Refining Ovarian Cancer Test Accuracy Scores:

A test accuracy study to validate new risk scores in women with symptoms of suspected ovarian cancer protocol

ROCkeTS Study

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FOR STUDY REGISTRATION, visit **https://rockets.medscinet.com** anytime or telephone:**0800 953 0274 (UK)** 9am to 5pm Mon – Fri (except University Closed days)

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University of Birmingham is the sponsor. Sudha Sundar is the Chief Investigator.

The University of Birmingham is responsible for obtaining necessary approvals, the Project Management Committee is jointly responsible for overseeing good clinical practice and the investigators are responsible for obtaining informed consent and care of the participants.

Signatures

The investigators and the sponsor have discussed this protocol. The investigators agree to perform the investigation and to abide by this protocol except in case of medical emergency or where departures from it are mutually agreed in writing.

Chief investigator		20/09/2018
Organisation	Signature	Date
Sponsor	For UoB sponsored trials, the sponsor will confirm approval of the protocol by signing the IRAS form and therefore a signature on the protocol is not required.	

Protocol amendments

Amendments

Amendment number:	Relevant Documents:	Changes summary
Original app	Protocol, PIS, Consent v1.1 15.12.2014;	n/a
1	Protocol, PIS update to V2.0 01.04.2015; Consent to V2.1 06.05.2015; review of patient CRFs V1.0 01.04.2015 and poster (no version number)	Clarification on target population, comparator, outcome measures, eligibility criteria, collection of USG variables and storage of confidential data.
3	Protocol update to V3.0 05.10.15, PIS and Consent to V3.0 23.11.15	Protocol amended to include addition of PMG member, clarification on biomarker assessments, eligibility criteria. Updated schedule of events. Addition of ultrasound image collection requirements and their uses. Consent amended to include new PIS version, addition of NIHR disclaimer, collection of scan images. PIS amended to clarify blood volume collection, protocol version, NIHR disclaimer, ultrasound collection and transfer, cancer registry statement.
8*	Protocol v4.0 05.04.2017	Increase of study recruitment duration.
11	Protocol v7.0 14.03.2018 PIS Premenopausal v6.0 02.02.2018 PIS Postmenopausal v6.0 02.02.2018	Protocol change to design, target population, sample size, source of potential participants, eligibility criteria, Protocol clarification on schedule of events & CRF completion, approaching patients for consent, timeline of study procedures/tests, IOTA certification requirement of scanners, data collection, death, AE reporting, archiving PIS split into pre and postmenopausal (premenopausal now required to be scheduled for surgery), sample use, contact details, complaints, NIHR disclaimer and acknowledgement, Consent: wording clarified.
13*	Protocol v8.0 20.09.2018	Increase of study recruitment duration. Correction of CRF name used to record death

* Non substantial amendment

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Abbreviations

AE	Adverse Event
BCTU	Birmingham Clinical Trials Unit at the University of Birmingham
CI	Chief Investigator
CRF	Case Report Form
DH	Department of Health
GCP	Good Clinical Practice
GP	General Practitioner
IOTA	International Ovarian Tumour Analysis
ISRCTN	International Standard Randomised Controlled Trial Number
NICE	National Institute for Health and Care Excellence
NPV	Negative Predictive Value
OC	Ovarian Cancer
PI	Principal Investigator – the local lead investigator for the ROCkeTS Study
PIS	Participant Information Sheet
PMG	Project Management Group
POG	Project Oversight Group
PPV	Positive Predictive Value
RCOG	Royal College of Obstetricians and Gynaecologists
RMI	Risk of Malignancy Index
ROC	Receiver Operating Curve
ROCkeTS	Refining Ovarian Cancer Test Accuracy Scores
ROMA	Risk of Ovarian Malignancy Algorithm
RR	Relative Risk
SAE	Serious Adverse Event
SOP	Standard Operating Procedure
UoB	University of Birmingham
UKCTOCS	U.K Collaborative Trial of Ovarian Cancer Screening
UKOPS	UK Ovarian Cancer Population Study
USG	Ultrasound

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1. INTRODUCTION

1.1. Ovarian Cancer background

Ovarian cancer (OC) has an annual incidence of 6500 women and causes 4400 deaths in the UK; the lifetime risk of developing OC is 1 in 54.[1] 80% of patients will present at advanced stage and all stage, 5 year survival rate is 40%. OC is predominantly a disease of older, post-menopausal women, however 1000 women under 50 will be diagnosed with OC annually.[1] International cancer bench marking project shows OC survival in the UK is significantly lower than other western countries; it is unclear as to whether this could be attributed to delay in diagnosis or differences in treatment received.[2]

1.2. Current diagnosis of Ovarian Cancer

National Institute for Health and Care Excellence (NICE) guidelines, in 2011 recommended sequential testing using serum Ca125 followed by pelvic ultrasound (USG) in women (particularly aged $\geq$50) presenting to primary care with symptoms on a persistent or frequent basis - persistent abdominal distension/'bloating', feeling full and/or loss of appetite, pelvic/abdominal pain, increased urinary urgency and/or frequency, unexplained weight loss, fatigue or changes in bowel habit. However these symptoms are very common[3,4] with abdominal bloating alone being documented in 16-30% of women presenting to General Practitioners (GPs).[5] Diagnostic challenges are considerable given (1) the low incidence of OC (a GP sees a woman with OC once in 3-5 years) (2) the low positive predictive value (PPV) of symptoms (only 1 in 400-600 symptomatic women have OC)[6,7] and (3) the lack of clear diagnostic pathways. Furthermore, NICE guidelines do not detail what USG abnormalities should prompt referral.

Use of this NICE guidance is extremely variable. A survey of 258 GPs report that the majority would refer patients on the basis of raised Ca125 even if the USG was normal.[8] A recent audit at City Hospital, Birmingham (unpublished) of 448 referrals through the 2 week wait clinics, reveals that the majority of referrals (90%) for suspected OC do not follow guidance. Referrals were heterogeneous in symptoms, in what the GPs considered were abnormal levels of Ca125 or abnormal USG. Two thirds of women referred were premenopausal. Ovarian masses are common in premenopausal women and up to 10% of women will undergo surgery during their lifetime for the presence of an ovarian mass.[9] Women with complex masses considered benign can undergo laparoscopic or conservative management, whereas women with malignancy who undergo thorough surgery by gynaecological oncologist have best outcomes.[10,11] Therefore, there are compelling health needs to improve early detection and reduce cancer mortality whilst minimising unnecessary intervention in women.

There is substantial literature on tests and scoring systems in women with ovarian masses presenting to secondary care. However, this literature is often derived in women with advanced stage cancer at secondary care. Literature is limited in studies of women with symptoms presenting to primary care, and no published studies of blood tests or USG in women with symptoms in primary care exist. Thus, deriving a score from a risk prediction model based on a combination of variables that include symptoms/existing serum test Ca125/new blood marker and additional details on USG, which may be used to improve the way patients are triaged both in primary care and secondary care, is a key gain of this

project. This may both improve early detection of OC and reduce the numbers of women unnecessarily referred to secondary care.

