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MIRRORS: a prospective cohort study assessing the feasibility of robotic interval debulking surgery for advanced-stage ovarian cancer

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ABSTRACT

Objective To establish the feasibility and safety of robotic interval debulking surgery following the MIRRORS protocol (robot-assisted laparoscopic assessment prior to robotic or open surgery) in women with advanced-stage ovarian cancer. MIRRORS is the first of three planned trials: MIRRORS, MIRRORS-RCT (pilot), and MIRRORS-RCT.

Methods The participants were patients with stage IIIc-IVb epithelial ovarian cancer undergoing neo-adjuvant chemotherapy, suitable for interval debulking surgery with a pelvic mass ≤8 cm. The intervention was robot-assisted laparoscopic assessment prior to robotic or open interval debulking surgery (MIRRORS protocol). The primary outcome was feasibility of recruitment, and the secondary outcomes were quality of life (EORTC QLQC30/OV28, HADS questionnaires), pain, surgical complications, complete cytoreduction rate (%), conversion to open surgery (%), and overall and progression-free survival at 1 year.

Results Overall, 95.8% (23/24) of patients who were eligible were recruited. Median age was 68 years (range 53–83). All patients had high grade serous histology and were BRCA negative. In total, 56.5% were stage IV, 43.5% were stage III, 87.0% had a partial response, while 13.0% had stable disease by RECIST 1.1. Median peritoneal cancer index was 24 (range 6–38). Following MIRRORS protocol, 87.0% (20/23) underwent robotic interval debulking surgery, and 13.0% (3/23) had open surgery. All patients achieved R<1 (robotic R0=47.4%, open R0=0%). No patients had conversion to open. Median estimated blood loss was 50 mL for robotic (range 20–500 mL), 2026 mL for open (range 2000–2800 mL) (p=0.001). Median intensive care length of stay was 0 days for robotic (range 0–8) and 3 days (range 3–13) for MIRRORS Open (p=0.012). The median length of stay was 1.5 days for robotic (range 1–17), 6 days for open (range 5–41) (p=0.012). The time to chemotherapy was as follows 18.5 days for robotic (range 13–28), 25 days for open (range 22–28) (p=0.139).

Conclusions Robotic interval debulking surgery appears safe and feasible for experienced robotic surgeons in patients with a pelvic mass ≤8 cm. A randomized controlled trial (MIRRORS-RCT) will determine whether MIRRORS protocol has non-inferior survival (overall and progression-free) compared with open interval debulking surgery.

WHAT IS ALREADY KNOWN ON THIS TOPIC

⇒ Retrospective studies have suggested that minimally invasive interval debulking surgery is feasible. There are no prospective trials on robotic interval debulking surgery for advanced ovarian cancer.

WHAT THIS STUDY ADDS

⇒ MIRRORS is a prospective cohort study assessing the feasibility of robotic interval debulking surgery for advanced-stage ovarian cancer. MIRRORS demonstrated the feasibility and safety of robotic interval debulking surgery in advanced stage ovarian cancer. MIRRORS is the first in a series of three planned trials culminating in a multicenter international randomized controlled trial of MIRRORS protocol versus standard open interval debulking surgery (MIRRORS-RCT).

HOW THIS STUDY MIGHT AFFECT RESEARCH, PRACTICE, OR POLICY

⇒ In the UK and Europe, the majority of patients with advanced ovarian cancer have interval debulking surgery performed through an open approach. If non-inferiority of robotic interval debulking surgery with regards to survival (overall and progression-free) is confirmed by an adequately powered randomized controlled trial, this could lead to a significant change in practice.

INTRODUCTION

Epithelial ovarian cancer, including cancers of the fallopian tube and peritoneum, is the sixth most common cancer in women in the UK, with around 7500 women diagnosed each year. More than 70% of women present with advanced stage disease (FIGO ≥stage III), and many are older and or frail, as incidence increases with age.[1] Standard treatment involves surgery and platinum-based chemotherapy. Complete resection of all visible tumor deposits (R0) is the strongest predictor of improved overall and progression-free survival. Best outcomes are seen in women where it is possible to remove all visible tumor deposits during primary surgery.[2]

Neoadjuvant chemotherapy is recommended in women with advanced stage disease, where upfront surgery would be unlikely to achieve removal of all visible disease, or when patients are not fit for primary surgery. Interval debulking surgery has been shown to have equivalent outcomes to primary surgery with reduced patient morbidity and mortality.[3 4] The ongoing TRUST trial is seeking to establish whether primary cytoreductive surgery is superior to interval debulking surgery in patients with advanced ovarian cancer.[5]

While surgical complications may prevent or delay patients from commencing chemotherapy,[6–11] minimally invasive surgery is associated with quicker recovery, shorter inpatient stay, reduced blood loss and need for transfusion, fewer wound complications, lower risk of thromboembolism and high dependency care requirements, and lower 30-day mortality in comparison with laparotomy.[6 12]

METHODS

Trial Design

MIRRORS (**M**inimally **I**nvasive **R**obotic surgery, **R**ole in optimal debulking **O**varian cancer, **R**ecovery and **S**urvival) is a prospective cohort feasibility study of robotic interval debulking surgery in women with advanced-stage epithelial ovarian cancer. MIRRORS is a stage 2a development study following the IDEAL framework.[13]

Patients with stage IIIC-IVb epithelial ovarian cancer (following review of imaging in the gynecological oncology multidisciplinary team meeting), and identified as suitable for interval debulking surgery having responded to neoadjuvant chemotherapy, were offered inclusion in the study. Patients with progressive disease on CT were excluded. Surgery commenced with an open entry laparoscopy using an Alexis wound protector (Applied Medical, Rancho Santa Margarita, CA, USA). A laparoscopic assessment of the abdomen and pelvis was performed using the Da Vinci robot endoscopic camera (Intuitive Surgical, Sunnyvale, CA, USA) by an experienced gynecological oncologist and robotic surgeon, followed by proceeding immediately to robotic or open interval debulking surgery (MIRRORS protocol). The decision to proceed with robotic interval debulking surgery or to proceed with an open approach was made by the lead operating surgeon, based on the laparoscopic findings. Cases such as those with extensive dense adhesions preventing safe port entry and full visualization of the abdomen, peritoneal disease covering the entire anterior abdominal wall around port sites, or extensive bowel mesenteric disease considered resectable via an open approach may be best suited to an open surgical approach. The aim of surgery was to remove all visible disease with conversion to open surgery if required. Robotic surgery was performed using the Da Vinci Si and Xi systems (Intuitive Surgical, Sunnyvale, CA, USA) (Figures 1 and 2).

Setting

MIRRORS was based at Royal Surrey NHS Foundation Trust, UK a gynecological cancer center and Intuitive Robotic Epicenter. Recruitment occurred between June 2020 and May 2021. The publication of this feasibility study was delayed due to both professional and academic commitments. MIRRORS was presented at both the British Gynecological Cancer Society Academic Meeting and International Gynecologic Cancer Society Conference in 2022. Following this, a successful grant application for MIRRORS-RCT (pilot), a follow-up study to MIRRORS, required time to complete sponsorship, ethics applications, and site set-up. The findings of MIRRORS presented here have contributed to the design of MIRRORS-RCT (pilot) and are informing the final design of MIRRORS-RCT.

Participants

Inclusion criteria

Women ≥18 years with Stage IIIc–IVb epithelial ovarian cancer suitable for interval debulking surgery with a pelvic mass ≤8cm.

Exclusion criteria

Women who lacked capacity to complete trial documentation or were not medically fit for laparoscopy, and women who required specialist surgical support whose recommendation was open surgery were excluded.

Outcomes

Primary outcome was recruitment (%). Recruitment (%) was defined as the number of patients consented for the MIRRORS study compared with the number identified by multidisciplinary team as eligible for inclusion in the study, expressed as a percentage. Secondary outcomes included surgical and post-operative complications, rate of conversion to open surgery once robot docked, rate of complete cytoreduction (R0) (percentage), pain, quality of life, and progression-free and overall survival.

Assessment of surgical and post-operative complications included both intraoperative and post-operative (classified by Clavien-Dindo classification) complications assessed at close of trial (15 months±7 days (recruitment and follow-up period)), with success being defined as complication rate not higher than for open interval debulking surgery.

Pain was assessed using a numeric rating scale (NRS11), mental well-being using the hospital anxiety and depression scale (HADS) and quality of life using the patient-reported outcome measure European Organization for Research and Treatment of Cancer (EORTC) validated quality of life questionnaire for ovarian cancer (QLQ-C30/QLQ-OV28) and analysed as per the EORTC scoring manual.[14 15] Unadjusted mean scores were compared between MIRRORS Open and MIRRORS Robot at each time point using linear regression (Stata Statistical Software Release 16), with results presented graphically. Questionnaires were completed at baseline, at day 1 post-surgery, 3–4 weeks post surgery, and 3 months post-surgery. Data were analysed in Microsoft Excel and IBM SPSS Statistics 26.

Kaplan-Meier survival curves were generated from date of diagnosis until date of first recurrence or death in months. Progression was defined as radiographic evidence of disease progression as per the Response Evaluation Criteria in Solid Tumors (RECIST) version 1.1, or by progressive serial elevation of CA125, as per the recommendations of the Gynecological Cancer Intergroup (GCIG), with the earliest date recorded.[16–18] As a prospective feasibility study there was no control arm. To provide reassurance that we were not seeing an increased number of early recurrences, a concurrent cohort (Not-MIRRORS, n=11) consisting of all women undergoing interval debulking surgery not recruited to MIRRORS, and a historical cohort (n=37), consisting of women who had undergone open interval debulking surgery in the 12 months immediately prior to MIRRORS were identified. Follow-up was for a minimum of 1 year for survival.

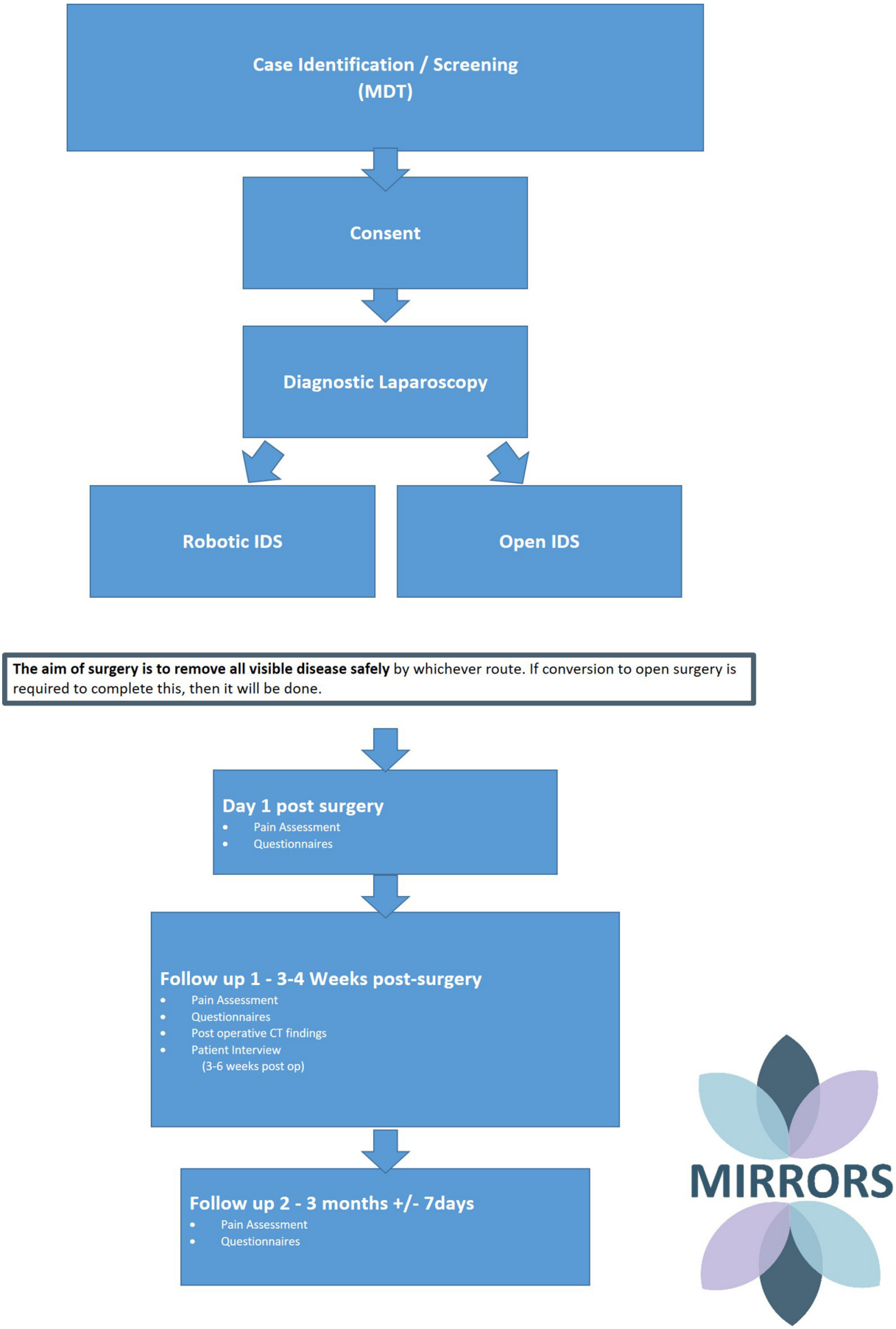

Figure 1 MIRRORS study flow diagram.

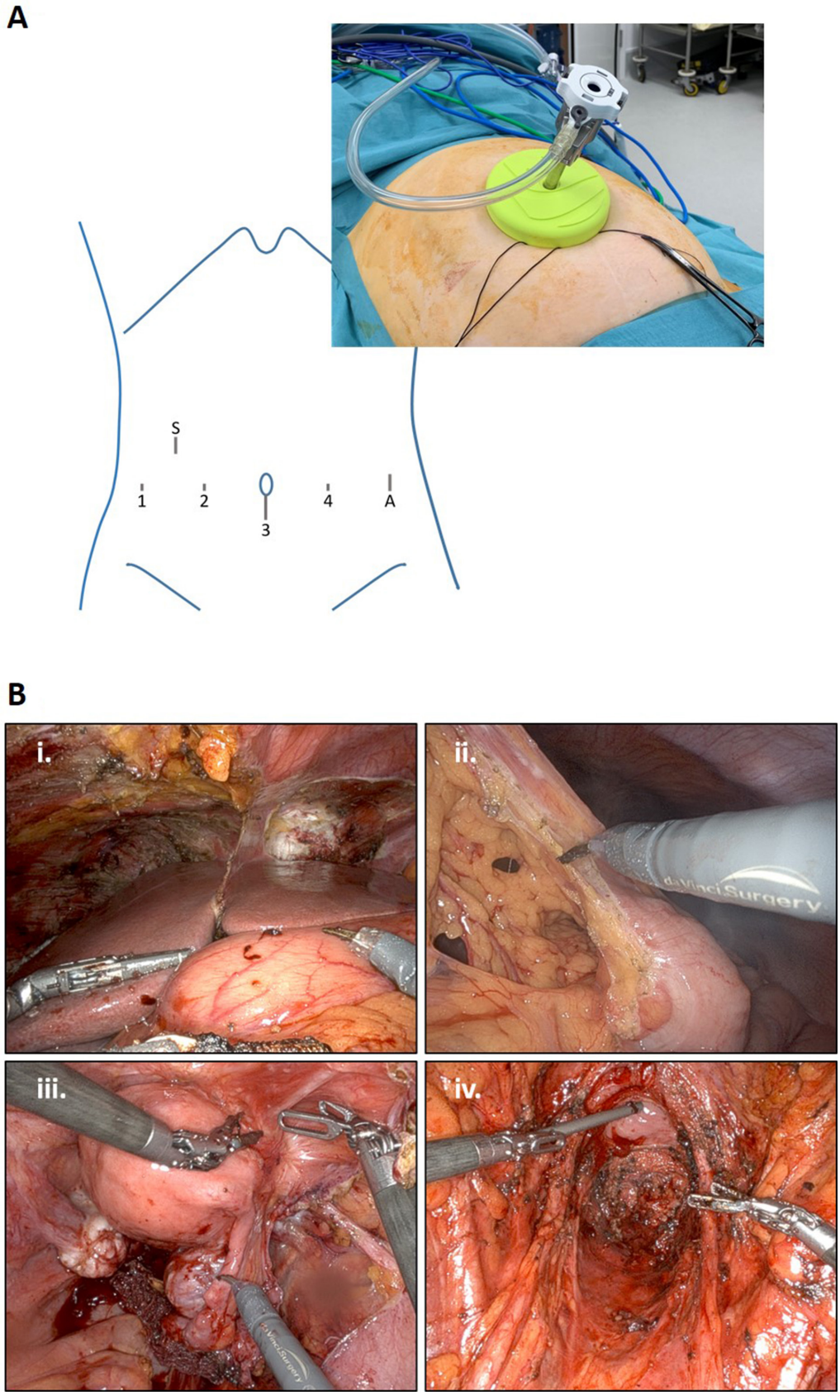

Figure 2 (A) MIRRORS protocol set-up and port placement (A=assistant port; S=port for stapler if required). (B) MIRRORS surgical images illustrating surgical procedures i. Appearance following right sided diaphragmatic stripping. ii. Supracolic omentectomy in progress. iii. Early operative appearance of pelvis; right-sided peritoneal stripping has been started. iv. Appearance of pelvis following full pelvic peritoneal stripping, radical hysterectomy, bilateral ureterolysis, bilateral salpingo-oophorectomy, and anterior resection prior to stapled end-to-end anastomosis.

Study Size

The sample size was set pragmatically to balance precision in the estimate of the pre-defined feasibility success criteria; at least 20% of those eligible accepting inclusion in the study, complication rate not higher for robotic interval debulking surgery than for open, and the conversion to open surgery rate not greater than 50% of the patient group deemed suitable for robotic interval debulking surgery following initial diagnostic laparoscopy. Inclusion of a minimum of 20 women in this initial feasibility study was targeted as sufficient to ensure these rates can be estimated within a standard error of less than 10%, providing maximal confidence intervals for percentage estimates of ±20%.

Trial Registration

Registered prior to first patient recruited at ClinicalTrials.gov: NCT04402333 (https://clinicaltrials.gov/ct2/show/study/NCT04402333). In accordance with the journal's guidelines, we will provide our data for independent analysis by a team selected by the Editorial Team for the purposes of additional data analysis, or for the reproducibility of this study in other centers, if such is requested.

RESULTS

During the recruitment period 35 of 44 women considered were found to be eligible for interval debulking surgery (one was later found unfit). Of these 35, 24 women fulfilled the inclusion/exclusion criteria for MIRRORS (68.6%). Overall, 23 of 24 eligible women were recruited (95.8%). Median age was 68 years (range 53–83). All patients recruited had high grade serous tumors and were BRCA negative, and 13 (56.5%) had stage IV disease (IVa: n=3, 13.0%; IVb: n=10, 43.5%). Following MIRRORS protocol, 20 women (87.0%) proceeded with robotic surgery and 3 (13.0%) with open surgery. There were no conversions to open surgery.

None of the patients had a complete response to chemotherapy by RECIST 1.1. The median peritoneal cancer index score was 24 (range 6–38) The diagnosis of stage IVb disease was based on the presence of extra abdominal lymph nodes on pre-operative imaging. In addition, of these patients presenting with stage IVb disease, one was diagnosed based on a supraclavicular lymph node biopsy, one had a biopsy-proven high-grade serous tumor breast metastasis, one had a histology-proven full thickness diaphragmatic deposit, another had a liver deposit resected involving the liver parenchyma on histology, and lastly, one had tumor in the resected umbilicus on histology. Peritoneal cancer index score was documented before and after surgery. MIRRORS did not find that the addition of a CT scan within 4 weeks of surgery improved on this assessment (Tables 1 and 2).

