CLINICAL STUDY PROTOCOL

Study Title:	The Impact of Multiparametric MRI on the Staging and Management of Patients with Suspected or Confirmed Ovarian Cancer
Short title:	MR in Ovarian Cancer (MROC)
Protocol Number:	C/33/2014
Sponsor:	Imperial College London
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The Protocol Development Group will hand over all responsibility for approving any subsequent amendments following the first version the protocol over to the Trial Management Group.

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ABBREVIATIONS

Abbreviation	Explanation
AE	Adverse Event
CI	Chief Investigator
CRF	Case Report Form
CCTS	Cancer (Research UK Imperial Centre): Clinical Trials Section
CSR	Clinical Study Report
CT	Computerised Tomography
CTCAE	Common Terminology Criteria for Adverse Events
DCE	Dynamic Contrast Enhanced
DWI	Diffusion Weight Imaging
ECOG	Eastern Cooperative Oncology Group
eCRF	Electronic Case Report Form
EDC	Electronic Data Capture
ICH GCP	International Conference on Harmonisation – Good Clinical Practice
ICHTB	Imperial College Healthcare NHS Tissue Bank
IDMC	Independent Data Monitoring Committee
IEC	Independent Ethics Committee
IRB	Institutional Review Board
MDT	Multi-disciplinary team
MedDRA	Medical Dictionary for Regulatory Activities
mL	Millilitre
mm	Millimetre
MpMRI	Multiparametric MRI
MRI	Magnetic Resonance Imaging
NCI-CTCAE	National Cancer Institute-Common Terminology Criteria for Adverse Events
NIHR	National Institute for Health Research
OC	Ovarian cancer
PCI	Peritoneal Cancer Index
PET	Positron Emission Tomography
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SOP	Standard Operating Procedure
SSPM	Study Specific Procedure Manual
TMG	Trial Management Group
TSC	Trial Steering Committee

TRIAL SUMMARY

Title:	MROC: The Impact of Multiparametric MRI on the Staging and Management of Patients with Suspected or Confirmed Ovarian Cancer
Diagnostic Tests:	(i) CT scan alone (ii) mpMRI alone (iii) CT scan in combination with mpMRI
Diagnostic Test Comparisons:	(i) CT alone to mpMRI alone (mpMRI as a replacement test to CT) (ii) CT alone to CT/mpMRI combined (mpMRI as an add on test to CT) All test comparisons are per patient unless specifically stated otherwise.
Trial Outcomes:	We note that the investigator team considers the first secondary outcome as of equal or greater importance to the primary outcome, but that the primary outcome is based on the order of the outcomes listed in the NIHR bid. The IDMC, TSC and TMG will be consulted on which outcome is clinically relevant to be the primary outcome.

Primary Objective		**Primary Outcome**
1.	To compare identification of advanced stage disease in women with suspected or confirmed Ovarian Cancer (OC).	Comparison of the diagnostic accuracy of advanced cancer stage based on radiological staging of women with suspected or confirmed OC. • Difference in sensitivity (per patient) • Difference in specificity (per patient) Comparisons: (i) mpMRI alone to CT alone (mpMRI as a replacement test to CT) (ii) CT/mpMRI combined to CT alone (mpMRI as an add on test to CT). Advanced stage: stage 3c/4 Non-advanced stage or benign: stage 1/2/3a/3b and benign Reference Standard: Staging defined in section 5.5.
Secondary Objectives		**Secondary Outcomes**
1.	To compare change in unsuccessful patient management (mainly resulting from avoidance of unnecessary cancer surgery).	Difference in proportion of patients avoiding unsuccessful patient management mostly resulting from (unnecessary) cancer surgery. mpMRI and CT will be compared against the reference standard for patient management decisions to determine unsuccessful treatment. Unsuccessful treatment is defined as: (a) sub-optimal/open-close cancer surgery or (b) over extensive surgery for benign disease or (c) no immediate surgery offered based on false positive imaging incorrectly detecting extensive spread of disease perceived as preventing successful surgery. Successful patient management is defined as: (i) optimal cancer surgery or (ii) appropriate surgery for benign or (iii) no immediate surgery as sub-optimal surgery predicted due to extensive spread of disease.

		Reference Standard: Patient Management Decisions further defined in section 5.5.
2.	To compare concordance of imaging findings and MDT decisions for surgical resectability	Comparison of image findings determining surgical resectability and the MDT decisions determining surgical resectability, per patient. Reference Standard: Patient Management further defined in section 5.5.
3.	To compare incremental cost and cost effectiveness using CT alone, mpMRI alone and mpMRI/CT combined.	Comparison of incremental cost and cost effectiveness accounting for categorisation into final surgical outcome, treatment costs & patient outcomes. If concordance: mean incremental cost per patient of management pathway. If discordance: mean incremental cost per patient of management pathway; mean incremental cost per patient of treatment pathway; mean incremental cost per patient of management pathway plus treatment pathway; mean quality adjusted life years (QALYs) gained per patient; incremental net monetary benefits. Reference Standard: Patient Management Decisions further defined in section 5.5
4.	To compare diagnostic accuracy of disease extent both per patient and per location.	Difference in sensitivity and specificity of peritoneal disease of diagnostic accuracy, per patient and per location. • PCI and peritoneal presence per patient • Site by site disease location Reference Standard: Peritoneal Disease Extent further defined in section 5.5.
5.	To compare MDT planning between local and external MDTs for surgical operation and patient care.	Comparison of MDT plans between local and external MDTs for treatment choice, ITU stay, length of operation, surgical expertise needed, per patient.
Sub-Study Objectives		**Sub-Study Outcomes**
1.	To evaluate inter-observer agreement of mpMRI for sites of disease and stage	Inter-observer agreement of mpMRI interpretation / reading for accurate diagnosis of referral for sites of disease and cancer stage; per patient and per location. Reference Standard: Disease Extent further defined in section 5.5.
2.	To compare mpMRI to conventional MRI	Comparison of mpMRI to conventional MRI (analyse for primary outcome and secondary outcomes 1 and 2 only) in order to determine incremental benefit. Reference Standard: Disease Extent further defined in section 5.5.

Design:	Multicentre prospective cohort study with internal pilot
Sample size:	645 women including approximately 475 women considered for primary surgery and approximately 170 women considered for delayed surgery
Inclusion criteria:	1. Written (signed and dated) informed consent prior to mpMRI scan^ and judged capable of co-operating with study requirements during treatment and follow-up; *^ A patient can be enrolled based on verbal consent with written consent to be obtained prior to the mpMRI scan* 2. Aged 18 years or over; (no upper limit); 3. Suspected ovarian, fallopian tube or primary peritoneal cancer. This can be contingent on imaging findings (either on ultrasound or CT) and/or a Risk Malignancy Index Score* (RMI) greater than 250; 4. Being considered for primary surgery or for delayed surgery following neoadjuvant chemotherapy (after 3 to 5 cycles) via the "NHS Cancer Pathway"; 5. Considered fit for surgery (by MDT or patient's surgeon).
Exclusion criteria:	1. Known contra-indication to MRI (e.g. claustrophobia, ferrous implants, cardiac pacemaker, inability to lie flat); 2. Known pregnancy; See section 4.3.2; 3. Medical or psychiatric illness that renders the patient unsuitable or unable to give informed consent; 4. Unable to undergo a CT scan with IV contrast due to allergy, renal failure or any other cause.

1. BACKGROUND AND RATIONALE

1.1. Ovarian Cancer (OC)

UK survival rates for ovarian cancer are worse than many similar countries. It is estimated that compared with the best in Europe, almost 2400 additional deaths occur within 5 years of diagnosis [1].it is imperative to improve NHS outcomes for ovarian cancer. Studies have evaluated the roles of initial surgery or chemotherapy in women with advanced disease. A meta-analysis by Bristow et al (81 studies, 6885 women) found that the factor with the greatest impact on survival was maximal surgical cytoreduction but only if residual sites of disease measured <2cm [2].

The EORTC 55971 study is the only completed randomised control trial (RCT), recruiting 718 women stage 3c/4 and reported no difference in overall or progression-free survival if surgery was performed before (primary surgery, PS) or after neoadjuvant chemotherapy (delayed surgery, DS) but a higher rate of serious adverse events in the initial surgery group [3]. Complete resection of all macroscopic disease at PS or DS was the strongest independent variable that predicted survival. It is clearly important to identify correctly those patients suitable for complete resection but to avoid surgery when it will be unsuccessful. Recent advances in MRI may now allow some improvement in patient selection for PS or DS.

The possibility of improved radiological delineation of the extent of disease now presents itself, potentially facilitating more accurate treatment stratification by the MDT. There is little economic evidence regarding which imaging modality is most cost-effective (http://www.crd.york.ac.uk/CRDWeb/HomePage.asp).

NICE guidance for the initial treatment of women with suspected OC comprises surgical resection of all macroscopic tumour, in those patients suitable for surgery, followed by chemotherapy [4].

However, most women present at FIGO stage 3/4 and immediate primary cytoreductive surgery (PS) may be impossible due to the extent of disease. If surgery is not considered possible, the patient undergoes neoadjuvant chemotherapy prior to reconsideration for delayed surgery (DS). The problem addressed by this study turns on the inability of the current standard, CT, to delineate disease extent accurately in all patients; resulting in difficulty when correctly selecting patients suitable for surgery, either at the stage of up-front surgery (PS) or following 3-5 cycles of neoadjuvant chemotherapy (DS). Currently 15-40% of women are subjected to unsuccessful surgery, evidenced by available literature and audit of our study centres. Inappropriate surgery with sub-optimal resection of disease is unlikely to benefit the patient and could delay chemotherapy treatment. Conversely, it is important that patients that could benefit from primary or delayed surgery are not categorized inappropriately as ‘not suitable for surgery’ based on CT, as surgical removal of disease is important to ensure the best overall outcome [2, 3].

