PAIRS

PARP **I**nhibitor **R**esistance **S**tudy

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CRUK Glasgow Clinical Trials Unit (CRUK CTU)

(Partner of Cancer Clinical Trials Unit Scotland (CaCTUS))

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Funder(s)

Wellbeing of Women

Supported by Artios Pharma Limited

This trial will be performed according to the UK Policy Framework for Health and Social Care 2017 (as amended) and World Medical Association Declaration of Helsinki Ethical Principles for Medical Research Involving Human Subjects 1964 (as amended)

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Role: Lead Biostatistician
Date:
Signature:

Name: Nicola Jensen
Role: Sponsor Representative
Date:
Signature:

Trial Summary

Title: **Pa**rp **I**nhibitor **R**esistance **S**tudy (PAIRS)

Background: The majority of prior work on mechanisms of PARP inhibitor (PARPi) resistance in ovarian cancer have been in *in vitro* systems. In this study, we want to establish a cohort of paired tumour samples (archival pre-PARPi sample and post-PARPi sample) to identify mechanisms of PARPi resistance and their relative frequencies. We will then determine if the identified resistance mechanisms can also be detected in circulating tumour DNA. Understanding PARPi resistance will allow us to spare patients unlikely to benefit from PARPi from treatment toxicity, develop strategies to prevent the emergence of resistance and to treat PARPi resistant disease. Ultimately, knowledge gained from this study will lead to more rational use of PARPi therapy.

Design: Multi-centre, non-randomised, sample collection study

Objectives:

Primary

To obtain tumour samples from 200 patients taken from high grade ovarian cancer (HGOC) tumours that have progressed on PARPi therapy and the matched archival primary tumour sample.

Exploratory

1. To interrogate the paired samples to define the PARPi resistance mechanisms that occur in HGOC patients and their relative proportions.
2. To examine ctDNA at progression to establish if resistance mechanisms identified in tissue samples can be detected in blood samples.
3. In Cohort A (patients currently receiving PARPi maintenance or progression free post PARPi maintenance) – to collect serial samples for isolation of ctDNA to detect and track emerging resistance in patients whose disease subsequently progresses.

Endpoints:

Primary

Number of PARPi resistant tumours and matched pre-PARPi tumour samples obtained.

Exploratory

1a. Homologous recombination repair (HRR) gene aberration status using whole exome sequencing (WES) and RNAseq in pre-PARPi tumour samples.

1b. Homologous recombination (HR) status in pre-PARPi tumour samples.

1c. Status of methylation of HRR genes in pre-PARPi tumour samples

1d. HRR gene aberration status in post-PARPi tumour sample using WES and RNAseq (where relevant).

1e. HR status in post-PARPi tumour samples for cases previously found to have HRD disease.

1f. Methylation status in post-PARPi tumour samples for cases previously found to have a methylation event in their pre-PARPi tumour.

1g. Status of other pathways implicated in PARPi resistance as determined by proteomic and other analysis.

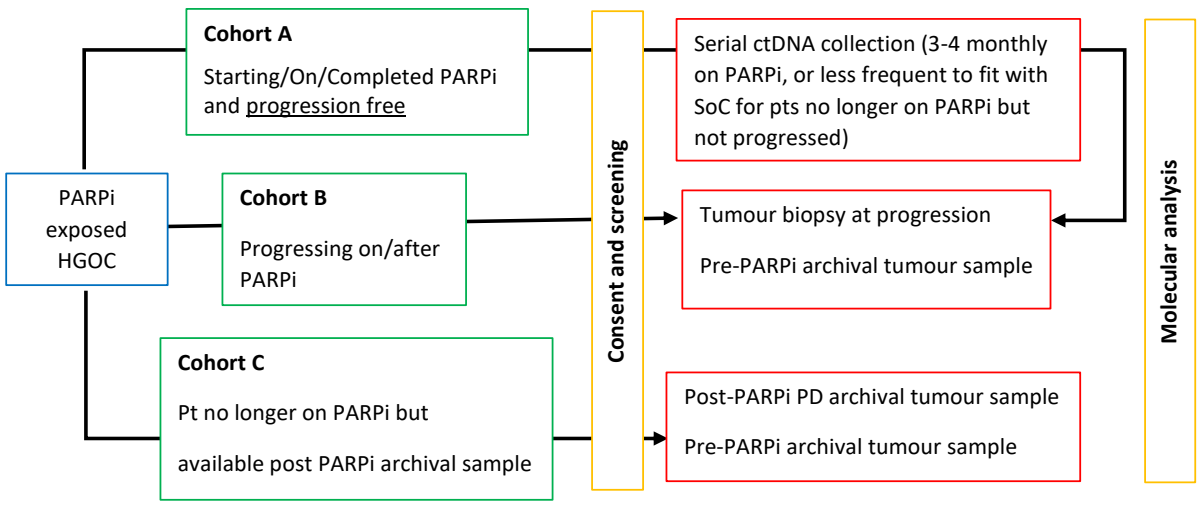
1h. Proportion of tumours with each resistance mechanism.