Two patients recruited to MIRRORS proved to have high-grade serous endometrial cancer (open: n=1, robotic: n=1). Of those confirmed to have epithelial ovarian cancer, complete cytoreduction (R0) was achieved in 47.4%, who had robotic interval debulking surgery. None of the open surgery cases achieved R0. Median estimated blood loss for the robotic group was 50 mL (range 20–500) versus 2026 mL (range 2000–2800) for the open surgery group (p=0.001). Median operating time was 358 min for robotic (range 168–698), 338 min for open (range 310–360), and 353 min for MIRRORS overall (range 168–698) (p=0.763). Robotic interval debulking procedures included bowel resection with stapled anastomosis (3/20, 15.0%), diaphragmatic stripping (12/20, 60.0%), full thickness diaphragmatic resection (1/20, 5.0%), and pelvic peritoneal stripping (14/20, 70.0%) (Figure 2B).

Median length of stay was 1.5 days (range 1–17) for robotic interval debulking surgery (n=20) and 6 days (range 5–41) for MIRRORS Open (n=3) (p=0.012). Median intensive care length of stay was 0 days for robotic (range 0–8) and 3 days (range 3–13) for MIRRORS Open (p=0.012). Median time to chemotherapy for robotic interval debulking surgery was 18.5 days (range 13–28), 25 days for open surgery (range 22–28), and 20.0 days (range 13–28) for the entire MIRRORS cohort (p=0.139).

There were no returns to the operating room, and the 30-day and 90-day mortality rates were zero. The most common reported minor complications were urinary tract infection in 5/23 (21.7%) patients (none culture-proven, as patients were treated empirically by their general practitioner), and surgical emphysema, which occurred in the first 4/20 (20.0%) patients undergoing robotic interval debulking surgery. Our surgical approach was subsequently adapted so that the patient was only in a steep head down position for resection of disease in the pelvis, and was then moved to a completely flat position for resection of disease in the upper abdomen. This successfully prevented further significant surgical emphysema.

Three women enrolled in MIRRORS experienced Clavien-Dindo complications ≥grade 3. One patient in the open group suffered a superficial wound breakdown, requiring vacuum-assisted wound closure therapy. In the robot group, one patient had a chest drain inserted on day 1 post-surgery to treat a pneumothorax following diaphragmatic stripping, and subsequently tested positive for SARS-CoV-2 day 3 post-surgery. A second patient in the robot group suffered a fractured neck of femur on day 46 post-surgery, and was readmitted for surgery (Table 1).

Median pain scores for robotic interval debulking surgery were lower than open across all time points. Overall (MIRRORS cohort n=23) median scores for anxiety and depression were in the normal range at all-time points across the study. Analysis of the EORTC validated quality of life questionnaires (QLQ) for ovarian cancer (QLQ-C30/QLQ-OV28) found the symptom scores for nausea (p=0.032) and pain (p=0.030) to be significantly lower in the robot group than in the open group (Figure 3).

Overall survival and progression-free survival for MIRRORS patients confirmed to have epithelial ovarian cancer was compared with the concurrent cohort Not-MIRRORS (n=11) and the historical cohort (n=37), and is presented in Figure 3C. No significant difference in overall (p=0.39) or progression-free survival (p=0.54) was observed.

DISCUSSION

Summary of Main Results

MIRRORS has confirmed the feasibility of robotic interval debulking surgery for women with advanced (stage IIIc-IVb) epithelial ovarian cancer with a pelvic mass ≤8 cm. The initial clinical assessment of suitability for robotic interval debulking surgery using the Da Vinci robot endoscopic camera proved accurate when performed immediately prior to the cytoreductive procedure, eliminating the need to arrange an additional surgical procedure, with 87.0% of MIRRORS cases undergoing robotic surgery with no conversions.

Table 1 MIRRORS demographics

		MIRRORS (n=23)				
		Median	Minimum	Maximum	N	%
Age (years)		68	53	83	23	100.0
Body mass index		24.2	15.2	38.9	23	100.0
Number of cycles of chemotherapy prior to surgery		3	3	6	23	100.0
ASA score	1				0	0.0
	2				7	30.4
	3				16	69.6
BRCA	Negative				21	91.3
	BRCA1				0	0.0
	BRCA2				0	0.0
	Not applicable (endometrial primary)				2	8.7
Tumor site	Endometrial				2	8.7
	Ovary				11	47.8
	Peritoneum				0	0.0
	Tube				10	43.5
Tumor type	Adenocarcinoma				0	0.0
	Clear cell				0	0.0
	MMMT				0	0.0
	Neuroendocrine				0	0.0
	Serous				23	100.0
Grade	3				23	100.0
Stage	IIIc				10	43.5
	IVa				3	13.0
	IVb				10	43.5
Chemotherapy regimen						
Carboplatin					1	4.3
Combined carboplatin and paclitaxel					21	91.3
Other regimen					1	4.3
Bevacizumab					1	4.3
PARP inhibitor					17	73.9
ECOG	0				9	39.1
	1				12	52.2
	2				2	8.7
Ethnicity	White British				20	87.0
	Any other white background				2	8.7
	Black Caribbean				1	4.4
Parity (n)	0				5	21.7
	1				2	8.7
	2				11	47.8
	3				2	8.7
	4				3	13.0
Smoking history	Ex-smoker				8	34.8
	Never smoked				13	56.5
	Smoker				2	8.7

Continued

Table 1 Continued

		MIRRORS (n=23)				
		Median	Minimum	Maximum	N	%
Number of previous abdominal surgeries	0				5	21.7
	1				8	34.8
	2				5	21.7
	3				2	8.7
	4				2	8.7
	5				1	4.4
Comorbidities						
Cardiac condition					4	17.4
Previous venous thromboembolism					3	13.0
Anemia					1	4.4
Diabetes					3	13.0
Vascular					1	4.4
Hypertension					6	26.1
Respiratory disease					6	26.1
Dermatology condition					2	8.7
Previous cancer					4	17.4
Musculoskeletal/rheumatology					5	21.7
Mental health					1	4.4
Endocrine/autoimmune					7	30.4
RECIST 1.1						
Complete response					0	0.0
Partial response					20	87.0
Stable disease					3	13.0

ASA, American Society of Anesthesiologists; ECOG, Eastern Cooperative Oncology Group; MIRRORS, Minimally Invasive Robotic surgery, Role in optimal debulking Ovarian cancer, Recovery and Survival; MMMT, malignant mixed mullerian tumors; PARP, poly-ADP ribose polymerase.

Women who underwent robotic interval debulking surgery described less pain and nausea post-operatively and spent less time in hospital with few requiring any intensive or high dependency care. Time to chemotherapy following surgery was shorter (18.5 days) for those undergoing robotic interval debulking surgery than for those undergoing open surgery (25 days). Overall time to chemotherapy for MIRRORS was 20 days. The findings of previous studies showing reduced blood loss and post-operative pain were confirmed.[19–23]

Results in the Context of Published Literature

Ovarian cancer management varies considerably both within the UK and internationally.[24 25] Retrospective studies have suggested that minimally invasive interval debulking surgery is feasible.[19 22 23] There are no prospective trials assessing the role of robotic interval debulking surgery for advanced ovarian cancer. The recently published CILOVE study, a phase II prospective multicenter feasibility study of laparoscopic interval debulking surgery, found that of 41 patients eligible for cytoreductive surgery, 32 (78.0%) were assessed as suitable for laparoscopy, and 9 (22.0%) suitable for open. Of these, 29/32 patients successfully underwent laparoscopic interval debulking surgery, with a conversion rate of 9.4%.[26] Up to 10 ports were used to achieve a very high rate of R0 of 97%. No benefit in reduction of length of stay or time to chemotherapy was found.

MISSION,[21] a prospective feasibility trial from 2016, assessed the early complication rate of minimally invasive interval debulking surgery. MISSION included women with complete clinical response and ECOG performance status <2, and excluded those with body mass index >40 kg/m^2 and ASA score III-IV. Of the 184 patients considered eligible for interval debulking surgery, 52 (28.3%) met the inclusion criteria. Of these, 30 (57.7%) patients had minimally invasive interval debulking surgery (26 laparoscopic and 4 robotic) with no conversions. Of the 30 patients undergoing minimally invasive surgery, median blood loss was 100 mL (range 50–200 mL) and median post-operative stay was 2 days (range 2–3). Feasibility was demonstrated in this select group, but the authors concluded that longer follow-up and larger numbers were required to show oncological equivalence.

The current LANCE trial is looking at the role of minimally invasive surgery (both standard laparoscopic and robotic) versus laparotomy in women with advanced high-grade epithelial ovarian cancer who have demonstrated complete or partial response to chemotherapy. LANCE excludes patients with 'small bowel or gastric tumor involvement, colon or rectal tumor involvement, diaphragmatic tumor

Table 2 Surgical outcomes

		MIRRORS Robotic N=20					MIRRORS Open N=3				
		Median	Minimum	Maximum	N	%	Median	Minimum	Maximum	N	%
Length of surgery (h:mm:ss) (knife to skin to skin closure complete)		5:58:00	2:47:59	11:38:00	20	100.0	5:37:59	5:10:00	5:59:59	3	100.0
Estimated blood loss (ml)		50.0	20	500	20	100.0	2026.0	2000	2800	3	100.0
Length of stay (days)		1.5	1	17	20	100.0	6.0	5.0	41.0	3	100.0
ITU (days)		0	0	8	20	100.0	3.0	3.0	13.0	3	100.0
Number of days to chemotherapy following surgery[†]		18.5	13	28	20	100.0	25.0	22	28	2	66.7
Return to theater					0	0.0				0	0.0
30-day mortality					0	0.0				0	0.0
90-day mortality					0	0.0				0	0.0
Residual disease*	0				9	47.4				0	0.0
	≤0.2				8	42.1				1	50.0
	>0.2 to ≤0.5				2	10.5				1	50.0
	>0.5 to ≤1				0	0.0				0	0.0
	>1				0	0.0				0	0.0
Intraoperative findings		Median	Minimum	Maximum			Median	Minimun	Maximun		
Peritoneal cancer index before		24	6	31			27	24	38		
Peritoneal cancer index after		2	0	11			4	3	10		
Length and position of longest Incision (cm)		3.5	2.5	7.0			35.0	34.0	35.0		
Intraoperative blood transfusion (units)		0	0	1[‡]			2	2	4		
Number of units of blood transfused post-op (units)		0	0	3			0	0	6		
Surgical procedures					N	%				N	%
Pelvic lymphadenectomy/ sampling					2	10.0				0	0.0
Para-aortic lymphadenectomy/ sampling					1	5.0				0	0.0
Pelvic peritoneal stripping					14	70.0				2	66.7
Abdominal peritoneal stripping					2	10.0				2	66.7
Large bowel resection±anastomosis					3	15.0				1	33.3
Diaphragmatic stripping					12	60.0				2	66.7
Full thickness diaphragmatic resection					1	5.0				1	33.3
Splenectomy					0	0.0				0	0.0
Liver resection					2	10.0				0	0.0
Small bowel resection and anastomosis					0	0.0				0	0.0
Stoma					0	0.0				0	0.0
Partial pancreatectomy					0	0.0				0	0.0
Pain score		Median	Minimum	Maximum			Median	Minimum	Maximum		
Pain score pre-surgery		0	0	7			0	0	2		
Pain score day 1		2	0	9			6	0	6		
Pain score follow-up 1 (3–4 weeks post-op)		0	0	8			4	2	4		
Pain score follow-up 2 (3 months post-op)		0	0	2			3	2	3		

Continued

Table 2 Continued

	MIRRORS Robotic N=20					MIRRORS Open N=3				
	Median	Minimum	Maximum	N	%	Median	Minimum	Maximum	N	%
Complications				N	%				N	%
Blood loss ≥1000 mL				0	0.0				3	100
Post-operative complications: day of discharge (Patients, n)				N	%				N	%
Grade 1				6	30.0				0	0.0
Grade 2				1	5.0				0	0.0
Grade 3a				1	5.0				1	33.3
Grade 3b				0	0.0				0	0.0
Post-operative complications: follow-up 1 (Patients, n)				N	%				N	%
Readmissions				0	0.0				0	0.0
Grade 1				3	15.0				0	0.0
Grade 2				3	15.0				2	66.7
Grade 3a				0	0.0				0	0.0
Grade 3b				0	0.0				0	0.0
Post-operative complications: follow-up 2 (Patients, n)				N	%				N	%
Readmissions				1§	5.0				0	0.0
Grade 1				0	0.0				1	33.0
Grade 2				4	20.0				0	0.0
Grade 3a				0	0.0				0	0.0
Grade 3b				1§	5.0				0	0.0

*Only tumour site ovary/peritoneum and tube.
†One patient in the MIRRORS Open IDS group received no adjuvant chemotherapy.
‡Low HB pre-operatively.
§1 patient in the MIRRORS Robot group suffered a fractured neck of femur on day 46 post-operatively and was admitted to hospital for surgical repair.
ITU, intensive therapy unit.

involvement, splenic or hepatic surface or parenchymal tumor involvement'.[27] The initial pilot results of the first 100 randomized patients has been presented with promising results, indicating that the study is feasible, and enrolment is ongoing in a definitive trial.[28] The unexpected findings of the LACC trial, finding lower rates of disease-free survival and overall survival in women undergoing minimally invasive radical hysterectomy for early stage cervical cancer, highlights the need for surgical randomized controlled trials.[29]

Complete resection of all visible disease and sensitivity to platinum-based chemotherapy is associated with the best survival outcomes.[3 30] There has been a move towards more radical procedures to attain complete resection of all visible tumor deposits (R0). There is some debate as to whether achieving R0 is a reflection of tumor biology, case selection, or the surgeon. 'Ultra-radical' surgery is associated with increased patient morbidity and reduced numbers of patients considered for surgery.[31] Many frail patients may not be suitable for such procedures but may benefit from a reduction in tumor burden. This group of women may have the most to gain from a robotic approach.

Strengths and Weaknesses

MIRRORS is a prospective cohort feasibility study of robotic interval debulking surgery. Recruitment proved to be feasible with a high rate of patient enrolment. With regards to intra-operative and post-operative complications, success for this feasibility study was pre-defined as the 'complication rate for robotic interval debulking surgery not exceeding that observed for open interval debulking surgery'. Initially it was anticipated that up to 50% of patients would successfully undergo robotic interval debulking surgery. A higher than expected number of patients successfully underwent robotic interval debulking surgery (87.0%) with less than expected (13.0%) undergoing open interval debulking surgery. Those undergoing open interval debulking surgery had a greater burden of disease by pre-operative peritoneal cancer index (PCI) score (open: median PCI 27 (range 24–38); robotic: median PCI24 (range 6–31)). Intraoperatively there were no complications in the robotic group, in the open group all three patients had blood loss >1000 mL. Grade 3 post-operative Clavien-Dindo complications occurred in 1/20 of the MIRRORS Robotic cohort, and in 1/3 of the MIRRORS Open group. As this was a feasibility study it was not powered to detect efficacy effects. Nevertheless, despite the very small number of open cases performed (n=3) compared with robotic (n=20), there appeared to be a significant difference in estimated blood loss, length of stay, length of stay in intensive care, and symptom scores for

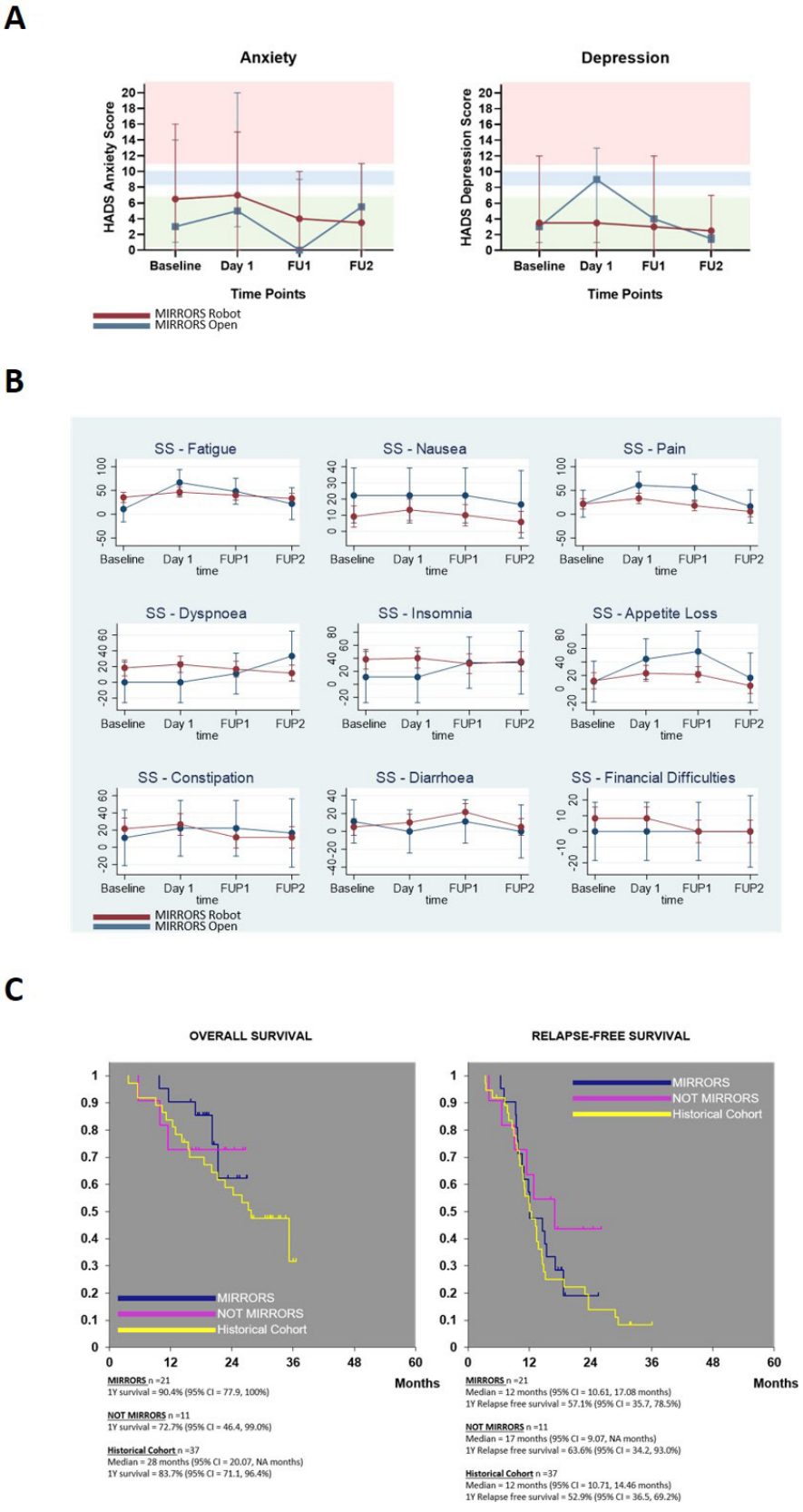

Figure 3 (A) Hospital Anxiety and Depression Scale (HADS) median and range HADS scores presented for MIRRORS Robot (n=20) and MIRRORS Open (n=3) at each time point. Scores: 0–7=normal range, 8–10=borderline, 11–21=high. (B) Quality of life outcomes EORTC QLQ-C30/QLQ-OV28 results. Mean and 95% CIs for each symptom score are presented for MIRRORS Open (n=3) and MIRRORS Robot (n=20) at each time point. (C) Overall survival and progression-free survival: Kaplan-Meier curves showing overall and progression-free survival for MIRRORS (excluding those found to be high-grade serous endometrial cancer on final histology) (n=21), Not-MIRRORS (n=11), and historical cohort (n=37).

nausea and pain in favor of robotic interval debulking surgery. A randomized controlled trial is required to assess whether there is a significant difference in outcomes for women undergoing surgery following the MIRRORS protocol compared with those undergoing standard open surgery.

For survival analysis, historical and contemporaneous control groups were used to provide some comparison and reassurance that there was no increase in early recurrences. This was reassuring with regards to immediate short-term surgical outcomes, but a randomized controlled trial is required to assess this. Retrospective analysis relies on the quality of input data, and may be subject to selection bias. Selection bias, with regards to the contemporaneous and historical comparative cohorts, has been limited, as operation notes for each procedure are produced within the dedicated database at the time of surgery.