In patients with a solitary complex ovarian mass, complete surgical cytoreduction is not a management issue, as this is achieved in almost every case. The problem here is that it can be very difficult to know if the lesion is cancer or not, as biopsy of these masses is contra-indicated due to the risk of upstaging disease. If a patient has a complex ovarian mass on US and the risk of malignancy index 1 (RMI 1: based on the ultrasound findings, CA-125 level and menopausal status) is greater than 250 (NICE guidance [4]), there is a risk that the patient will undergo cancer surgery inappropriately, removing both ovaries, the uterus, omentum and extensive sampling of the peritoneum to stage supposed cancer [4]. Such an outcome is devastating in pre-menopausal patients, particularly those wishing fertility preservation.

Each of these problems affects patient outcome and care adversely. CT does not prevent these failures of treatment categorisation.

1.2. Multiparametric Magnetic Resonance Imaging (mp-MRI)

There is good evidence that mpMRI characterises adnexal masses accurately [5]**.** However, there is limited evidence regarding how mpMRI impacts on clinical decision-making for complex adnexal masses suspected of being cancer. Evidence is sparse concerning the optimal imaging modality (comparing CT and MRI) for OC staging and management [4]. Recent technical developments in MRI, including diffusion weighted imaging (DWI) and technical improvements in dynamic-contrast-enhanced (DCE) MRI have led to small single centre studies investigating mpMRI for advanced ovarian cancer, particularly those evaluating response to chemotherapy treatment [6-8]. DWI MRI is likely to be useful to detect peritoneal disease. In addition, developments in small bowel MR imaging (Taylor HTA11/23/01) and peritoneal imaging [9] suggest likely improvements in the depiction of the bowel wall, often a very challenging area when detecting disseminated peritoneal carcinomatosis by CT. An on-going multicentre study is investigating DWI for response assessment (DISCOVAR), but this does not include stage or surgical resectability as outcome measures.

1.3. Rationale

The aim of this study is to evaluate the possibility of mpMRI providing an improved radiological assessment for the classification and delineation of the extent of disease for patients with suspected ovarian cancer compared to standard of care CT assessment, potentially facilitating more accurate decisions regarding patient management by the MDT. Currently there is little economic evidence regarding which imaging modality is most cost-effective in this situation.

2. STUDY OBJECTIVES AND ENDPOINTS

2.1. Primary Objective and Outcomes

Objective	Outcomes
1. To compare identification of advanced staged disease in women with suspected or confirmed Ovarian Cancer (OC).	Comparison of the diagnostic accuracy of advanced cancer stage based on radiological staging of women with suspected or confirmed OC • Difference in sensitivity (per patient) • Difference in specificity (per patient) Comparisons (i) mpMRI alone to CT alone (mpMRI as a replacement test to CT) (ii) CT/mpMRI combined to CT alone (mpMRI as an add on test to CT). Advanced stage: stage 3c/4 Non-advanced stage or benign: stage 1/2/3a/3b and benign Reference Standard: Staging defined in section 5.5

2.2. Secondary Objectives and Outcomes

For all secondary objectives we will be comparing:
i) mpMRI alone to CT alone (mpMRI as a replacement test to CT)
ii) CT/mpMRI combined to CT alone (mpMRI as an add on test to CT)

Objective	Outcomes
1. To compare change in unsuccessful patient management (mainly resulting from avoidance of unnecessary cancer surgery).	Difference in proportion of patients avoiding unsuccessful patient management mostly resulting from (unnecessary) cancer surgery. mpMRI and CT will be compared against the reference standard for patient management decisions to determine unsuccessful treatment. Unsuccessful treatment is defined as: (a) sub-optimal/open-close cancer surgery or (b) over extensive surgery for benign disease or (c) no immediate surgery offered based on false positive imaging incorrectly detecting extensive spread of disease perceived as preventing successful surgery. Successful patient management is defined as: (i) optimal cancer surgery or (ii) appropriate surgery for benign or (iii) no immediate surgery as sub-optimal surgery predicted due to extensive spread of disease. Reference Standard: Patient Management Decisions further defined in Section 5.5.
2. To compare concordance of	Comparison of image findings determining surgical resectability

imaging findings and MDT decisions for surgical resectability	and the MDT decisions determining surgical resectability, per patient. Reference Standard: Patient Management further defined in section 5.5.
3. To compare incremental cost and cost effectiveness using CT alone, mpMRI alone and mpMRI/CT combined.	Comparison of incremental cost and cost effectiveness accounting for categorisation into final surgical outcome, treatment costs & patient outcomes. If concordance: mean incremental cost per patient of management pathway. If discordance: mean incremental cost per patient of management pathway; mean incremental cost per patient of treatment pathway; mean incremental cost per patient of management pathway plus treatment pathway; mean quality adjusted life years (QALYs) gained per patient; incremental net monetary benefits. Reference Standard: Patient Management Decisions further defined in section 5.5.
4. To compare diagnostic accuracy of disease extent both per patient and per location.	Difference in sensitivity and specificity of peritoneal disease of diagnostic accuracy, per patient and per location. • PCI and peritoneal presence per patient • Site by site disease location. • Reference Standard: Peritoneal Disease Extent further defined in section 5.5.
5. To compare MDT planning between local and external MDTs for surgical operation and patient care	Comparison of MDT plans between local and external MDTs for treatment choice, ITU stay, length of operation, surgical expertise needed, per patient.

2.3. Sub-Study Objectives and Outcomes

Objective	Outcome
1. To evaluate inter-observer agreement of mpMRI for sites of disease and stage	Inter-observer agreement of mpMRI interpretation / reading for accurate diagnosis of referral for sites of disease and stage; per patient and per location. Reference Standard: Disease Extent further defined in section 5.5
2. To compare mpMRI to conventional MRI	Comparison of mpMRI to conventional MRI (analyse for primary outcome and secondary outcomes 1 and 2 only) in order to determine incremental benefit. Reference Standard: Disease Extent further defined in section 5.5

3. STUDY DESIGN

3.1. Overall study design

This is a multicentre study to compare the diagnostic accuracy of

i) mpMRI alone to CT alone (mpMRI as a replacement test to CT)

ii) CT/mpMRI combined to CT alone (mpMRI as an add on test to CT).

for evaluating tumour stage, disease extent and patient management decisions arising from imaging results of disease stage and extent for patients with suspected or confirmed ovarian cancer.

645 women who are being considered for ovarian cancer surgery (including approximately 475 women considered for primary surgery and approximately 170 women considered for delayed surgery) will be recruited to this study across the UK. The study will initially open as an internal pilot recruiting patients from 3 sites for a period of 6 months to assess study feasibility and refine logistics (image reporting, data completion, etc.).

If the results of this pilot support study progression, all additional sites will be opened and recruitment will continue until our sample size has been reached. All site set-up processes at other sites will continue during the internal pilot study to ensure a smooth transition from one phase to the other.

3.2. Study Flow Chart

The patient pathway is likely to differ between participating sites to a variable degree, contingent on local variations in practice. Figure 1 describes the expected flow of events; however, this may be adjusted locally in order to optimise recruitment. All staging assessments and treatment decisions must occur within the timeframes specified in the current NHS Cancer Pathway Guidelines at the time the patient is recruited.

There must be no delay to cancer treatment as a direct result of participation in this study.

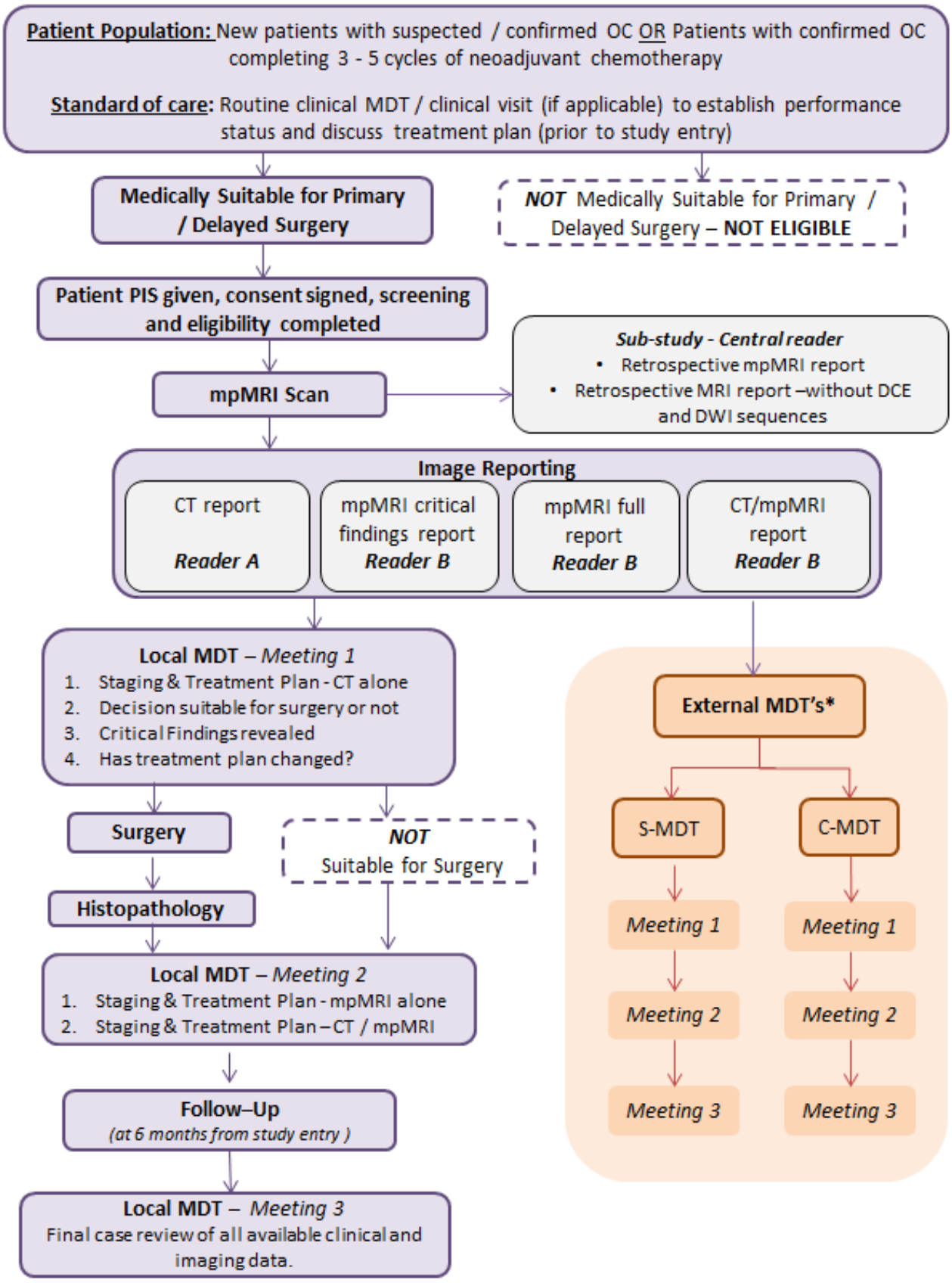

Figure 1: Study Flow Chart

***External MDT's will review each imaging modality (CT, mpMRI, CT and mpMRI combined) at 3 separate meetings to determine theoretical staging and treatment plans. These meetings will occur at approximately 3 month intervals. The order in which the images are reviewed will be randomly allocated by CCTS.**