2. Proportion of patients where resistance mechanism can be identified in ctDNA.

3. Proportion of patients where resistance mechanism can be identified in ctDNA prior to detection of disease progression by standard clinical assessments.

Population: Patients with high grade epithelial ovarian cancer who are being/ have been treated with a PARP inhibitor will be recruited to 3 cohorts (A, B and C).

PArp Inhibitor Resistance Study (PAIRS) scheme



PARPi=PARP inhibitor, ctDNA= circulating tumour DNA, HGOC=high grade ovarian cancer, Pt=patient, PD=progressive disease, SoC=standard of care

Eligibility: **Inclusion Criteria- all patients**

1. Age ≥ 16 years.
2. Histological diagnosis of high-grade serous, high-grade endometrioid or carcinosarcoma of the ovary, primary peritoneum or fallopian tube.
3. Availability of formalin-fixed, paraffin-embedded tissue taken at the time of original diagnosis of high grade serous ovarian cancer. This may be primary surgical debulking specimen OR core biopsy. For those with only a core biopsy from time of diagnosis, availability of specimen taken at interval debulking surgery is also requested.
4. Prior treatment with a PARP inhibitor or about to commence maintenance PARPi therapy (cohort A). PARPi can be single agent or in combination with bevacizumab. If PARPi is in combination with a different agent as part of a clinical trial, the patient may still be eligible but this should be confirmed with the Cancer Research UK Glasgow Clinical Trials Unit prior to patient registration.

Inclusion Criteria- cohort A

1. About to commence, currently receiving PARPi as maintenance therapy or completed PARPi maintenance with no intervening treatment before study entry.
2. Patients need to be progression free (defined by no evidence of GCIG Ca125 progression or radiological progression). Patients who have progressed in a single site that could be considered a sanctuary site (i.e. brain metastasis) should be discussed with CTU to determine eligibility.
3. No contraindication to biopsy.
4. Ability to provide written informed consent prior to participating in the study and any study related procedures being performed.
5. Willingness to comply with trial procedures.
6. Life expectancy > 3 months.

Inclusion Criteria- cohort B

1. Patients need to have radiologically-defined progressive disease on/after PARPi. If progression is in a single site that could be considered a sanctuary site (i.e. brain metastasis), the case should be discussed with CTU to determine eligibility since recruitment to cohort A may be preferred.
2. Patients must have progressing disease deemed suitable for imaging-guided biopsy (ultrasound or CT) by an experienced radiologist or suitable for intra-operative biopsy during secondary debulking surgery as determined by an experienced gynaecological oncology surgeon. Other biopsies, such as skin

deposits, are also acceptable. However this must be confirmed with the Cancer Research UK Glasgow Clinical Trials Unit prior to patient registration (for cohort B).

3. No contraindication to biopsy.
4. No systemic anti-cancer treatment (SACT) commenced post PARPi (patients continuing PARPi after surgical resection of a progressing lesion can be included). Patients who have received 1-2 cycles of SACT whilst awaiting surgery may still be eligible for the study, please contact CTU to discuss prior to registration.
5. Ability to provide written informed consent prior to participating in the study and any study related procedures being performed.
6. Willingness to comply with trial procedures.
7. Life expectancy > 3 months.

Inclusion Criteria- cohort C

1. Patients need to have had a lesion which radiologically progressed on/after PARPi.
2. Archival tumour of a lesion progressing post PARPi must be available.
3. Ability to provide written informed consent prior to participating in the study and any study related procedures being performed. Patients with available archival pre and post-PARPi tumour samples, who are no longer living may be identified by their clinical team and registered for the study if samples were collected under generic research consent (or equivalent).

Exclusion Criteria – all patients

1. Ovarian, primary peritoneal or fallopian tube cancer of low grade serous, grades 1 or 2 endometrioid, clear cell or mucinous subtypes.
2. Borderline/low malignant potential tumours.
3. Any non-epithelial ovarian malignancy.
4. Original diagnosis of high grade serous cancer made on cytology only.
5. Discontinued PARPi for toxicity within 3 months of starting PARPi. (exclusion applies to cohort B & C only). Patients who are recruited to cohort A at initiation of PARPi and subsequently discontinue within 3 months for toxicity will be replaced. Cohort A patients who progress and discontinue PARPi within 3 months will be included in the analysis and will not be replaced
6. Any other severe concurrent disease which may increase the risk associated with trial participation.

7. Any psychological, familial, sociological or geographical considerations potentially hampering compliance with the trial and follow up schedule.

Procedure:

Cohort A and B-

Imaging-guided (Ultrasound or CT), intra-operative or other suitable biopsies will be taken for research purposes from women who have a tumour progressing on PARPi, meet the eligibility criteria and who give written, informed consent.