1.3. The need for a new algorithm to test for OC

Currently an average size NHS trust will receive about 100 urgent referrals a year for suspected OC. This translates, to approximately 10,000 referrals each year in the UK through the rapid access referral system alone for suspected OC; approximately 2000 will be diagnosed with OC. National Cancer intelligence network data shows that currently OC diagnosis is made in women presenting through diverse routes – 2 week referrals, routine GP referrals, cross specialty referrals with a third of patients presenting as emergency presentations.[12] Thus risk prediction models must be assessed in a heterogeneous study population in all these settings.

Optimal diagnostic pathways and risk scores generated will be highly relevant in the NHS to streamline referrals for women with suspected OCs. New scores may enable a stage shift in cancer presentations, helping the Department of Health (DH) aim for cancer mortality targets. Optimal diagnostic pathways for premenopausal women with suspected OC/complex ovarian mass and raised CA125 are not defined. In addition, a gynaecology consultant clinic will see 2 new referrals for premenopausal women with complex ovarian mass per week. Most will remain under follow-up for 12 months and undergo regular scans. ROCkeTS provides a unique opportunity to derive and validate a clinical risk score that can reliable triage patients, save resource, build a dataset in this population and can change practice. Providing USG training and regular quality assessments as part of study recruitment, will also embed quality enhanced USG in the participating sites – this is likely to disseminate across the NHS.

It is also important to stratify patients into premenopausal and postmenopausal women. Whilst the risk of OC is higher in postmenopausal women, two thirds of patients referred through the rapid access pathway are premenopausal women. Current recommended best practice for premenopausal women (Royal College of Obstetricians and Gynaecologists (RCOG) guidance[9]) with a complex ovarian mass is to assess risk of malignancy using the Risk of Malignancy Index (RMI), 200 threshold, even though the score was derived for postmenopausal women and the use of logistic regression models in a different population is flawed.

1.4. The ROCkeTS project

The ROCkeTS project aims to derive and validate new tests/risk prediction models that estimate the probability of having OC in women with symptoms. **This protocol refers to the prospective study only.**

This project will be conducted in four interlinked Phases

1. Phase 1 will be to undertake systematic reviews of the accuracy of tests and risk prediction models used for identifying OC in women with suspected OC.
2. Simultaneously, in Phase 2 we will undertake refinement of an existing risk prediction model based on additional predictions within existing large datasets. For Phase 2, we have identified 3 datasets UKCTOCS, UKOPS and International Ovarian Tumour Analysis (IOTA) that are relevant to primary care and secondary care settings in post and premenopausal women.

3. **Phase 3 Prospective study,** based on the evidence from Phases 1 and 2 , the most promising tests and risk prediction models for post and menopausal women will be externally validated, in a prospective study comprising newly presenting premenopausal and postmenopausal patients. In order to conduct this complex project as effectively as possible, we will start recruitment to the Phase 3 study and banking of samples from patients concomitant with Phases 1 and 2.
4. In Phase 4, we will develop models of pathways and cost comparisons of alternative testing. Pathways will incorporate the differences in patient management guided by different thresholds of the risk prediction models, that inform the minimum predicted probability that flags a diagnosis of OC.

1.4.1 ROCkeTS prospective study

The ROCkeTS prospective study: patients entering the study will complete a symptom questionnaire, donate a sample of blood and undergo an USG scan. Patients who undergo surgery will have their histology details recorded for the study, for patients who do not undergo surgery wellbeing will be ascertained at 12 months follow-up after presentation by a clinic visit or a telephone call. These data will be used at the end of the study to validate the novel risk prediction models developed in Phases 1 and 2.

FOR THE PURPOSE OF THIS PROTOCOL, THE TERM OVARIAN CANCER INCLUDES FALLOPIAN TUBE CANCER, PRIMARY PERITONEAL CANCER

1.4.2 Risks and benefits

There are no vulnerable groups or risks associated with this project that would prolong/complicate the Ethics or R&D approval processes as there is no intervention and all participants follow their normal care pathway,

2. ROCKETS STUDY DESIGN

2.1. Aim of the study

- To derive and validate risk prediction models that estimate the probability of having OC for women with symptoms suggestive of OC for postmenopausal and premenopausal women.
- To identify optimal risk thresholds for the models that can guide patient management.

2.2. Design

ROCkeTS study is a single arm prospective cohort diagnostic test accuracy study to evaluate existing & novel risk prediction models for post-menopausal women with symptoms. For premenopausal women, a similar cohort design has been used for the study up until Version 4.0 of the protocol. As of Version 5.0 of the protocol the design has been altered to become a prospective diagnostic case- control study, with recruitment focused on women undergoing surgery/biopsy for suspected ovarian cancer or adnexal mass. This change is necessary due to the very low prevalence of ovarian cancer observed.

A test accuracy study compares measurements obtained by index tests with those obtained by a reference standard. In this way the accuracy of index tests can be estimated. A reference standard is a test (or combination of tests) that confirms or refutes the presence or absence of disease beyond reasonable doubt..

Here, the reference standard will be histology of tissues taken from patients who proceed to surgery or biopsy or follow-up at a minimum of 12 months after presentation. The accuracy of the index test will be compared against that of the comparator test – the existing standard risk prediction score RMI.

In ROCkeTS, the index test (risk prediction models) will be derived in phases 1 and 2 and validated at the end of the study. Therefore we will collect symptom questionnaires, blood and USG data in the study to be analysed and validated at the end of the study.

2.3. Components of the new risk prediction model/s

We identify biochemical markers, symptom indices and USG as likely components of a novel risk prediction model, as these may be implemented across primary and secondary care.

2.3.1 Symptoms

Case-control studies demonstrate that symptom questionnaires have good diagnostic accuracy; Symptom scores need to be refined for use by patients in primary care.[13,14] However the duration of symptoms preceding diagnosis is uncertain.[14] Symptom questionnaires may help triage prior to referral and would also help standardise symptoms for any prediction model. This is particularly important, given the subjective nature of eliciting symptoms through unstructured clinical history taking and the existing audit evidence that they are interpreted variably. A robust symptom score that can triage referral based on a questionnaire may be very useful.

2.3.2 Biochemical markers

A number of serum biomarkers tests and multiple-marker based algorithms (ROMA, OVA1) have been identified in the last decade. Abnormal He4 biomarker levels is a novel test that may improve risk stratification for OC. A recent systematic review reports that He4 shows improved diagnostic performance to Ca125, however studies showed considerable heterogeneity.[15]

All study biomarker assessments will not be available to the participant's medical team. All study biomarker assessments will not be tested in real time with the participant's standard care.

2.3.3 Ultrasound based models –IOTA risk prediction models

DH has a policy of increasing access to USG in primary care.[15] Timmerman group suggest IOTA USG 'm rules' may be most accurate in triaging women.[16,17] However, 'm' rules are not in common practice and have not been extensively validated in non-specialist hands.