Implications for Practice and Future Research

More randomized controlled trials are needed to assess the role of minimally invasive interval debulking surgery. The LANCE trial aims to answer this question for selected women undergoing either laparoscopic or robotic surgery who have demonstrated complete or partial response to chemotherapy.[27 28] MIRRORS-RCT will look to assess the role of robotic interval debulking surgery in women with a pelvic mass ≤8 cm.

CONCLUSIONS

Robotic interval debulking surgery appears to be safe and feasible in women with a pelvic mass ≤8 cm. Extensive disease on the small bowel mesentery or serosa or on parts of the anterior abdominal wall next to ports may not be amenable to robotic resection. Where disease is limited to the pelvic peritoneum, the rectosigmoid colon, paracolic gutters, and diaphragmatic peritoneum, the robotic platform facilitates resection of disease particularly in patients with high body mass index.

The planned MIRRORS-RCT trial aims to establish whether survival, patient morbidity, and quality of life are non-inferior in women undergoing MIRRORS protocol (robot-assisted laparoscopic assessment proceeding to robotic or open interval debulking surgery) compared with standard open interval debulking surgery with a pelvic mass ≤8 cm. Should non-inferiority be confirmed, a significant change in practice could result.

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Correction notice This article has been corrected since it was first published. Information was missing from the Acknowledgements and Ethics approval sections and has now been added.

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Contributors Conceptualization: CU and SB-M. Study design: CU, SB-M, SSS, and AM. Data collection: CU, HA, JR, JC, JCh, PE, and SB-M. Data interpretation: CU, KB, AT, JC, JCh, PE, SS, AM, and SB-M. Drafting and/or editing manuscript: CU, HA, KB, JR, AT, JC, JCh, PE, SSS, AM, and SB-M. All authors approve and agree to be accountable for all aspects of the work. CU and SB-M are the guarantors and accept full responsibility for the finished work and the conduct of the study.

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Competing interests CU is Vice President of the The Young European Advocates of Robotic Surgery (YEARS) which is part of the Society of European Robotic Gynaecological Surgery (SERGS) HA: none, KB: none, JR: none, AT: none, JC: none. JC is a proctor for Intuitive Surgical Ltd, the manufacturers of Da VinciTM surgical robots. As such, he has received payment and travel expenses within the past three years for surgical proctoring on robotic gynecological surgery at other hospitals around the UK, as he is an acknowledged expert in this field. He also occasionally gives paid lectures on behalf of pharmaceutical companies. PE: none, SSS: none, AM: Consulting or Advisory Role (EISA Pharma, GlaxoSmithKline, Ipsen) Research Funding (Merck) Travel, Accommodations, Expenses (Merck). SB-M is a proctor for Intuitive Surgical Ltd, the manufacturers of Da VinciTM surgical robots. As such, he has received payment and travel expenses within the past three years for surgical proctoring on robotic gynaecological surgery at other hospitals around the UK and in the EU, as he is an acknowledged expert in this field. SB-M has recently been appointed Vice President (President Elect) of the British and Irish Association of Robotic Gynaecological Surgeons (BIARGS).

Patient consent for publication Consent was obtained for all surgical images.

Ethics approval MIRRORS was approved by the London Riverside Research Ethics Committee (Ref: 20/LO/0262 IRAS project ID: 261933). MIRRORS was performed in accordance with the Declaration of Helsinki. Written informed consent was obtained from all participants prior to them taking part. Historical and concurrent comparison data were assessed as part of a registered service evaluation project with Royal Surrey NHS Foundation Trust (No: SU-CA-21-22-037).

Provenance and peer review Not commissioned; externally peer reviewed.

Data availability statement Data are available upon reasonable request. All data relevant to the study are included in the article or uploaded as supplementary information. The datasets generated from this current study will be available upon request from Christina Uwins (Christina.Uwins@nhs.net) as raw anonymized data for up to 5 years following completion of the study. Participants have given their consent for the information collected from this study to be used to support other research in the future and to be shared anonymously with other researchers.

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MIRRORS

(Minimally **I**nvasive **R**obotic Surgery, **R**ole in Optimal Debulking **O**varian Cancer, **R**ecovery & **S**urvival)

A prospective Feasibility Study (non-randomised) of robotic interval debulking surgery in Ovarian Cancer

Sponsor	Royal Surrey NHS Foundation Trust
Funder	GRACE Charity
Protocol Version and Date	V1.3 16/01/2020
Chief Investigator	Mr Simon Butler-Manuel
Trial Management Group	
Statistical Oversight	Professor Simon Skene, University of Surrey

Uwins C, *et al. Int J Gynecol Cancer* 2024;0:1–12. doi: 10.1136/ijgc-2024-005265

Signature Page

The undersigned confirm that the following protocol has been agreed and accepted and that the Principal Investigator agrees to conduct the study in compliance with the approved protocol and will adhere to the principles outlined in the Declaration of Helsinki, the International Conference on Harmonisation Topic E6: Guideline for Good Clinical Practice (ICH GCP), any relevant SOPs, and other regulatory requirements.

I agree to ensure that the confidential information contained in this document will not be used for any other purpose other than the evaluation or conduct of the investigation without the prior written consent of the Sponsor.

I also confirm that I will make the findings of the study publicly available through publication or other dissemination tools without any unnecessary delay and that an honest, accurate and transparent account of the study will be given; and that any discrepancies from the study as planned in this protocol will be explained.

For and on behalf of the Study Sponsor:

Signature: ..... Date: ...../...../.....

Name (please print):

Position: .....

Chief Investigator:

Date: 16/01/2020

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Uwins C, *et al. Int J Gynecol Cancer* 2024;0:1–12. doi: 10.1136/ijgc-2024-005265

1. Glossary

AE	Adverse Event
CRF	Case Report Form
GCP	Good Clinical Practice
ICF	Informed Consent Form
ICH	International Conference on Harmonisation
ISF	Investigator Site File
PI	Principal Investigator
SAE	Serious Adverse Event
SOP	Standard Operating Procedure
SUSAR	Suspected Unexpected Serious Adverse Reaction
TMF	Trial Master File

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3 Protocol Summary

Title: **Minimally Invasive Robotic Surgery, Role in Optimal Debulking Ovarian Cancer, Recovery & Survival** *A prospective Feasibility Study (non-randomised) of robotic interval debulking surgery in Ovarian Cancer*	
Short title	**MIRRORS**
Sponsor	Royal Surrey NHS Foundation Trust, Egerton Road, Guildford GU2 7XX
Funder reference	
Clinical trials / ISRCTN	
Design	Prospective feasibility study of Robotic assisted interval debulking surgery (IDS) in ovarian cancer
Primary objectives	Feasibility of robotic surgery as defined by: 1. Ability to recruit patients 2. Acceptability to patients 3. Quality of life 4. Maximal macroscopic debulking rate (R=0 rate) 5. Rate of conversion to open surgery
Secondary objectives Ancillary Study:	1. Overall Survival 2. Progression free survival 3. Cost comparison of Robotic minimally invasive interval debulking surgery vs Open. 4. To evaluate staging and assessment of operability via Robotic surgery using Diagnostic laparoscopy Peritoneal angiography / perfusion assessment using Indocyanine green (ICG) in patients with advanced ovarian cancer
Target accrual	20 Robotic IDS completed
Inclusion criteria	Adult women ≥18 years with Stage III and IV Ovarian cancer undergoing Neo-adjuvant Chemotherapy. Considered suitable for IDS ≤8cm pelvic mass Open surgery not required for other surgical speciality intervention
Exclusion criteria	• Extensive disease requiring liver and upper Gastro-intestinal surgical support will exclude patients if an open surgical approach is considered necessary. • Lacking capacity to the extent they are unable to understand or complete trial documentation / questionnaires.
Number of sites	1
Duration of recruitment	1 year
Duration of patient follow-up	3 months post-surgery
Definition of end of trial	Once final patient data collection has occurred and data queries have been resolved. Length of trial 18months

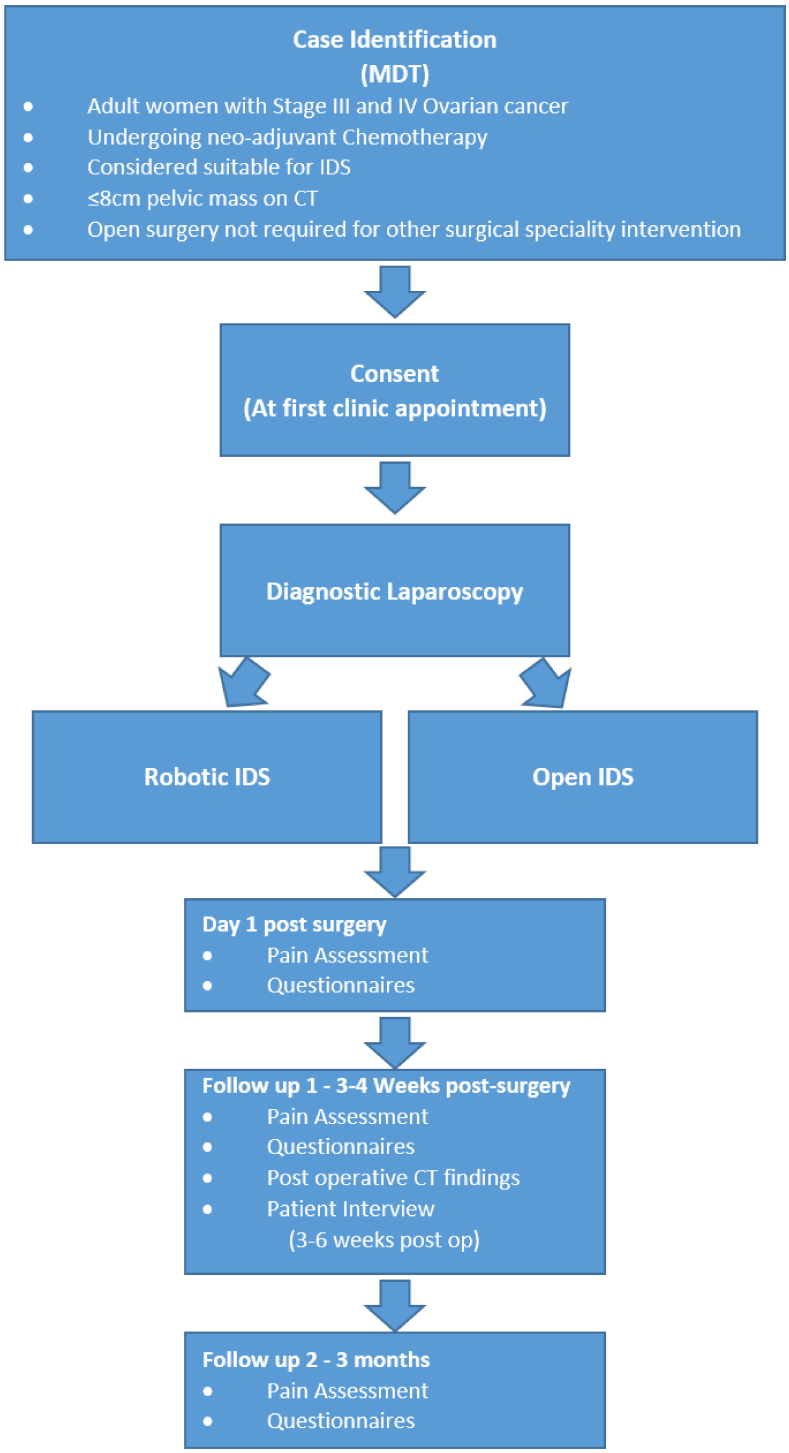

Figure 1 - MIRRORS Flow Diagram

4 Study Schedule

Investigations	**Baseline**	**Day of Surgery**	**Day 1 Post surgery**	**Day of Discharge**	**Follow up 1 (3-4 weeks post surgery)**	**Follow up 2 - End of Trial Visit 3 Months post op +/- 7 days**	**Survival and Recurrence follow up (no visit required)**
Patient Demographics [a]	**x**						
Informed consent	**x**						
Baseline Data[b]	**x**						
Patient Interview at 3-6 weeks post op					**X done 3-6 weeks post op**		
Pain assessment • Numeric Rating Scale (NRS) Patient rates the pain from 0 (no pain) to 10 (worst pain)	**x**		**x**		**x**	**x**	
Questionnaires: • EORTC QLQ C30 • EORTC QLQ OV28 • HADs	**x**		**x**		**x**	**x**	
Surgical data[c]:		**x**					
Inpatient Stay[d]:				**x**			
Reported Post operative Surgical Complications Classified by the Clavien-Dindo Classification				**x**	**x**	**x**	
Record any Surgical Readmission • Cause of readmission • Number of days readmitted					**x**	**x**	
Patient Status[e]: • Alive without recurrence • Alive Following recurrence (date) • Dead (date and cause of death)				**x**	**x**	**x**	**x**
Time to adjuvant chemotherapy (days) Date of first cycle after Robotic IDS (aim ≤14 days)					**x**	**x**	

a) Patient Demographic - The following demographic data will be collected:
   - Date of birth
   - Ethnicity

b) Baseline Data – The following baseline data will be collected:
   - ECOG performance status (Eastern Cooperative Oncology Group)
   - Weight
   - Height
   - BMI
   - Smoking status
   - Co-morbidities previous and current medical conditions
   - Concomitant medications
   - Parity
   - Previous abdominal surgery including caesarean sections
   - BRACA Status when available
   - Chemotherapy Regimen
   - RECIST Response from pre IDS CT
   - Number of cycles of chemotherapy prior to Surgery (minimum 3)
   - Size of pelvic mass on CT scan in cm

c) Surgical Data:
   - Date of Surgery
   - Peritoneal Cancer Index Score (PCI) at Laparoscopy.
   - Suitable for robotic IDS Yes/No, If not reason
   - Mode of Surgery (Open / Robotic)
   - Reason for conversion if applicable
   - Operation Title
   - ASA Grade
   - Time Skin incision to Time Skin closure
   - Length and position of longest Incision
   - Mode of specimen retrieval (Mini Laparotomy / Through vagina)
   - Surgical $C0_2$ pneumoperitoneum operating pressure mmHg
   - Peritoneal Cancer Index Score (PCI) score after debulking surgery complete
   - Estimated Blood Loss (EBL)
   - Number of units of blood transfused
   - Maximal diameter of macroscopic residual disease in cm and categorised as
     - R=0
     - R<0.2
     - R<0.5
     - R<1
     - R>1
   - Site of Largest residual disease using same categories as for PCI (see table below)
   - Intraoperative complications
   - Histopathological diagnosis
   - Grade
   - FIGO Stage

} Available by Follow up 1

d) Inpatient Stay data to be completed prior to discharge:
- Total Number of units of blood transfused post op
- Number of Days ITU Care required
- Date of admission and Date of Discharge
- Length of stay (Days admission following surgery – Day of surgery = Day 0)
- Post-operative complications classified by the Clavien-Dindo Classification

e) Follow up

- Post Operative CT findings
- Alive without recurrence
- Alive with recurrence
- Date of recurrence if applicable
- Date of Death
- Cause of Death

5 Background

Ovarian cancer (which includes cancer of the fallopian tube & peritoneum) is the 6th most common cancer in women in the UK with around 7,300 women diagnosed each year. 1-year survival in England ranges from 98.7% (stage1) to 51.4% (stage IV) (NCIN 2015). Sadly, more than 70% of patients with newly diagnosed ovarian cancer will present with advanced disease (FIGO stage-III or IV disease (BGCS 2017)). A woman's risk of developing ovarian cancer before the age of 75 is estimated at 1.12% in the UK (Ferlay 2019). The incidence of ovarian cancer increases with age with most women presenting between the ages of 65-69. Many of these women are also frail (Cancer Research UK).

Current standard treatment for advanced ovarian cancer involves surgery and chemotherapy. The aim of surgery is to assess how far the cancer has spread (staging) and to remove as much visible disease as possible (ideally all of it) as this is associated with the longest survival. Unfortunately, as most women present with advanced disease this is often not always possible. Women with advanced stage cancer are usually treated with 3 cycles of chemotherapy (known as “neo-adjuvant chemotherapy”) to reduce the amount of tumour, before having any surgery. Surgery following chemotherapy is called “Interval debulking surgery”. The aim of surgery is to remove as much of the tumour that remains after chemotherapy as possible. Treatment is then completed with 3 further cycles of chemotherapy following surgery.

Ovarian cancer surgery is usually performed through a vertical incision on the abdomen from just above the pubic bone to above the belly button and sometimes up towards the bottom of the breastbone, depending on how far the cancer has spread. A larger incision is required if there is tumour in the upper parts of the abdomen.

Minimally invasive surgery, uses multiple small cuts on the abdomen to insert ports through which instruments and a camera are passed. Surgery is performed under direct vision, with carbon dioxide gas inflating the abdomen to lift the abdominal wall upwards to provide the space underneath in which the surgeons can operate. Robotic surgery is a further development in minimally invasive surgery which adds mechanical assistance and support of the instruments. Performing surgery through smaller cuts is generally less painful and has been found to enhance recovery with reduced length of stay in hospital, reduced blood loss, so avoiding blood transfusion, infections and blood clots in the legs or lungs (Walker et al 2009, Kornblith et al 2009, Feuer et al, Kumar et al, 2013, Mahdi et al, 2016). Larger more complex operations generally carry greater risks of surgical complications, and these complications may delay or prevent women from re-starting their chemotherapy. It is impossible to remove large cysts or masses through such keyhole incisions and so this form of surgery is not suitable for everyone with ovarian cancer.

The role of robotic surgery in ovarian cancer treatment is uncertain but robotics has the potential to lessen the impact and reduce the adverse effects of surgery on some women with ovarian cancer. It may be particularly helpful for women at high risk of anaesthetic complications including those who are overweight, the elderly and women with other pre-existing medical conditions.

A systematic review and meta-analysis by Cardenas-Goicoechea *et al* 2019 looking at the feasibility of achieving complete cytoreductive surgery after neoadjuvant chemotherapy for stage IIIC -IV ovarian cancer patients identified 6 studies (3 prospective and 3 retrospective). Of the prospective trials two compared open surgery vs laparoscopy (Tozzi et al 2016, Favero et al 2015) and one looked at the outcomes following laparoscopic or Robotic interval debulking surgery (Gueli Alletti et al 2016). The retrospective trials included one looking at Robotic surgery (Ackroyd et al, 2017) one comparing open vs lap/robotic (Melamed et al 2017) and one looking at outcomes following laparoscopic interval debulking surgery (Corrado et al, 2015). In total, these studies included 3231 patients, 567 in the minimally invasive group and 2664 in the laparotomy group. Most of the patients included in the meta-analysis related to the study by Melamed et al 2017 (450/567 of the Minimally invasive group and 2621/2664 in the open group). Cardenas-Goicoechea et al (2019) created two pooled groups, one of minimally invasive surgery and one for laparotomies. They found that complete cytoreductive surgery after neoadjuvant chemotherapy is feasible and safe in selected patients. No statistical difference was found between the groups for their complete cytoreductive surgery rate.

Melamed et al 2017 used a national cancer database to identify a cohort of patients with stage IIIC to IV epithelial ovarian cancer who underwent interval debulking surgery following neoadjuvant chemotherapy between 2010-2012 this study included 2621 patients in the open group and 450 in the combined laparoscopy/robotic group. In comparison the other studies included in the meta-analysis by Cardenas-Goicoechea et al (2019) had 10-30 patients in the minimally invasive groups. Follow-up for all the studies ranged from 15 to 36 months. Common exclusion criteria in these studies were residual tumour in porta hepatis and bowel serosa, patients >70 years, elevated tumour markers, BMI >40 and ASA score III-IV. Melamed *et al* (2017) concluded that patients selected for laparoscopic debulking may have a lower burden of disease than those chosen for laparotomy. Postoperative hospitalisation was slightly shorter in the laparoscopy group (4 vs 5 days).