4. PATIENT SELECTION AND RECRUITMENT

4.1. Site Inclusion

In this study there will be two types of sites: “recruiting sites” and “MDT sites”. Recruiting sites will also act as MDT sites for other recruiting sites.

4.1.1 Recruiting Sites

Recruiting sites must fulfil the following criteria:

1. Gynae-Oncology specialist centre (defined by fulfilling annual MDT peer review requirements) undertaking surgical and non-surgical treatment of ovarian cancer with a full range of expertise including imaging, surgery, medical oncology and histopathology.
2. MRI scanner (1.5 or 3T) capable of fulfilling the mpMRI sequences required by the protocol. mpMRI sequences will be certified by the Sponsor who will undertake study specific quality assurance at all recruiting sites.
3. Gynae-Oncology core MDT radiologists able and willing to report CT images for the study and, if possible, interpret study mpMRI and undertake study-specific training. Training will be undertaken by “remote buddy” reporting of mpMRI cases between a previously trained radiologist with double reporting of 10 retrospective training mpMRI data sets (with DCE and DWI). A further 5 retrospective mpMRI data sets will be assessed with a minimum of 4/5 being within reasonable agreement.

These sites will be required to:

- Conduct patient recruitment, trial imaging, follow-up schedules and all requirements of the trial protocol.
- Conduct local MDTs to generate and discuss patient management decisions.
- Carry out standard of care treatment plan.
- Collect & report image and clinical data as required in the protocol.
- Act as an external MDT site (see section 4.1.1.2)

4.1.2 MDT Sites

MDT sites must fulfil the following criteria:

- Gynae-oncology specialist centre (defined by fulfilling annual MDT peer review requirements) undertaking surgical and non-surgical treatment of ovarian cancer with a full range of expertise including imaging, surgery, medical oncology and histopathology.

These sites will be required to:

- Conduct external MDTs to evaluate patient management decisions.
- Record the decisions on patient management from MDTs

4.1.3 Classification of Sites

Both local and external MDT sites will be classified into either:

1) A Surgical MDT (S-MDT)
2) A Chemotherapy MDT (C-MDT)

This decision will be based on whether they have a high percentage (>50% based on a minimum of 3 months data) of patients, with stage 3c or 4 disease, allocated routinely either to upfront surgery (S-MDT)

or upfront chemotherapy (C-MDT). The classification of the site will be initially determined by the Sponsor, from data obtained during feasibility, and will be reviewed by the IDMC annually.

4.2 Screening and Enrolment

4.2.1 Screening

Potentially eligible patients will be identified by local investigators, predominantly during local MDT meetings at recruiting sites. Some patients, undergoing neo-adjuvant chemotherapy, may be identified during routine clinic visits although such patients would normally be re-discussed in the MDT meeting prior to decision for surgery, at which point they can also be identified.

A complete record of all patients who are screened for the study should be recorded on the screening log. Copies of this log should be sent to the Sponsor at regular intervals and originals stored in the Investigator Site File.

4.2.2 Informed Consent

Patients will be seen by a healthcare professional after a suspected diagnosis of ovarian cancer, based upon abnormal clinical findings. At this appointment, the diagnosis is explained along with the need for further tests to determine staging. Due to the urgent need to stage the patient quickly in order for treatment to start as soon as possible, these tests are usually performed within a very short time period. There is no scheduled return outpatient appointment (OPA) during this staging process. Instead patients are next seen face to face after the local MDT has made a decision about their treatment.

Therefore, patients that have been identified as being potentially eligible during the local MDT will be approached during their first OPA. They will be provided with the Patient Information Sheet (PIS) and invited to enter the study by a healthcare professional listed on the delegation log. A explanation of the study will be given and any contra-indications to MRI will need to be identified during initial discussions with the PIS.

The consent process from then onwards has been left deliberately flexible in order to accommodate the needs of individual patients and variations in site requirements. The flowcharts (Figure 2) below describe three different options for obtaining written informed consent from patients, each of which ensures that patients have a minimum of 24 hours to consider their participation in the trial before any trial-specificprocedures i.e. mpMRI.

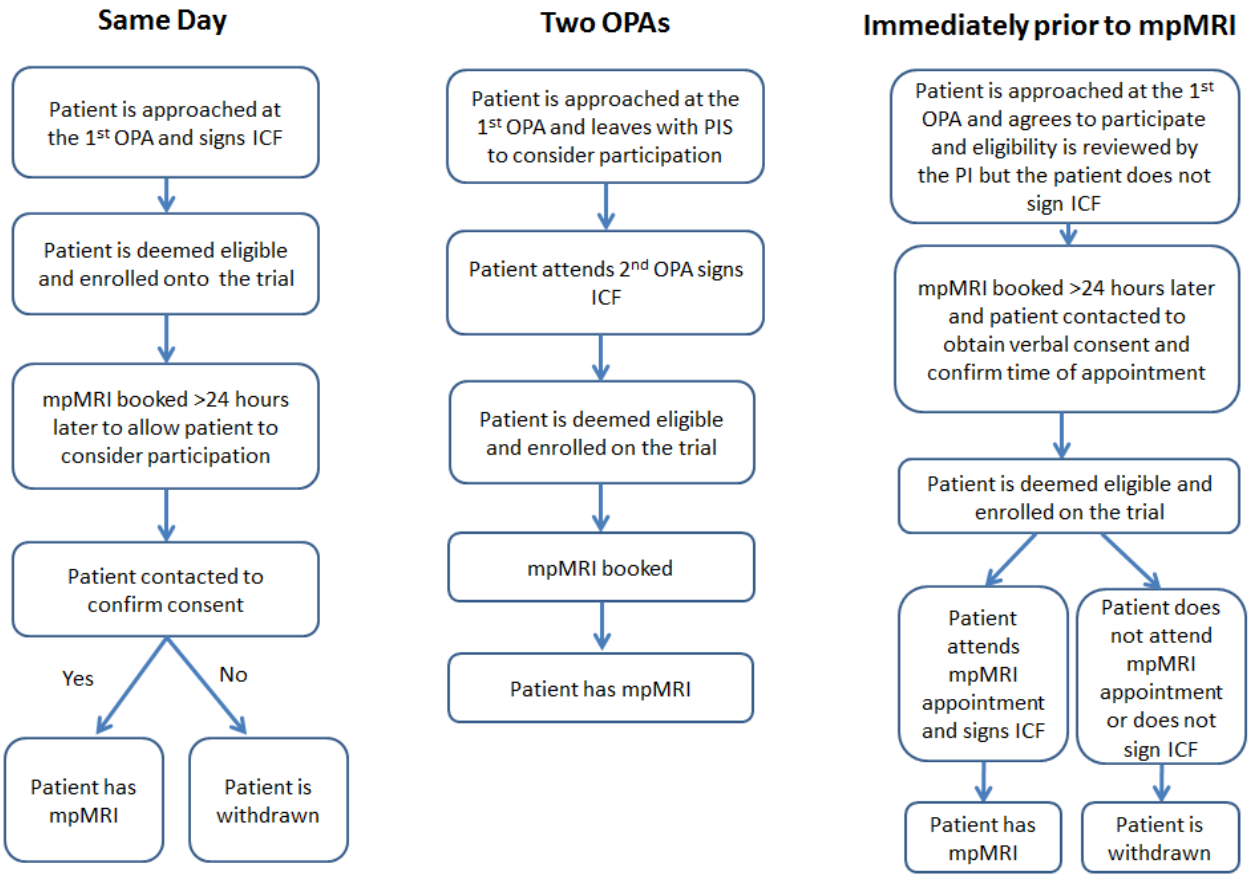

Figure 2: Informed Consent Process

Written informed consent using the current approved version of the consent form for the trial must be obtained before any trial-specific procedures (mpMRI) are conducted. The discussion and consent process must be documented in the patient notes. The right of the patient to refuse to participate in the trial without giving reasons must be respected. All patients are free to withdraw at any time. Subjects who withdraw prior to having their mpMRI scan will be replaced.

Site staff are responsible for:

- Checking that the correct approved version of the patient information sheet and informed consent form are used;
- Checking that information on the informed consent form is complete and legible;
- Checking that the patient has completed/initialled all relevant sections and signed and dated the informed consent form correctly;
- Checking that an appropriate member of staff has countersigned and dated the informed consent form to confirm that they provided information to the patient;
- Checking that an appropriate member of staff has made dated entries in the patient's medical notes relating to the informed consent process (i.e. information given, consent signed etc.);
- Following registration:
    - Completing all required fields, including the patient trial number, on all copies of the consent form. Copies should then be filed in the patient's medical notes and investigator site file.
    - Providing the patient with a copy of their signed informed consent form and patient information sheet.