Cohorts A, B and C-

Blood will be taken to examine circulating markers of PARPi resistance.

- Serially (3-4 monthly on treatment, or less frequent to fit with standard of care for patients no longer on treatment but not progressed) for cohort A
- At progression for cohort B
- At recruitment for cohort C if the patient is surviving

Archival tissue will be accessed.

Associated clinical data will be recorded.

Duration: 3 year recruitment period followed by 6 month follow-up.

Table of Contents

Abbreviations

AE	Adverse Event
BRCA1/2m	Breast Cancer gene 1/2 mutation
CA125	Cancer Antigen 125
CaCTUS	Cancer Clinical Trials Unit Scotland
CI	Chief Investigator
CRF	Case Report Form
CRUK	Cancer Research United Kingdom
CTC	Clinical Trial Coordinator
ctDNA	Circulating Tumour DNA
CTIMP	Clinical Trial of an Investigational Medicinal Product
CTU	Clinical Trials Unit
FIGO	The International Federation of Gynecology and Obstetrics
HR	Homologous Recombination
HRR	Homologous Recombination Repair
HGOC	High Grade Ovarian Cancer
IDMC	Independent Data Monitoring Committee
ISF	Investigator Site File
IMP	Investigational Medicinal Product
NGS	Next Generation Sequencing
NIMP	Non Investigational Medicinal Product
PARP	Poly (ADP-ribose) polymerase
PI	Principal Investigator
PNF	Pregnancy Notification Form
PM	Project Manager
PV	Pharmacovigilance
R&D	Research and Development
RAE	Related Adverse Reaction
REC	Research Ethics Committee
RNAseq	Ribonucleic Acid Sequencing
RSI	Reference Safety Information
SAE	Serious Adverse Event
SUSAR	Suspected Unexpected Serious Adverse Reaction
SOP	Standard Operating Procedure

TSC	Trial Steering Committee
UTSC	Umbrella Trials Steering Committee
WES	Whole Exome Sequencing