IOTA – The International Ovarian Tumour Analysis (IOTA) collaboration have conducted 5 previous prospective studies to derive standardization of USG description of adnexal pathology. The group have developed USG based novel risk prediction models using prospectively collected large databases to determine the optimal approach to characterize adnexal pathology preoperatively. A two-step strategy using the IOTA simple rules (image below) supplemented with subjective assessment of USG findings when the rules do not

apply, also reached excellent diagnostic performance (sensitivity 90%, specificity 93%) and misclassified fewer malignancies than did the RMI. A pilot validation of a three step strategy (simple descriptors/simple rules/subjective assessment) to triage benign from malignant masses demonstrated improved diagnostic performance over the RMI, even with USG examiners of varying levels of experience and training as would be the case in routine NHS practice.[16-18]

Many adnexal masses have a typical USG appearance and can therefore be easily correctly classified even by relatively inexperienced USG examiners. IOTA group have established simple rules based on a number of clearly defined USG features that can guide examiners. Using these simple rules no risk estimates are produced, but tumours are classified as benign, malignant or unclassifiable. The simple rules consist of five USG features of malignancy (M-features) and five USG features suggestive of a benign mass (B-features) see Figure 1. These features with corresponding USG images are shown in this image. A mass is classified as malignant if at least one M-feature and none of the B-features are present, and vice versa. If no B- or M-features are present, or if both B- and M-features are present, then the rules are considered inconclusive (unclassifiable mass) and a different diagnostic method should be used.

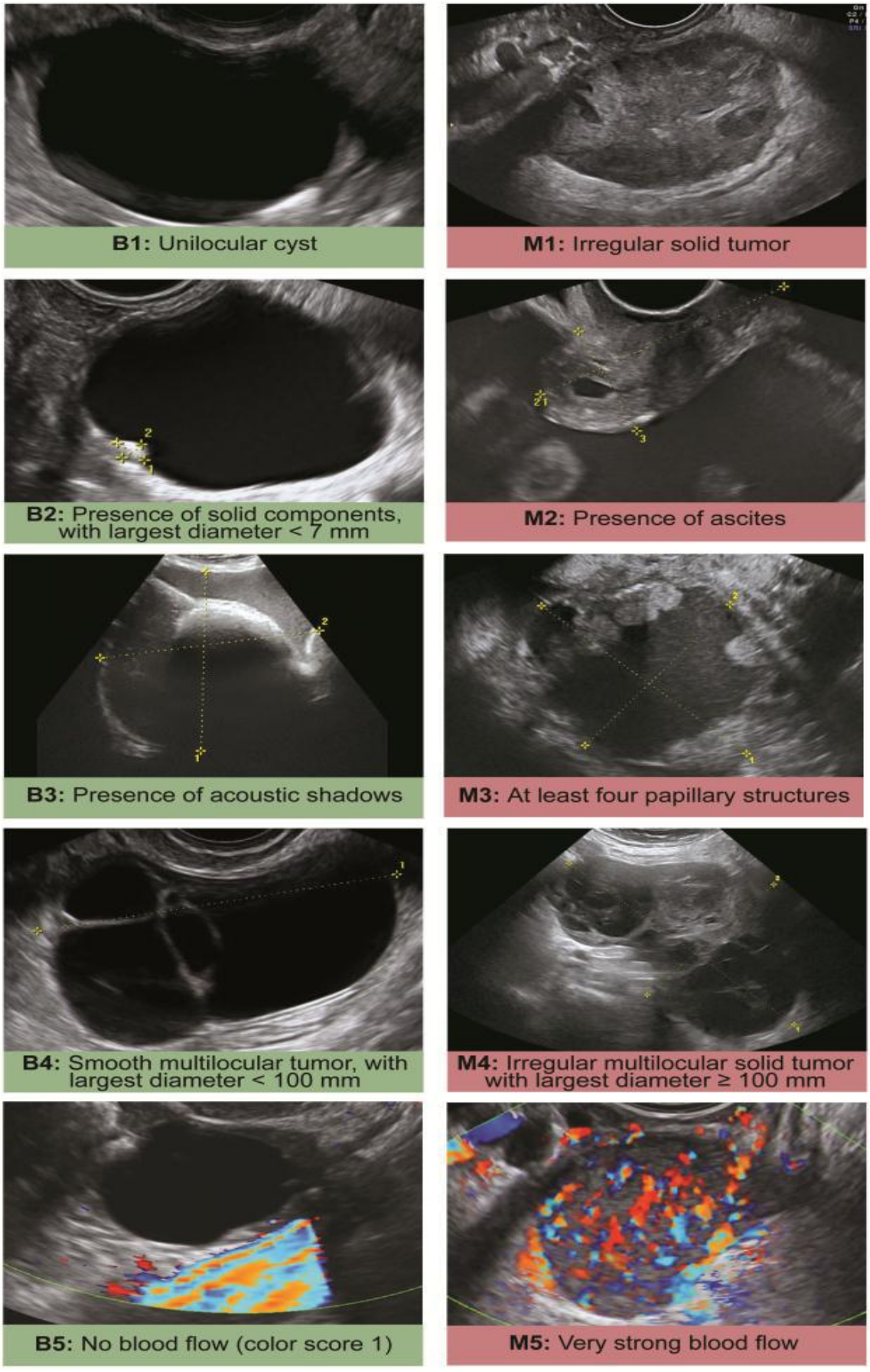


Figure 1. Illustrative examples of the use of IOTA 'm' malignancy rules are illustrated by USG images. B1–B5, benign features; M1–M5, malignant features.

2.4. Setting

Recruiting from 20-30 sites within the UK. Secondary care – Outpatients: 2 week referrals, USG clinics, routine GP referrals, cross specialty referrals. Inpatients: emergency presentations to secondary care.

2.5. Target Population

Postmenopausal women who have been referred to secondary care with symptoms of suspected OC.

As of Protocol Version 5.0: Premenopausal women who have been referred to secondary care with symptoms of suspected OC undergoing surgery/biopsy for adnexal mass.

Symptoms are as defined by NICE which include but not restricted to, persistent or frequent abdominal distension, feeling full (early satiety) and/or loss of appetite, pelvic or abdominal pain, increased urinary urgency and/or frequency. Symptoms listed here are not an exhaustive list.

2.6. Comparator

RMI at cut off 250.

2.7. Outcome measures and costs

Validation of a risk prediction model and tests for estimating the probability of OC in women with suspected OC; key outcome measures are the accuracy of the tests and models in terms of their discrimination ability (e.g. sensitivity, specificity) and calibration (observed versus predicted probabilities), and the identification of thresholds to guide patient management decisions.

Reference standard for the study will be histology of tissue taken at surgery or biopsy in women who are managed surgically following study enrolment.

Study data collection will be undertaken prospectively for all participants in order to inform the costs for each pathway.

Following giving consent, at baseline, the participants, and the local study team will complete a series of CRFs (see table 1) including:

1) Participant Baseline CRF
2) Registration form

A surgery CRF should only be completed where histology is attempted from tissue taken at surgery or biopsy. Should histology from one of these procedures come back as unknown, but is identified at a later date from a subsequent surgery/histology, the surgery CRF should be updated. The surgery CRF will completed by the clinical team.

If no surgery CRF has been completed by 12 months post study entry, the 12 month Clinical CRF will be completed by the clinical team after either a clinic visit or a telephone call to the participant or from medical records.

If no surgery CRF has been completed by 12 months post study entry, the Participant 12 month CRF will be completed, this will be sent directly to the participant from the Birmingham Clinical Trials Unit with a freepost return envelope.

If insufficient information is available through the medical records and from the participant the GP will be contacted to ensure that all available data are collected.