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Readmission, death within 90 days and suboptimal debulking did not differ between the two groups.

Magrina *et al* in 2011 published a retrospective case-control analysis of 25 patients with epithelial ovarian cancer undergoing robotic surgical treatment between March 2004 and December 2008. A comparison was made with similar patients treated by laparoscopy and laparotomy and matched by age, BMI and type of procedures between January 1999 and December 2006. Mean operating times were longer for robotic surgery compared to laparoscopy or laparotomy, and mean blood loss reduced at 164mls vs 266.7 vs 1307ml respectively. Magrina *et al* concluded that laparoscopy and robotics were preferable to laparotomy for patients with ovarian cancer requiring primary tumour excision alone or with one additional major procedure classed as intestinal resection, full thickness diaphragm resection, liver resection or splenectomy. Laparotomy was found to be preferable for patients requiring 2 or more additional major procedures.

A further study by Magrina et al in 2013 compared secondary cytoreduction by laparoscopy (9) laparotomy (33) or robotics (10) in patients with recurrent ovarian cancer. Laparoscopy and robotics were found to have reduced blood loss and hospital stay with no difference observed for operating time, complications, complete debulking and survival. They concluded that laparotomy was preferable for patients with widespread peritoneal implants, multiple sites of recurrence and or extensive adhesions but in a selected group of patients laparoscopic or robotic secondary cytoreduction was feasible without compromising survival.

Fagotti et al (2019) recently published the results of The International Mission Study which was a retrospective multicentre study to investigate minimally invasive interval debulking surgery (either laparoscopic or Robotic) in patients with stage III-IV advanced epithelial ovarian cancer. This study included a total of 127 patients who underwent minimally invasive interval debulking surgery. Following minimally invasive interval debulking surgery, 96% of their patients had no visible residual tumour (R=0), the rest were resected to tumour deposits < 1cm (R<1). Median reported blood loss was 100ml (range 70-1320) Median time to discharge was 2 days (range 1-33 days). Conversion rate to laparotomy was 3.9%. There were no defined exclusion criteria as these varied between centres depending on the patient. Standard cytoreduction surgery was defined as hysterectomy, salpingo-oophorectomy omentectomy and peritoneal biopsies. All patients not having standard intraperitoneal cytoreduction and with a follow up time less than 6 months were excluded from the study. This retrospective multicentre trial followed the publication of the MISSION Trial in 2016. The MISSION trial looked at the feasibility and early complication rate of minimally invasive interval debulking surgery (both laparoscopic and Robotic), in stage III-IV epithelial ovarian cancer patients after neoadjuvant chemotherapy. The trial only included patients with epithelial ovarian cancer with complete clinical response (assessed by the RECIST criteria (Eisenhauer et al. 2009)) and ECOG performance status <2. Women with BMI >40kg/m^2 and ASA score III-IV were excluded. Of 184 patients considered eligible for IDS, 52 met the inclusion criteria and were enrolled in the study. Of these 52 patients 22 had laparotomies following surgical evaluation. Of the 30 patients who went on to have minimally invasive interval debulking surgery Median blood loss was 100ml (range 50-200ml) and Median post-operative stay 2 days (range 2-3 days).

Abitbol *et al* (2019) recently published the results of their study looking at the impact of introducing robotic surgery in their centre for interval cytoreduction of selected patients with stage III-IV ovarian

cancer. This study compared patients having surgery in the period from November 2008-2014 (post the introduction of Robotic surgery) to patients having surgery between January 2006 and November 2008 (pre Robotic area n=22). A total of 91 patients were selected to undergo interval cytoreduction either via robotic surgery (n=57) or laparotomy (n=34) after neoadjuvant chemotherapy. The median survival was 42.8+/- 3.1 months in the period where both robotic surgery and laparotomy were offered compared with 37.9+/-9.8 months in the time period preceding, when only laparotomy was performed (p=0.6). All patients undergoing robotic interval debulking surgery achieved cytoreduction to <1cm residual disease and 82% had no residual disease. The median blood loss was 100ml (range 10-1250ml), median hospital stay was 1 day (range 1-17 days) and median time to adjuvant chemotherapy was 13 days (range 6-75 days) in the robotic cohort.

Our own department in 2009 (Madhuri et al) published a case report of laparoscopic interval debulking surgery for stage 4 primary fallopian tube carcinoma in a woman who had achieved a good response to carboplatin and paclitaxel chemotherapy. Laparoscopic total hysterectomy, bilateral salpingo-oophorectomy and stripping of the surrounding pelvic peritoneum and supracolic omentectomy was performed. All visible disease was excised, blood loss was 200ml and she was discharged the following day with chemotherapy restarting 2 days post-operatively. This patient survived 44 months from surgery with first recurrence at 16 months.

Since 2009, we have now performed over 1200 gynaecological oncology robotic operations here in the Academic Department of Gynaecological Oncology and have by far the greatest robotics experience in the UK. The majority of these operations have been performed for women with uterine (womb) cancers. Our introduction of robotics has revolutionised our practice, particularly with regards to womb cancer. This has resulted in patient benefits and enhanced recovery in this group. Robotic surgery in our department has been found to be associated with a lower number of complications than standard laparoscopic keyhole surgery or open surgery. Indeed, many women previously thought not fit for surgery at all, are now recommended robotic surgery.

To date, we have only performed a relatively small number of operations for ovarian cancer using robotic surgery. Looking at our own work, between January 2010 and December 2018 we performed 950 operations for ovarian cancer of which 31 were performed using the Da Vinci Robot. Of these, just 3 cases were Interval debulking procedures.

Other indications included:

- 15 for completion/staging
- 7 for recurrent disease
- 1 for fertility sparing
- 2 initially thought to be CAH / Corpus cancer
- 3 for suspicious cysts

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When compared to patients undergoing similar open procedures (hysterectomy removal of both tubes and ovaries and removal of the omentum +/- appendix) (464 in this time period), patients undergoing Da Vinci Robot Assisted surgery for ovarian cancer lost significantly less blood (median blood loss 50ml Robotic and 800ml open), spent less time in hospital (Median length of stay Robotic 1 day, open 6 days) and had a lower 30 day mortality rate (0 for Robotic, 3 for open surgery 0.65%).

Although the numbers are small with regards to Robotic surgery and ovarian cancer the values presented for blood loss and length of stay correlate well with those we found for Robotic vs Open surgery for Womb cancer in the same time period: Robotic: 631 operations Median blood loss 50 ml. Median Length of stay 1 day, 30-day Mortality 1/631 (0.16%); Open: 154 operations, Median blood loss 500 ml, Median length of stay 6 days, 30-day Mortality 4/154 (2.6%).

6 Rationale for study

For all except 1a disease, standard treatment involves surgery to both stage and remove the volume of disease (debulking) and chemotherapy. Complete resection of all macroscopic disease (at primary or interval surgery) is the strongest independent variable in predicting overall survival (Vergote et al. 2010, Kehoe et al. 2015). Sensitivity to platinum-based chemotherapy is the other principal variable which determines survival.

Minimally invasive surgery offers the potential benefits of enhanced recovery with reduced length of stay, reduced blood loss avoiding blood transfusion, reduced pain, infections and thromboembolic complications. Surgical complications may prevent or delay patients from commencing chemotherapy. Robotic surgery provides anaesthetic benefits of low pressure pneumoperitoneum and is more ergonomic for the surgeons allowing them to perform longer and more complex surgery via a minimal access route. Robotic minimally invasive surgery is open to more patients such as those at high risk of anaesthetic complications including those suffering from obesity, the elderly & those with medical comorbidities with fewer resulting complications and readmissions.

The reduced length of stay associated with minimally invasive surgery positively impacts on the availability of bed resources in the NHS. Additionally, reduced readmissions, reduced HDU/ITU rates also reduces costs. Minimally invasive surgery including both Laparoscopic surgery and Robotic surgery already has an established role in the treatment of Endometrial cancer (Jorgensen et al. 2018, Walker et al. 2009). These patients benefit from the improved recovery associated with the minimally invasive surgical route. Ovarian cancer in contrast is still predominantly treated with extensive open surgery with associated long recovery times affecting quality of life in patients, many of whom are elderly and or frail.

As described before there is an increasing body of retrospective evidence with regards to the feasibility and safety of minimally invasive interval debulking surgery for ovarian cancer, of which many have grouped laparoscopy and Robotic surgery together. Minimally invasive interval debulking

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surgery still remains controversial in Britain. To investigate the feasibility of Robotic interval debulking surgery, with the generous support of GRACE Charity, we are proposing establishing a new UK based prospective feasibility study **M**inimally **I**nvasive **R**obotic Surgery, **R**ole in Optimal Debulking **O**varian Cancer, **R**ecovery & **S**urvival (**MIRRORS**). The aim of this study is to establish the role of Robotic Minimally invasive interval debulking surgery for advanced ovarian cancer. We are interested in discovering whether the benefits seen with regards to recovery and quality of life in Robotic assisted surgery for womb cancer can be provided for women with advanced ovarian cancer with equivalent overall survival and progression free survival. This trial is the first step towards launching a British multicentre randomised control trial of Robotic interval debulking surgery for ovarian cancer in the future. Given Royal Surrey's investment and now 10 years of experience in Robotic surgery, we see this exciting new trial and possible future national randomised controlled trial as complementary to Royal Surrey's ambitious "True North" objectives of staying at the cutting edge of safety and quality improvement and the vision of becoming a Nationally celebrated, community focused health care (service).

In contrast to many of the previous studies, based on our 10 years of robotic experience, we have kept the inclusion criteria wide, not restricting by BMI or patient comorbidities. With this in mind the study will be offered to all adult women with ovarian cancer who have been identified through our multi-disciplinary team meeting as being suitable for interval debulking surgery after 3 cycles of chemotherapy. A Pelvic Mass >8cm and extensive disease which would require liver, upper Gastro-intestinal or other surgical support will exclude patients if an open surgical approach is deemed necessary.

Robotic surgery is unlikely to be suitable in all cases of ovarian cancer, particularly those with large pelvic masses or extensive disease around the upper part of the abdomen, however, it has the potential to provide significant recovery and quality of life benefits to a selected group of our patients.

7 Trial Objectives

To assess the feasibility of obtaining consent from women and acceptability of Robotic interval debulking surgery for advanced ovarian cancer. Women deemed suitable for interval debulking surgery will be identified through the Gynaecological Oncology MDT. The aim is to recruit women over a period of 1 year aiming for a total of 20 women who undergo Minimally Invasive Robotic Interval debulking surgery for advanced ovarian cancer. The main outcomes are feasibility of the recruitment process and acceptability of the questionnaires and numeric rating pain scale (NRS-11) as assessed by completion rate and patient interviews. Acceptability to surgeons will be assessed though a national questionnaire distributed via the British Gynaecological Cancer Society. Qualitative interviews with women will be conducted to provide an insight into Women's experiences of taking part. Thematic Analysis using NVIVO will be used to analyse the data.

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Quantitative data will be collected pre op, prior to discharge, at follow up at 3-4 weeks and at 3 months. The outcomes from this feasibility study will include the knowledge to set up national multi-centre randomised controlled trial to investigate whether robotic surgery does have a role in interval debulking advanced ovarian cancer and whether in a sub-selected group of women it is non inferior (with regards to overall survival and progression free survival) to traditional open interval debulking surgery.

Hypothesis: in selected cases of ovarian cancer, following neoadjuvant chemotherapy, minimally invasive robotic surgery provides maximal debulking surgery and improved patient outcomes.

Null Hypothesis: Robotic surgery is not suitable for the treatment of ovarian cancer following neoadjuvant chemotherapy. It is not possible to achieve maximal debulking surgery and patient outcomes are not improved.

This study's primary objectives are to investigate the role of Minimally Invasive Robotic Interval debulking surgery in selected patients for the management of their Ovarian cancer. Specifically:

7.1 Primary objectives

To demonstrate the feasibility of selecting candidate women and successfully completing robotic interval debulking surgery as defined by:

1. Ability to recruit patients
2. Acceptability of procedure to patients
3. Success of Surgery; measured by the Maximal macroscopic debulking rate (R=0 rate)

7.2 Primary outcomes

- Number of patients consented compared to number identified by MDT
- Quality of life as assessed by EORTC QLQ C30 and OV28 and HADs validated questionnaires
- R=0 Rate
- Rate of Conversion to Open surgery and documented reason
- % patients fully filling out trial questionnaires

Population: The study will be offered to all adult women with ovarian cancer who have been identified through our multi-disciplinary team meeting as being suitable for interval debulking surgery after 3 cycles of chemotherapy. A Pelvic Mass >8cm and extensive disease requiring liver and upper Gastro-intestinal surgical support or any other surgery requiring an open approach will exclude patients if an open surgical approach is considered necessary.

Intervention: Robotic assisted minimally invasive interval debulking surgery.

7.3 Secondary objectives

1. Overall Survival
2. Progression free survival
3. Cost comparison of Robotic minimally invasive interval debulking surgery vs Open
4. To evaluate staging and assessment of operability via Robotic surgery using Diagnostic laparoscopy

7.4 Secondary Outcomes

1. Overall Survival measured in Months from the date of surgery up to 3 months from the last patient and longer term follow-up for survival and disease progression.
2. Progression free survival in Months from the date of surgery
3. Cost of Robotic minimally invasive interval debulking to the hospital compared to a similar open procedure measured in GBP £
4. Percentage of Patient considered suitable for Robotic interval debulking surgery based on initial diagnostic laparoscopy who are successfully debulked to R=0

7.5 Success Criteria

- At least 20% of people eligible for the study will accept inclusion in the study.
- Complication rate is not higher than for open interval debulking surgery
- Conversion to open surgery rate not greater than 50% in patient group deemed suitable for Robotic IDS following initial diagnostic laparoscopy.

7.6 Exploratory objectives

Outcome measure	Measurement Variable	Analysis Metric	Method of aggregation	timepoint
Length and position of longest incision (midline / transverse)	Centimetres Position: • Midline • Transverse		Median and range (number and percentage done in Midline vs transverse)	Immediately following completion of surgery
Mode of specimen retrieval	Mini laparotomy Through Vagina		% patients requiring Mini laparotomy to remove specimen	Immediately following completion of surgery
Surgical C02 pneumoperitoneum operating pressure	mmHg		Median and Range	Immediately following completion of surgery
Estimated Blood Loss (EBL)	Millilitres (ml)		Median and range	At completion of surgery
Number of units of blood transfused post operatively	Number of units		Median and range	Documented on day of discharge
Number of days requiring ITU care	Number of days from date of surgery to date suitable for stepdown care		Median and Range	Documented on day of discharge
Length of stay	Number of days in hospital following operation		Median and range	Documented on day of discharge
Surgical Readmission rate and cause	Readmitted yes or no Reasons for readmission Number of days readmitted		Number and Percentage of patients requiring readmission	Up to including 30 days post surgery. Day of surgery = Day 0

Outcome measure	Measurement Variable	Analysis Metric	Method of aggregation	timepoint
Maximal diameter of macroscopic residual disease	Measured in Centimetres	• R=0 • R<0.2 • R<0.5 • R<1 • R>1	Percentage and median number of patients achieving R0 Median and range of maximal diameter of macroscopic residual disease.	Immediately following completion of surgery
Effectiveness of Debulking surgery - comparison of pre-operative and post-operative disease burden	**Peritoneal Cancer Index (PCI)** Score: Score: LS 0 = no tumour seen LS 1 Tumour ≤ 0.5cm LS 2 Tumour > 0.5cm ≤ 5.0cm LS 3 Tumour >5.0 cm or confluence 0. Central region 1. Right Upper 2. Epigastrium 3. Left Upper 4. Left Flank 5. Left Lower 6. Pelvis 7. Right Lower 8. Right Flank 9. Upper Jejunum 10. Lower Jejunum 11. Upper Ileum 12. Lower Ileum	Change from baseline to completion of tumour resection	% difference	At the start of surgery as part of initial assessment following entry into abdominal cavity and once surgery completed prior to removing camera and closing skin incisions.

Outcome measure	Measurement Variable	Analysis Metric	Method of aggregation	timepoint
Site of Largest residual disease	0. Central region 1. Right Upper 2. Epigastrium 3. Left Upper 4. Left Flank 5. Left Lower 6. Pelvis 7. Right Lower 8. Right Flank 9. Upper Jejunum 10. Lower Jejunum 11. Upper Ileum 12. Lower Ileum	`		Immediately following completion of surgery
Surgery to Chemotherapy interval in days aiming for ≤ 14 days post op (currently week 3 post op for laparotomies)	Day number post-surgery that chemotherapy recommenced. Day of surgery = Day 0	< 3 weeks	Median and Range	Within 8 weeks post surgery

Outcome measure	Measurement Variable	Analysis Metric	Method of aggregation	timepoint
Patient reported outcome will be assessed using:	ECOG performance status (Eastern Cooperative Oncology Group) HADs questionnaire European Organisation for Research and Treatment of Cancer Quality of Life questionnaires QLQ - OV28 QLQ - C30 Open ended white space questions to assess what is important to patients	Score at each time point	Standard deviation Number of patient assessed at each time point	At Preoperative appointment Day 1 post op 3-4 weeks post surgery 3 months post surgery

Outcome measure	Measurement Variable	Analysis Metric	Method of aggregation	Timepoint
Intra-operative & Post-operative complications	Clavien-Dindo Classification **Grades** **Definition** Grade I Any deviation from the normal postoperative course without the need for pharmacological treatment or surgical, endoscopic and radiological interventions Allowed therapeutic regimens are: drugs as antiemetics, antipyretics, analgetics, diuretics and electrolytes and physiotherapy. This grade also includes wound infections opened at the bedside. Grade II Requiring pharmacological treatment with drugs other than such allowed for grade I complications. Blood transfusionsand total parenteral nutritionare also included. Grade III Requiring surgical, endoscopic or radiological intervention - IIIa Intervention not under general anesthesia - IIIb Intervention under general anesthesia Grade IV Life-threatening complication (including CNS complications)* requiring IC/ICU-management - IVa single organ dysfunction (including dialysis) - IVb Multiorgandysfunction Grade V Death of a patient (Dindo et al 2004)			Time of surgery On discharge First post op review

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8 Trial design

Prospective feasibility study of adult women with stage III-IV ovarian cancer (including peritoneal and fallopian tube cancer) considered suitable for interval debulking surgery following discussion in MDT with pelvic mass ≤8cm and no anticipated requirement for open surgery e.g upper abdominal / colorectal surgery expected.

Study aims

- To gather preliminary information on the use of robotic surgery in the treatment of ovarian cancer following adjuvant chemotherapy (the intervention) and the feasibility of conducting a full-scale national randomised control trial

8.1 Eligibility criteria

Participants identified as suitable and willing to have robotic interval debulking surgery will be consented for both open surgery and robotic assisted laparosopic surgery. Initial diagnostic laparoscopic assessment will be carried out. If it is deemed feasible, surgery will proceed robotically alternatively, if it is determined that full debulking surgery to zero macroscopic residual disease is best carried out though open surgery and the patient has consented for this then this will be done

8.2 Inclusion

- Adult women, capable of giving informed consent, with Stage III and IV Ovarian cancer undergoing Neo-adjuvant Chemotherapy.
- Considered suitable for IDS
- ≤8cm pelvic mass
- Open surgery not required for other surgical speciality intervention to achieve removal of all visible disease
- Able to understand and complete trial documentation / questionnaires and comply with the protocol.

8.3 Exclusion

- Open surgery required for other surgical speciality interventions to achieve removal of all visible disease
- Unable to understand and complete trial documentation / questionnaires and comply with the protocol.

9 Trial procedures

9.1 Recruitment

Participants will be identified in MDT and the trial discussed in clinic.

A participant information sheet will be provided and the study explained in person. Participants agreeing to be included will sign a consent form. Following consent participants will be asked to complete baseline questionnaires.