Trial Flow Chart

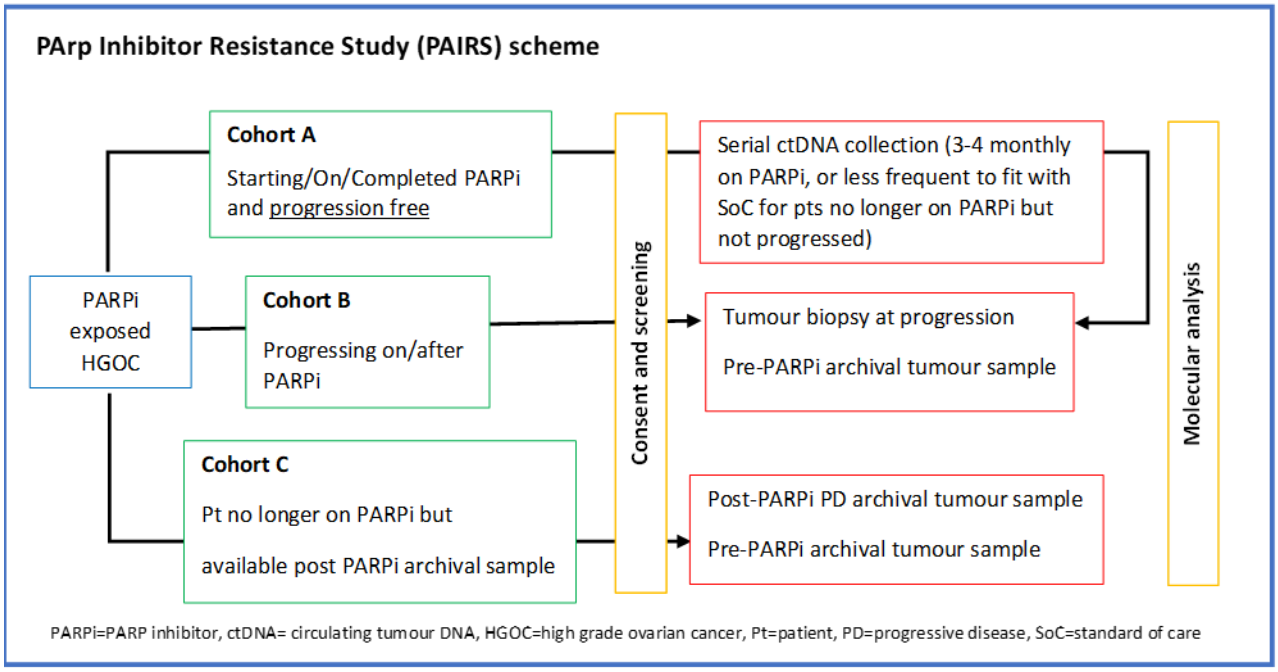


Figure 1: Study Scheme

Schedule of Assessments

	Cohort A			
	Cohort B		Cohort B	Cohort B
	Cohort C[1]			Cohort C
	Consent visit[2]	On tx visit[3]	Progression visit	Follow-up visit[4]
Written informed consent	X			
ECOG performance status	X[5]			
Histology	X			
FIGO stage	X[5]			
Document prior SACT[6]	X			
Response to prior SACT[7]	X			
Surgical procedure(s)[8]	X			
Surgical outcome[9]	X			
Known genetic results[10]	X			
Archival pre-PARPi tumour[11]	X			
Radiological disease assessment[12]	X	X	X	X
Ca125[13]	X[5]	X	X	X
PARPi start details and indication[14]	X			
PARPi compliance		X		
Basis of progression on PARPi[15]			X	
Haematology[13]			X	
Biochemistry[13]			X	
ct DNA	X[16]	X[21]	X[17]	
Germline DNA sample	X[16]			
Core biopsy/resection specimen[18]			X	
Serious adverse events[19]			X	
Subsequent therapies and responses[20]				X
Survival status				X

[1]Patients who are no longer living could be recruited to cohort C if they have available archival tumour samples pre and at progression on PARPi if generic research consent allow use of their samples and associated data for research.
[2]Remote consent and data collection are permitted
[3]Every 3-4 months to fit with standard of care assessments
[4] At 6 months post progression on PARPi and/or at final data-cut. For patients yet to progress follow-up will be at final data-cut. This visit can be performed virtually or at clinic attendance.
[5]At diagnosis
[6]Drugs, schedule, start date, stop date
[7]Clinical, radiological, biochemical, histological (if chemotherapy response score reported on delayed primary surgery specimen). This also includes the date of progression following SACT and the basis of progression (all or some of clinical, radiological and/or biochemical).
[8]Including dates
[9]Complete cytoreduction, optimal, sub-optimal for each procedure
[10]Germline and/or somatic BRCA1/2 and any other genes sequenced and HRD status if known.
[11]Core, primary surgical specimen, interval debulking specimen.

[12]Dates of standard of care imaging and disease sites and measurements on each should be recorded including initial diagnostic imaging and all subsequent.
[13]Sample collected as per standard of care
[14]To include name of PARPi and starting dose and date as well as indication for PARPi (1st-line maintenance, 2nd or subsequent line maintenance, treatment)
[15] Based on standard of care clinical assessment, imaging and Ca125. Please detail if progression was all or some of clinical, radiological or biochemical.
[16] All Cohorts except unconsented (deceased) Cohort C.
[17]ctDNA sample to be taken before biopsy
[18]If having secondary surgery study biopsy can be taken at that time. See lab manual for instructions.
[19] Only SAEs which are related to study biopsy and unexpected need to be reported.
[20] Drugs, schedule, start date, stop date, PARPi stop date and dose at stopping, adverse events leading to dose reductions, response (clinical, biochemical and radiological), progression free survival
[21] For cohort A patients no longer on PARPi but have not progressed, ctDNA collection can be less frequent to fit with standard of care assessments.

1 INTRODUCTION

1.1 Background

High grade serous ovarian cancer (HGSOC) is the most common histological type of ovarian cancer (approx[19]. 70% of epithelial tumours). Typically, it presents late and causes significant morbidity and mortality. Traditionally, treatment includes cytoreductive surgery and platinum-based chemotherapy [1]. In recent years the addition of maintenance PARPi therapy has achieved an improvement in ovarian cancer outcome in the first-line [2-4] and relapsed disease settings [5-7] , delaying the relapse of disease by a median of three years in one study [3]. In the first-line maintenance setting, patients in response to chemotherapy may receive either olaparib[19] monotherapy, if they have a BRCA1/2 mutated tumour, or niraparib, which may be used regardless of BRAC1/2 status, or olaparib[19] in combination with bevacizumab, which may be used in patients with homologous recombination defective (HRD) tumours. In the second-line maintenance setting, patients in response to chemotherapy may receive either niraparib or rucaparib. Although PARPis are now standard of care for most patients, some patients who are eligible for PARPi maintenance will not benefit (but suffer drug related side-effects) and many patients will benefit initially but develop disease resistance to PARPi.

In order to maximise the utility of PARP inhibitors, a number of *in vitro* studies have investigated causes of PARPi resistance. Identified mechanisms include:

1) Secondary mutations that restore reading frame of BRCA1, BRCA2 or RAD51C [8-10]
2) Hypomorphic forms of BRCA1 secondary to exon skipping [11,12]
3) Stabilisation of BRCA1/2 variants by HSP90 [13]
4) Reversion of BRCA1 or RAD51C epigenetic silencing [14]
5) Removal of end resection barrier during homologous recombination repair (HRR) (secondary to loss of 53BP1, REV7, RIF1, PTIP, Artemis, Shieldin, CST) [15]
6) Stabilisation of the replication fork (loss of CHD4, MLL3/4, MRE11, PTIP, EZH2, PARP1, MUS81; overexpression of miR-493-p) [16]
7) Decreased PARP trapping (loss of PARP1) [17]
8) Increased drug export (overexpression of P-glycoprotein) [18]

However, with the exception of secondary BRCA1/2 mutations [19,20] and reversal of BRCA1 or RAD51C methylation [14,21], these have not been validated in patients.