Participation in the ROCkeTS study is completed on receipt of a completed surgery CRF if the participant does not have surgery then a completed 12 month clinical and participant CRF will be used as the participant completion.

2.8. Schedule of Events & CRF Completion

Table 1:

	Screening	Baseline	≤ 12 months
Eligibility Check	x[1]		
Valid Informed Consent	x[1]		
Registration Form CRF		x	
Online registration		x[2]	
GP Letter		x	
Blood sample		x[3]	
IOTA USG		x[3]	
Ultrasound CRF		Post USG	
Participant Baseline CRF		x[3]	
Surgery CRF			Post-surgery/biopsy
Outcome CRF			12 months – *only required if histology not obtained*
Participant 12 month CRF [4]			12 months – *only required if histology not obtained*

[1] See section 'Approaching Potential Participants to Consent'.

[2] It is acceptable to delay registration until blood sample, IOTA USG & Participant Baseline CRF are complete.

[3] Blood sample, IOTA USG and Participant Baseline CRF should all be captured within 3 months of whichever of the following occurred first: presentation, IOTA USG (see section 5.1).

[4] Requested by and sent directly to BCTU.

2.9. Sample Size

Due to the expected difference in performance in pre and postmenopausal women, separate sample sizes have been computed.

For postmenopausal women: Cohort study design. Performance of RMI is assumed to be 70% sensitive and 90% specific.37 A sample size of n= 1760 will have 90% power to detect a 13% difference in sensitivity between the preferred ROCkeTS test (83% sensitivity) and current practice test Risk of malignancy index at threshold 250 (70%

sensitivity) at the 5% significance level, allowing for a moderate positive correlation between test errors.

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For premenopausal women: Diagnostic Case-control study design. Performance of RMI is assumed to be sensitivity of 72% and a specificity of 46% (see rationale below). A sample size of 568 women will have 90% power to detect at the 5% significance level a difference of 10% from a baseline of 46% specificity (assuming uncorrelated test errors). This sample size has now been achieved.

Recruitment of premenopausal women will now focus on those more likely to have OC – ie those on the surgical pathway until we have 100 women identified as having OC (which will be adequate events to model 10 predictor variables based on the 10 events per variable rule of thumb) we predict that we will require 420 premenopausal women to achieve this.

3. SELECTION OF PARTICIPANTS

3.1. Source of potential participants

Patients referred as Outpatients; either as 2 week or routine referrals, USG clinics, inpatient and emergency presentation to secondary care. The whole spectrum of the suspected ovarian cancer population should be considered for ROCkeTS.

These should be new patients only, i.e. first presentation to the service; patients who are on routine follow up in the secondary care service as part of standard practice should not be approached for recruitment.

Premenopausal participants must be proceeding to surgery/biopsy for suspected ovarian cancer or adnexal mass.

3.2. Inclusion and Exclusion Criteria

Inclusion criteria for pre and postmenopausal women:

- Women referred with symptoms of suspected OC (typical referral symptoms are defined in section 2.5 of the protocol).

- Aged between 16 and 90 years. Both pre and postmenopausal are included.

  Menopause is defined as >12 months without menstruation. Those no longer menstruating >12 months for reasons such as contraception or hysterectomy should have their menopausal status categorised according to age; <50 years premenopausal, 51+ years postmenopausal.

- In addition women must have test results from one of the following;
  1) A raised Ca125 test result (even if imaging has not been done yet)
  2) Abnormal imaging result showing a lesion (even if CA125 test is not raised).
  3) Both a raised CA125 test and an abnormal imaging result showing a lesion

- Patients able to provide informed consent.

Additional inclusion criteria for PREmenopausal women:

- All above inclusion criteria AND must be scheduled to undergo surgery/biopsy for suspected OC or adnexal mass.

FOR THIS STUDY WE FOLLOW THE IOTA DEFINITION OF A LESION; A LESION IS PART OF AN OVARY OR AN ADNEXAL MASS THAT IS JUDGED TO BE INCONSISTENT WITH NORMAL PHYSIOLOGICAL FUNCTION.

Exclusion criteria for pre and postmenopausal women:

- USG reveals simple ovarian cysts < 5cm in size (very low risk of malignancy) and patient does not have a raised CA125.

- Patients who are pregnant..

- Previous ovarian malignancy.

- Active non ovarian malignancy – Women with a past history of cancer are only eligible if there are no documented persistent or recurrent disease and have not received treatment for this in the last 12 months. This exclusion does not apply to patients with premalignant disease e.g. cervical intra-epithelial neoplasia or patients receiving Tamoxifen/other drugs to prevent breast cancer recurrence.

Additional exclusion criteria for POSTmenopausal women:

- Patients who decline transvaginal scan.

3.3. Approaching potential participants for consent

Potential participants will be approached at their clinic appointment or whilst they are inpatients in hospital. If they are interested they will be supplied the information sheet and be given the opportunity to ask any questions. As this is a minimal risk study, observational, diagnostic test accuracy study potential participants are allowed to consent on the day of approach. Participants may choose to have the opportunity to take time and reflect on decision and then consent at a later date.

Participants who potentially fulfil the inclusion criteria for this study must have their eligibility confirmed by medically qualified doctor with access to and a full understanding of the potential participant's medical history. Eligible patients may also be identified at scan departments but again must have their eligibility confirmed by medically qualified doctor. Patients who are admitted into hospital as emergencies and undergoing investigations for OC will be approached to give informed consent. In our experience, these patients are

unwell enough to need hospital stay but are not critically unwell to the extent that they cannot fully understand the implications of consent.

Consent should be sought under unhurried circumstances – however can be obtained on the same day the potential participant is approached (i.e. the potential participant may choose to consent on the day that they receive their information sheet or take time to reflect and consent at a later date), when entry criteria are fulfilled. Consent will be sought as follows:

- A participant information sheet will be given to all women referred through rapid access 2 week wait clinics, USG and outpatient clinics for suspected OC. This participant information sheet and posters on the study will also be made generally available and prominently displayed in various areas within the participating hospitals and their primary care practices – including clinics, corridors, MDT meeting rooms, ultrasound rooms, offices. PISs are also available via the trial website All women presenting as acute admissions to hospital, will be offered the participant information sheet and the option of study participation, unless deemed inappropriate by the attending clinical team for clinical reasons. However wherever possible the patient should make the decision on whether to receive the study information or not.
- Where necessary, appropriate trust interpreters will be asked to aid discussion relating to study participation. Patients who do not understand English are eligible to enter the study provided an interpreter can fully explain the consent form, participant information sheet and symptom questionnaire to them.
- The initial approach to the potential participant will be through their clinician or appropriately trained person delegated the responsibility to approach patients to discuss the study. The consent form will be signed by the patient prior to any blood samples being taken and counter signed by the person delegated the responsibility of taking consent.
- If the scan is part of the standard care pathway, participants may receive an USG prior to consent as part of usual care. Data from these scans can be collected retrospectively into the study if the site already follows the IOTA models/rules for scanning following a participant consenting to join the trial. As the Royal College of Obstetricians and Gynaecologists has recommended IOTA rules in their guidance on management of women with cysts, it is likely that at some sites patients will have the scan performed prior to study entry. Prospective collection of ultrasound scan data will be used at centres that do not use the IOTA rules as part of the trusts standard practice where no prior scan has been performed. This flexibility is important as it will reduce additional burden on both participant and the trial centre.
- For patients who have already attended a hospital visit and who have not been given a Patient information sheet, provided a clinician has confirmed eligibility for inclusion into the study, the research nurse can approach them by phone to provide information about the study .