4.2.3 Enrolment

Once the consent form has been signed, or the patient has given verbal consent, the potential patient will be assessed for eligibility by the principal investigator or delegate and if eligible will be enrolled into the study and assigned a unique identifier number by the Sponsor. A complete record of all patients enrolled, must be recorded on the enrolment log which will be maintained at each site. The principal investigator, or delegate, is responsible for ensuring that this record includes the allocated trial ID as well as the patient identifiable data including name, hospital number and date of birth.

4.3 Patient Selection

Eligible patients who take part in the study must meet all of the listed inclusion criteria and satisfy none of the exclusion criteria.

4.3.1 Inclusion Criteria

Patients must fulfil all of the following criteria:

1. Written (signed and dated) informed consent prior to mpMRI scan^ and judged capable of co-operating with study requirements during treatment and follow-up;
   ^ A patient can be enrolled based on verbal consent with written consent to be obtained prior to the mpMRI scan
2. Aged 18 years or over; (no upper limit);
3. Suspected ovarian, fallopian tube or primary peritoneal cancer. This can be contingent on imaging findings (either on ultrasound or CT) and/or a Risk Malignancy Index Score* (RMI) greater than 250;
4. Being considered for primary surgery or for delayed surgery following neoadjuvant chemotherapy (typically after 3 to 5 cycles) via the "NHS Cancer Pathway"[10].
5. Considered fit for surgery (by MDT or patient's surgeon).

** RMI combines three pre-surgical features: serum CA125 (CA125), menopausal status (M) and ultrasound score (U). The RMI is a product of the ultrasound scan score, the menopausal status and the serum CA125 level (IU/ml); RMI = U x M x CA125*

- *The ultrasound result is scored 1 point for each of the following characteristics: multilocular cysts, solid areas, metastases, ascites and bilateral lesions. U = 0 (for an ultrasound score of 0), U = 1 (for an ultrasound score of 1), U = 3 (for an ultrasound score of 2–5).*
- *The menopausal status is scored as 1 = pre-menopausal and 3 = post-menopausal. The classification of 'post-menopausal' is a woman who has had no period for more than 1 year or a woman over 50 who has had a hysterectomy.*
- *Serum CA125 is measured in IU/ml.*

4.3.2 Exclusion criteria

Patients who meet one or more of the following exclusion criteria will <u>not</u> be considered eligible for this study:

1. Known contra-indication to MRI (e.g. claustrophobia, ferrous implants, cardiac pacemaker, inability to lie flat);
2. Known pregnancy; See section 4.3.2;
3. Medical or psychiatric illness that renders the patient unsuitable or unable to give informed consent;
4. Unable to undergo a CT scan with IV contrast due to allergy, renal failure or any other cause.

4.3.3 Pregnancy and Birth Control

MRI poses a theoretical risk to the foetus, particularly in the first trimester, due to local acoustic and heating effects. However the risk is generally deemed very small and significantly less than the risk of ionising radiation imparted by CT (i.e. standard imaging investigations).

A woman of childbearing potential (WCBP) is a sexually mature woman (i.e. any female who has ever experienced menstrual bleeding) and who has not undergone a hysterectomy or who has not been postmenopausal for 24 consecutive months (i.e. who has had menses at any time in the preceding 24 consecutive months). The need to perform a pregnancy test in WCBP will be decided as part of the patient's routine clinical care, given the risk to pregnancy from standard of care staging investigations and subsequent treatment. There is no requirement to perform a pregnancy test purely contingent on recruitment to the trial if this would not have been performed as part of standard clinical care.

There is no requirement for additional contraceptive advice to patients over and above that routinely given as part of their routine clinical care, given their diagnosis of ovarian cancer.

Patients are excluded if they are known to be pregnant.

4.3.4 Withdrawal from Study

Withdrawal refers to the discontinuation of the patient from the study. This can occur for the following reasons:

- Patient decision – prior to the mpMRI scan
- Lost to follow-up
- Death
- PI decision

If the patient is withdrawn from the study the primary reason as well as the date of withdrawal must be recorded in the eCRF.

5 STUDY PLAN AND PROCEDURES

5.1 Study Overview

There is no treatment component to this trial.

Once a patient has been enrolled onto the study, they will undergo an mpMRI scan as soon as practically possible. In accordance with the timelines stipulated in the NHS Cancer Pathway, the patient will then be discussed at the local MDT to determine the most appropriate treatment pathway. This will initially be based upon information gathered from the CT scan alone. After a decision has been reached, any critical mpMRI finding will be revealed to the local MDT who will then determine if this changes their original decision. Approximately 3 months after the patient's enrolment on the study, the local MDT will review the full mpMRI report and the combined CT/mpMRI and record theoretical treatment plans based on the imaging findings. These will not impact on patient treatment. For further details, refer to section 5.2.6.

In parallel, each patients imaging and clinical information will be reviewed by two external MDTs (one S-MDT and one C-MDT). This will be separate from the patient treatment pathway and not have any effect on the patients treatment. Each imaging modality (CT, mpMRI, combined CT/mpMRI) will be viewed in a random order at the external MDTs, with a gap of approximately 3 months between each review. For each modality, a separate theoretical treatment plans will be recorded. For further details, refer to section 5.2.7.

Approximately 6 months after the patient's enrolment on the study, the local MDT will review all available information regarding the treatment the patient underwent and the associated outcomes to determine the reference standard for the patient. This meeting will not have an effect on the patient's treatment.

The schedule of study assessments is presented in Table 2.

5.2 Patient demographics, history and other clinical tests

5.2.1 Demographic Data and Medical History

Demographic data and other characteristics will be recorded and will include date of birth, race/ethnicity and NHS number. A relevant medical history will be obtained including details of previous and current medication, relevant surgical history and pre-surgery tumour characteristics, if available.

5.2.2 ECOG Performance Status

Performance status will be assessed during eligibility checks, according to ECOG criteria as follows:

0	Fully active, able to carry on all pre-disease activities without restriction
1	Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature. For example, light housework, office work
2	Ambulatory and capable of all self-care but unable to carry out any work activities. Up and about more than 50% of waking hours
3	Capable of only limited self-care, confined to bed or chair 50% or more of waking hours
4	Completely disabled. Cannot carry on any self-care. Totally confined to bed or chair
5	Death

Table 1: ECOG Performance Status

5.2.3 CA125 Assessment

CA125 assessments will be conducted as part of the patient's standard of care and within the timelines depicted in the protocol. All CA125 results should be recorded in the study database.

Table 2: Schedule of Assessments

Activity / Assessment	(Local) Recruiting Site								MDT Sites
	Screening	Study Imaging	Local MDT Meeting 1	Surgery	Histopathology	Local MDT Meeting 2	Follow-up (6 months later)	Local MDT Meeting 3	External MDT Meetings
Informed Consent[1]	X								
Demographic Data	X								
Medical / Surgical History	X								
ECOG	X								
CA125[2]	X								
CEA[2]	X								
CT Scan[3]	X								
mpMRI Scan		X							
CT Reporting		X							
mpMRI Reporting		X							
CT/mpMRI Reporting		X							
Adverse Events[4] (NCI-CTCAE v4.03)		X							
Record of proposed treatment plans			X						
Surgical eCRF completion				X					
Histopathology eCRF completion					X				
Record of theoretical treatment plans						X[5]			X[6]
Record of actual treatments and outcomes							X		
Review of all imaging and clinical outcome data								X	

1-If informed consent is taken on the day the PIS is provided to the patient, consent must be re-confirmed either by telephone or face to face prior to the mpMRI scan; if consent is signed immediately prior to mpMRI scan, the verbal agreement on the telephone must be obtained following receipt of the PIS in order to screen for inclusion and exclusion criteria.

2- The CA125 and CEA levels recorded during routine diagnostic tests can be used for this trial

3- The standard of care CT scan from the point of referral should be used for this trial. If a patient has had a CT at another hospital and this is not available, a local CT scan would need to performed as part of the standard of care management pathway of the patient and would not be done only for the purposes of the study.

4- AE's will be collected at the mpMRI scan and for a total of 24hours after. Only AE's ≥ grade 2 and related to the mpMRI scan will be recorded.

5- Local MDT 2– Review of the mpMRI scan alone followed by review of the combined CT/mpMRI scans. This MDT will occur after surgery has taken place and decisions will not be clinically undertaken.

6- Each patient will be assigned to one S-MDT and one C-MDT; each MDT will review CT alone, mpMRI alone and mpMRI in combination with CT. There will be at least 3 months between an MDT reviewing each imaging modality. The suggested treatment plans will be collected but will not be feedback to the patient's local site and decisions will not be clinically undertaken.

5.3 Diagnostic imaging tests

Recruited patients will undergo both CT and mpMRI scanning at their recruitment sites.

5.3.1 CT Scanning

The imaging manual specifies the requirements of CT scanning in the trial. In brief, the standard of care CT scans from the point of referral will be used for the study assessment of CT. CT scans with intravenous contrast enhancement at the portal venous phase and of the abdomen and pelvis or chest abdomen and pelvis will be required. In those relatively infrequent cases where the patient has not had CT at the time of recruitment, then this will be performed at the study centre, as per local policy. Information on details of CT scanning and use of contrast will be collected as part of the study.

5.3.2 mpMRI Scanning

The imaging manual specifies full details of mpMRI scanning in the trial. In brief, during the site set up the study physicists will perform quality assurance on all mpMRI sequences. Details of the QA process and the imaging sequences to be used in this study can be found in the Imaging SSPM.

Approximately 2 hours prior to the scan patients will be requested to drink 1 litre of pineapple juice. Immediately prior to the start of the mpMRI, an antiperistaltic agent will be given as per local practice.

N.B. If a patient is unable to drink the pineapple juice or take the antiperistaltic they would still be eligible have the mpMRI scan and participate in the study.