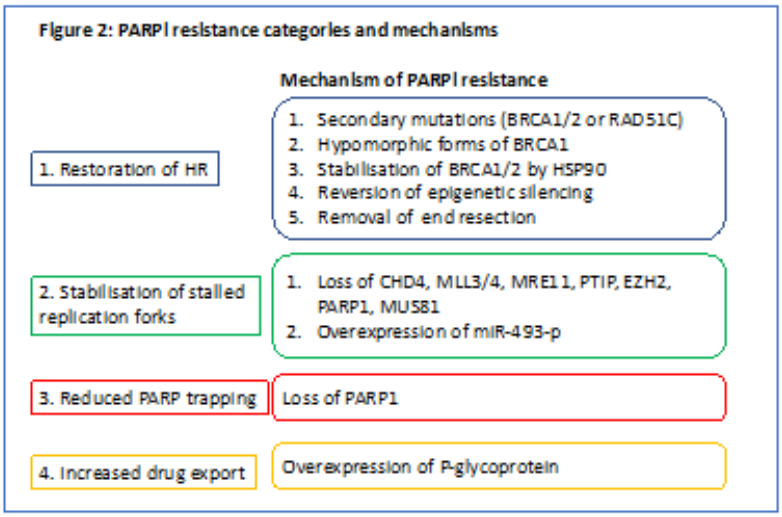


Figure 2: PARPi resistance categories and mechanisms

1.2 Trial Rationale and Hypothesis

This study aims to build a cohort of paired tumour samples (pre-PARPi and post-PARPi) to allow us to comprehensively assess the mechanisms of PARPi resistance, many of which have only been reported in *in vitro* studies and report their relative frequencies.

A better understanding of the resistance mechanisms which operate in patients and their relative frequency would improve our ability to prevent them arising or allow the development of therapies to abrogate this process. Additionally, the ability to identify patients harbouring resistant clones and therefore unlikely to respond to PARPi therapy would save the patient toxicity and considerable financial cost of delivering an ineffective therapy. Moreover, some of the resistance mechanisms are likely to predict future platinum resistance (those which result in restoration of HRR) whereas others are likely to be compatible with a further response to platinum. Hence, knowledge of the actual resistance mechanisms operating will maximise the utility of PARP inhibitors, minimise toxicity and unnecessary expenditure and facilitate individualisation of care in terms of post-PARPi therapy.

2 TRIAL OBJECTIVES

2.1 Primary Objective

To obtain tumour samples from 200 patients taken from HGOC tumours that have progressed on PARPi therapy and the matched archival primary tumour sample.

2.2 Exploratory Objective(s)

1. To interrogate the paired samples to define the PARPi resistance mechanisms that occur in HGOC patients and their relative proportions.

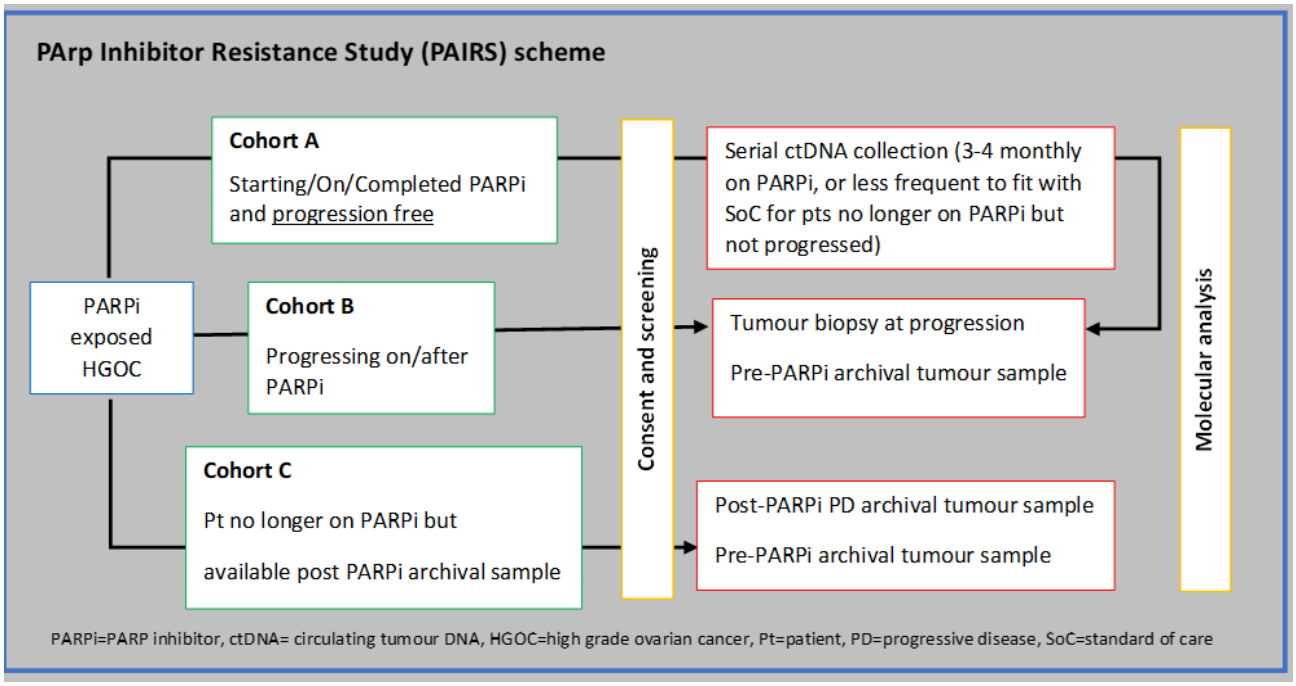
2. To examine ctDNA at progression to establish if resistance mechanisms identified in tissue samples can be detected in blood samples.
3. In Cohort A – (patient's currently receiving PARPi maintenance or progression free post PARPi maintenance))-to collect serial samples for isolation of ctDNA to detect and track emerging resistance in patients whose disease subsequently progresses.