3.4. Obtaining consent

The participant's written informed consent to participate in the study will be obtained before entry and after a full explanation has been given of the study. Participant information sheets and consent forms will be provided so that patients can find out more about the study before deciding whether or not to participate. Patients will be assigned a study trial number after registration.

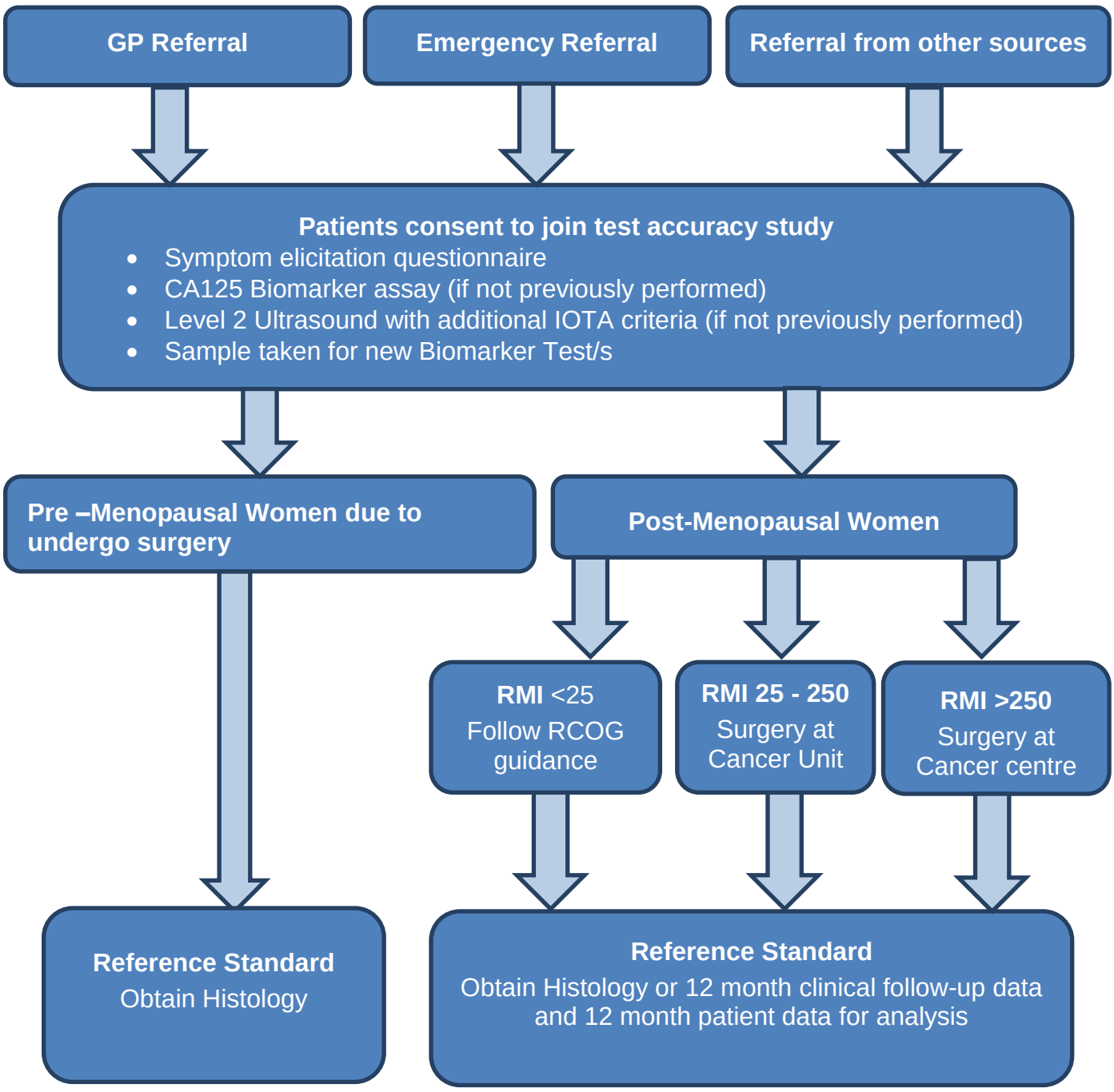
The initial participant information sheet was reviewed by 4 research advocates (patients) from Target ovarian cancer and the patient co-applicant on the study team

3.4.1 Informing the participant's GP

The participant's GP should be notified; with the participant's consent and a specimen "GP Letter" is supplied.

4. RECRUITMENT

4.1. Flow chart



4.2. Recruitment

In order to obtain the large number of participants necessary for the reliable evaluation of the index tests, the study will need the participation of more than one centre. To make these practicable, study procedures need to be kept simple, with the minimal extra workload placed on participating clinicians, beyond that required to manage their patients. This will be achieved by simple entry procedures, early consent of women, the use of standard local testing regimens, minimising documentation and streamlining data collected procedures. Regular newsletters will keep collaborators informed of study progress, and

regular meetings will be held to report progress of the study and to address any problems encountered in the conduct of the study.

4.3. Organisation of Recruitment

Recruitment will be organised and supported by dedicated research nurses, who will work with local lead investigators and lead sonographer/radiologist. We believe that that the following strategy is likely to be successful in achieving maximum recruitment.

- Each participating centre has nominated an interested local lead clinician and imaging lead who will take responsibility for ensuring IOTA implementation, training and quality assurance is organised at the site. Sites recruiting to ROCKETS will demonstrate competency in IOTA rules/models of ultrasound. Training may be delivered online or face to face. Where appropriate, sites will receive a site visit from a person nominated by the IOTA team.
- Identification of appropriate research staff (doctors, clinical nurse specialists, research nurses, sonographers). A nurse at each site with responsibility for consent and study specific procedures.
- As part of the standard care pathway participants may receive an USG prior to consent, the data from these scans can be collected retrospectively if the scan centre already follows the IOTA rules, this is likely at some centres as the use of IOTA rules is recommended by the RCOG. Prospective collection of ultrasound scan data will be used at centres that do not use the IOTA rules in trusts standard practice. This flexibility is important as it will help reduce additional burden on both participant and the trial centre.
- Appointment of a trials unit co-ordinator at BCTU, who will liaise with all the coordinating research nurses at each site and coordinate the screening at this hospital, provide training and trouble-shoot recruitment and follow-up problems.
- Provision of simple written study information, supported by face to face discussion with clinical staff.
- Provision of regular feedback on progress in study recruitment, including individual hospital teams' performance and progress against targets.
- Regular newsletters to all relevant staff involved in the study.

4.4. Other management at discretion of local doctors

Apart from the study tests, all other aspects of participant management are entirely at the discretion of the local doctors and as per the RCOG guidelines for management of these participants.[9,19] Treating clinicians will be asked to record their treatment recommendations as per standard care and after any additional USG information in order to assess the impact of this test on care pathways.