Prior to imaging a surface phased array coil should be used to cover the entire abdomen and pelvis, for the internal pilot scans the area will be extended to include the chest. Information on details of mpMRI scanning and patient preparation will be collected as part of the study.

5.3.3 Study Image Upload

If the standard of care CT is acquired prior to recruitment, which is likely to be the case, this will be anonymised and up-loaded to the study database Mint Lesion™ along with the anonymised mpMRI image. For full details on uploading image data to the database please refer to the Data Collection SSPM.

5.3.4 Study Image Reporting:

Two radiologists (Reader A and Reader B) will report the scans prior to the first local MDT (Meeting 1) review following enrolment. If a recruiting site is unable to provide two blinded readers, CCTS can assign a central reader to report the patient's mpMRI and combined CT/mpMRI.

- ***Reader A*** will report the CT scan whilst remaining blinded to the mpMRI scan and will provide:
  - A full CT report (for the local and external MDTs)

- ***Reader B*** will report the mpMRI scan whilst remaining blinded to the CT scan and will need to provide:
  - A full mpMRI report (for the external MDT and Local MDT Meeting 2)
  - A ***'Critical Findings Report'*** (for the local MDT Meeting 1) which would include any mpMRI findings that would present a contra-indication to cytoreductive surgery that was planned following CT assessment. (NB. In some cases, surgery may go ahead despite such findings being present. This decision will be made by the Local MDT on a case-by-case basis.

  The critical findings report will include information such as:
    - Benign adnexal mass with AdnexMR score of 1,2, 3 or 4
    - Unequivocal solid organ parenchymal metastatic disease

- Unequivocal invasion of solid organ or duodenum
- Unequivocal tumour infiltration of major vasculature
- Distant metastases, excluding pleura
- Pulmonary embolus
- Bowel Invasion
- Primary tumour arising from another organ
- Any other significant safety concern

If the mpMRI report is being read by a "buddy reader" not located at the local site, instructions will be sent on how to contact the local PI should any urgent clinical findings arise regarding patient safety.

Once the CT and mpMRI reports have been completed, Reader B will then be given access to all the imaging data and produce the 'combined CT/mpMRI report'.

All imaging reports will be directly entered into the image report eCRF, located in the study Mint Lesion™ database. For full details on eCRF completion requirements and access to the database, please refer to the Data Collection SSPM.

Radiologists reporting images as part of the study will be reporting as part of their normal clinical practice. Prior radiologist experience will be recorded including years of experience and previous number of reports in last 12 months of CT, MRI and mpMRI as appropriate. mpMRI training will be completed for all mpMRI readers.

5.3.5 Local MDT

Once CT, mpMRI and combined reporting has been completed and entered into the database, the patient will be reviewed at the local MDT to discuss the stage of the cancer and patient's management.

Meeting 1:

- The local MDT will determine the stage of the cancer and an initial treatment plan based upon information gathered from the CT scan alone.
- After the above decisions have been reached and during the same meeting, any critical mpMRI finding (see 5.2.4 for details of critical findings report) will be revealed to the local MDT who will then decide if this impacts the initial treatment plan.
    - *N.B.The MRI scan itself will not be available to the local MDT at this stage, in case it incorrectly influences patient management.*

Meeting 2:

- Approximately 3 months after enrollment, the local MDT will meet again to determine theoretical staging and treatment plans based upon the mpMRI alone.
- After the above decisions have been reached and recorded in the study Mint Lesion™ database, the combined CT/mpMRI report will be reveleaed to the local MDT and a second theoretical staging plan will be completed.
- Neither of these plans will have any impact upon patient management.

Meeting 3:

- Approximately 6 months after enrolment, the local MDT will review all available information (including all imaging, surgery, histology and cytology available for the patient), to form a final consensus regarding what the patient's optimal treatment plan would have been.

All data will be captured on the treatment plan eCRF, Mint Lesion™, by the local MDT in real time. For full details on eCRF completion requirements, please refer to the Data Collection Manual.

5.3.6 External MDT

Each patient case will be randomly allocated by the Sponsor to two external MDTs:

i) One MDT with a high percentage (>50%) of up-front surgery (S-MDT) in patients with Stage 3c to 4 disease
ii) One MDT with a high percentage (>50%) of up-front chemotherapy (C-MDT) in patients with Stage 3c to 4 disease

Each external MDT will review each of the three imaging modalities (CT alone, mpMRI alone, combined CT/mpMRI), for each patient, at three separate meetings. The associated report and relevant baseline clinical data (age, ECOG and CA125 at study entry) will also be available. The order in which the three images are reviewed will be randomly allocated and the meetings must occur at least three months apart. For each modality, the external MDT will record a theoretical patient stage, peritoneal disease extent and management plan. Treatment plans recorded by the external MDTs will not be reported back to local sites and therefore will not affect patient treatment.

All data will be captured on the eCRF, mint Lesion™, by the external MDT in real time. For full details on eCRF completion requirements, please refer to the Data Collection Manual.

5.3.7 Record of Trial Outcomes

A record of actual treatment received since enrolment on the study and associated outcomes will be recorded on the outcomes eCRF. These will include :

- Radiologist interpretation of patient imaging, including imaging stage and extent of disease (peritoneal diease presence, PCI, individual sites of peritoneal diease, individual sites of non-peritoneal disease spread).

- Details of surgery planned at MDT meetings based on imaging reports and MDT discussion.

- Details of the surgery and surgical outcome recorded at end of surgical procedure directly into the eCRF if the patient underwent surgery.

- If the surgery differed from the planned surgery indicated by the MDT, the reason for change will be indicated (due to patient unstable in theatre, much more widespread disease, unresectable site of disease, found benign lesion not cancer (such as a degenerating fibroid).

- Post-operative requirements, if the patients underwent surgery.

- Histopathology, if the patient underwent surgery.

- Neoadjuvant chemotherapy, if the patient underwent neoadjuvant chemotherapy.

- Details of the treatments (including additional scans, histology, cytology and visits that patients have received / attended will be collected after 6 months from the study entry and recorded in the outcomes eCRF for all patients.
    - Anonymised copies of patients' reports / results may be requested by the Sponsor in cases where the patient case is to be reviewed by the expert study panel as part of the IDMC study review.

5.4 Sub-Study Comparison of MRI and mpMRI Reporting

A substudy will include additional interpretations of anonymised mpMRI images with and without the functional sequences., to compare mpMRI and MRI reporting. This substudy will enrol at least 5% of all patients (at least 35 patients).

Reporting will include blinded interpretation in randomised order of images from the same patient using mpMRI and MRI with functional sequences (DWI and DCE) excluded in order to replicate interpretation of a conventional MRI series. Blinded interpretation of mpMRI.

5.5 Reference Standards

The following reference standards will be used:

5.5.1 Reference Standard for Staging

FIGO classification determined at the final case review after 6 months by local MDT (L-MDT Meeting 3), with all clinical and imaging information available (i.e. imaging, surgery, histology and cytology) since the patient was enrolled up until 6 month follow up. Individual sites of metastasis will be reported.

5.5.2 Reference Standard for Peritoneal Disease Extent

Peritoneal disease extent will be determined at the final case review after 6 months by local MDT (L-MDT Meeting 3), with all clinical and imaging information available (i.e. imaging, surgery, histology and cytology) from patient enrollment up to 6 months follow-up.
Review will record disease extent per patient (PCI and presence of peritoneal disease) and peritoneal disease extent site by site disease (metastasis of tumour).

5.5.3 Reference Standard for Patient Management Decisions

Treatment plan considered to be the most appropriate for the patient, determined at the final case review after 6 months by local MDT (L-MDT Meeting 3), with all clinical and imaging information available (i.e. imaging, surgery, histology and cytology) from patient enrollment up to 6 months follow-up.

- CT imaging will be used by MDT to guide patient management, except where specific trial management rules apply (where would be unethical not to use MR imaging results in patient management).
- For CT: % successful surgery in patients where CT results refer for surgery. If critical findings report or extent of disease refers patient to delayed surgery, then reference panel will use delayed surgery and all imaging and test results to opine on potential for success at primary surgery.
- For MR: % successful surgery in patients if MR results had been used to refer for surgery. If MR predicts disease too extensive for primary surgery, these patients would not be included in % success based on MR. If CT predicts spread too great for primary surgery but MR does not, reference panel will use delayed surgery and all imaging and test results to opine on potential for success at primary surgery.

5.6 Exploratory Research

At sites which routinely collect surgical samples for research purposes and have procedures and staff in place to manage this, patients will be given the opportunity to consent to the collection, storage and subsequent use of tissue samples for research. All samples will be linked anonymised and identified only by the trial ID and unique sample number allocated by CCTS.

5.6.1 Tissue collection

Sites that are able to perform fresh frozen sampling will be offered the opportunity to take part in tissue collection. Participation in this part of the study is not mandatory and non-participation would not prevent the site from becoming a recruiting site.

Sites participating in tissue collection would be required to provide fresh frozen tissue from the standard of care ovarian surgery for all consenting patients. Tissue samples from the main tumour, the omentum and peritoneum should be collected if available.

At the end of the study, custody of the samples will be transferred to the Imperial College Healthcare Tissue Bank for long-term storage. This will allow the samples to be used in future ethically approved studies which may involve the samples being sent outside of the UK for analysis.

5.6.2 Chain of Custody of Biological Samples

In all cases, patients will be consented for the collection and use of their biological samples for research purposes subsequently, and a full chain of custody will be maintained for all samples throughout their lifecycle. The Investigator at each site will be responsible for maintaining a record of full traceability of biological samples collected from patients while these are in storage at the site, either until shipment or disposal. Anyone with sample custody (e.g. sub-contracted service provider) will keep full traceability of samples from receipt to further shipment or disposal (as appropriate). Imperial College London will maintain overall oversight of the entire lifecycle via internal monitoring procedures and monitoring of study sites. Samples retained for further use will be registered with Imperial College Healthcare NHS Tissue Bank (ICHTB).