All screened patients will have the following anonymised basic information collected:

- Date of Birth / Age
- Ethnicity
- Reason not eligible
- Reason for declining if eligible but declined

9.2 Patient identification

Participants will be identified in MDT where all patients with ovarian cancer are discussed prior to interval debulking surgery. Participants will be consented during their post MDT visit to clinic and will be followed up during their normal scheduled appointment times.

9.3 Screening

There will be no additional screening bloods or investigations beyond that already done as part of the surgical work up.

9.4 Consent

The Principal Investigator (PI) (Mr Butler-Manuel) retains overall responsibility for the conduct of research at the site, this includes the taking of informed consent of participants. Any person delegated responsibility to participate in the informed consent process will be authorised, trained

and competent to participate according to the ethically approved protocol, principles of Good Clinical Practice (GCP) and Declaration of Helsinki.

Informed consent will be obtained prior to any data being collected.

The right of a woman to refuse participation without giving reasons will be respected at all times. Participants are free to withdraw at any time from the trial without giving reasons and without prejudicing their further treatment. All participants will be provided with an information leaflet complete with a contact point where she may obtain further information about the trial. Data and samples collected up to the point of withdrawal will only be used after withdrawal if the participant has consented for this. Intention to utilise such data is outlined in the consent literature. Where a participant is required to re-consent or new information is required to be provided to a participant it is the responsibility of the PI to ensure this is done in a timely manner. The PI takes responsibility for ensuring that all vulnerable participants are protected and participate voluntarily in an environment free from coercion or undue influence

Consent process:

- Discussion will occur following initial pre surgical clinic appointment between the potential participant and an individual knowledgeable about the research, the nature and objectives of the trial and possible risks associated with their participation. The Gynaecological Oncology CNS will be present to provide support for the potential participant and to help protect the potential participant's interests minimising any risk of coercion.
- Written information in the form of a patient information leaflet and consent document, approved by the REC and be in compliance with GCP, local regulatory requirements and legal requirements, will be provided.
- Potential participants will have the opportunity to ask questions
- Potential participants must be capable of giving consent.
- The Participant must:
    - Understand the purpose and nature of the research
    - Understand what the research involves, its benefits (or lack of benefits), risks and burdens
    - Understand the alternatives to taking part
    - Be able to retain the information long enough to make an effective decision.
    - Be able to make a free choice
    - Be capable of making this particular decision at the time it needs to be made (though their capacity may fluctuate, and they may be capable of making some decisions but not others depending on their complexity)

A person is assumed to have the mental capacity to decide unless it is shown to be absent. Mental capacity is considered to be lacking if, in a specific circumstance, a person is unable to decide for him or herself because of impairment or a disturbance in the functioning of their mind or brain.

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9.5 Additional consent provision for ancillary studies

Participation in the ancillary research is not required for participation in the trial

9.5.1 MIRRORS ICG - Peritoneal angiography / perfusion assessment using Indocyanine green (ICG) in patients with advanced ovarian cancer.

Indocyanine green (ICG) is an intravenous fluorescent dye used for cardiac, circulatory, microcirculatory and tissue perfusion diagnostics (See attached Summary of Product Characteristics for Verdye 5mg/ml, section 4.2 “Measurement of tissue perfusion” pg 3). ICG is used for diagnostics only. After intravenous injection ICG does not undergo any significant extra hepatic or enterohepatic circulation and does not pass into urine or cerebrospinal fluid. Indocyanine green is not metabolised and stays within blood vessels when given intravenously (Verdye 5mg/ml Summary of Product Characteristics).

In our Gynaecological oncology department, we regularly use ICG for sentinel lymph node assessment in endometrial cancer and have also used it in vulval and cervical cancer for the same purpose. Other therapeutic indications include assessment of perfusion in skin flaps and bowel anastomoses. At Royal Surrey NHS Foundation Trust, it is given intravenously for angiography in ophthalmology (see attached patient information leaflet). The incidence of adverse events is low (1 in 10 000-42,000 patients (Pruimboom et al 2019).

Within ophthalmology ICG dye is used to detect choroidal neovascularisation (formation of new blood vessels) which is seen in age related macular degeneration. The anatomy of these new vessels is abnormal and is characterised by large size with varying diameters and convolutedness (Solass, W. et al., 2016). Peritoneal inflammation and cancer invasion also causes neovascularisation with abnormal blood vessel patterns seen over the surface of peritoneal metastatic deposits (Solass, W. et al., 2016).

ICG binds to serum proteins and behaves like a macromolecule in the circulation. Macromolecules are known to accumulate in tumour tissue due to increased vascular permeability and reduced drainage. This phenomenon is called the “enhanced permeability and retention” (EPR) effect and has been observed in most solid tumours (Pruimboom et al 2019).

Tummers et al (2015) observed the effects of intravenous ICG in 10 patients suspected of ovarian cancer undergoing primary surgery. Of these 10 patients only 2 had metastasis and only one of these had stage 3 or above disease. Tummers et al (2015) found that in the 2 patients with metastatic disease all the metastatic deposits fluoresced under near infrared light therefore 100% sensitivity.

Standard ovarian cancer surgery involves careful assessment of the abdominal and pelvic cavities, identifying and removing all tumour deposits and taking biopsies. This is to both debulk the disease and to stage it. Survival in ovarian cancer is strongly associated with removing all visible tumour.

For this Ancillary study, we are proposing to use ICG fluorescent dye to look at the blood vessel pattern of the peritoneum (angiography) in the patients enrolled in the MIRRORS Study. We will inject 20mg of ICG dye in 10ml of water for injection intravenously (maximum of 0.5mg/kg). Following injection of ICG, the peritoneal surfaces of the abdominal and pelvic cavity will be searched under normal white light in order to identify any tumour deposits. The abdominal cavity will then be examined under near infrared light (using Da Vinci robot Firefly Fluorescence imaging mode) looking for areas of abnormal vasculature and peritoneal metastases. All visibly abnormal areas will be removed and sent to histopathology as is our standard surgical practice. **The ICG will not be used to guide where biopsies are taken or tissue is removed only clinically abnormal tissue or lymph nodes will be removed regardless of the effect of the ICG on them.** We will observe and record whether or not any lesions that are removed fluoresced under near infrared light.

Women agreeing to take part in the MIRRORS study will be asked whether they also wish to take part in this ancillary study. **Participation in this ancillary research is not required for participation in the trial.** Inclusion criteria will be the same as for the MIRRORS Study. Exclusion criteria will be: Severe renal insufficiency GFR< 55ml/min, known allergy to iodine or ICG and hyperthyroidism. The **aim** of this ancillary study is to observe the perfusion of the peritoneum in women with advanced ovarian cancer and observe how changes in the pattern of perfusion relate to any metastatic deposits.

- Biological specimens for this ancillary study will be acquired with consent, transferred and stored during the trial.
- The specimens will be used for ethically approved research as part of this study on ovarian cancer.
- Participants will be consented for the use of specimens in future research related to ovarian cancer
- Participants will be consented to be contacted by trial investigators for further informational and consent-related purposes
- Withdrawal from the ancillary research is possible. Any material provided will be disposed of in accordance with hospital regulations.
- Specimens used in any separate study outside of the pathology department will be coded so that participants cannot be identified from them.
- Withdrawal prior to any research being performed will result in the material being disposed of in accordance with hospital regulations.
- The results of the trial and any ancillary studies will be disseminated in a public event, to which all trial participants will be invited.

10 Trial Procedures, baseline data and assessments

Investigations	Baseline	Day of Surgery	Day 1 Post surgery	Day of Discharge	Follow up 1 (3-4 weeks post surgery)	Follow up 2 - End of Trial Visit 3 Months post op +/- 7 days	Survival and Recurrence follow up (no visit required)
Patient Demographics [a]	x						
Informed consent	x						
Baseline Data[b]	x						
Patient Interview at 3-6 weeks post op					X done 3-6 weeks post op		
Pain assessment • Numeric Rating Scale (NRS) Patient rates the pain from 0 (no pain) to 10 (worst pain)	x		x		x	x	
Questionnaires: • EORTC QLQ C30 • EORTC QLQ OV28 • HADs	x		x		x	x	
Surgical data[c]:		x					
Inpatient Stay[d]:				x			
Reported Post operative Surgical Complications Classified by the Clavien-Dindo Classification				x	x	x	
Record any Surgical Readmission • Cause of readmission • Number of days readmitted					x	x	
Patient Status[e]: • Alive without recurrence • Alive Following recurrence (date) • Dead (date and cause of death)				x	x	x	x
Time to adjuvant chemotherapy (days) Date of first cycle after Robotic IDS (aim ≤14 days)					x	x	

e) Patient Demographic - The following demographic data will be collected:
- Date of birth
- Ethnicity

f) Baseline Data – The following baseline data will be collected:
- ECOG performance status (Eastern Cooperative Oncology Group)
- Weight
- Height
- BMI
- Smoking status
- Co-morbidities previous and current medical conditions
- Concomitant medications
- Parity
- Previous abdominal surgery including caesarean sections
- BRACA Status when available
- Chemotherapy Regimen
- RECIST Response from pre IDS CT
- Number of cycles of chemotherapy prior to Surgery (minimum 3)
- Size of pelvic mass on CT scan in cm

g) Surgical Data:
- Date of Surgery
- Peritoneal Cancer Index Score (PCI) at Laparoscopy.
- Suitable for robotic IDS Yes/No, If not reason
- Mode of Surgery (Open / Robotic)
- Reason for conversion if applicable
- Operation Title
- ASA Grade
- Time Skin incision to Time Skin closure
- Length and position of longest Incision
- Mode of specimen retrieval (Mini Laparotomy / Through vagina)
- Surgical $C0_2$ pneumoperitoneum operating pressure mmHg
- Peritoneal Cancer Index Score (PCI) score after debulking surgery complete
- Estimated Blood Loss (EBL)
- Number of units of blood transfused
- Maximal diameter of macroscopic residual disease in cm and categorised as
  - R=0
  - R<0.2
  - R<0.5
  - R<1
  - R>1
- Site of Largest residual disease using same categories as for PCI (see table below)
- Intraoperative complications
- Histopathological diagnosis
- Grade
- FIGO Stage

} Available by Follow up 1

h) Inpatient Stay data to be completed prior to discharge:

- Total Number of units of blood transfused post op
- Number of Days ITU Care required
- Date of admission and Date of Discharge
- Length of stay (Days admission following surgery – Day of surgery = Day 0)
- Post-operative complications classified by the Clavien-Dindo Classification

f) Follow up

- Post Operative CT findings
- Alive without recurrence
- Alive with recurrence
- Date of recurrence if applicable
- Date of Death
- Cause of Death

10.1 Follow up

Follow up will follow that described in the Gynaecology Tumour Site Specific Group Constitution for advanced ovarian cancer with any additional visits depending on clinical need. The final trial follow-up visit will occur at 3 months coinciding with the normal clinic appointment. Following this time only survival and recurrence data will be collected as per established departmental internal audit.

Patients who cannot be contacted and whose GP's or local hospital cannot verify their status will be considered 'lost to follow-up'. If visits or data collection time-points are missed, with consent, patients will be phoned and questionnaires completed over the telephone by an appropriately trained individual knowledgeable about the research and the nature and objectives of the trial.

10.2 Withdrawal criteria

Participants are free to withdraw from the study at any time without giving any reason for doing so. The coordinating team should be informed so a record of all withdrawals can be maintained.

Participants who choose to withdraw will be asked for their reasons which will be recorded if they choose to divulge them. These participants will be followed up with regards to survival and overall survival as per established departmental internal audit.

If a patient withdraws from the study following surgery – They will continue to be followed up with regards to survival and recurrence but not with the questionnaire part of the study as per established departmental internal audit.

10.3 End of trial

Recruitment will be for 1 year. The trial will close once final patient data collection has occurred and data queries have been resolved. This will be around 1 year and 3 months from opening (i.e. to gather 90day mortality and post operative assessments following surgery). Patients will continue to be followed up as per established departmental internal audit.

11 Adverse events

An adverse event (AE) is an unfavourable symptom or disease temporarily associated with the trial treatment, whether or not it is related to the trial treatment.

A Serious adverse event (SAE) as an adverse event that:

- Results in death
- Is life-threatening
- Requires in-patient hospitalisation or prolongs existing hospitalisation
- Results in persistent or significant disability/incapacity
- Is otherwise considered to be medically significant by the investigator
- All Adverse events and Serious adverse events must be documented on the patient case report form (CRF).

List of Serious Adverse Events

- Severe Anaesthetic complications / anaphylactic reactions resulting in prolongation of hospitalisation
- Intraoperative or post operative bleeding requiring blood transfusion
- Injury to bladder / bowel / blood vessels / ureters / other visceral organ
- Thromboembolism including pulmonary embolism and deep vein thrombosis.
- Need to return to theatre
- Post operative infection resulting in the prolongation of hospitalisation
- Respiratory arrest
- Myocardial infarction
- Cardiac arrhythmia
- Cardiac arrest
- Wound dehiscence / port site herniation / bowel strangulation requiring return to theatre

11.1 Adverse reactions associated with Indocyanine Green (ICG) dye:

Severe allergic reaction: Very rare (affects fewer than one in every 10,000 patients) symptoms include (Diagnostic Green, Verdye 5mg/ml patient information leaflet):

- tightness in the throat
- itchy skin
- blotchy skin
- nettle-rash
- coronary artery spasm
- facial swelling (facial oedema)
- breathing difficulties - tightness and/or pain in the chest
- faster heart beat

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- a fall in blood pressure and shortness of breath
- heart failure (cardiac arrest)
- restlessness - feeling sick (nausea)
- feeling of warmth - flushes.

11.2 Reporting procedures

With regards to Suspected unexpected Serious Adverse Reactions (SUSAR) a sponsor or investigator should take appropriate urgent safety measures in order to protect research participants against any immediate hazard to their health or safety, without prior authorisation from a regulatory body.

The main Research Ethics Committee (REC) must be notified immediately (maximum within 3 days) in the form of a substantial amendment, that such measures have been taken and the reasons why. Copies of the information should be provided to the REC that approved the study using the REC safety reporting cover sheet.

Only reports of Serious Adverse Events (SAEs) that are: **related** to the study (Robotic surgery only) and **unexpected** (ie not listed in the protocol as an expected occurrence should be emailed to the REC using the **Non-CTIMP safety report to REC form.** These should be sent within 15 days of the chief investigator becoming aware of the event. (Health Research Authority 2019)

An annual progress report, signed by the chief investigator will be submitted to the REC which gave the favourable opinion 12 months after the date on which the favourable opinion was given. An electronic copy will be emailed to the REC within 30 days of the end of the reporting period.

12 Statistics and data analysis

12.1 Sample size calculation

Aim: The over-riding aim of the study is to demonstrate the feasibility and acceptability of robotic assisted interval debulking surgery (IDS) in the treatment of ovarian cancer. The sample size has been set pragmatically to give precision in the estimate of pre-defined feasibility criteria parameters such as consent rate, robotic operation rate and success rate (target debulking of R=0 achieved). The study will attempt to recruit 20 women, identified as suitable by MDT over a one year period, to be operated on robotically. Up to 20 women will ensure rates described above can be estimated within a standard error of less than 10%.

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12.2 Planned recruitment rate

This is a feasibility study with a view to doing a national randomised control trial following it if it is feasible. This trial will demonstrate the ability to recruit women to the study. The planned recruitment rate is 2 patients per month.

12.3 Statistical analysis plan

As a feasibility study, emphasis will be on descriptive statistics, including confidence intervals to give a measure of precision. No formal statistical comparisons will be undertaken. As is good practice, a formal statistical analysis plan will be prepared in advance of the data being seen at the end of the trial.

13 Data handling

13.1 Data collection tools and source document identification

Data will be collected on to Case Report Forms (CRF) and trial questionnaires at each of the defined time points and saved in the departments password protected Gynaecological Oncology database.

Survival and Progression data will be collected at each clinic as per current internal audit

To maximise completeness of data participants will be consented to be contacted by telephone so that any missing information can be acquired eg missing questionnaires.

Records of all participating patients (with sufficient information to link records e.g., CRFs, hospital records and samples), all original signed informed consent forms and copies of the CRF pages will be kept.

13.2 Access to data

Direct access will be granted to authorised representatives from the Sponsor, host institution and the regulatory authorities to permit trial-related monitoring, audits and inspections- in line with participant consent.

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13.3 Archiving

- Archiving will be authorised by the Sponsor following submission of the end of trial report
- The sponsor will be responsible for archiving patient questionnaires and CRFs. The site is responsible for the archiving of patient records if necessary.
- All essential documents will be archived for a minimum of 5 years after completion of the trial
- Destruction of essential documents will require authorisation from the Sponsor

13.4 Monitoring, audit & inspection

The study will be overseen by Royal Surrey NHS Foundation Trust. Research governance monitoring and auditing will take place and research conducted in line with Good Clinical Practice guidelines and NHS Research Governance Framework. Regular monitoring of recruitment, informed consent, data quality, and complaints will be carried out by Royal Surrey NHS Foundation Trust, the sponsor. A quarterly report will be provided to the sponsor by the research team.

14 Ethical and regulatory considerations

14.1 Research Ethics Committee (REC) review & reports

- Before the start of the trial, approval will be sought from a REC for the trial protocol, informed consent forms and other relevant documents e.g. Advertisements and GP information letters
- Substantial amendments that require review by REC will not be implemented until the REC grants a favourable opinion for the trial (note that amendments may also need to be reviewed and accepted by the MHRA and/or NHS R&D departments before they can be implemented in practice at sites)
- All correspondence with the REC will be retained in the Trial Master File/Investigator Site File
- An annual progress report (APR) will be submitted to the REC within 30 days of the anniversary date on which the favourable opinion was given, and annually until the trial is declared ended
- It is the Chief Investigator's responsibility to produce the annual reports as required.
- The Chief Investigator will notify the REC of the end of the trial
- If the trial is ended prematurely, the Chief Investigator will notify the REC, including the reasons for the premature termination
- Within one year after the end of the trial, the Chief Investigator will submit a final report with the results, including any publications/abstracts, to the REC

14.2 Peer review

Three individual experts in the field have reviewed the trial who are external to Royal Surrey NHS Foundation Trust.

14.3 Public and Patient Involvement

The Study Protocol and patient information leaflets have been circulated amongst a number of women with gynaecological cancers though GRACE Charity for their feedback prior to submission. The results of this study will be published in peer reviewed journals and presented at conferences. A public event where all participants will be invited will be held to disseminate the findings. Participant confidentiality will be protected. Information will also be disseminated through GRACE Charity who is supporting this research and the media.

Additionally, Qualitative interviews with women will be conducted to provide an insight into Women's experiences of taking part.

14.4 Protocol compliance

- Prospective, planned deviations or waivers to the protocol are not allowed under the UK regulations on Clinical Trials and must not be used e.g. It is not acceptable to enrol a participant if they do not meet the eligibility criteria or restrictions specified in the trial protocol
- Accidental protocol deviations can happen at any time. They must be adequately documented on the relevant forms and reported to the Chief Investigator and Sponsor immediately.
- Deviations from the protocol which are found to frequently recur are not acceptable, will require immediate action and could potentially be classified as a serious breach.

14.5 Data protection and patient confidentiality

All investigators and trial site staff must comply with the requirements of the Data Protection Act 1998 with regards to the collection, storage, processing and disclosure of personal information and will uphold the Act's core principles.

- Personal information will be collected, kept secure, and maintained.

- In general, this will involve:
    - The creation of coded, depersonalised data where the participant's identifying information is replaced by an unrelated sequence of characters
    - Secure maintenance of the data and the linking code in separate locations using encrypted digital files within password protected folders and storage media
    - Limiting access to the minimum number of individuals necessary for quality control, audit, and analysis

- All essential documents will be archived for a minimum of 5 years after completion of the trial
- The Chief investigator will be the data custodian

14.6 Financial and other competing interests

None

14.7 Indemnity

Indemnity for all patients recruited to the study will be provided by the sponsor. All recruited patients are NHS patient of RSCH Foundation Trust.

