear Prof. Strath

Thank you for your correspondence regarding request for Yellow Card data.

Firstly, to provide some background the MHRA is a government agency which is responsible for the regulation of medicines and medical devices in the UK. The Yellow Card Scheme was established in 1964 and collates spontaneous 'suspected' Adverse Drug Reactions (ADR) reports associated with drug substances from healthcare professionals, companies and members of the public. These reports are held on a database and are available in the form of Drug Analysis Prints which can be downloaded from our website www.mhra.gov.uk/daps.

I am pleased to provide you with the total number & breakdown of suspected Adverse Drug Reports (ADRs) received per year for the period 01/01/1996 – 31/12/2013 in UK. Please see table 1.

Table 1:

Year	Total number of reports
1996	17107
1997	16623
1998	18042
1999	18482
2000	33145
2001	21444
2002	17590
2003	19190
2004	19933
2005	21834
2006	21424
2007	21190
2008	25029
2009	25462
2010	23305
Total	**319800**

When interpreting this data it is important to take the following points into consideration:

The number of reports received via the Yellow Card Scheme does not directly equate to the number of people who suffer adverse reactions to drugs for a number of reasons, as this scheme is associated with an unknown and variable level of under-reporting - i.e. not all reports of suspected ADRs are reported as it is not mandatory for healthcare professionals to report suspected ADRs to the MHRA.

Please be aware that ADR reporting rates are influenced by the seriousness of reactions, their ease of recognition, the extent of use of a particular drug, and may be stimulated by promotion and publicity about a drug. In addition the number of reports received should not be used as a basis for determining incidence of a reaction as neither the total number of reactions occurring, nor the number of patients using the drug is known.

Further more we currently provide two categories of data requests i.e category I(a/b) and II. Category I a/b data are releasable under the provisions of the Freedom of Information Act (FOIA) 2000. Category 1a comprises anonymised aggregated data e.g. Drug Analysis Prints (DAPs) which I've mentioned above. Category 1b data requests comprises a pre-defined basic set of case details such as patient age categories; the proportion of males and/or females who experienced the reaction; the suspected drug or drugs; the dose and duration of the suspected drug(s) and the suspected adverse drug reaction(s) (see the Yellow Card application form Annex D for further details)
http://www.mhra.gov.uk/Committees/IndependentScientificAdvisoryCommitteeforMHRAdatabaseresearch/index.htm.
Please note if you request large quantities of data there may be a charge.

I hope this has been helpful, if you still require additional information, do not hesitate to contact me.

Yours Sincerely,

Olutoyin Agbaje
Signal Assessor
Vigilance Intelligence and Research Group
MHRA - Floor 3.O BPR

Cc: Rauf Pathan - Therapeutic Team Co-ordinator.

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Appendix VI

Approval Letter 3

The following appendix contains the approval Letter 3

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Robert Gordon University
Schoolhill, Aberdeen
AB10 1FR
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MHRA
151 Buckingham Palace Road
Victoria
London SW1W 9SZ
United Kingdom
www.mhra.gov.uk

18/09/2013

Dear Prof. Strath

Thank you for your recent correspondence requesting a break down of the number of Yellow Card reports received per year.

Firstly, to provide some background the MHRA is a government agency which is responsible for the regulation of medicines and medical devices in the UK. The Yellow Card Scheme was established in 1964 and collates spontaneous 'suspected' Adverse Drug Reactions (ADR) reports associated with drug substances from healthcare professionals, companies and members of the public. These reports are held on a database and are available in the form of Drug Analysis Prints (DAPs) which can be downloaded from our website www.mhra.gov.uk/daps.

I am pleased to provide you with the total number of suspected spontaneous UK Adverse Drug Reaction (ADRs) reports received per year between the time periods of **01/01/1963 – 31/12/1995 & 01/01/2011 – 31/12/2012** . Please see annex 1.