6 ADVERSE EVENT REPORTING

6.1 Definition of an adverse event (AE)

An AE is any untoward medical occurrence in a patient or clinical trial patient. An AE can therefore be any unfavourable and unintended sign (including an abnormal laboratory finding), symptom, whether or not considered related to the research proposed in this protocol.

For this study only AE's ≥ grade 2 and considered related to the mpMRI scan and occurring within 24 hours from the mpMRI scan will be recorded.

6.2 Recording of adverse events

AEs for mpMRI will be collected during the study , from the patients mpMRI scan until 24 hours after. Should an AE relating the mpMRI scan occur the patient will be followed up according to local practice until the event has stabilised or resolved.

Possible recognised MRI AEs include:

- Vomiting (after pineapple juice)
- Allergic Reaction to IV contrast (e.g.: nausea, rash, anaphylaxis etc)
- Anxiety / panic attack or other event as a result of claustrophobia

Any AEs which remain on-going at 24 hours after the mpMRI should be followed up by the Investigator, or delegate, for as long as medically indicated, but without further recording in the eCRF.

6.2.1 Severity of adverse events

Severity is a measure of intensity whereas seriousness is defined by the criteria in section 6.3. Severity will be assessed using the grading scales found in the National Cancer Institute CTCAE version 4.03 for all adverse events with an assigned CTCAE term. For those events without assigned CTCAE grades, the recommendation on page 1 of the CTCAE that converts mild, moderate and severe into CTCAE grades should be used. A copy of the CTCAE version 4.03 can be downloaded from the Cancer Therapy Evaluation Program website.

6.2.2 Causality of adverse events

The Investigator will assess causal relationship between study procedures and each AE.

Unrelated: No evidence of any causal relationship

Unlikely: There is little evidence to suggest there is a causal relationship (e.g. the event did not occur within a reasonable time after a study procedure). There is another reasonable explanation for the event (e.g. the patient's clinical condition, other concomitant treatment).

Possible: There is some evidence to suggest a causal relationship (e.g. because the event occurs within a reasonable time after a study procedure). However, the influence of other factors may have contributed to the event (e.g. the patient's clinical condition, other concomitant treatments).

Probable There is evidence to suggest a causal relationship and the influence of other factors is unlikely.

Definite: There is clear evidence to suggest a causal relationship and other possible contributing factors can be ruled out.

6.3 Definitions of Serious Adverse Events (SAE)

An SAE is an AE occurring during any part of the study that meets one or more of the following criteria:

- Results in death;
- Is life-threatening*;
- Requires hospitalisation or prolongation of existing inpatient's hospitalisation**;
- Results in persistent or significant disability or incapacity;
- Is a congenital abnormality or birth defect;

** "Life-threatening" in the definition of "serious" refers to an event in which the patient was at risk of death at the time of the event; it does not refer to an event which hypothetically might have caused death if it were more severe.*
*** "Hospitalisation" means any unexpected admission to a hospital department. It does not usually apply to scheduled admissions that were planned before study inclusion or visits to casualty (without admission).*
Medical judgement should be exercised in deciding whether an adverse event/reaction is serious in other situations. Important adverse events/reactions that are not immediately life-threatening, or do not result in death or hospitalisation but may jeopardise a patient, or may require intervention to prevent one of the other outcomes listed in the definition above should also be considered serious.

If an Investigator is notified of any SAEs, including death, at any time after a patient has completed the study and he/she considers there is a reasonable possibility that the event is related to the mpMRI scan, the Investigator should notify CCTS.

The following details will be collected in the CRF for each AE:

- AE description / diagnosis
- Date of onset and date of resolution
- CTCAE grade maximum intensity
- Seriousness (see section 6.2.1)
- Causality rating (see section 6.2.2)
- Action taken
- Outcome

6.4 Reporting of SAEs

SAEs for mpMRI will be collected during the study , from the patients mpMRI scan until 24 hours after. SAE's should be reported within 24 hours of the Principal Investigator or designee becoming aware of the event, of all SAEs occurring during the study, must be performed as detailed in the Safety Reporting Manual. If the investigator becomes aware of safety information that appears to be related to the mpMRI scan even after an individual patient has completed the study, this should also be reported to Cancer Research UK Imperial Centre: Clinical Trials Section.

The SAE should be reported electronically to the study team at Cancer Research UK Imperial Centre: Clinical Trials Section via the Mint Lesion database as detailed in the Safety Reporting Manual.

All SAEs will be reviewed by the Chief Investigator or designated representative to confirm relatedness and expectedness. Following documented assessment by the CI, the completed SAE form will be sent by fax to

Sponsor by the study team at Cancer Research UK Imperial Centre: Clinical Trials Section within the pre-specified timelines.

Reports of related and unexpected SAEs should be submitted within 15 days of the Chief Investigator becoming aware of the event, using the NRES SAE form for non-IMP studies. The Chief Investigator must also notify the Sponsor of all SAEs.

Local investigators should report any SAEs as required by their Local Research Ethics Committee, Sponsor and/or Research & Development Office.

SAEs that are related and unexpected will be notified to the relevant Research Ethics Committee by Cancer Research UK Imperial Centre: Clinical Trials Section in accordance with local policies.

7 STATISTICAL ANALYSES

7.1 Sample Size and Power Considerations

With 645 women with ovarian cancer for whom surgery is considered (NICE guidance: RMI>250 and imagine findings) and performance fit for surgery, there is 90% power for the two main outcomes specified:

1. Primary Outcome: Change in staging - need 475 women considered for primary surgery
2. Secondary Outcome 1: To compare change in unsuccessful patient management (mainly resulting from avoidance of unnecessary cancer surgery).- need 475 women considered for primary surgery and 170 women considered for delayed surgery.

The justification for only recruiting women with performance fit for surgery is that in women who are not clinically fit for surgery, the initial treatment offered is always neoadjuvant chemotherapy regardless of staging or imaging results. These women may subsequently become fit for surgery following 3 or 4 cycles of chemotherapy and they can be considered for study entry at the second recruitment stage.

The power calculation has been informed from NICE Evidence review, published data and an audit conducted in 2014 of data collected from 5 participating sites (University Hospitals Birmingham NHS Foundation Trust (UHB), Imperial College Healthcare NHS Trust (ICHNT), Lancashire Teaching Hospitals NHS Trust (LTH), Gateshead Health NHS Trust (GHNT) and University College London Hospitals NHS Foundation Trust (UCLH)). N.B. Anonymised results from this audit will be made available as appropriateto the TSC, TMG and IDMC.

This study is powered on the primary outcome and first secondary outcome, as specified in section 2, (change in staging and change in management plans). The study design has increased power by comparing both imaging modalities in the same patients and by each imaging modality being interpreted by a radiologist blinded to other imaging modality.

The primary outcome is powered powered for a difference between CT and MRI in the detection of advanced ovarian cancer (stage 3c/4) versus non-advanced cancer or benign (stage 1/2/3a/3b or benign mass) at 90% power, both compared to a reference standard of cancer stage.

Sample size for recruitment: 475 women (greater than 468) with RMI>250 and imaging findings indication OC (with 10% loss to FU).

Assumptions:

- 6% increase in sensitivity (92% CT, 98% MRI [Ref 10]) based on 48% prevalence of advanced ovarian cancer in women with performance status sufficient for surgery, and;
- 8% increase in specificity of correct staging (MR 91%, CT 83% [Ref 10]) at a prevalence of 52% for benign and non advanced cancer.
- Prevalence assumptions based on distribution of cancer staging 62% advanced staging (CRUK Ovarian Cancer Incident Statistics 2012, audit UCLH & ICHNT) and prevalence of staged cancers in recruited women of 70% (3 centres in study audit: 78%, 76%, 65%).

The first secondary outcome is powered to compare change in patient management through avoidance of unnecessary cancer surgery using CT and MRI. Imaging findings will be compared to a reference standard for patient management decisions.

Unsuccessful treatment is defined as:

(a) sub-optimal/open-close cancer surgery or
(b) over extensive surgery for benign disease or

(c) no immediate surgery offered based on false positive imaging incorrectly detecting extensive spread of disease perceived as preventing successful surgery.

Successful patient management is defined as:

(i) optimal cancer surgery or
(ii) appropriate surgery for benign or
(iii) no immediate surgery as sub-optimal surgery predicted due to extensive spread of disease.

Sample size for recruitment: 645 women with suspected or confirmed ovarian cancer for whom surgery is considered (475 with RMI>250, imaging findings with performance level fit for primary surgery and 170 considered for delayed surgery) including 10% LFU.

Assumptions:

- 645 recruited women will include 68% women referred for immediate surgery following CT imaging (at least 427 women, expect 439 of 645 women).
- Powered on 4% decrease in unsuccessful patient management (CT 11%, MR 7%, 6% positive with both CT and MR.
- Expected reduction of women referred for unsuccessful surgeries from 68 (CT) to 47 (MR) based on imaging results, 10% LFU).

7.1.1 Sub-Studies Sample Size

Two sub-studies are planned (i) to evaluate inter-observer agreement of mpMRI (ii) comparison of mpMRI to conventional MRI. These studies will conduct additional interpretations of annonymised stored study images which will not be used to inform womens' diagnosis or treatment. No extra women will be enrolled for these substudies and there will be no additional procedures for patients as part of these substudies.

Both studies will enroll radiologists with similar experience to those reading CT and MRI images in NHS practice. Training will be given to those radiologists reading mpMRI.

The inter-observer agreement study will include images from at least 10% of women enrolled for each sub-study (i.e. images from at least 65 women).

The comparison of mpMRI to conventional MRI will include at least 5% of women enrolled (i.e. images from at least 35 women).

7.2 Data Analysis

Final analysis will be performed at the end of the study and interim analysis will be determined by the IDMC.

Full details of the statistical analysis are included in the statistical analysis plan (SAP). A final draft will be locked prior to transfer of data prior to final analysis.