4.5. Conduct and Withdrawal

The conduct of the study will be in accordance with the Research Governance Framework for Health and Social Care and/or the Research Governance Framework for Health and Community Care. The participant's written informed consent to participate in the study must be obtained before any study procedures or questionnaires are completed. The women's GP will be notified of her participation in the study with her consent (GP letter).

Participants will be free to withdraw from the study at any time without any effect on standard of care, data and samples provided up to the point a participant withdraws will be

retained unless the participant expressly requests their removal. This is because analysis will be based on all recruited participants and per protocol.

5. STUDY PROCEDURES AND TESTS

5.1. The Index tests

There are 3 index tests that will be performed in the prospective single arm test accuracy study. All 3 index tests should all be done within 3 months of one another – the clock starting at either presentation or at the point the first index test is done – whichever occurs first.

1. Whilst symptoms are routinely elicited and recorded as part of a clinical assessment at presentation to secondary care, this is not standardised and involves the doctor transcribing elicited symptoms from the participant. Study - Participants entering the study will complete a symptom elicitation questionnaire, anxiety questionnaire and a general CRF including resource usage

2. A transabdominal and transvaginal USG is performed for all patients suspected of OC as part of NICE guidelines. This is usually performed by trained ultrasonographers who report the scan as per routine.

   Ultrasonographers will record the USG variables and score the USG using a scoring system called the IOTA 'm' rules.[16,18] The IOTA rules have been recommended by the RCOG in women with ovarian cysts in their guidelines.[9] For most women in the study, this will only mean some additional data being collected during their USG appointment, for sites that use these rules in standard practice already it may mean data collection only with no additional work for the sonographer. For a small number of women, this may mean an additional USG scan after consent. Some sites will have already used IOTA 'm' rules as part of standard care, at these sites it may be possible to collect retrospective USG data after consent. Surgery should be planned within 120 days after USG.

   For premenopausal women participating in the study – an additional transvaginal scan recording IOTA variables is desirable but not mandatory as the study team recognise that in women on the surgical pathway, timelines may not permit scheduling of an additional transvaginal scan. If a transvaginal scan recording IOTA variables has been performed within 120 days prior to the surgery then that scan can be used to provide information for ROCkeTS

3. Participants will have an additional blood sample taken at baseline for biomarker assessment at the end of the study. Treating doctors will be blinded to any new biomarker assessments done as part of this study, this is because all biomarker assessments are not being performed in real time. Details of blood sample collection will be provided in the lab manual.

5.2. Quality assurance of index tests

The study team recognise that USG in particular is subjective and operator dependent. Therefore only those sonographers/doctors who are IOTA certified may perform USG as part of the ROCkeTS study . Sites will commit to undergoing quality assurance as part of this.

Quality assurance of testing will begin with a clearly documented staff training programme. A register of staff who have been trained, and their competence assessed will be maintained, and only staff whose names appear on this list will be permitted to undertake testing. Staff will also receive a site visit and assessment of their competence. Competence will be assessed by those authorised by the IOTA team.

As part of ROCkeTS, sites will be required to upload ultrasound images to the ROCkeTS study database for each participant enrolled in the study. We require at least 5 images per participant (but more can be supplied), but it is expected that the images should show all aspects of the IOTA standards reported.

5.3. Reference standard/Follow-up Schedule

Reference standard for the study will be histology of tissue taken at surgery or biopsy in women who are managed surgically following study enrolment. Outcome of participants referred for suspected OC that do not undergo surgery will be assessed by a follow-up visit at 12 months or by a telephone call or a questionnaire from the research nurse at 12 months, as per the local investigators' discretion and clinical assessment. Wellbeing will be ascertained at this follow-up.

5.4. Study Duration

We anticipate recruitment of 2748 participants by end of February 2019, with a maximum of 12 months follow-up from the last participant entering the study.

5.5. Sample acquisition, Storage and Transport

Please refer to the laboratory manual.

5.6. Data collection

All information will be collected on standard proformas (Table 1) and identified by study number, initials and date of birth. Registration Form, Participant Baseline CRF, Ultrasound CRF, Surgery CRF, and Outcome CRF will be entered by the relevant site directly into the study database via a web interface. Images obtained from ultrasounds will be anonymised and uploaded by the relevant site directly into the study database via a web interface.
The coordinating centre (BCTU) will send the Participant 12 month CRF directly to the participant's home, requesting the completed form is returned directly to it. Upon receipt the BCTU will enter data directly into the study database via a web interface.

We aim to collect a minimal demographic dataset including age, ethnicity, parity, GP details and significant medical/surgical history. We aim to use the NHS number as the primary identifier when linking to national registries and to track individuals throughout the NHS. Some additional data will be collected at follow-up.

Data will be collected on relevant medical, obstetric and gynaecological, surgical history, emotional impact as well as information on the symptoms that prompted GP referral or investigation. USG information will be collected. Data on the reference diagnosis will be obtained from the histopathology form and a structured template to assess wellbeing for participants who do not undergo surgery will be developed in association with the participating sites.

5.6.1 Death

If a participant dies prior to histology data being provided to the Trials Office (if available), inform the Trials Office immediately via a Change of Status form. This is to ensure that the Participant 12 months CRF is not sent to the home of the deceased.

5.7. Analysis

5.7.1 Test accuracy

We will report estimates of sensitivity, specificity, c-statistic (area under Receiver operating curve (ROC) curve), PPV and Negative Predictive value (NPV) and for models a calibration plot. Also, in terms of our new model, its improvement over existing models will be summarised by comparing the c-statistic and the calibration; further, we will summarised the net-reclassification index for each new predictor that existing models omitted.

The risk prediction models derived in the ROCkeTS project phases 1 and 2, will each produce a predicted risk of OC by 12 months for all the individuals in our study. Therefore, we will compare the observed outcome at 12 months with this predicted risk. The calibration (in terms of calibration slope) and discrimination (e.g. c-statistic) will be evaluated for the models derived and identified in Phases 1 and 2, and their performance compared to the existing RMI model. The calibration will be shown visually by grouping women into deciles ordered by predicted risk and considering the agreement between the mean predicted risk and the observed events in each decile.

5.7.2 Cost consequence analysis

Resource usage for each of the diagnostics will be broken down and displayed along with their unit costs alongside the outcomes for each pathway. The resource usage will include the different types of tests administered, the number of inpatient and outpatient consultations, and any operative procedures undertaken. This approach will help to show which are the major cost drivers for each of the diagnostic pathways and will be collected as part of the clinical CRF.

6. ADVERSE EVENT REPORTING

There are no foreseeable risks of mortality or significant morbidity associated with testing. Every effort will be made to minimise any risk through training. **Therefore only serious adverse events[*] (SAEs) believed to be associated with any study procedures should be reported**. SAEs should be reported via fax to the Study Office

The collection and reporting Serious Adverse Events (SAEs) will be in accordance with Good Clinical Practice (GCP) and the Research Governance Framework 2005.

Safety will be assessed continuously throughout the study. Safety monitoring has been delegated by the Sponsor (University of Birmingham) to the BCTU. There are no

[*] For the purposes of this study, "**serious**" adverse events are those occurring in participants which are fatal, life-threatening, disabling or require some form of medical or surgical treatment.

Investigational Medicinal Products being used as part of the ROCkeTS study and the tests evaluated in the study are not being used to determine patient management. A risk assessment of the ROCkeTS study has been performed with all testing considered to be of low risk.