When interpreting this data it is important to take the following points into consideration:

- The number of reports received via the Yellow Card Scheme does not directly equate to the number of people who suffer adverse reactions to drugs for a number of reasons, as this scheme is associated with an unknown and variable level of under-reporting - i.e. not all reports of suspected ADRs are reported as it is not mandatory for healthcare professionals to report suspected ADRs to the MHRA.
- Please be aware that ADR reporting rates are influenced by the seriousness of reactions, their ease of recognition, the extent of use of a particular drug, and may be stimulated by promotion and publicity about a drug. In addition the number of reports received should not be used as a basis for determining incidence of a reaction as neither the total number of reactions occurring, nor the number of patients using the drug is known.
- Further more we currently provide two categories of data requests i.e category I(a/b) and II. Category I a/b data are releasable under the provisions of the Freedom of Information Act (FOIA) 2000. Category 1a comprises anonymised aggregated data e.g. DAPs which I've mentioned above. Category 1b data requests comprises a pre-defined basic set of case details such as patient age categories; the proportion of males and/or females who experienced the reaction; the suspected drug or drugs; the dose and duration of the suspected drug(s) and the suspected adverse drug reaction(s). http://www.mhra.gov.uk/Committees/IndependentScientificAdvisoryCommitteeforMHRAdatabaseresearch/index.htm.

Please note if you request large quantities of data there may be a charge. I hope this has been helpful, if you still require additional information, do not hesitate to contact me.

Yours Sincerely

Olutoyin Agbaje
Signal Assessor - VRMM

Medicines and Healthcare Products Regulatory Agency

MHRA
Cc: –Sharon Jethwa- Signal Management Team Co-ordinator.

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Annex 1.

Year	Total number of UK ADR reports
1963	21
1964	1296
1965	3737
1966	2228
1967	3234
1968	3193
1969	3911
1970	3317
1971	2711
1972	3554
1973	3308
1974	4470
1975	4505
1976	6071
1977	10894
1978	11412
1979	10516
1980	9680
1981	11172
1982	11118
1983	12127
1984	12998
1985	12601
1986	15270
1987	16305
1988	18378
1989	18561
1990	17869
1991	19930
1992	20118
1993	18030
1994	17514
1995	17618
2011	25133
2012	26038


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Appendix VII

Research Protocol (Yellow Card)

The following appendix contains the research protocol for the Yellow Card Scheme

Okechukwu Obisike Ndu
PhD student (1010078)
School of Pharmacy & Life Sciences

RESEARCH PROTOCOL (Version 3 –*February 25, 2013)*

PROJECT TITLE: A descriptive analysis of yellow card reports on paediatric Natural Product Complementary & Alternative Medicines

RESEARCH TEAM: Okechukwu Ndu, James McLay, Lorna McHattie, Alison Strath, Lesley Diack

1.0 BACKGROUND TO THE STUDY: The World Health Organisation defines Complementary and Alternative Medicine (CAM) as 'a broad set of health care practices that are not part of a country's own tradition, and are not integrated into the dominant health care system' (1). The Cochrane Collaboration defines CAM in a similar way (2), and classifies it (3) based essentially on the model put forth by the National Center for Complementary and Alternative Medicine (4) into five major categories: natural product-based therapies (like herbal and homeopathic medicines, dietary supplements, and probiotics), mind-body medicine therapies (like meditation, yoga, and guided imagery), manipulative and body-based practices (like spinal manipulation, massage, and acupuncture), alternative (or whole) medical systems (like Anthroposophic medicine, homeopathy, and traditional Chinese medicine), and other therapies (such as energy medicine and various forms of healings). While CAM use has been found to be increasing across the world in both adults and children (5-11), most surveys have found the natural product CAM therapies (NP-CAM) to be the most popular of all therapies used (12-15). With their popularity has, however, come a growing emphasis on safety issues surrounding their regulation and use (16-22). In the UK, the main system for drug safety monitoring is the Medicines and Healthcare

Products regulatory Agency (MHRA) through its Yellow Card Scheme (17,23,24). But despite various initiatives aimed at stimulating the reporting of NP-CAM-associated suspected adverse drug reactions (such as including CAM providers, community pharmacists, nurses and even patients themselves as accredited reporters in the scheme), the number of reports related to NP-CAM has been reported to be low (17,25). While studies have summarized the adverse drug reports to the MHRA with respect to various drug classes (26-29) and children (30-35), none has thus far focused on NP-CAM. The current study proposes to fill this gap. Pharmacovigilance data on NP-CAM reported to the MHRA from its inception in July, 1964 until July, 2012 has been obtained, and will form the basis of the study.

2.0 PROPOSED METHOD: The study is proposed to follow a descriptive retrospective method of database analysis.

2.1 AIM: To analyse reports of suspected adverse drug reactions (ADRs) related to NP-CAM in subjects aged up to 18 years in the UK Yellow Card Scheme (YCS).