7.2.1 Missing, Unused and Spurious Data

For the primary analysis, missing data will be derived from overlapping fields in the eCRFs and by multiple imputation based on other recorded data including outcome data for the primary and secondary outcomes.

A sensitivity analysis will be included based on complete case data for each outcome. Imputation methods for missing data in the primary endpoint and secondary endpoints will be fully documented in the SAP.

7.2.2 Deviations from the Statistical Plan

Any deviation(s) from the final statistical plan in the final analysis will be described and justification given in the final report.

7.2.3 Primary Analysis

Primary Outcome 1: To compare the staging of women with suspected Ovarian Cancer (OC) using standard of care CT alone, mpMRI alone, and CT/mpMRI combined.

- Comparison of the diagnostic accuracy of advanced cancer stage based on radiological staging of women with suspected OC

(i) Difference in sensitivity (per patient)
(ii) Difference in specificity (per patient)

- Staging results will be grouped based on combined FIGO stages (i) advanced stage (stage 3c/4) (ii) non-advanced/benign (stage 1/2/3a/3b and benign).
- Imaging staging from CT, mpMRI and combined CT/mpMRI will be defined based on MDT interpretation.
- Test comparisons
  (i) mpMRI alone to CT alone (mpMRI as a replacement test to CT)
  (ii) CT/mpMRI combined to CT alone (mpMRI as an add on test to CT)
- Paired comparison of radiology based staging for each strategy against the reference standard for staging based on grouping of FIGO staging classificati
- Reference standard for staging will be according to section 5.5
- Overlapping data fields and imputation will be used to account for missing data and imperfect data
- Analysis will use multilevel logistic regression, clustered by patient and site.
- Results will be expressed as estimates of sensitivity and specificity with 95% CI calculated, allowing for data clustering by patient.
- Descriptive tables and analyses will be specified in the SAP
- Data analysis will be conducted in STATA 13.

7.2.4 Secondary Outcome Analyses

For all secondary objectives we will be comparing

i) mpMRI alone to CT alone (mpMRI as a replacement test to CT)
ii) CT/mpMRI combined to CT alone (mpMRI as an add on test to CT).

Secondary Outcome 1: To compare change in unsuccessful patient management (mainly resulting from avoidance of unnecessary cancer surgery).

- Difference in proportion of patients avoiding unsuccessful patient management mostly resulting from (unnecessary) cancer surgery. mpMRI and CT will be compared against the reference standard for patient management decisions to determine unsuccessful treatment.

- Unsuccessful treatment is defined as (a) sub-optimal/open-close cancer surgery or (b) over extensive surgery for benign disease or (c) no immediate surgery offered based on false positive imaging incorrectly detecting extensive spread of disease perceived as preventing successful surgery.

- Successful patient management is defined as (i) optimal cancer surgery or (ii) appropriate surgery for benign or (iii) no immediate surgery as sub-optimal surgery predicted due to extensive spread of disease.
- Reference Standard: Patient Management Decisions further defined in Section 5.5.
- Paired comparison of proportions of using multilevel logistic regression.
- Subgroup analysis: women with benign disease.
- Descriptive analysis (a) women referred for PS, including women found to have benign disease (b) chemotherapy plus delayed surgery (c) histology ovarian cancer.

Secondary Outcome 2: To compare concordance of imaging findings and MDT decisions for surgical resectability

- Comparison of image findings determining surgical resectability and the MDT decisions determining surgical resectability, per patient.
- Reference Standard: Patient Management further defined in section 5.5.
- Paired comparison of proportions of imaging findings against MDT decisions for surgical resectability using multilevel logistic regression, clustered by patient.
- Descriptive analysis (a) primary surgery (b) chemotherapy plus delayed surgery (c) histologically benign (d) histology ovarian cancer.

Secondary Outcome 3: To compare incremental cost and cost effectiveness using CT alone, mpMRI alone and mpMRI/CT combined

- Comparison of incremental cost and cost effectiveness accounting for categorisation into final surgical outcome, treatment costs and patient outcomes.
- Analyses will conform to accepted economic evaluation methods [11]. All costs will be assessed from the perspective of the NHS and personal social services costs (PSS).
- If concordance: mean incremental cost per patient of management pathway.
- If discordance: mean incremental cost per patient of management pathway; mean incremental cost per patient of treatment pathway; mean incremental cost per patient of management pathway plus treatment pathway; mean quality adjusted life years (QALYs) gained per patient; incremental net monetary benefits.
- Full details of the health economics analysis can be found in the health economics analysis plan.

Secondary Outcome 4: To compare diagnostic accuracy of disease extent both per patient and per location

- Difference in sensitivity and specificity of site-specific disease, per patient and per location.
- Per patient outcomes: PCI and peritoneal presence.
- Per location: Site by site disease.
- Reference Standard: Peritoneal Disease Extent and Reference Standard for Staging (refer to section 5.5).
- Paired comparison of proportions of using multilevel logistic regression, clustered by patient.
- Disease locations will be defined in the SAP.

Secondary Outcome 5: To compare MDT planning between local and external MDTs for surgical operation and patient care

- Comparison of MDT plans between local and external MDTs for treatment choice, ITU stay, length of operation, surgical expertise needed, per patient.

- This will be a description of how often pre-treatment plans compare between MDT sites, without comparison to a reference standard. For each patient there will be comparison to a S-MDT and a C-MDT.

7.2.5 Sub-Studies Analysis

Sub-Study Outcome 1: To evaluate Inter-observer agreement of mpMRI for sites of disease and stage

- Inter-observer agreement of mpMRI interpretation for accurate diagnosis of referral for sites of disease and cancer stage; per patient (PCI and presence of peritoneal disease) and per location (site specific).
- Reference Standard: Disease Extent further defined in section 5.5.

Sub-Study Outcome 2: To compare mpMRI to conventional MRI

- Comparison of mpMRI to conventional MRI (analyse for primary outcome and secondary outcomes 1 and 2 only) in order to determine incremental benefit.
- Reference Standard: Disease Extent further defined in section 5.5.

7.2.6 Interim Analysis

Interim analyses to assess any potential harms arising from use of mpMRI, will be conducted on instruction from the Independent Data Monitoring Committee (IDMC). Any potential harms arising from mpMRI would be due to inappropriate additional use of invasive tests such as tissue biopsy or withholding surgery due to false positive mpMRI results. After the internal pilot, the IDMC will also assess the feasibility of the study. In addition, interim analyses of prevalence of OC and OC stages will be followed to check sample size estimates. There are no planned stopping rules for this study, as it compares radiological imaging methods in current clinical use in the NHS and in order to influence NHS practice, study results will need to be conducted in a sufficient number of patients to be statistically reliable and also for face validity and sufficient to influence clinical practice. These interim analyses are not based on the study primary outcomes and so do not affect study power.

7.2.7 Reduction of Bias in Imaging Interpretation and Reporting

Scans	Methods Used to Reduce Bias
CT and mpMRI radiologist interpretation	Anonymised images will be accessed via different user accouts with defined user permissions for reader A or reader B interpretation within trial. Different readers report CT and mpMRI scans. If the recruiting site is unable to assign two different blinded readers, CCTS will assign a "buddy" reader from a different centre for mpMRI and/or combined. Anonymised image, so access to prior clinical information or patient scans is appropriate to trial. Results locked onto eCFR.
CT/ mpMRI radiologist interpretation	Reader A and B will have access only to their own images for interpretation. Reader B will only be able to complete combined read after CT alone report is locked. Anonymised image, so access to prior clinical information or patient scans is appropriate to trial.
Local MDT	CT based staging and treatment plan will be locked on eCRF before, mpMRI critical findings report is revealed. This blinds local MDT to MRI report findings for CT based decisions. Reader B will not disclose any information regarding the mpMRI, other that that in the criticial findings report,during the first local MDT meeting.
External MDT	Anonymised patient reports are presented in randomly allocated, with only one imaging report for each participant per MDT meeting. Order of imaging reports randomly allocated for each patients. Each patient will be allocated to one C-MDT and one S-MDT. Patient reports are sent to separate centres to local MDT. Approximately 3 month intervals between reports for the same patient based on different imaging system. MDT treatment decision eCRFs are locked and not accessible except to CCTS after each MDT meeting.
Reference standard for treatment, staging and treatment extent	Review of all reports by local MDT and blinded to external MDT decisions.

8 REGULATORY, ETHICAL AND LEGAL ISSUES

8.1 Declaration of Helsinki

The investigator will ensure that this study is conducted in full conformity with the principles of the 1964 Declaration of Helsinki and any subsequent revisions.

8.2 Good Clinical Practice

The study will be conducted in accordance with the guidelines laid down by the International Conference on Harmonisation for Good Clinical Practice (ICH GCP E6 guidelines).

8.3 Independent Ethics Committee/Institutional Review Board Approval

8.3.1 Initial Approval

Prior to the enrolment of patients, the IEC/IRB must provide written approval of: the conduct of the study at named sites, the protocol and any amendments, the Patient Information Sheet and Consent Form, any other written information that will be provided to the patients, any advertisements that will be used and details of any patient compensation.

8.3.2 Approval of Amendments

Proposed amendments to the protocol and aforementioned documents must be submitted to the IEC/IRB for approval. Amendments requiring IEC/IRB approval may be implemented only after a copy of the IEC/IRB's approval letter has been obtained.

Amendments that are intended to eliminate an apparent immediate hazard to patients may be implemented prior to receiving Sponsor or IEC/IRB approval. However, in this case, approval must be obtained as soon as possible after implementation.

8.3.3 Annual Safety Reports and End of Trial Notification

The IEC/IRB will be sent annual safety updates in order to facilitate their continuing review of the study (reference. ICH GCP E6 Section 3.1.4) and will also be informed about the end of the trial, within the required timelines.

8.4 Insurance

The Sponsor has civil liability insurance, which covers this study in the United Kingdom.