3 TRIAL DESIGN

This multi-centre, non-randomised, sample collection study will be performed according to the UK Policy Framework for Health and Social care 2017 (as amended).

Patients with high grade epithelial ovarian cancer who are being/have been treated with a PARP inhibitor will be recruited to 3 cohorts (A, B and C).

Cohort A will recruit patients initiating PARPi treatment or progression free on PARPi. Cohort B will recruit patients on or after a PARPi who have disease progression and have not completed subsequent lines of therapy. Patients who have received 1-2 cycles of SACT whilst awaiting surgery may still be eligible, however, this must be discussed with CTU prior to registration. Cohort C will recruit patients who have archival tumour tissue available from prior to PARPi and at/after progression on a PARPi.



3.1 Trial Population

We aim to obtain tumour samples from 200 patients with high-grade epithelial ovarian cancer whose disease has progressed on or after PARPi. We estimate that we will require to recruit approximately 260 patients to obtain 200 PARPi progression tumour samples. Appropriate patients will be identified by ovarian cancer multidisciplinary team members at each participating site and be referred to the study investigators who will review eligibility and discuss the study with potential participants and obtain informed consent.

3.2 Inclusion Criteria

Inclusion Criteria- all patients

1. Age ≥ 16 years.
2. Histological diagnosis of high-grade serous, high-grade endometrioid or carcinosarcoma of the ovary, primary peritoneum or fallopian tube.
3. Availability of formalin-fixed, paraffin-embedded tissue taken at the time of original diagnosis of high grade serous ovarian cancer. This may be primary surgical debulking specimen OR core biopsy. For those with only a core biopsy from time of diagnosis, availability of specimen taken at interval debulking surgery is also requested.
4. Prior treatment with a PARP inhibitor or about to commence maintenance PARPi therapy (cohort A). PARPi can be single agent or in combination with bevacizumab. If PARPi is in combination with a different agent as part of a clinical trial, the patient may still be eligible but this should be confirmed with the Cancer Research UK Glasgow Clinical Trials Unit prior to patient registration.

Inclusion Criteria- cohort A

1. About to commence, currently receiving PARPi as maintenance therapy or completed PARPi maintenance with no intervening treatment before study entry.
   Patients need to be progression free (defined by no evidence of GCIG Ca125 progression or radiological progression). Patients who have progressed in a single site that could be considered a sanctuary site (i.e. brain metastasis) should be discussed with CTU to determine eligibility.
2. No contraindication to biopsy.
3. Ability to provide written informed consent prior to participating in the study and any study related procedures being performed.
4. Willingness to comply with trial procedures.
5. Life expectancy > 3 months.

Inclusion Criteria- cohort B

1. Patients need to have radiologically-defined progressive disease on/after PARPi. If progression is in a single site that could be considered a sanctuary site (i.e. brain metastasis), the case should be discussed with CTU to determine eligibility since recruitment to cohort A may be preferred.
2. Patients must have progressing disease deemed suitable for imaging-guided biopsy (ultrasound or CT) by an experienced radiologist or suitable for intra-operative biopsy during secondary debulking surgery as determined by an experienced gynaecological oncology surgeon. Other biopsies, such as skin deposits, are also acceptable. However, this must be confirmed with the Cancer Research UK Glasgow Clinical Trials Unit prior to patient registration (for cohort B).
3. No contraindication to biopsy.
4. No SACT commenced post PARPi (patients continuing PARPi after surgical resection of a progressing lesion can be included). Patients who have received 1-2 cycles of SACT whilst awaiting surgery may still be eligible for the study, please contact CTU to discuss prior to registration.
5. Ability to provide written informed consent prior to participating in the study and any study related procedures being performed.
6. Willingness to comply with trial procedures.
7. Life expectancy > 3 months.