2.2 SPECIFIC OBJECTIVES:

(i) To characterize NP-CAM-related YCS reports in terms of patient demography, dates of reports, type, presentation, and mode of administration of the products concerned, variety and (perceived) seriousness of ADRs, nature, clinical classification, duration and outcome of the reported events, and reporter status;

(ii) To investigate the relationship between patient and reporter-related factors and ADR nature and outcome.

(ii) To identify and highlight areas of potential concern for further investigation.

2.3 STUDY SETTING: The database of reports on subjects aged up to 18 years submitted to the MHRA through its YCS from July, 1964 to July, 2012 will be the focus of the study. All such reports made within the period shall be considered irrespective of the specific geographical location of origin within the UK.

2.4 ANALYSIS OF RESULTS: The results of the study will be analysed statistically in line with the study objectives. Descriptive statistics (means, medians, proportions, etc.) will be used to characterise the subjects of the ADRs, the type of reporter involved, the ADRs reported and their outcomes, as well as the NP-CAM associated. Inferential statistics will be used to investigate the relationships between patient and reporter-related factors and the number quality and outcome of ADRs reported at 95 % level of significance. All analyses will be carried out using SPSS 17.0.

2.5 RESEARCH GOVERNANCE: To ensure that the study is carried out to the highest ethical standards and in conformity with Robert Gordon University's research ethics committee guidelines, as well as the requirements of the MHRA Independent Scientific Advisory Committee (ISAC), approval for the study will be obtained from the Robert Gordon University School of Pharmacy & Life Sciences Ethics committee. As there is no intention to contact the patients, reporters or healthcare professionals involved, there will be no need for approval by the North of Scotland Research Ethics Committee. All procedures will conform to the School of Pharmacy & Life Sciences standard operating procedures for data collection. All data obtained will be stored in SPSS format in a password-protected university computer under the oversight of the principal researcher (ON), and will be processed, used and stored in line with the Data Protection Act of 1998. No third parties will have access to the data. At the end of the study, all related data will be deleted from the password-protected computer used. Apart from the PhD thesis resulting from the study, any research outputs accruing from the results of

this study will be submitted to the MHRA at least four calendar weeks prior to publication for any necessary regulatory actions.

3.0 WORK PLAN TIME-LINES: The study is proposed to commence by April 1, 2013, and end by the end of June, 2013, over a period of three months.

NOTE: Application has been made for the release of non-identifiable NP-CAM-related patient dispensing data from the Information Services Division (ISD) of the Scottish NHS. If the application is successful, the data will be studied and analysed in line with the above-stated provisions.

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Appendix VIII

Focus Group Topic Guide I

The following appendix contains the focus group topic guide I

Okechukwu Obisike NDU (1010078)

PhD student

A QUESTIONNAIRE PRE-TEST FOCUS GROUP
FOR A SURVEY OF PARENTS ON
THE USER-PERCEIVED EFFECTIVENESS AND SAFETY OUTCOMES OF
COMPLEMENTARY & ALTERNATIVE MEDICINE IN SCHOOL-AGED CHILDREN
GUIDELINE FOR FOCUS GROUP DISCUSSION

SWITCH ON THE AUDIO RECORDER ***CHECK FOR THE "ON" LIGHT ON THE AUDIO RECORDER***	Date	Time 00:00

A: INTRODUCTORY REMARKS (Time allotted: 5 minutes)

Hi, everybody. My name is Okeh NDU, and I am currently in my third year of doctoral research in the School of Pharmacy & Life Sciences under the supervision of Drs. Lesley Diack and Lorna McHattie, and Prof. Alison Strath. I am privileged to have Lorna here with me today to co-facilitate today's focus group. I thank you all very much for coming to attend this focus group pre-test.