6.1. Definition of a Serious Adverse Event

The definition of an SAE is an untoward event that:

- results in death;
- is life-threatening*;
- requires hospitalisation** or prolongation of existing hospitalisation;
- results in persistent or significant disability or incapacity;
- Consists of a congenital anomaly/ birth defect
- or, is otherwise considered medically significant by the Investigator

*The term “life-threatening” 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.

** Patients must be formally admitted – waiting in out-patients or A&E does not constitute an SAE (even though this can sometimes be overnight). Similarly, planned hospitalisations that clearly are not related to the condition under investigation or hospitalisations/prolongation of hospitalisation due to social reasons should not be considered as SAEs.

6.2. Reporting Period

The main theoretically possible recognised reportable SAEs associated with this study relates to the blood sample being taken, USG conducted or distress following completion of baseline questionnaire. SAEs occurring within 24 hours of one of these events should be reported immediately upon awareness to the ROCkeTS Study Office on an SAE form. The assessment of relatedness and expectedness is a clinical decision based on all available information at the time.

SAEs outside of this timeframe can also be reported if it is the opinion of the Investigator that there is a possible causal relationship to another aspect of the study. An assessment of relatedness and expectedness will also be undertaken by the Chief Investigator (or designee).

6.3. Reporting Procedure – At Site

SAEs believed associated with any study procedures will be notifiable to the ROCkeTS Trial Office **immediately and within 24hours of becoming aware of the event**. On becoming aware that a participant has experienced said SAE, the Investigator (or delegate) must complete, date and sign an SAE Form. The form should be faxed to the ROCkeTS Trial Office using one of the numbers listed below. The Investigator will also be asked to provide a categorisation of seriousness and causality (continue reading for further details).

Fax SAE Forms to the Trials Office and inform trial team of fax submission, via telephone or email

For contact details, refer to the 'ROCkeTS Study Office' section at the front of this protocol.

For SAE Forms completed by a member of the site trial team other than the Principal Investigator (PI), the PI will be required to countersign the original SAE Form to confirm agreement with the causality and seriousness/severity assessments. The form should then be returned to the Trials Office and a copy kept in the Site File.

Investigators should also report SAEs to their own Trust in accordance with local practice.

6.4. Causality assessment

AEs defined as serious and which require reporting as an SAE should be reported on an SAE Form. When completing the form, the PI (or delegate) will be asked to define the causality and the severity of the AE.

Causality (relatedness) will be categorised according to the following coding system:

1=Unrelated to study treatment or procedure*
2=Unlikely to be related to study treatment or procedure*
3=Possibly related to study treatment or procedure
4=Probably related to study treatment or procedure
5=Definitely related to study treatment or procedure

Table 2 provides a definition for each relatedness category.

Table 2: Definitions of relatedness.

Category	Definition	Causality
Definitely	There is clear evidence to suggest a causal relationship, and other possible contributing factors can be ruled out	Related
Probably	There is evidence to suggest a causal relationship, and the influence of other factors is unlikely	
Possibly	There is some evidence to suggest a causal relationship. However, the influence of other factors may have contributed to the event (e.g. the patient's clinical condition, other concomitant events or medication)	
Unlikely	There is little evidence to suggest there is a causal relationship. There is another reasonable explanation for the event (e.g. the patient's clinical condition, other concomitant events or medication)	Unrelated
Unrelated	There is no evidence of any causal relationship	

6.5. Assessment of Expectedness

Expectedness will be assessed by the CI or designee using this study protocol as the reference document. Table 3 gives definitions of expectedness with respect to SAEs.

Table 3: Definitions of expectedness

Category	Definition
Expected	An adverse event that is classed in nature as serious and which is consistent with known information about the study related procedures or that is clearly defined in this protocol
Unexpected	An adverse event that is classed in nature as serious and which is not consistent with known information about the study related procedures

6.6. Provision of follow-up information

Participants should be followed up until resolution or stabilisation of the event. Follow-up information should be provided on a new SAE Form, making sure to include the SAE reference number, provided by the Trials Unit upon receipt of the initial SAE.

6.7. Reporting procedure – ROCkeTS Trial Office

On receipt the Trials Office will allocate each SAE a unique reference number which will be forwarded to the site as proof of receipt within 1 working day. The SAE reference number will be quoted on all correspondence and follow-up reports regarding the SAE.

On receipt of an SAE Form, seriousness and causality (relatedness to the study intervention) will be assessed independently by the Clinical Lead. Further information may be immediately requested from the clinical team at site. The Clinical Lead will not overrule the causality or seriousness assessment given by the site PI, but may add additional comment on these.

An SAE judged to have a reasonable causal relationship with the study treatment will be regarded as a related SAE. The Clinical Lead or delegate will assess all related SAEs for expectedness. If the event is it will be classified as **an unexpected and related SAE**.

6.8. Reporting procedure to Research Ethics Committee (REC)

SAEs categorised by a CI or the Clinical Lead as both believed to be associated with study participation and “unexpected” will be subject to expedited reporting to the REC by the ROCkeTS Trial Office within 15 days after the Trial Office has been notified. A copy will also be sent to the University of Birmingham Research Governance Team at the same time.

The ROCkeTS Trial Office (on behalf of the CI) will inform all PIs of relevant information about SAEs that could adversely affect the safety of participants.

The REC will be notified immediately if a significant safety issue is identified during the course of the study.

The University of Birmingham Research Governance Team will also be informed at the time that the REC is informed.

6.9. Investigators

Details of all Unexpected and Related SAEs and any other safety issue which arises during the course of the study will be reported to Principal Investigators by BCTU. A copy of any such correspondence should be filed in the Site File.

7. DATA ACCESS AND QUALITY ASSURANCE

7.1. Confidentiality of personal data

Personal data and sensitive information required for the ROCkeTS Study will be collected directly from study participants and hospital notes. Participants will be informed about the transfer of this information to the ROCkeTS study office at the BCTU and asked for their consent. The data will be entered onto a secure computer database, either directly via the internet using secure socket layer encryption technology or indirectly from paper by BCTU staff. Study database will be held in a secure internet facility, through an ISO 9001 accredited and FDA compliant Integrated Trial Management System (MedSciNet).

Participants will also be informed that, and consent to, their blood samples, being transferred from local centres to the central laboratory. Samples will only be identified by their study number. Central laboratory staff will not have access to personal data. Blood samples, which have been transferred from local centres to the central laboratory, will only be identified by their study number.

All personal information received in paper format for the study will be held securely and treated as strictly confidential according to BCTU policies. All staff involved in the ROCkeTS Study (clinical, academic, BCTU) share the same duty of care to prevent unauthorised disclosure of personal information. No data that could be used to identify an individual will be published.

Data will be stored on a secure server under the provisions of the Data Protection Act and/or applicable laws and regulations.

Access to data will be restricted by usernames and passwords at two levels (the computer require username and password for access; following this the Integrated Trial Management System will require a username and password to obtain access to data. The necessary study data will be encrypted. No study data will be held in handheld media, laptops, personal computers, or other similar media.