8.5 Informed consent

The Principal Investigator at each site will:

- Ensure that each patient is given full and adequate oral and written information about the study including the background, purpose and risks/benefits of participation.
- Ensure that each patient is notified that they are free to withdraw from the study at any time.
- Ensure that each patient is given the opportunity to ask questions and allowed sufficient time to read and understand the information sheet.

- Ensure each patient provides signed, dated informed consent before undergoing any study specific procedure.
- Ensure the original copy of the signed, dated Informed Consent Form is stored in the Investigator site file and a copy is also filed in the medical records.
- Ensure that each patient receives a copy of the signed, dated Informed Consent Form.

8.6 Contact with General Practitioner

It is not necessary for the GP to be contacted concerning this study. If the patient requests that the investigator communicate with the GP regarding the study, it is the principal investigator's responsibility to consider this and the decision should be documented in the patient notes.

8.7 Data Protection

The principal investigator must ensure that the patient's privacy is maintained. On the eCRF or other documents submitted to the Sponsors, patients will be identified by a trial ID number only. Documents that are not submitted to the Sponsor (e.g. signed informed consent form) should be kept in a strictly confidential file by the principal investigator.

The investigator shall permit direct access to patients' records and source document for the purposes of monitoring, auditing, or inspection by the Sponsor, authorised representatives of the Sponsor and IECs / IRBs.

Precautions will be taken to ensure that patient confidentiality is preserved at all times. The patient consent form will identify those individuals who will require access to patient data and identifiable details and obtain appropriate permission from the consenting patient.

8.8 End of Trial

The end of the trial is defined as the last data capture (i.e. the last external MDT) of the last patient undergoing the study. This is expected to be approximately 9 months after the last patient is enrolled.

8.9 Study Documentation and Data Storage

The investigator must retain essential documents until notified by the Sponsor (Imperial College London), and at least for ten years after study completion, as per Imperial College London policy. Patient files and other source data (including copies of protocols, CRFs, original reports of test results, correspondence, records of informed consent, and other documents pertaining to the conduct of the study) must be kept for the maximum period of time permitted by the institution. Documents should be stored in such a way that they can be accessed/data retrieved at a later date. Attention should be given to security and environmental risks.

No study document will be destroyed without prior written agreement between the Sponsor and the investigator. Should the investigator wish to assign the study records to another party or move them to another location, written agreement must be obtained from the Sponsor.

9 DATA AND STUDY MANAGEMENT

9.1 Source Data

All original records and certified copies of original records of clinical findings, observations, or other activities necessary for the reconstruction and evaluation of the trial are classified as source data. Source data are contained in source documents; these are defined as: original documents, data, and records e.g., hospital records, clinical and office charts, laboratory notes, memoranda, patients' diaries or evaluation checklists, recorded data from automated instruments, copies or transcriptions certified after verification as being accurate copies, microfiches, photographic negatives, microfilm or magnetic media, x-rays, patient files, and records kept at the laboratories and at medico-technical departments involved in the clinical trial.

For the purpose of this study information entered directly into the eCRF as part of the image reporting, treatment plan, surgery and histopathology eCRFs will be classified as source data. eCRF's may be completed by central readers in EU countries that are trained as MROC investigators and delegated to this task.

9.2 Language

CRFs will be in English. Generic names for concomitant medications should be recorded in the eCRF wherever possible. All written material to be used by patients must use vocabulary that is clearly understood, and be in the language appropriate for the study site.

9.3 Data Collection

In compliance with Good Clinical Practice (GCP), the medical records/medical notes should be clearly marked and allow easy identification of a patient's participation in the clinical trial.

The Investigator (or delegated member of the site study team) must record all data relating to protocol procedures into the MROC electronic data collection system as indicated by the Data Collection Manual.

9.4 Electronic Recording of Data

Full details for procedures for data collection will be provided in the Data Collection Manual.

9.5 Data Management

Data management will be performed by the CCTS using the data capture systems. The system allows for real time oversight of trial activity including adverse event reporting.

AE data will be coded using the Medical Dictionary for Regulatory Activities (MedDRA) system organ class and preferred term, and CTCAE grade.

Data queries will be raised for inconsistent, impossible or missing data. All entries to the study database will be available in an audit trial.

9.6 Study Management Structure

9.6.1 Independent Trial Steering Committee

An independent Trial Steering Committee (TSC) will be convened including as a minimum an independent Chair, an independent statistician, independent clinician, the Chief Investigator and trial coordinator. The

role of the TSC will be to provide overall supervision of the trial progress and, as necessary, advice to the Trial Management Group on operational issues.

9.6.2 Trial Management Group

An internal Trial Management Group (TMG) will be convened including the Chief Investigator, co-investigators and identified key collaborators, the trial statistician and trial coordinator. Principle Investigators and key study personnel may be invited to join the TMG as appropriate to ensure representation from a range of sites and professional groups.

Notwithstanding the legal obligations of the Sponsor and Chief Investigator, the TMG will have operational responsibility for the conduct of the trial. Further details regarding the responsibilities, membership and timing of meetings will be defined in the TMG charter.

9.6.3 Independent Data Monitoring Committee

An Independent Data Monitoring Committee (IDMC) consisting of an independent chair, independent statistician and independent clinician and will define its role and conduct with reference to recommendations for IDMC conduct from the DAMOCLES charter [12] and specific recommendations for IDMC for diagnostic accuracy studies.

The IDMC will be convened to assess whether there are any safety issues that should be brought to the participants' attention, any reasons for the trial not to continue, to assess quality and to advise on evaluation of sample size assumptions during trial recruitment. Reccomendations from the IDMC will be reported back to the TSC.

9.7 Monitoring

The study will be monitored periodically to assess the progress of the study, verify adherence to the protocol, ICH GCP E6 guidelines and other national/international requirements and to review the completeness, accuracy and consistency of the data.

Monitoring procedures and requirements will be documented in a Monitoring Plan. Monitoring will be proportionate to the objective, purpose, design, size, complexity, blinding, endpoints and risks associated with the clinical trial. The appropriate level and nature of monitoring required for the clinical trial will be assessed by undertaking a formal risk assessment analysis of the study.

9.8 Quality Control and Quality Assurance

Quality Control will be performed according to Imperial College London internal Standard Operating Procedures. The study may be audited by a Quality Assurance representative of the Sponsor. All necessary data and documents will be made available for inspection.

Quality assurance of the study site MRI scanners and the acquired scans will be undertaken by the Sponsor. A QA completion document for each MRI scanner to be used will be filed in the Trial Master File and the Investigator Site File.

9.9 Disclosure of Data and Publication

Information concerning the study, patent applications, processes, scientific data or other pertinent information is confidential and remains the property of the Sponsor. The investigator may use this information for the purposes of the study only.

If the patient consents to having their NHS number collected, this will be held securely and centrally by CCTS, Imperial College London. CCTS will preserve patient confidentiality and will not disclose or reproduce any information by which patients could be identified. Data will be stored in a secure manner and CCTS are registered in accordance with the Data Protection Act 1998. Researchers conducting ethically-approved studies may apply for access to this information in order to obtain long-term follow up data regarding disease status.

In order to allow the use of the information derived from this clinical study, the investigator understands that he/she has an obligation to provide complete test results and all data developed during this study to the Sponsor. External verbal or written discussion of results prior to study completion and the final CSR, should only be undertaken with written consent from the Sponsor.

Therefore all information obtained as a result of the study will be regarded as CONFIDENTIAL, at least until appropriate analysis and review by the investigator(s) is completed.

Investigators may only present data separately to the total data available externally, with the permission of the CI, TMG, TSC and IDMC and not less than 6 months after the publication of the main results.

All investigators that contribute to patient recruitment, data collection or analysis will be included as named authors, identifiable in PubMed, under the title of 'MROC investigators'. Those investigators that actively take part in manuscript preparation will form writing groups for particular publications and may be named authors representing the MROC investigators.

10 REFERENCES

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12. Damocles Study Group, N.H.S.H.T.A.P., *A proposed charter for clinical trial data monitoring committees: helping them to do their job well.* Lancet, 2005. **365**(9460): p. 711-22.

11 SIGNATURE PAGES

SIGNATURE PAGE 1 (Chief Investigator)

The signature below constitutes approval of this protocol by the signatory.

I agree to the terms of this study protocol. I will conduct the study according to all stipulations of the protocol including all statements regarding confidentiality, and according to the principles of Good Clinical Practice (GCP) and local regulations.

Study Title: MROC: The Impact of Multiparametric MRI on the Staging and Management of Patients with Suspected or Confirmed Ovarian Cancer

Protocol Number: C/33/2014

Signed: _____

Professor Andrea Rockall
Professor of Radiology
Imperial College London

Date: _____

SIGNATURE PAGE 2 (Sponsor)

The signature below constitutes approval of this protocol by the signatory.

Study Title: MROC: The Impact of Multiparametric MRI on the Staging and Management of Patients with Suspected or Confirmed Ovarian Cancer

Protocol Number: C/33/2014

Signed: _____

Becky Ward
Research Governance Manager
Imperial College London

Date: _____

SIGNATURE PAGE 3 (STATISTICIAN)

The signature below constitutes approval of this protocol by the signatory.

Study Title: MROC: The Impact of Multiparametric MRI on the Staging and Management of Patients with Suspected or Confirmed Ovarian Cancer

Protocol Number: C/33/2014

Signed: _____

Dr Susan Mallett
Senior Lecturer in Medical Statistics
University of Birmingham

Date: _____

SIGNATURE PAGE 5 (INVESTIGATOR)

The signature of the below constitutes agreement of this protocol by the signatory and provides the necessary assurance that this study will be conducted at his/her investigational site according to all stipulations of the protocol including all statements regarding confidentiality.

Study Title: MROC: The Impact of Multiparametric MRI on the Staging and Management of Patients with Suspected or Confirmed Ovarian Cancer

Protocol Number: C/33/2014

Address of Institution: _____

_____

_____

Signed: _____

Print Name and Title: _____

Date: _____