14.8 Amendments

If the sponsor wishes to make a substantial amendment to the REC application or the supporting documents, the sponsor must submit a valid notice of amendment to the REC for consideration. The REC will provide a response regarding the amendment within 35 days of receipt of the notice. It is the sponsor's responsibility to decide whether an amendment is substantial or non-substantial for the purposes of submission to REC.

14.9 Dissemination policy

- The data arising and results of the trial will be the intellectual property of The Department of Gynaecological Oncology at Royal Surrey NHS Foundation Trust.
- On completion of the trial, the data will be analysed and tabulated and a final trial report prepared.
- GRACE Charity be acknowledged within any publications.
- The results of this study will be published in peer reviewed journals and presented at conferences. A public event where all participants will be invited will be held to disseminate the findings. Participant confidentiality will be protected. Information will also be disseminated through GRACE Charity who is supporting this research and the media.

14.10 Authorship eligibility guidelines and any intended use of professional writers

Current authors include people directly involved in the development of the trial protocol.

Miss Christina Uwins

Mr Simon Butler-Manuel

Dr Agnieszka Michael

Professor Simon Skene

Mr Anil Tailor

Dr Thumuluru Kavitha Madhuri

Mr Jayanta Chatterjee

Miss Patricia Ellis

As per the ICMJE recommendations authors will fulfil the following criteria (Sahni & Aggarwal 2018.):

- Substantial contributions to the conception or design of the work; or the acquisition, analysis, or interpretation of data for the work; AND
- Drafting the work or revising it critically for important intellectual content; AND
- Final approval of the version to be published; AND
- Agreement to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

Further authors may be added throughout the trial but they will only be added if a personal contribution to the running of the trial or analysis of the data has been made.

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MIRRORS

(Minimally **I**nvasive **R**obotic Surgery, **R**ole in Optimal Debulking **O**varian Cancer, **R**ecovery & **S**urvival)

A prospective Feasibility Study (non-randomised) of robotic interval debulking surgery in Ovarian Cancer

Sponsor	Royal Surrey NHS Foundation Trust
Funder	GRACE Charity
Protocol Version and Date	V1.3 16/01/2020
Chief Investigator	Mr Simon Butler-Manuel
Trial Management Group	
Statistical Oversight	Professor Simon Skene, University of Surrey

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Signature Page

The undersigned confirm that the following protocol has been agreed and accepted and that the Principal Investigator agrees to conduct the study in compliance with the approved protocol and will adhere to the principles outlined in the Declaration of Helsinki, the International Conference on Harmonisation Topic E6: Guideline for Good Clinical Practice (ICH GCP), any relevant SOPs, and other regulatory requirements.

I agree to ensure that the confidential information contained in this document will not be used for any other purpose other than the evaluation or conduct of the investigation without the prior written consent of the Sponsor.

I also confirm that I will make the findings of the study publicly available through publication or other dissemination tools without any unnecessary delay and that an honest, accurate and transparent account of the study will be given; and that any discrepancies from the study as planned in this protocol will be explained.

For and on behalf of the Study Sponsor:

Signature: ..... Date: ...../...../.....

Name (please print):

Position: .....

Chief Investigator:

Date: 16/01/2020

Signature:
Name: (please print):
Mr. Simon A. Butler-Manuel MD FRCS FRCOG
Clinical Director and Consultant in Gynaecological Oncology
TPD for Subspecialty Training in Gynaecological Oncology, Guildford
Honorary Senior Lecturer, University of Surrey
Director, Intuitive Epicenter for Gynaecological Robotic Training, Guildford

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1. Glossary

AE	Adverse Event
CRF	Case Report Form
GCP	Good Clinical Practice
ICF	Informed Consent Form
ICH	International Conference on Harmonisation
ISF	Investigator Site File
PI	Principal Investigator
SAE	Serious Adverse Event
SOP	Standard Operating Procedure
SUSAR	Suspected Unexpected Serious Adverse Reaction
TMF	Trial Master File

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Table of Contents

2 Contacts

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Sponsor	Royal Surrey County Hospital NHS Foundation Trust Egerton Road, Guildford GU2 7XX
Funder(s)	**GRACE Charity** Registered Charity No. 1109997 Call: 01306 730872 Email: info@grace-charity.org.uk **GRACE** Department of Gynaecological Oncology Royal Surrey NHS Foundation Trust Egerton Road Guildford Surrey GU2 7XX
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Key Protocol Contributors	**Dr Agnieszka Michael PhD MRCP** Clinical Reader and Consultant Medical Oncologist School of Biosciences and Medicine University of Surrey
Statistician	**Professor Simon Skene** Professor of Medical Statistics | Director of Surrey Clinical Trials Unit and Clinical Research Facility School of Biosciences and Medicine University of Surrey

3 Protocol Summary

Title: **Minimally Invasive Robotic Surgery, Role in Optimal Debulking Ovarian Cancer, Recovery & Survival** *A prospective Feasibility Study (non-randomised) of robotic interval debulking surgery in Ovarian Cancer*	
Short title	**MIRRORS**
Sponsor	Royal Surrey NHS Foundation Trust, Egerton Road, Guildford GU2 7XX
Funder reference	
Clinical trials / ISRCTN	
Design	Prospective feasibility study of Robotic assisted interval debulking surgery (IDS) in ovarian cancer
Primary objectives	Feasibility of robotic surgery as defined by: 1. Ability to recruit patients 2. Acceptability to patients 3. Quality of life 4. Maximal macroscopic debulking rate (R=0 rate) 5. Rate of conversion to open surgery
Secondary objectives Ancillary Study:	1. Overall Survival 2. Progression free survival 3. Cost comparison of Robotic minimally invasive interval debulking surgery vs Open. 4. To evaluate staging and assessment of operability via Robotic surgery using Diagnostic laparoscopy Peritoneal angiography / perfusion assessment using Indocyanine green (ICG) in patients with advanced ovarian cancer
Target accrual	20 Robotic IDS completed
Inclusion criteria	Adult women ≥18 years with Stage III and IV Ovarian cancer undergoing Neo-adjuvant Chemotherapy. Considered suitable for IDS ≤8cm pelvic mass Open surgery not required for other surgical speciality intervention
Exclusion criteria	• Extensive disease requiring liver and upper Gastro-intestinal surgical support will exclude patients if an open surgical approach is considered necessary. • Lacking capacity to the extent they are unable to understand or complete trial documentation / questionnaires.
Number of sites	1
Duration of recruitment	1 year
Duration of patient follow-up	3 months post-surgery
Definition of end of trial	Once final patient data collection has occurred and data queries have been resolved. Length of trial 18months

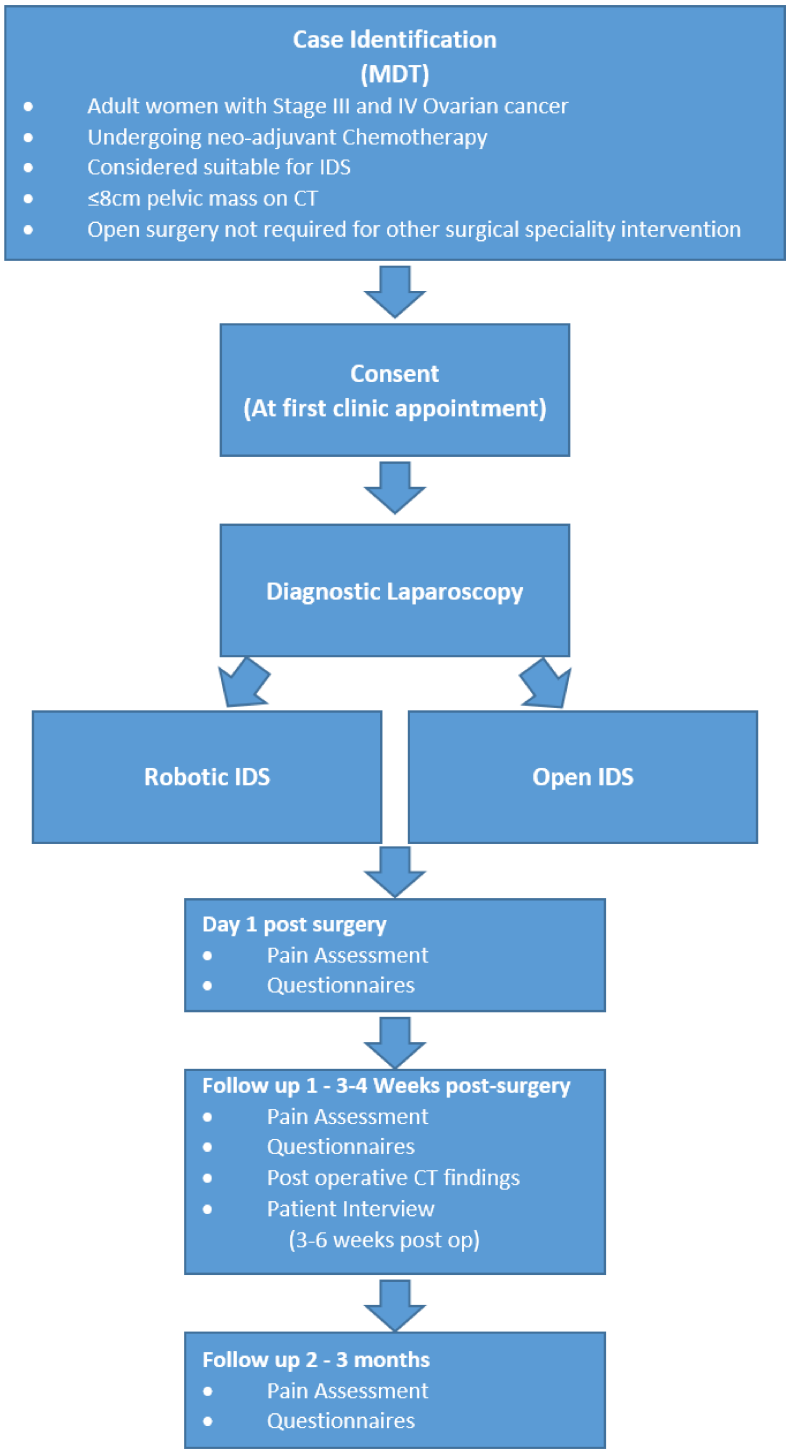

Figure 1 - MIRRORS Flow Diagram

4 Study Schedule

Investigations	**Baseline**	**Day of Surgery**	**Day 1 Post surgery**	**Day of Discharge**	**Follow up 1 (3-4 weeks post surgery)**	**Follow up 2 - End of Trial Visit 3 Months post op +/- 7 days**	**Survival and Recurrence follow up (no visit required)**
Patient Demographics [a]	**x**						
Informed consent	**x**						
Baseline Data[b]	**x**						
Patient Interview at 3-6 weeks post op					**X done 3-6 weeks post op**		
Pain assessment • Numeric Rating Scale (NRS) Patient rates the pain from 0 (no pain) to 10 (worst pain)	**x**		**x**		**x**	**x**	
Questionnaires: • EORTC QLQ C30 • EORTC QLQ OV28 • HADs	**x**		**x**		**x**	**x**	
Surgical data[c]:		**x**					
Inpatient Stay[d]:				**x**			
Reported Post operative Surgical Complications Classified by the Clavien-Dindo Classification				**x**	**x**	**x**	
Record any Surgical Readmission • Cause of readmission • Number of days readmitted					**x**	**x**	
Patient Status[e]: • Alive without recurrence • Alive Following recurrence (date) • Dead (date and cause of death)				**x**	**x**	**x**	**x**
Time to adjuvant chemotherapy (days) Date of first cycle after Robotic IDS (aim ≤14 days)					**x**	**x**	

a) Patient Demographic - The following demographic data will be collected:
   - Date of birth
   - Ethnicity

b) Baseline Data – The following baseline data will be collected:
   - ECOG performance status (Eastern Cooperative Oncology Group)
   - Weight
   - Height
   - BMI
   - Smoking status
   - Co-morbidities previous and current medical conditions
   - Concomitant medications
   - Parity
   - Previous abdominal surgery including caesarean sections
   - BRACA Status when available
   - Chemotherapy Regimen
   - RECIST Response from pre IDS CT
   - Number of cycles of chemotherapy prior to Surgery (minimum 3)
   - Size of pelvic mass on CT scan in cm

c) Surgical Data:
   - Date of Surgery
   - Peritoneal Cancer Index Score (PCI) at Laparoscopy.
   - Suitable for robotic IDS Yes/No, If not reason
   - Mode of Surgery (Open / Robotic)
   - Reason for conversion if applicable
   - Operation Title
   - ASA Grade
   - Time Skin incision to Time Skin closure
   - Length and position of longest Incision
   - Mode of specimen retrieval (Mini Laparotomy / Through vagina)
   - Surgical $C0_2$ pneumoperitoneum operating pressure mmHg
   - Peritoneal Cancer Index Score (PCI) score after debulking surgery complete
   - Estimated Blood Loss (EBL)
   - Number of units of blood transfused
   - Maximal diameter of macroscopic residual disease in cm and categorised as
     - R=0
     - R<0.2
     - R<0.5
     - R<1
     - R>1
   - Site of Largest residual disease using same categories as for PCI (see table below)
   - Intraoperative complications
   - Histopathological diagnosis
   - Grade
   - FIGO Stage

} Available by Follow up 1

d) Inpatient Stay data to be completed prior to discharge:
- Total Number of units of blood transfused post op
- Number of Days ITU Care required
- Date of admission and Date of Discharge
- Length of stay (Days admission following surgery – Day of surgery = Day 0)
- Post-operative complications classified by the Clavien-Dindo Classification

e) Follow up

- Post Operative CT findings
- Alive without recurrence
- Alive with recurrence
- Date of recurrence if applicable
- Date of Death
- Cause of Death

5 Background

Ovarian cancer (which includes cancer of the fallopian tube & peritoneum) is the 6th most common cancer in women in the UK with around 7,300 women diagnosed each year. 1-year survival in England ranges from 98.7% (stage1) to 51.4% (stage IV) (NCIN 2015). Sadly, more than 70% of patients with newly diagnosed ovarian cancer will present with advanced disease (FIGO stage-III or IV disease (BGCS 2017)). A woman's risk of developing ovarian cancer before the age of 75 is estimated at 1.12% in the UK (Ferlay 2019). The incidence of ovarian cancer increases with age with most women presenting between the ages of 65-69. Many of these women are also frail (Cancer Research UK).

Current standard treatment for advanced ovarian cancer involves surgery and chemotherapy. The aim of surgery is to assess how far the cancer has spread (staging) and to remove as much visible disease as possible (ideally all of it) as this is associated with the longest survival. Unfortunately, as most women present with advanced disease this is often not always possible. Women with advanced stage cancer are usually treated with 3 cycles of chemotherapy (known as “neo-adjuvant chemotherapy”) to reduce the amount of tumour, before having any surgery. Surgery following chemotherapy is called “Interval debulking surgery”. The aim of surgery is to remove as much of the tumour that remains after chemotherapy as possible. Treatment is then completed with 3 further cycles of chemotherapy following surgery.

Ovarian cancer surgery is usually performed through a vertical incision on the abdomen from just above the pubic bone to above the belly button and sometimes up towards the bottom of the breastbone, depending on how far the cancer has spread. A larger incision is required if there is tumour in the upper parts of the abdomen.

Minimally invasive surgery, uses multiple small cuts on the abdomen to insert ports through which instruments and a camera are passed. Surgery is performed under direct vision, with carbon dioxide gas inflating the abdomen to lift the abdominal wall upwards to provide the space underneath in which the surgeons can operate. Robotic surgery is a further development in minimally invasive surgery which adds mechanical assistance and support of the instruments. Performing surgery through smaller cuts is generally less painful and has been found to enhance recovery with reduced length of stay in hospital, reduced blood loss, so avoiding blood transfusion, infections and blood clots in the legs or lungs (Walker et al 2009, Kornblith et al 2009, Feuer et al, Kumar et al, 2013, Mahdi et al, 2016). Larger more complex operations generally carry greater risks of surgical complications, and these complications may delay or prevent women from re-starting their chemotherapy. It is impossible to remove large cysts or masses through such keyhole incisions and so this form of surgery is not suitable for everyone with ovarian cancer.

The role of robotic surgery in ovarian cancer treatment is uncertain but robotics has the potential to lessen the impact and reduce the adverse effects of surgery on some women with ovarian cancer. It may be particularly helpful for women at high risk of anaesthetic complications including those who are overweight, the elderly and women with other pre-existing medical conditions.

A systematic review and meta-analysis by Cardenas-Goicoechea *et al* 2019 looking at the feasibility of achieving complete cytoreductive surgery after neoadjuvant chemotherapy for stage IIIC -IV ovarian cancer patients identified 6 studies (3 prospective and 3 retrospective). Of the prospective trials two compared open surgery vs laparoscopy (Tozzi et al 2016, Favero et al 2015) and one looked at the outcomes following laparoscopic or Robotic interval debulking surgery (Gueli Alletti et al 2016). The retrospective trials included one looking at Robotic surgery (Ackroyd et al, 2017) one comparing open vs lap/robotic (Melamed et al 2017) and one looking at outcomes following laparoscopic interval debulking surgery (Corrado et al, 2015). In total, these studies included 3231 patients, 567 in the minimally invasive group and 2664 in the laparotomy group. Most of the patients included in the meta-analysis related to the study by Melamed et al 2017 (450/567 of the Minimally invasive group and 2621/2664 in the open group). Cardenas-Goicoechea et al (2019) created two pooled groups, one of minimally invasive surgery and one for laparotomies. They found that complete cytoreductive surgery after neoadjuvant chemotherapy is feasible and safe in selected patients. No statistical difference was found between the groups for their complete cytoreductive surgery rate.

Melamed et al 2017 used a national cancer database to identify a cohort of patients with stage IIIC to IV epithelial ovarian cancer who underwent interval debulking surgery following neoadjuvant chemotherapy between 2010-2012 this study included 2621 patients in the open group and 450 in the combined laparoscopy/robotic group. In comparison the other studies included in the meta-analysis by Cardenas-Goicoechea et al (2019) had 10-30 patients in the minimally invasive groups. Follow-up for all the studies ranged from 15 to 36 months. Common exclusion criteria in these studies were residual tumour in porta hepatis and bowel serosa, patients >70 years, elevated tumour markers, BMI >40 and ASA score III-IV. Melamed *et al* (2017) concluded that patients selected for laparoscopic debulking may have a lower burden of disease than those chosen for laparotomy. Postoperative hospitalisation was slightly shorter in the laparoscopy group (4 vs 5 days).

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Readmission, death within 90 days and suboptimal debulking did not differ between the two groups.

Magrina *et al* in 2011 published a retrospective case-control analysis of 25 patients with epithelial ovarian cancer undergoing robotic surgical treatment between March 2004 and December 2008. A comparison was made with similar patients treated by laparoscopy and laparotomy and matched by age, BMI and type of procedures between January 1999 and December 2006. Mean operating times were longer for robotic surgery compared to laparoscopy or laparotomy, and mean blood loss reduced at 164mls vs 266.7 vs 1307ml respectively. Magrina *et al* concluded that laparoscopy and robotics were preferable to laparotomy for patients with ovarian cancer requiring primary tumour excision alone or with one additional major procedure classed as intestinal resection, full thickness diaphragm resection, liver resection or splenectomy. Laparotomy was found to be preferable for patients requiring 2 or more additional major procedures.

A further study by Magrina et al in 2013 compared secondary cytoreduction by laparoscopy (9) laparotomy (33) or robotics (10) in patients with recurrent ovarian cancer. Laparoscopy and robotics were found to have reduced blood loss and hospital stay with no difference observed for operating time, complications, complete debulking and survival. They concluded that laparotomy was preferable for patients with widespread peritoneal implants, multiple sites of recurrence and or extensive adhesions but in a selected group of patients laparoscopic or robotic secondary cytoreduction was feasible without compromising survival.