The online database will be maintained according to prescribed security policies of BCTU or MedSciNet. These cover assignment of passwords, encryption, database immediate back−up, off−site back−up and disaster recovery processes. Electronic data will be backed up every 24 hours to both local and remote media in encrypted format. Paper-based data (e.g. signed consent forms) will be kept in locked filing cabinets at each site.

Individual participant information obtained as a result of this study is considered confidential. Each participant will be allocated a unique study number at recruitment. This database will be encrypted and include off-site back-up and disaster recovery processes.

7.2. In-house Data Quality Assurance

7.2.1 Monitoring and Audit

Investigators and their host Trusts will be required to permit study-related monitoring and audits to take place by the ROCkeTS Study Team or sponsor, providing direct access to source data and documents as requested. Trusts may also be subject to inspection by the Research and Development Manager of their own Trust and should do everything requested by the Chief Investigator (CI) in order to prepare and contribute to any inspection or audit. Study participants will be made aware of the possibility of external audit of data they provide in the PIS.

7.2.2 Statistical monitoring throughout the study

The prevalence of OC in the study will be constantly monitored and sample size calculations will be reviewed to check if the study has accrued enough samples and data to report.

7.2.3 Project Oversight Group

The Project Oversight Group (POG) provides independent supervision for the study, providing advice to the Chief and Co- Investigators and the Sponsor on all aspects of the study and affording protection for participants by ensuring the study is conducted according to the Research Governance Framework for Health and Social Care and/or the Research Governance Framework for Health and Community Care.

If the Chief and Co-Investigators are unable to resolve any concern satisfactorily, Principal Investigators (PI), and all others associated with the study, may write through the Study Office to the chairman of the POG, drawing attention to any concerns they may have or about any other matters thought relevant.

7.3. Long-term storage of data

After the end of the study, the site files from each centre should be archived by the NHS Trust as per regulations for a non-CTIMP.

All data will be stored for at least 20 years. Any queries or concerns about the data, conduct or conclusions of the study can also be resolved in this time.

Study data will be stored within the BCTU under controlled conditions for at least 3 years after closure. Long-term offsite data archiving facilities will be considered for storage after this time. The BCTU has standard processes for both hard copy and computer database legacy archiving.

7.3.1 Data Sharing

There are data sharing agreements in place between the IOTA and UKCTOCS groups and the ROCkeTS Trial Team. Over the duration of the study data will be shared between these groups. All data shared between groups will be fully anonymised and has been clearly explained in the PIS and consent form.

8. ORGANISATION AND RESPONSIBILITIES

To ensure the smooth running of the study and to minimise the overall procedural workload, it is proposed that each participating centre should designate individuals who would be chiefly responsible for local co-ordination of clinical and administrative aspects of the study.

All investigators are responsible for ensuring that any research they undertake follows the agreed protocol, for helping care professionals to ensure that participants receive appropriate care while involved in research, for protecting the integrity and confidentiality of clinical and other records and data generated by the research, and for reporting any failures in these respects, adverse drug reactions and other events or suspected misconduct through the appropriate systems.

8.1. Local Co-ordinator at each centre

Each Centre should nominate a clinical lead Doctor and an USG lead; one of whom will act as the local PI and bear responsibility for the conduct of research at their centre. The responsibilities of the local PI will be to ensure that all medical and nursing staff involved in the care of participants are well informed about the study and trained in study procedures, including obtaining informed consent. The local PI should liaise with the Study Coordinator on logistic and administrative matters connected with the study. The USG lead will take responsibility for co-ordinating IOTA USG delivery within the research study.

8.2. Nursing Co-ordinator at each centre

Each participating centre should also designate one nurse as local Nursing Coordinator. This person would be responsible for ensuring that all eligible participants are considered for the study, that patients are provided with study information sheets, and have an opportunity to discuss the study if required. The nurse may be responsible for collecting the baseline participant data and for administering the follow-up evaluations. Again, this person would be sent updates and newsletters, and would be invited to training and progress meetings.

8.3. The Study Office

The BCTU Study Office is responsible for providing all study materials, including the study folders containing printed materials and the update slides. These will be supplied to each collaborating centre, after relevant ethics committee approval has been obtained. Additional supplies of any printed material can be obtained on request. The Study Office is responsible for collection and checking of data (including reports of SAEs thought to be due to study investigations), for reporting of serious and unexpected AEs to the sponsor and/ or regulatory authorities and for analyses. The Study Office will help resolve any local problems that may be encountered in study participation.

8.4. Research Governance

The conduct of the study will be according to the Research Governance Framework for Health and Social Care and/or the Research Governance Framework for Health and Community Care.

All centres will be required to sign an Investigator's Agreement, detailing their commitment to accrual, compliance, Good Clinical Practice (GCP), confidentiality and publication. Deviations from the agreement will be monitored and the POG will decide whether any action needs to be taken, e.g. withdrawal of funding, suspension of centre.

The Study Office will ensure researchers not employed by an NHS organisation hold an NHS honorary contract for that organisation.

8.5. Regulatory and Ethical Approval

8.5.1 Ethical and Trust Management Approval

Trust R&D departments will conduct local governance checks and assess the facilities and resources needed to run the study, in order to give host site permission. The Study Office is able to help the local PI in the process of the site specific assessment by completing much of Site Specific Information section of the standard IRAS form as possible. The local PI will be responsible for liaison with the Trust management with respect to locality issues and obtaining the necessary signatures at their Trust.

As soon as Trust approval has been obtained, the Study Office will send a folder containing all study materials to the local PI. Potential study participants can then start to be approached.

8.6. Funding and Cost implications

The research costs of the study are funded by a grant from the National Institute of Health research awarded to the University of Birmingham.

The study has been designed to minimise extra 'service support' costs for participating hospitals, with no extra visits to hospital and no extra tests. Additional NHS service support costs associated with the study, e.g. gaining consent, aliquoting extra blood samples etc, are estimated in the Site Specific Information section of the standard IRAS form.

8.7. Indemnity

There are no special arrangements for compensation for non-negligent harm suffered by participants as a result of participating in the study. The study is not an industry-sponsored study and so ABPI/ABHI guidelines on indemnity do not apply. The normal NHS indemnity liability arrangements for research detailed in HSG96(48) will operate in this case.

However, it should be stressed that in terms of negligent liability, NHS Trust hospitals have a duty of care to a patient being treated within their hospital, whether or not that patient is participating in a clinical study. Apart from defective products, legal liability does not arise where there is non-negligent harm. NHS Trusts may not offer advance indemnities or take out commercial insurance for non-negligent harm.

As Sponsor, the University is responsible for the general conduct of the study and shall indemnify the Clinical Centre against any claims arising from any negligent act or omission by the University in fulfilling the Sponsor role in respect of the Study.

8.8. Publication

A meeting will be held after the end of the study to allow discussion of the main results among the collaborators prior to publication. The success of the study depends entirely on the wholehearted collaboration of a large number of doctors, nurses and others. For this reason, chief credit for the main results will be given not to the committees or central organisers but to all those who have collaborated in the study.

8.9. Ancillary studies

It is requested that any proposals for formal additional studies of the effects of the study treatments on some participants (e.g. special investigations in selected hospitals) be referred to the Project Management Committee for consideration. In general, it would be preferable for the study to be kept as simple as possible, and add-on studies will need to be fully justified.

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