Inclusion Criteria- cohort C

1. Patients need to have had a lesion which had radiologically progressed on/after PARPi.
2. Archival tumour of a lesion progressing post PARPi must be available.
3. Ability to provide written informed consent prior to participating in the study and any study related procedures being performed. Patients with available archival pre and post-PARPi tumour samples, who are no longer living may be identified by their clinical team and registered for the study if samples were collected under generic research consent (or equivalent). This will only be in sites where local procedures allow.

3.3 Exclusion Criteria – all patients

1. Ovarian, primary peritoneal or fallopian tube cancer of low grade serous, grades 1 or 2 endometrioid, clear cell or mucinous subtypes.
2. Borderline/low malignant potential tumours.
3. Any non-epithelial ovarian malignancy.
4. Original diagnosis of high grade serous cancer made on cytology only.
5. Discontinued PARPi for toxicity within 3 months of starting PARPi. (Exclusion applies to cohort B & C only). Patients who are recruited to cohort A at initiation of PARPi and subsequently discontinue within 3 months for toxicity will be replaced. Cohort A patients who progress and discontinue PARPi within 3 months will be included in the analysis and will not be replaced.

6. Any other severe concurrent disease which may increase the risk associated with trial participation.
7. Any psychological, familial, sociological or geographical considerations potentially hampering compliance with the trial and follow up schedule.

There will be no exception to the eligibility requirements at the time of registration. Queries in relation to the eligibility criteria should be addressed via contact with the CTU prior to registration. Patients are eligible for the trial if all the inclusion criteria are met and none of the exclusion criteria apply.

3.4 Identification of participants and consent

Ovarian cancer teams at each site will be made aware of the study and asked to identify any of their patients who may be suitable participants. Participants will be given an information sheet to consider usually for at least 24 hours and the research team will arrange to discuss the study with the potential participants to ensure patients understand the commitment required to fulfil the trial requirements. Only patients with capacity to give informed consent will be included in cohort A and B. During the consent process, patients will be made aware that participation is voluntary and they can leave the trial at any time without their standard care being affected. No activities related to the trial may be undertaken until consent has been obtained. Consent may be taken remotely for this study (See Section 11.2.1).

For cohort C, suitable patients who have archival pre-PARPi and post PARPi tumour samples available will be identified by clinical teams. If the patients are living, then the consent process will proceed as per cohort A and B. If the patient has passed away, then the patient may be registered for inclusion in the study (analysis of tissue and associated clinical data) if the tissue was previously collected under a generic research consent (or equivalent).

Eligibility confirmation and consent to the study must be taken by a member of the research team who is delegated to perform those tasks on the delegation log.

3.5 Registration

Patients cannot be registered to the trial until the site has been activated to begin recruitment. To register a patient on the trial, contact the CRUK Glasgow Clinical Trials Unit. Registration to the trial can be performed by either telephone or email on the following number/email:

Telephone Number: 0141 301 7201

Email: ggc.recruitment.crukglasgowctu@nhs.scot

The patient's eligibility criteria will be checked and, if eligible, a trial number will be allocated at this point.

All patients must be registered onto the trial prior to commencement of study procedures.

The patient's GP will be informed of their involvement in the trial.

3.6 Withdrawal

3.6.1 Withdrawal from Trial

Patients will be withdrawn from the study for the following reasons:

- Patient decision to withdraw consent.
- Development of a medical or psychiatric condition that would make biopsy contraindicated in the opinion of the investigator.

If the patient withdraws their consent to any further participation in the study, the level of consent withdrawal will be clearly documented in the source data. If this occurs:

- Withdrawal of consent will be clearly documented, along with the level of consent withdrawal (for example no further procedures but continued access to clinical data/samples versus no procedures or data/sample access) and the reason (if the patient has given any)
- A consent withdrawal notification form will be completed
- The consent withdrawal notification form will be sent to the CRUK Glasgow Clinical Trials Unit
- If patient requests absolute withdrawal with no further contact with the study team, no further data will be collected on the patient from that point onwards.

Patients will be replaced in the study for the following reasons:

- Biopsy is deemed technically not feasible by radiologist undertaking biopsy
- Insufficient or inadequate material obtained
- Biopsy indicates a different type of ovarian cancer (i.e. not HGOC)

For the safety of all trial participants, SAEs (which meet the requirements for reporting as detailed below) will continue to require to be reported and follow-up information for SAEs that have already been reported be provided, even once consent for trial participation has been withdrawn.