Fagotti et al (2019) recently published the results of The International Mission Study which was a retrospective multicentre study to investigate minimally invasive interval debulking surgery (either laparoscopic or Robotic) in patients with stage III-IV advanced epithelial ovarian cancer. This study included a total of 127 patients who underwent minimally invasive interval debulking surgery. Following minimally invasive interval debulking surgery, 96% of their patients had no visible residual tumour (R=0), the rest were resected to tumour deposits < 1cm (R<1). Median reported blood loss was 100ml (range 70-1320) Median time to discharge was 2 days (range 1-33 days). Conversion rate to laparotomy was 3.9%. There were no defined exclusion criteria as these varied between centres depending on the patient. Standard cytoreduction surgery was defined as hysterectomy, salpingo-oophorectomy omentectomy and peritoneal biopsies. All patients not having standard intraperitoneal cytoreduction and with a follow up time less than 6 months were excluded from the study. This retrospective multicentre trial followed the publication of the MISSION Trial in 2016. The MISSION trial looked at the feasibility and early complication rate of minimally invasive interval debulking surgery (both laparoscopic and Robotic), in stage III-IV epithelial ovarian cancer patients after neoadjuvant chemotherapy. The trial only included patients with epithelial ovarian cancer with complete clinical response (assessed by the RECIST criteria (Eisenhauer et al. 2009)) and ECOG performance status <2. Women with BMI >40kg/m^2 and ASA score III-IV were excluded. Of 184 patients considered eligible for IDS, 52 met the inclusion criteria and were enrolled in the study. Of these 52 patients 22 had laparotomies following surgical evaluation. Of the 30 patients who went on to have minimally invasive interval debulking surgery Median blood loss was 100ml (range 50-200ml) and Median post-operative stay 2 days (range 2-3 days).

Abitbol *et al* (2019) recently published the results of their study looking at the impact of introducing robotic surgery in their centre for interval cytoreduction of selected patients with stage III-IV ovarian

cancer. This study compared patients having surgery in the period from November 2008-2014 (post the introduction of Robotic surgery) to patients having surgery between January 2006 and November 2008 (pre Robotic area n=22). A total of 91 patients were selected to undergo interval cytoreduction either via robotic surgery (n=57) or laparotomy (n=34) after neoadjuvant chemotherapy. The median survival was 42.8+/- 3.1 months in the period where both robotic surgery and laparotomy were offered compared with 37.9+/-9.8 months in the time period preceding, when only laparotomy was performed (p=0.6). All patients undergoing robotic interval debulking surgery achieved cytoreduction to <1cm residual disease and 82% had no residual disease. The median blood loss was 100ml (range 10-1250ml), median hospital stay was 1 day (range 1-17 days) and median time to adjuvant chemotherapy was 13 days (range 6-75 days) in the robotic cohort.

Our own department in 2009 (Madhuri et al) published a case report of laparoscopic interval debulking surgery for stage 4 primary fallopian tube carcinoma in a woman who had achieved a good response to carboplatin and paclitaxel chemotherapy. Laparoscopic total hysterectomy, bilateral salpingo-oophorectomy and stripping of the surrounding pelvic peritoneum and supracolic omentectomy was performed. All visible disease was excised, blood loss was 200ml and she was discharged the following day with chemotherapy restarting 2 days post-operatively. This patient survived 44 months from surgery with first recurrence at 16 months.

Since 2009, we have now performed over 1200 gynaecological oncology robotic operations here in the Academic Department of Gynaecological Oncology and have by far the greatest robotics experience in the UK. The majority of these operations have been performed for women with uterine (womb) cancers. Our introduction of robotics has revolutionised our practice, particularly with regards to womb cancer. This has resulted in patient benefits and enhanced recovery in this group. Robotic surgery in our department has been found to be associated with a lower number of complications than standard laparoscopic keyhole surgery or open surgery. Indeed, many women previously thought not fit for surgery at all, are now recommended robotic surgery.

To date, we have only performed a relatively small number of operations for ovarian cancer using robotic surgery. Looking at our own work, between January 2010 and December 2018 we performed 950 operations for ovarian cancer of which 31 were performed using the Da Vinci Robot. Of these, just 3 cases were Interval debulking procedures.

Other indications included:

- 15 for completion/staging
- 7 for recurrent disease
- 1 for fertility sparing
- 2 initially thought to be CAH / Corpus cancer
- 3 for suspicious cysts

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When compared to patients undergoing similar open procedures (hysterectomy removal of both tubes and ovaries and removal of the omentum +/- appendix) (464 in this time period), patients undergoing Da Vinci Robot Assisted surgery for ovarian cancer lost significantly less blood (median blood loss 50ml Robotic and 800ml open), spent less time in hospital (Median length of stay Robotic 1 day, open 6 days) and had a lower 30 day mortality rate (0 for Robotic, 3 for open surgery 0.65%).

Although the numbers are small with regards to Robotic surgery and ovarian cancer the values presented for blood loss and length of stay correlate well with those we found for Robotic vs Open surgery for Womb cancer in the same time period: Robotic: 631 operations Median blood loss 50 ml. Median Length of stay 1 day, 30-day Mortality 1/631 (0.16%); Open: 154 operations, Median blood loss 500 ml, Median length of stay 6 days, 30-day Mortality 4/154 (2.6%).

6 Rationale for study

For all except 1a disease, standard treatment involves surgery to both stage and remove the volume of disease (debulking) and chemotherapy. Complete resection of all macroscopic disease (at primary or interval surgery) is the strongest independent variable in predicting overall survival (Vergote et al. 2010, Kehoe et al. 2015). Sensitivity to platinum-based chemotherapy is the other principal variable which determines survival.

Minimally invasive surgery offers the potential benefits of enhanced recovery with reduced length of stay, reduced blood loss avoiding blood transfusion, reduced pain, infections and thromboembolic complications. Surgical complications may prevent or delay patients from commencing chemotherapy. Robotic surgery provides anaesthetic benefits of low pressure pneumoperitoneum and is more ergonomic for the surgeons allowing them to perform longer and more complex surgery via a minimal access route. Robotic minimally invasive surgery is open to more patients such as those at high risk of anaesthetic complications including those suffering from obesity, the elderly & those with medical comorbidities with fewer resulting complications and readmissions.

The reduced length of stay associated with minimally invasive surgery positively impacts on the availability of bed resources in the NHS. Additionally, reduced readmissions, reduced HDU/ITU rates also reduces costs. Minimally invasive surgery including both Laparoscopic surgery and Robotic surgery already has an established role in the treatment of Endometrial cancer (Jorgensen et al. 2018, Walker et al. 2009). These patients benefit from the improved recovery associated with the minimally invasive surgical route. Ovarian cancer in contrast is still predominantly treated with extensive open surgery with associated long recovery times affecting quality of life in patients, many of whom are elderly and or frail.

As described before there is an increasing body of retrospective evidence with regards to the feasibility and safety of minimally invasive interval debulking surgery for ovarian cancer, of which many have grouped laparoscopy and Robotic surgery together. Minimally invasive interval debulking

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surgery still remains controversial in Britain. To investigate the feasibility of Robotic interval debulking surgery, with the generous support of GRACE Charity, we are proposing establishing a new UK based prospective feasibility study **M**inimally **I**nvasive **R**obotic Surgery, **R**ole in Optimal Debulking **O**varian Cancer, **R**ecovery & **S**urvival (**MIRRORS**). The aim of this study is to establish the role of Robotic Minimally invasive interval debulking surgery for advanced ovarian cancer. We are interested in discovering whether the benefits seen with regards to recovery and quality of life in Robotic assisted surgery for womb cancer can be provided for women with advanced ovarian cancer with equivalent overall survival and progression free survival. This trial is the first step towards launching a British multicentre randomised control trial of Robotic interval debulking surgery for ovarian cancer in the future. Given Royal Surrey's investment and now 10 years of experience in Robotic surgery, we see this exciting new trial and possible future national randomised controlled trial as complementary to Royal Surrey's ambitious "True North" objectives of staying at the cutting edge of safety and quality improvement and the vision of becoming a Nationally celebrated, community focused health care (service).

In contrast to many of the previous studies, based on our 10 years of robotic experience, we have kept the inclusion criteria wide, not restricting by BMI or patient comorbidities. With this in mind the study will be offered to all adult women with ovarian cancer who have been identified through our multi-disciplinary team meeting as being suitable for interval debulking surgery after 3 cycles of chemotherapy. A Pelvic Mass >8cm and extensive disease which would require liver, upper Gastro-intestinal or other surgical support will exclude patients if an open surgical approach is deemed necessary.

Robotic surgery is unlikely to be suitable in all cases of ovarian cancer, particularly those with large pelvic masses or extensive disease around the upper part of the abdomen, however, it has the potential to provide significant recovery and quality of life benefits to a selected group of our patients.

7 Trial Objectives

To assess the feasibility of obtaining consent from women and acceptability of Robotic interval debulking surgery for advanced ovarian cancer. Women deemed suitable for interval debulking surgery will be identified through the Gynaecological Oncology MDT. The aim is to recruit women over a period of 1 year aiming for a total of 20 women who undergo Minimally Invasive Robotic Interval debulking surgery for advanced ovarian cancer. The main outcomes are feasibility of the recruitment process and acceptability of the questionnaires and numeric rating pain scale (NRS-11) as assessed by completion rate and patient interviews. Acceptability to surgeons will be assessed though a national questionnaire distributed via the British Gynaecological Cancer Society. Qualitative interviews with women will be conducted to provide an insight into Women's experiences of taking part. Thematic Analysis using NVIVO will be used to analyse the data.

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Quantitative data will be collected pre op, prior to discharge, at follow up at 3-4 weeks and at 3 months. The outcomes from this feasibility study will include the knowledge to set up national multi-centre randomised controlled trial to investigate whether robotic surgery does have a role in interval debulking advanced ovarian cancer and whether in a sub-selected group of women it is non inferior (with regards to overall survival and progression free survival) to traditional open interval debulking surgery.

Hypothesis: in selected cases of ovarian cancer, following neoadjuvant chemotherapy, minimally invasive robotic surgery provides maximal debulking surgery and improved patient outcomes.

Null Hypothesis: Robotic surgery is not suitable for the treatment of ovarian cancer following neoadjuvant chemotherapy. It is not possible to achieve maximal debulking surgery and patient outcomes are not improved.

This study's primary objectives are to investigate the role of Minimally Invasive Robotic Interval debulking surgery in selected patients for the management of their Ovarian cancer. Specifically:

7.1 Primary objectives

To demonstrate the feasibility of selecting candidate women and successfully completing robotic interval debulking surgery as defined by:

1. Ability to recruit patients
2. Acceptability of procedure to patients
3. Success of Surgery; measured by the Maximal macroscopic debulking rate (R=0 rate)

7.2 Primary outcomes

- Number of patients consented compared to number identified by MDT
- Quality of life as assessed by EORTC QLQ C30 and OV28 and HADs validated questionnaires
- R=0 Rate
- Rate of Conversion to Open surgery and documented reason
- % patients fully filling out trial questionnaires

Population: The study will be offered to all adult women with ovarian cancer who have been identified through our multi-disciplinary team meeting as being suitable for interval debulking surgery after 3 cycles of chemotherapy. A Pelvic Mass >8cm and extensive disease requiring liver and upper Gastro-intestinal surgical support or any other surgery requiring an open approach will exclude patients if an open surgical approach is considered necessary.

Intervention: Robotic assisted minimally invasive interval debulking surgery.

7.3 Secondary objectives

1. Overall Survival
2. Progression free survival
3. Cost comparison of Robotic minimally invasive interval debulking surgery vs Open
4. To evaluate staging and assessment of operability via Robotic surgery using Diagnostic laparoscopy

7.4 Secondary Outcomes

1. Overall Survival measured in Months from the date of surgery up to 3 months from the last patient and longer term follow-up for survival and disease progression.
2. Progression free survival in Months from the date of surgery
3. Cost of Robotic minimally invasive interval debulking to the hospital compared to a similar open procedure measured in GBP £
4. Percentage of Patient considered suitable for Robotic interval debulking surgery based on initial diagnostic laparoscopy who are successfully debulked to R=0

7.5 Success Criteria

- At least 20% of people eligible for the study will accept inclusion in the study.
- Complication rate is not higher than for open interval debulking surgery
- Conversion to open surgery rate not greater than 50% in patient group deemed suitable for Robotic IDS following initial diagnostic laparoscopy.

7.6 Exploratory objectives

Outcome measure	Measurement Variable	Analysis Metric	Method of aggregation	timepoint
Length and position of longest incision (midline / transverse)	Centimetres Position: • Midline • Transverse		Median and range (number and percentage done in Midline vs transverse)	Immediately following completion of surgery
Mode of specimen retrieval	Mini laparotomy Through Vagina		% patients requiring Mini laparotomy to remove specimen	Immediately following completion of surgery
Surgical C02 pneumoperitoneum operating pressure	mmHg		Median and Range	Immediately following completion of surgery
Estimated Blood Loss (EBL)	Millilitres (ml)		Median and range	At completion of surgery
Number of units of blood transfused post operatively	Number of units		Median and range	Documented on day of discharge
Number of days requiring ITU care	Number of days from date of surgery to date suitable for stepdown care		Median and Range	Documented on day of discharge
Length of stay	Number of days in hospital following operation		Median and range	Documented on day of discharge
Surgical Readmission rate and cause	Readmitted yes or no Reasons for readmission Number of days readmitted		Number and Percentage of patients requiring readmission	Up to including 30 days post surgery. Day of surgery = Day 0

Outcome measure	Measurement Variable	Analysis Metric	Method of aggregation	timepoint
Maximal diameter of macroscopic residual disease	Measured in Centimetres	• R=0 • R<0.2 • R<0.5 • R<1 • R>1	Percentage and median number of patients achieving R0 Median and range of maximal diameter of macroscopic residual disease.	Immediately following completion of surgery
Effectiveness of Debulking surgery - comparison of pre-operative and post-operative disease burden	**Peritoneal Cancer Index (PCI)** Score: Score: LS 0 = no tumour seen LS 1 Tumour ≤ 0.5cm LS 2 Tumour > 0.5cm ≤ 5.0cm LS 3 Tumour >5.0 cm or confluence 0. Central region 1. Right Upper 2. Epigastrium 3. Left Upper 4. Left Flank 5. Left Lower 6. Pelvis 7. Right Lower 8. Right Flank 9. Upper Jejunum 10. Lower Jejunum 11. Upper Ileum 12. Lower Ileum	Change from baseline to completion of tumour resection	% difference	At the start of surgery as part of initial assessment following entry into abdominal cavity and once surgery completed prior to removing camera and closing skin incisions.

Outcome measure	Measurement Variable	Analysis Metric	Method of aggregation	timepoint
Site of Largest residual disease	0. Central region 1. Right Upper 2. Epigastrium 3. Left Upper 4. Left Flank 5. Left Lower 6. Pelvis 7. Right Lower 8. Right Flank 9. Upper Jejunum 10. Lower Jejunum 11. Upper Ileum 12. Lower Ileum	`		Immediately following completion of surgery
Surgery to Chemotherapy interval in days aiming for ≤ 14 days post op (currently week 3 post op for laparotomies)	Day number post-surgery that chemotherapy recommenced. Day of surgery = Day 0	< 3 weeks	Median and Range	Within 8 weeks post surgery

Outcome measure	Measurement Variable	Analysis Metric	Method of aggregation	timepoint
Patient reported outcome will be assessed using:	ECOG performance status (Eastern Cooperative Oncology Group) HADs questionnaire European Organisation for Research and Treatment of Cancer Quality of Life questionnaires QLQ - OV28 QLQ - C30 Open ended white space questions to assess what is important to patients	Score at each time point	Standard deviation Number of patient assessed at each time point	At Preoperative appointment Day 1 post op 3-4 weeks post surgery 3 months post surgery

Outcome measure	Measurement Variable	Analysis Metric	Method of aggregation	Timepoint
Intra-operative & Post-operative complications	Clavien-Dindo Classification **Grades** **Definition** Grade I Any deviation from the normal postoperative course without the need for pharmacological treatment or surgical, endoscopic and radiological interventions Allowed therapeutic regimens are: drugs as antiemetics, antipyretics, analgetics, diuretics and electrolytes and physiotherapy. This grade also includes wound infections opened at the bedside. Grade II Requiring pharmacological treatment with drugs other than such allowed for grade I complications. Blood transfusionsand total parenteral nutritionare also included. Grade III Requiring surgical, endoscopic or radiological intervention - IIIa Intervention not under general anesthesia - IIIb Intervention under general anesthesia Grade IV Life-threatening complication (including CNS complications)* requiring IC/ICU-management - IVa single organ dysfunction (including dialysis) - IVb Multiorgandysfunction Grade V Death of a patient (Dindo et al 2004)			Time of surgery On discharge First post op review

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8 Trial design

Prospective feasibility study of adult women with stage III-IV ovarian cancer (including peritoneal and fallopian tube cancer) considered suitable for interval debulking surgery following discussion in MDT with pelvic mass ≤8cm and no anticipated requirement for open surgery e.g upper abdominal / colorectal surgery expected.

Study aims

- To gather preliminary information on the use of robotic surgery in the treatment of ovarian cancer following adjuvant chemotherapy (the intervention) and the feasibility of conducting a full-scale national randomised control trial

8.1 Eligibility criteria

Participants identified as suitable and willing to have robotic interval debulking surgery will be consented for both open surgery and robotic assisted laparosopic surgery. Initial diagnostic laparoscopic assessment will be carried out. If it is deemed feasible, surgery will proceed robotically alternatively, if it is determined that full debulking surgery to zero macroscopic residual disease is best carried out though open surgery and the patient has consented for this then this will be done

8.2 Inclusion

- Adult women, capable of giving informed consent, with Stage III and IV Ovarian cancer undergoing Neo-adjuvant Chemotherapy.
- Considered suitable for IDS
- ≤8cm pelvic mass
- Open surgery not required for other surgical speciality intervention to achieve removal of all visible disease
- Able to understand and complete trial documentation / questionnaires and comply with the protocol.

8.3 Exclusion

- Open surgery required for other surgical speciality interventions to achieve removal of all visible disease
- Unable to understand and complete trial documentation / questionnaires and comply with the protocol.

9 Trial procedures

9.1 Recruitment

Participants will be identified in MDT and the trial discussed in clinic.

A participant information sheet will be provided and the study explained in person. Participants agreeing to be included will sign a consent form. Following consent participants will be asked to complete baseline questionnaires.

All screened patients will have the following anonymised basic information collected:

- Date of Birth / Age
- Ethnicity
- Reason not eligible
- Reason for declining if eligible but declined

9.2 Patient identification

Participants will be identified in MDT where all patients with ovarian cancer are discussed prior to interval debulking surgery. Participants will be consented during their post MDT visit to clinic and will be followed up during their normal scheduled appointment times.

9.3 Screening

There will be no additional screening bloods or investigations beyond that already done as part of the surgical work up.

9.4 Consent

The Principal Investigator (PI) (Mr Butler-Manuel) retains overall responsibility for the conduct of research at the site, this includes the taking of informed consent of participants. Any person delegated responsibility to participate in the informed consent process will be authorised, trained

and competent to participate according to the ethically approved protocol, principles of Good Clinical Practice (GCP) and Declaration of Helsinki.

Informed consent will be obtained prior to any data being collected.