We are here to discuss issues around a questionnaire on Complementary & Alternative Medicine (CAM) use in children that I have designed for on-line completion by parents of schoolchildren. The aim of this discussion is to find out whether, from your perspective as parents, this CAM questionnaire actually elicits the type of information it is intended to draw out from study participants; and where it does not, why that is so; and finally, how it could be better presented in order to achieve its objectives. Your input will be taken on board in further development of the questionnaire. Please note that, because we are having this discussion as a focus group of parents, we would like to hear your views and opinions as it pertains to you as a parent. As such, there are no right or wrong answers. The overall aim of this process is not to reach a consensus on

any matter, but to get all shades of opinions on every aspect of the questionnaire that can help us ensure a more robust research process. Generally, I will try to provide a bit of structure to the discussion, more-or-less in line with the topic guide I have distributed; but, please, feel free to contribute your ideas whenever an issue you consider important is raised. We will be keeping an audio record of this discussion so that I don't have to take notes; and so I encourage us all to try our very best to speak out loud, so that the Marantz® will be able to catch what we say clearly irrespective of where we are seated. In the end, I will summarize all that has been said into a report. In doing so, I want to assure us all of these two facts:

(i) I will not refer to any participant by name; and

(ii) The information generated from this discussion will be kept confidential, and used only for research purposes. And I plead with everyone present to do likewise as well.

Before we go into the discussion phase, **please, can I confirm that we have all completed and returned the consent form for participating in this focus group?**

DOES ANYONE HAVE ANY QUESTIONS ABOUT ALL I HAVE SAID SO FAR?

B: THE DISCUSSION (Time allotted: 45 minutes)

QUESTION ONE: As a parent, what was your **first impression** of the questionnaire?

As a parent –**if you received this link in the mail from your child's school**- what would you think of the idea of a CAM survey?

(3 MINUTES)

QUESTION TWO: What **did you think of the quantity and quality of the information** provided **in the ntroductory/invitation page**?

(5 MINUTES)

-Is the information there **sufficient**?

-Is the **definition of CAM** given sufficient/effective? **Did you understand it**?

-What about the **lists of CAM practices and products provided?** Did you go through them? **Were they helpful?**

-Do you think there is **any hint of coercion involved** in the invitation page?

QUESTION THREE: What was your **general impression of the section on parent demographics?** -Was there any item there you **felt was out of place**? **(10 MINUTES)**

If so, which? Why so? How would it be phrased to be more acceptable to you?

QUESTION FOUR: How did you understand the questions on **CAM use in schoolchildren**?

-Was there **any confusion**? **(10 MINUTES)**

-What **do you think you were supposed to do** there?

-Would you have **felt uncomfortable if you had been asked the purpose** for which the CAM was used?

-What about the questions on outcomes associated with CAM use? **How did you understand them?**

QUESTION FIVE: What do you think of **the general statements on opinions surrounding CAM use?**

-What did you **understand** them to mean? **(10 MINUTES)**

-Was there any you felt uncomfortable with?

-Did you think any of them was leading?

-Do you think any needs re-wording?

QUESTION SIX: What **potential problems do you think parents could encounter** in completing the questionnaire in its current form?

QUESTION SEVEN: In what way did your completing the questionnaire **affect your general impression on CAM use –especially with respect to children? (2 MINUTES)**

WRAP-UP QUESTION: Does **ANYBODY have ANY OTHER COMMENTS on any part of the questionnaire, or on the survey as a whole?**

C: CONCLUSION (5 MINUTES)

Once more, let me express my deep gratitude to you for honouring this invitation, and for your great co-operation in this entire exercise. **Please, take the next few minutes to complete a brief EVALUATION QUESTIONNAIRE** to let us know your views of this focus group discussion. **FINALLY, SHOULD YOU BE INVITED TO TAKE THIS SURVEY AGAIN THROUGH YOUR CHILD'S SCHOOL, PLEASE, DO NOT BOTHER TO DO SO.**

THANK YOU FOR YOUR TIME! *****SWITCH OFF THE AUDIO RECORDER***** *****CHECK FOR THE RED LIGHT ON THE AUDIO RECORDER*****	**Discussion concluded at:** 00:00

Appendix IX

Focus Group Topic Guide II

The following appendix contains the focus group topic guide II

Okechukwu O. NDU (1010078)

PhD student

TITLE OF STUDY:

PERCEIVED EFFECTIVENESS & SAFETY OF COMPLEMENTARY & ALTERNATIVE MEDICINE USE BY STUDENTS IN ABERDEEN

-A FOCUS GROUP STUDY

OCTOBER 18, 2013

@ABERDEEN COLLEGE, GALLOWGATE, ABERDEEN

TOPIC GUIDE

1. What were your first impressions of this survey?
2. In what ways could we stimulate public interest in the survey?
3. How could the survey be distributed so as to reach you or potential participants more easily?
4. What could be done to make completing the questionnaire more acceptable to fresh participants?
5. Is there any aspect of CAM use that you think has been overlooked in this questionnaire?

Appendix X

Paper-Based Questionnaire

The following appendix contains a sample of the paper-based questionnaire.

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Complementary & Alternative Medicine (CAM) Use among Children in North-East Scotland - A Parent Survey

Thank you for your interest in this survey. Please note that your views and opinions are welcome whether or not you have used CAM for your child/children.

WHAT IS CAM?

CAM refers to practices and products that people use along with or in place of conventional medicine to maintain general health & well-being, or to prevent, treat or manage specific health conditions. There are various types of CAM products and practices, including various supplements, special diets and herbal and homeopathic remedies, as well as various exercises and other self-help practices that are used to promote health. Some of these are so familiar, commonplace or ordinary that most people do not even realise they are CAM.

This CAM use survey will take you about 5-10 minutes to complete.

Thank you for your time.

SECTION ONE: GENERAL INFORMATION ABOUT YOU

This section asks general information about you and your children.

Q1. Your parental status is:

- *Father or male guardian* ☐
- *Mother or female guardian* ☐

Q2. Your age falls within:

- *16-29 years* ☐
- *30-44 years* ☐
- *45-59 years* ☐
- *60 years and above* ☐

Q3. Your marital status is:

- *Single* ☐
- *Cohabiting* ☐
- *Civil union/Partnership* ☐
- *Married* ☐
- *Separated* ☐
- *Divorced* ☐
- *Widowed* ☐

Q4. Where do you live?

- *Aberdeen* ☐
- *Aberdeenshire* ☐
- *Dundee* ☐
- *Rest of Angus* ☐
- *Moray* ☐
- *Perth & Kinross* ☐
- *Fife* ☐

Q5. The first part of your postcode is:

Postcode (e. g. AB 10) ☐

Q6. Your ethnic origin is:

- ***White Scottish*** ☐
- ***Other White British***
  - *English* ☐
  - *Irish* ☐
  - *Welsh* ☐
  - *Other White British* ☐
- ***Other White*** ☐
- ***Black British*** ☐
- ***Other Black***
  - *African* ☐
  - *Caribbean* ☐
  - *Other* ☐
- ***Chinese British*** ☐
- ***Other Chinese*** ☐
- ***Other Asian British***
  - *Bangladeshi* ☐
  - *Indian* ☐
  - *Pakistani* ☐
  - *Other* ☐
- ***Other Asian*** ☐
- ***Mixed racial background***
  - *White & Black African* ☐
  - *White & Black Caribbean* ☐
  - *White & Asian* ☐
  - *White & other mixed background* ☐
  - *Other mixed background* ☐
- ***Any other ethnic origin*** ☐

Q7. Would you be inclined to describe yourself as a person of faith?

- *Yes* ☐
- *No* ☐
- *I don't know* ☐

Q8. Your highest educational qualification is:

- *No formal qualifications* ☐
- *Secondary/High school* ☐
- *College* ☐
- *University* ☐

Q9. Would you have preferred to take this survey online (e-mail/Facebook) instead of on paper?

- *Yes, I prefer the online mode* ☐
- *No, I prefer the paper mode* ☐
- *Well, I don't really mind* ☐
- *I don't know* ☐

Q10. Which of the following types of CAM products have you ever used for your child/children?

- *Herbal medicinal products (including herbal teas)* ☐
- *Dietary supplements (e.g. Omega 3, multivitamins)* ☐
- *Probiotics (e. g. Yogurts)* ☐
- *Special diets (e. g. Gluten-free, Ketogenic, Atkins)* ☐
- *Aromatherapy (e. g. Olbas oil, Calrub, Tea tree oil)* ☐
- *Homeopathic products* ☐
- *Bach flower remedies* ☐
- *Traditional Chinese Medicines* ☐
- *Ayurveda/Kampo/Other traditional medicines* ☐
- *They have used others not listed above* ☐
- *They have NOT used any CAM products* ☐

Q11. Which of the following types of non-product CAM therapies have you ever used for your child/children?