The right of a woman to refuse participation without giving reasons will be respected at all times. Participants are free to withdraw at any time from the trial without giving reasons and without prejudicing their further treatment. All participants will be provided with an information leaflet complete with a contact point where she may obtain further information about the trial. Data and samples collected up to the point of withdrawal will only be used after withdrawal if the participant has consented for this. Intention to utilise such data is outlined in the consent literature. Where a participant is required to re-consent or new information is required to be provided to a participant it is the responsibility of the PI to ensure this is done in a timely manner. The PI takes responsibility for ensuring that all vulnerable participants are protected and participate voluntarily in an environment free from coercion or undue influence

Consent process:

- Discussion will occur following initial pre surgical clinic appointment between the potential participant and an individual knowledgeable about the research, the nature and objectives of the trial and possible risks associated with their participation. The Gynaecological Oncology CNS will be present to provide support for the potential participant and to help protect the potential participant's interests minimising any risk of coercion.
- Written information in the form of a patient information leaflet and consent document, approved by the REC and be in compliance with GCP, local regulatory requirements and legal requirements, will be provided.
- Potential participants will have the opportunity to ask questions
- Potential participants must be capable of giving consent.
- The Participant must:
    - Understand the purpose and nature of the research
    - Understand what the research involves, its benefits (or lack of benefits), risks and burdens
    - Understand the alternatives to taking part
    - Be able to retain the information long enough to make an effective decision.
    - Be able to make a free choice
    - Be capable of making this particular decision at the time it needs to be made (though their capacity may fluctuate, and they may be capable of making some decisions but not others depending on their complexity)

A person is assumed to have the mental capacity to decide unless it is shown to be absent. Mental capacity is considered to be lacking if, in a specific circumstance, a person is unable to decide for him or herself because of impairment or a disturbance in the functioning of their mind or brain.

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9.5 Additional consent provision for ancillary studies

Participation in the ancillary research is not required for participation in the trial

9.5.1 MIRRORS ICG - Peritoneal angiography / perfusion assessment using Indocyanine green (ICG) in patients with advanced ovarian cancer.

Indocyanine green (ICG) is an intravenous fluorescent dye used for cardiac, circulatory, microcirculatory and tissue perfusion diagnostics (See attached Summary of Product Characteristics for Verdye 5mg/ml, section 4.2 “Measurement of tissue perfusion” pg 3). ICG is used for diagnostics only. After intravenous injection ICG does not undergo any significant extra hepatic or enterohepatic circulation and does not pass into urine or cerebrospinal fluid. Indocyanine green is not metabolised and stays within blood vessels when given intravenously (Verdye 5mg/ml Summary of Product Characteristics).

In our Gynaecological oncology department, we regularly use ICG for sentinel lymph node assessment in endometrial cancer and have also used it in vulval and cervical cancer for the same purpose. Other therapeutic indications include assessment of perfusion in skin flaps and bowel anastomoses. At Royal Surrey NHS Foundation Trust, it is given intravenously for angiography in ophthalmology (see attached patient information leaflet). The incidence of adverse events is low (1 in 10 000-42,000 patients (Pruimboom et al 2019).

Within ophthalmology ICG dye is used to detect choroidal neovascularisation (formation of new blood vessels) which is seen in age related macular degeneration. The anatomy of these new vessels is abnormal and is characterised by large size with varying diameters and convolutedness (Solass, W. et al., 2016). Peritoneal inflammation and cancer invasion also causes neovascularisation with abnormal blood vessel patterns seen over the surface of peritoneal metastatic deposits (Solass, W. et al., 2016).

ICG binds to serum proteins and behaves like a macromolecule in the circulation. Macromolecules are known to accumulate in tumour tissue due to increased vascular permeability and reduced drainage. This phenomenon is called the “enhanced permeability and retention” (EPR) effect and has been observed in most solid tumours (Pruimboom et al 2019).

Tummers et al (2015) observed the effects of intravenous ICG in 10 patients suspected of ovarian cancer undergoing primary surgery. Of these 10 patients only 2 had metastasis and only one of these had stage 3 or above disease. Tummers et al (2015) found that in the 2 patients with metastatic disease all the metastatic deposits fluoresced under near infrared light therefore 100% sensitivity.

Standard ovarian cancer surgery involves careful assessment of the abdominal and pelvic cavities, identifying and removing all tumour deposits and taking biopsies. This is to both debulk the disease and to stage it. Survival in ovarian cancer is strongly associated with removing all visible tumour.

For this Ancillary study, we are proposing to use ICG fluorescent dye to look at the blood vessel pattern of the peritoneum (angiography) in the patients enrolled in the MIRRORS Study. We will inject 20mg of ICG dye in 10ml of water for injection intravenously (maximum of 0.5mg/kg). Following injection of ICG, the peritoneal surfaces of the abdominal and pelvic cavity will be searched under normal white light in order to identify any tumour deposits. The abdominal cavity will then be examined under near infrared light (using Da Vinci robot Firefly Fluorescence imaging mode) looking for areas of abnormal vasculature and peritoneal metastases. All visibly abnormal areas will be removed and sent to histopathology as is our standard surgical practice. **The ICG will not be used to guide where biopsies are taken or tissue is removed only clinically abnormal tissue or lymph nodes will be removed regardless of the effect of the ICG on them.** We will observe and record whether or not any lesions that are removed fluoresced under near infrared light.

Women agreeing to take part in the MIRRORS study will be asked whether they also wish to take part in this ancillary study. **Participation in this ancillary research is not required for participation in the trial.** Inclusion criteria will be the same as for the MIRRORS Study. Exclusion criteria will be: Severe renal insufficiency GFR< 55ml/min, known allergy to iodine or ICG and hyperthyroidism. The **aim** of this ancillary study is to observe the perfusion of the peritoneum in women with advanced ovarian cancer and observe how changes in the pattern of perfusion relate to any metastatic deposits.

- Biological specimens for this ancillary study will be acquired with consent, transferred and stored during the trial.
- The specimens will be used for ethically approved research as part of this study on ovarian cancer.
- Participants will be consented for the use of specimens in future research related to ovarian cancer
- Participants will be consented to be contacted by trial investigators for further informational and consent-related purposes
- Withdrawal from the ancillary research is possible. Any material provided will be disposed of in accordance with hospital regulations.
- Specimens used in any separate study outside of the pathology department will be coded so that participants cannot be identified from them.
- Withdrawal prior to any research being performed will result in the material being disposed of in accordance with hospital regulations.
- The results of the trial and any ancillary studies will be disseminated in a public event, to which all trial participants will be invited.

10 Trial Procedures, baseline data and assessments

Investigations	Baseline	Day of Surgery	Day 1 Post surgery	Day of Discharge	Follow up 1 (3-4 weeks post surgery)	Follow up 2 - End of Trial Visit 3 Months post op +/- 7 days	Survival and Recurrence follow up (no visit required)
Patient Demographics [a]	x						
Informed consent	x						
Baseline Data[b]	x						
Patient Interview at 3-6 weeks post op					X done 3-6 weeks post op		
Pain assessment • Numeric Rating Scale (NRS) Patient rates the pain from 0 (no pain) to 10 (worst pain)	x		x		x	x	
Questionnaires: • EORTC QLQ C30 • EORTC QLQ OV28 • HADs	x		x		x	x	
Surgical data[c]:		x					
Inpatient Stay[d]:				x			
Reported Post operative Surgical Complications Classified by the Clavien-Dindo Classification				x	x	x	
Record any Surgical Readmission • Cause of readmission • Number of days readmitted					x	x	
Patient Status[e]: • Alive without recurrence • Alive Following recurrence (date) • Dead (date and cause of death)				x	x	x	x
Time to adjuvant chemotherapy (days) Date of first cycle after Robotic IDS (aim ≤14 days)					x	x	

e) Patient Demographic - The following demographic data will be collected:
- Date of birth
- Ethnicity

f) Baseline Data – The following baseline data will be collected:
- ECOG performance status (Eastern Cooperative Oncology Group)
- Weight
- Height
- BMI
- Smoking status
- Co-morbidities previous and current medical conditions
- Concomitant medications
- Parity
- Previous abdominal surgery including caesarean sections
- BRACA Status when available
- Chemotherapy Regimen
- RECIST Response from pre IDS CT
- Number of cycles of chemotherapy prior to Surgery (minimum 3)
- Size of pelvic mass on CT scan in cm

g) Surgical Data:
- Date of Surgery
- Peritoneal Cancer Index Score (PCI) at Laparoscopy.
- Suitable for robotic IDS Yes/No, If not reason
- Mode of Surgery (Open / Robotic)
- Reason for conversion if applicable
- Operation Title
- ASA Grade
- Time Skin incision to Time Skin closure
- Length and position of longest Incision
- Mode of specimen retrieval (Mini Laparotomy / Through vagina)
- Surgical $C0_2$ pneumoperitoneum operating pressure mmHg
- Peritoneal Cancer Index Score (PCI) score after debulking surgery complete
- Estimated Blood Loss (EBL)
- Number of units of blood transfused
- Maximal diameter of macroscopic residual disease in cm and categorised as
  - R=0
  - R<0.2
  - R<0.5
  - R<1
  - R>1
- Site of Largest residual disease using same categories as for PCI (see table below)
- Intraoperative complications
- Histopathological diagnosis
- Grade
- FIGO Stage

} Available by Follow up 1

h) Inpatient Stay data to be completed prior to discharge:

- Total Number of units of blood transfused post op
- Number of Days ITU Care required
- Date of admission and Date of Discharge
- Length of stay (Days admission following surgery – Day of surgery = Day 0)
- Post-operative complications classified by the Clavien-Dindo Classification

f) Follow up

- Post Operative CT findings
- Alive without recurrence
- Alive with recurrence
- Date of recurrence if applicable
- Date of Death
- Cause of Death

10.1 Follow up

Follow up will follow that described in the Gynaecology Tumour Site Specific Group Constitution for advanced ovarian cancer with any additional visits depending on clinical need. The final trial follow-up visit will occur at 3 months coinciding with the normal clinic appointment. Following this time only survival and recurrence data will be collected as per established departmental internal audit.

Patients who cannot be contacted and whose GP's or local hospital cannot verify their status will be considered 'lost to follow-up'. If visits or data collection time-points are missed, with consent, patients will be phoned and questionnaires completed over the telephone by an appropriately trained individual knowledgeable about the research and the nature and objectives of the trial.

10.2 Withdrawal criteria

Participants are free to withdraw from the study at any time without giving any reason for doing so. The coordinating team should be informed so a record of all withdrawals can be maintained.

Participants who choose to withdraw will be asked for their reasons which will be recorded if they choose to divulge them. These participants will be followed up with regards to survival and overall survival as per established departmental internal audit.

If a patient withdraws from the study following surgery – They will continue to be followed up with regards to survival and recurrence but not with the questionnaire part of the study as per established departmental internal audit.

10.3 End of trial

Recruitment will be for 1 year. The trial will close once final patient data collection has occurred and data queries have been resolved. This will be around 1 year and 3 months from opening (i.e. to gather 90day mortality and post operative assessments following surgery). Patients will continue to be followed up as per established departmental internal audit.

11 Adverse events

An adverse event (AE) is an unfavourable symptom or disease temporarily associated with the trial treatment, whether or not it is related to the trial treatment.

A Serious adverse event (SAE) as an adverse event that:

- Results in death
- Is life-threatening
- Requires in-patient hospitalisation or prolongs existing hospitalisation
- Results in persistent or significant disability/incapacity
- Is otherwise considered to be medically significant by the investigator
- All Adverse events and Serious adverse events must be documented on the patient case report form (CRF).

List of Serious Adverse Events

- Severe Anaesthetic complications / anaphylactic reactions resulting in prolongation of hospitalisation
- Intraoperative or post operative bleeding requiring blood transfusion
- Injury to bladder / bowel / blood vessels / ureters / other visceral organ
- Thromboembolism including pulmonary embolism and deep vein thrombosis.
- Need to return to theatre
- Post operative infection resulting in the prolongation of hospitalisation
- Respiratory arrest
- Myocardial infarction
- Cardiac arrhythmia
- Cardiac arrest
- Wound dehiscence / port site herniation / bowel strangulation requiring return to theatre

11.1 Adverse reactions associated with Indocyanine Green (ICG) dye:

Severe allergic reaction: Very rare (affects fewer than one in every 10,000 patients) symptoms include (Diagnostic Green, Verdye 5mg/ml patient information leaflet):

- tightness in the throat
- itchy skin
- blotchy skin
- nettle-rash
- coronary artery spasm
- facial swelling (facial oedema)
- breathing difficulties - tightness and/or pain in the chest
- faster heart beat

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- a fall in blood pressure and shortness of breath
- heart failure (cardiac arrest)
- restlessness - feeling sick (nausea)
- feeling of warmth - flushes.

11.2 Reporting procedures

With regards to Suspected unexpected Serious Adverse Reactions (SUSAR) a sponsor or investigator should take appropriate urgent safety measures in order to protect research participants against any immediate hazard to their health or safety, without prior authorisation from a regulatory body.

The main Research Ethics Committee (REC) must be notified immediately (maximum within 3 days) in the form of a substantial amendment, that such measures have been taken and the reasons why. Copies of the information should be provided to the REC that approved the study using the REC safety reporting cover sheet.

Only reports of Serious Adverse Events (SAEs) that are: **related** to the study (Robotic surgery only) and **unexpected** (ie not listed in the protocol as an expected occurrence should be emailed to the REC using the **Non-CTIMP safety report to REC form.** These should be sent within 15 days of the chief investigator becoming aware of the event. (Health Research Authority 2019)

An annual progress report, signed by the chief investigator will be submitted to the REC which gave the favourable opinion 12 months after the date on which the favourable opinion was given. An electronic copy will be emailed to the REC within 30 days of the end of the reporting period.

12 Statistics and data analysis

12.1 Sample size calculation

Aim: The over-riding aim of the study is to demonstrate the feasibility and acceptability of robotic assisted interval debulking surgery (IDS) in the treatment of ovarian cancer. The sample size has been set pragmatically to give precision in the estimate of pre-defined feasibility criteria parameters such as consent rate, robotic operation rate and success rate (target debulking of R=0 achieved). The study will attempt to recruit 20 women, identified as suitable by MDT over a one year period, to be operated on robotically. Up to 20 women will ensure rates described above can be estimated within a standard error of less than 10%.

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12.2 Planned recruitment rate

This is a feasibility study with a view to doing a national randomised control trial following it if it is feasible. This trial will demonstrate the ability to recruit women to the study. The planned recruitment rate is 2 patients per month.

12.3 Statistical analysis plan

As a feasibility study, emphasis will be on descriptive statistics, including confidence intervals to give a measure of precision. No formal statistical comparisons will be undertaken. As is good practice, a formal statistical analysis plan will be prepared in advance of the data being seen at the end of the trial.

13 Data handling

13.1 Data collection tools and source document identification

Data will be collected on to Case Report Forms (CRF) and trial questionnaires at each of the defined time points and saved in the departments password protected Gynaecological Oncology database.

Survival and Progression data will be collected at each clinic as per current internal audit

To maximise completeness of data participants will be consented to be contacted by telephone so that any missing information can be acquired eg missing questionnaires.

Records of all participating patients (with sufficient information to link records e.g., CRFs, hospital records and samples), all original signed informed consent forms and copies of the CRF pages will be kept.

13.2 Access to data

Direct access will be granted to authorised representatives from the Sponsor, host institution and the regulatory authorities to permit trial-related monitoring, audits and inspections- in line with participant consent.

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13.3 Archiving

- Archiving will be authorised by the Sponsor following submission of the end of trial report
- The sponsor will be responsible for archiving patient questionnaires and CRFs. The site is responsible for the archiving of patient records if necessary.
- All essential documents will be archived for a minimum of 5 years after completion of the trial
- Destruction of essential documents will require authorisation from the Sponsor

13.4 Monitoring, audit & inspection

The study will be overseen by Royal Surrey NHS Foundation Trust. Research governance monitoring and auditing will take place and research conducted in line with Good Clinical Practice guidelines and NHS Research Governance Framework. Regular monitoring of recruitment, informed consent, data quality, and complaints will be carried out by Royal Surrey NHS Foundation Trust, the sponsor. A quarterly report will be provided to the sponsor by the research team.

14 Ethical and regulatory considerations

14.1 Research Ethics Committee (REC) review & reports

- Before the start of the trial, approval will be sought from a REC for the trial protocol, informed consent forms and other relevant documents e.g. Advertisements and GP information letters
- Substantial amendments that require review by REC will not be implemented until the REC grants a favourable opinion for the trial (note that amendments may also need to be reviewed and accepted by the MHRA and/or NHS R&D departments before they can be implemented in practice at sites)
- All correspondence with the REC will be retained in the Trial Master File/Investigator Site File
- An annual progress report (APR) will be submitted to the REC within 30 days of the anniversary date on which the favourable opinion was given, and annually until the trial is declared ended
- It is the Chief Investigator's responsibility to produce the annual reports as required.
- The Chief Investigator will notify the REC of the end of the trial
- If the trial is ended prematurely, the Chief Investigator will notify the REC, including the reasons for the premature termination
- Within one year after the end of the trial, the Chief Investigator will submit a final report with the results, including any publications/abstracts, to the REC

14.2 Peer review

Three individual experts in the field have reviewed the trial who are external to Royal Surrey NHS Foundation Trust.

14.3 Public and Patient Involvement

The Study Protocol and patient information leaflets have been circulated amongst a number of women with gynaecological cancers though GRACE Charity for their feedback prior to submission. The results of this study will be published in peer reviewed journals and presented at conferences. A public event where all participants will be invited will be held to disseminate the findings. Participant confidentiality will be protected. Information will also be disseminated through GRACE Charity who is supporting this research and the media.

Additionally, Qualitative interviews with women will be conducted to provide an insight into Women's experiences of taking part.

14.4 Protocol compliance

- Prospective, planned deviations or waivers to the protocol are not allowed under the UK regulations on Clinical Trials and must not be used e.g. It is not acceptable to enrol a participant if they do not meet the eligibility criteria or restrictions specified in the trial protocol
- Accidental protocol deviations can happen at any time. They must be adequately documented on the relevant forms and reported to the Chief Investigator and Sponsor immediately.
- Deviations from the protocol which are found to frequently recur are not acceptable, will require immediate action and could potentially be classified as a serious breach.

14.5 Data protection and patient confidentiality

All investigators and trial site staff must comply with the requirements of the Data Protection Act 1998 with regards to the collection, storage, processing and disclosure of personal information and will uphold the Act's core principles.

- Personal information will be collected, kept secure, and maintained.

- In general, this will involve:
    - The creation of coded, depersonalised data where the participant's identifying information is replaced by an unrelated sequence of characters
    - Secure maintenance of the data and the linking code in separate locations using encrypted digital files within password protected folders and storage media
    - Limiting access to the minimum number of individuals necessary for quality control, audit, and analysis

- All essential documents will be archived for a minimum of 5 years after completion of the trial
- The Chief investigator will be the data custodian

14.6 Financial and other competing interests

None

14.7 Indemnity

Indemnity for all patients recruited to the study will be provided by the sponsor. All recruited patients are NHS patient of RSCH Foundation Trust.

14.8 Amendments

If the sponsor wishes to make a substantial amendment to the REC application or the supporting documents, the sponsor must submit a valid notice of amendment to the REC for consideration. The REC will provide a response regarding the amendment within 35 days of receipt of the notice. It is the sponsor's responsibility to decide whether an amendment is substantial or non-substantial for the purposes of submission to REC.

14.9 Dissemination policy

- The data arising and results of the trial will be the intellectual property of The Department of Gynaecological Oncology at Royal Surrey NHS Foundation Trust.
- On completion of the trial, the data will be analysed and tabulated and a final trial report prepared.
- GRACE Charity be acknowledged within any publications.
- The results of this study will be published in peer reviewed journals and presented at conferences. A public event where all participants will be invited will be held to disseminate the findings. Participant confidentiality will be protected. Information will also be disseminated through GRACE Charity who is supporting this research and the media.

14.10 Authorship eligibility guidelines and any intended use of professional writers

Current authors include people directly involved in the development of the trial protocol.

Miss Christina Uwins

Mr Simon Butler-Manuel

Dr Agnieszka Michael

Professor Simon Skene

Mr Anil Tailor

Dr Thumuluru Kavitha Madhuri

Mr Jayanta Chatterjee

Miss Patricia Ellis

As per the ICMJE recommendations authors will fulfil the following criteria (Sahni & Aggarwal 2018.):

- Substantial contributions to the conception or design of the work; or the acquisition, analysis, or interpretation of data for the work; AND
- Drafting the work or revising it critically for important intellectual content; AND
- Final approval of the version to be published; AND
- Agreement to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

Further authors may be added throughout the trial but they will only be added if a personal contribution to the running of the trial or analysis of the data has been made.

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