- *Acupuncture/Acupressure* ☐
- *Biofeedback* ☐
- *Breathing exercises* ☐
- *Chiropractic/ Osteopathy* ☐
- *Guided imagery* ☐
- *Hypnosis* ☐
- *Healing (e. g. Reiki, Spiritual, Faith/Prayer* ☐
- *Massage* ☐
- *Mickel therapy* ☐
- *Music therapy* ☐
- *Reflexology* ☐
- *Shiatsu* ☐
- *Sunflower Method* ☐
- *Yoga* ☐
- *They have used others not listed above* ☐
- *They have NOT used any CAM practices* ☐

Q12. If your children have used any other CAM types than those listed above, please enter them here:

☐

Q13. Please provide the following general information on your children:

Child	Age in years (e. g. 10)	Sex (√)		Ever used CAM (√)		Used CAM in last 12 months (√)	
		M	F	Yes	No	Yes	No
1							
2							
3							
4							
5							

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SECTION TWO: DETAILED INFORMATION ON CAM USE IN CHILDREN

This section seeks detailed information about your child/children's use of CAM. If you have not used any CAM types for them, then proceed to Section three.

Q14. For each of the CAM products and/or practices your child/children have used please indicate how recently they (have) used it, how you found out about it, your perception of the degree of helpfulness and discomfort (if any) that resulted, as well as the specific type of discomfort (if any) experienced.

For clarity, please enter the specific names of CAM products used –e. g. Echinacea, Yogurt, Evening Primrose, Honey, Melatonin, etc.. For CAM practices, enter such terms as Acupuncture, Art therapy, Kinesiology, Pilates, Yoga, etc. with no further description.

Feel free to use more than one line for each entry where necessary.

S/ No	Specific name of each CAM type used (e.g. Echinacea, Rescue remedy, Facial massage, etc.)	Used in the last 12 months		Used more than 12 months ago		How did you find out about it? (Family, friend, doctor, nurse, internet, etc.)	How helpful was it? (√)					How much discomfort did it cause? (√)					What discomfort (if any) did it cause?
		Yes (√)	No (√)	Yes (√)	No (√)		A lot	A little	Not sure	Not much	Not at all	A lot	A little	Not sure	Not much	Not any	
1																	
2																	
3																	
4																	
5																	
6																	
7																	
8																	
9																	
10																	
11																	
12																	
13																	
14																	
15																	

Q15. If (any of) your children has stopped using any of the CAM you have listed, please indicate why they did so?
(Please tick all that apply.)

- *We haven't stopped using any*☐
- *They got better, so don't need it any more*☐
- *We decided to try something else*☐
- *The CAM caused too much discomfort*☐
- *The CAM was too expensive*☐
- *The CAM was no longer available /accessible*☐
- *We stopped for some other reasons*☐
- *No special reason: we just stopped*☐

Q16. Would you say that you achieved the main purpose for which your child/children used the therapies you found helpful?

- *We didn't find any helpful*☐
- *Yes*☐
- *No*☐

Q17. Would you recommend any of the CAM types to other parents?

- *Yes*☐
- *No*☐

Q18. If (any of) your children experienced any form of discomfort with any of the CAM you used, who did you inform of the incident?
(Please tick all that apply.)

- *They didn't experience any discomfort*☐
- *Nobody*☐
- *Family members/Friends*☐
- *The pharmacist/health shop staff*☐
- *A CAM therapist*☐
- *A doctor*☐
- *Any other health professional*☐
- *The MHRA*/Yellow Card Scheme*☐
- *Some other person*☐

***MHRA –Medicines & Healthcare products Regulatory Agency**

SECTION THREE: YOUR PERSONAL USE AND OPINIONS ON CAM

This section enquires of your personal use of, opinions on, and attitudes towards CAM.

Q19. If you have ever used any CAM therapies for yourself, please let us know which ones (as much as you can remember), and how helpful you found them. If you have never used CAM for yourself, please proceed to Q20 below to complete the survey.

S/ No	CAM type used	How helpful was it? (√)					S/ No	CAM type used	How helpful was it? (√)				
		A lot	A little	Not sure	Not much	*Not at all*			A lot	A little	Not sure	Not much	Not at all
1							*11*						
2							*12*						
3							*13*						
4							*14*						
5							*15*						
6							*16*						
7							*17*						
8							*18*						
9							*19*						
10							*20*						

Q20. For each statement below of some general attitudes towards CAM use, please tick the option that best describes how much you agree or disagree. Please note that there are no right or wrong answers.

	General statement about CAM use	Strongly disagree	Disagree	Not sure	Agree	Strongly agree	I don't know
1	I think CAM may be used in adults, but not in children.						
2	I believe certain health conditions are better managed with CAM than with conventional medicines prescribed by medical doctors.						
3	I think CAM should not be used together with conventional medicines prescribed by medical doctors.						
4	I believe CAM can cause harmful side effects						
5	I think CAM should be available on the NHS.						
6	I believe CAM is generally safer than conventional medicines prescribed by medical doctors.						
7	I think CAM users should inform their doctors that they use CAM.						
8	I believe CAM is generally more effective than conventional medicines prescribed by medical doctors.						
9	I think there is need for more information on CAM therapies.						
10	I believe people should be allowed to make up their own minds on using CAM.						

THANK YOU FOR PARTICIPATING IN THIS SURVEY.
Please return the completed survey to us in the envelope provided.

Appendix XI

Ethics Committee Approval letter

The following appendix contains the ethics committee approval letter

ROBERT GORDON UNIVERSITY
SCHOOL OF PHARMACY AND LIFE SCIENCES
ETHICAL APPROVAL FORM FOR UNDERGRADUATE, TAUGHT MSc, PhD AND EXTERNAL PROJECTS

SECTION 1 – to be completed

Research Student Name	OKECHUKWU NDU (1010078)
Study Coordinator	Lesley Diack
Research Project Title	Prevalence and user perceived effectiveness and safety of complementary and alternative medicine in young people in aberdeen

SECTION 2 – to be completed by the School Research Ethics Committee Date submitted to panel: 25 February 2013

Indicate Yes or No to each question and comment as appropriate.	**Panel member 1**	**Panel member 2**	**Panel member 3**	**Student Response**
Is the research question clear?	Yes	Yes	YES	
Is the project scientifically robust?	Yes	Yes, although maybe family structure such as single parent or divorced, number of siblings etc should be covered in the questionnaire as this might impact on the use of CAM. In the case of divorced parents, who do you ask if the responsibility of looking after the child is shared?	YES	
Are the procedures for obtaining informed consent clear and appropriate? If an audit does the student have approved access to information?	Yes	Yes	YES	
Is the extent of participant involvement clear?	Yes	Yes	YES	
Are the recruitment procedures ethical and appropriate?	Yes	Yes	YES	
Are the inclusion and exclusion criteria relevant and appropriate?	Yes	Yes	YES, but could be clearer/more specific.	
Is the extent and type of participant involvement ethical? (consider issues of unnecessary invasiveness, exposure, undue stress, anxiety and concern, inappropriate time commitments)	Yes	Yes	YES	
Are there clear procedures for ensuring compliance with the Data Protection Act?	Yes	Yes, although dissemination of findings is not mentioned	YES	

Please check the boxes below with your decision	**Panel member 1**	**Panel member 2**	**Panel member 3**
1. Approved – submit to LREC / MREC as appropriate and provide copy of approval letter to supervisor OR provide supervisor with evidence that submission not necessary	☒	☒	☒
2. NOT Approved – MINOR ISSUES approval subject to submitting a response, to ethics review panel via supervisor, addressing minor issues outlined above	☐	☐	☐
3. NOT approved – MAJOR ISSUES serious issues of concern to be addressed and whole proposal to be resubmitted via supervisor for further ethical review.	☐	☐	☐
4. NOT approved – UNETHICAL the study is unethical and a re-submission will not be considered.	☐	☐	☐
Comments:			

SECTION 3 - OVERALL ETHICAL DECISION to be completed by Chair of School Research Ethics Committee

1. Approved – submit to LREC / MREC as appropriate and provide copy of approval letter to supervisor OR
   provide supervisor with evidence that submission to LREC / MREC not necessary ☒
2. NOT Approved – MINOR ISSUES: subject to submitting a response, to ethics review panel via supervisor, addressing minor issues outlined above ☐
3. NOT approved – MAJOR ISSUES: there are serious issues of concern to be addressed and whole proposal to be resubmitted via supervisor for further ethics panel review. ☐
4. NOT approved – UNETHICAL: the study is completely unethical and a re-submission will not be considered. ☐

Signed (on behalf of the School Research Ethics Committee) **Dr Morag McFadyen** **Date: 22/03/2013**

Membership: Dr Stuart Cruickshank, Dr Lesley Diack (Chair), Dr Marie Goua, Dr Graeme Kay, Dr Morag McFadyen, Mrs Katie Maclure, Dr Stephen Macmanus, Dr Colin Thompson, Dr Anita Weidmann, Dr Wendy Wrieden.