3.6.2 Withdrawal due to Loss of Capacity

Patients who lose capacity during the course of their participation in the study to such an extent that they are unable to comply with the protocol procedures shall be withdrawn from the study (though samples collected up to that point would still be analysed). All other study processes, including safety assessments,

should continue. No patient whether they have capacity or not will continue on the study if it is unsafe to do so in the opinion of the Principal or Chief Investigator, or the Umbrella Trial Steering Committee.

4 TRIAL PROCEDURES

4.1 Trial Endpoints

4.1.1 Primary Endpoint

Number of PARPi resistant tumours and matched pre-PARPi tumour samples obtained.

4.1.2 Exploratory Endpoints

1a. HRR gene aberration status using WES and RNAseq in pre-PARPi tumour samples.

1b. HR status in pre-PARPi tumour samples.

1c. Status of methylation of HRR genes in pre-PARPi tumour samples.

1d. HRR gene aberration status in post-PARPi tumour sample using WES and RNAseq (where relevant).

1e. HR status in post-PARPi tumour samples for cases previously found to have HRD disease.

1f. Methylation status in post-PARPi tumour samples for cases previously found to have a methylation event in their pre-PARPi tumour.

1g. Status of other pathways implicated in PARPi resistance as determined by proteomic and other analysis.

1h. Proportion of tumours with each resistance mechanism.

2. Proportion of patients where resistance mechanism can be identified in ctDNA.

3. Proportion of patients where resistance mechanism can be identified in ctDNA prior to detection of disease progression by standard clinical assessments.

4.2 Trial Schedule

Please consult the schedule of events table.

Consent visit: Consent and baseline data collection (**all cohorts**)

Data collection to include the following-

- ECOG performance status at diagnosis (Appendix 2)
- Histology
- FIGO stage at diagnosis
- Document prior SACT (including drugs, schedule, start date, stop date)
- Response to prior SACT (clinical, radiological*, biochemical** and histological (if chemotherapy response score reported on delayed primary surgery specimen)). This also includes the date of

progression following SACT and the basis of progression (all or some of clinical, radiological and/or biochemical).

- Surgical procedure and outcome (dates, procedure and outcome (complete cytoreduction, optimal, sub-optimal))
- Known genetic results (germline and somatic, HRD)
- Archival pre-PARPi tumour request (once patient registered and study ID known)
- Radiological disease assessment*- dates of scans from initial diagnosis and all subsequent and sites and measurements of disease (where available)
- Ca125** at diagnosis and subsequent including dates and values
- PARPi name, start date and dose and indication for PARPi (1st-line maintenance, 2nd or subsequent line maintenance, treatment)
- ctDNA sample collection for all patients except unconsented (deceased) Cohort C patients
- Germline DNA sample collection for all patients except unconsented (deceased) Cohort C patients
-

On treatment visit: On PARPi (**cohort A only,** *visit occurs every 3-4 months to fit with standard of care reviews)*

- Radiological disease assessments (as per standard of care imaging)- dates, sites and measurements of disease (where available)
- Ca125 (as per standard of care response assessment, dates and values since baseline assessment to be included)
- PARPi compliance
- ctDNA collection (if patient is no longer on PARPi but has not progressed, ctDNA collection can be less frequent to fit with standard of care assessments.)

Progression visit: (**cohort A and B**). *To take place within 4 weeks of progression as determined by standard of care assessments.*

- Radiological disease assessments (as per standard of care imaging - dates, sites and measurements of disease (where available))
- Ca125 (as per standard of care response assessment, dates and values since baseline assessment to be included))
- Basis of PARPi progression. Based on standard of care clinical assessment, imaging and Ca125 please detail if progression was all or some of clinical, radiological or biochemical.
- Haematology and biochemistry (as per standard of care assessment)
- ctDNA collection (must be before biopsy)
- Core biopsy/ resection specimen. See lab manual for instructions.

- Continuous AE assessment after biopsy (to detect only serious, unexpected events related to study biopsy which require reporting)

Follow-up visits: (**all cohorts**). 6 months after progression on PARPi and/or at final data cut for patients yet to progress

*Radiological disease assessments (as per standard of care imaging - dates, sites and measurements of disease (where available))

**Ca125 (as per standard of care follow-up, dates and values since baseline assessment to be included))

- Subsequent chemotherapy details (including drugs, schedule, start date, stop date)
- Subsequent chemotherapy response (clinical, radiological*, biochemical** and histological). This also includes the date of progression following SACT and the basis of progression (all or some of clinical, radiological and/or biochemical).
- Continuous AE assessment after biopsy (to detect only serious, unexpected events, related to biopsy which require reporting)
- Survival status

NB: This follow up visit can take place virtually or at a clinic attendance

4.3 Laboratory Tests

The PAIRS lab manual details the handling, storage, destruction and packaging instructions for the following research samples collected as study procedures:

- ctDNA
- Germline DNA sample
- Archival pre-PARPi tumour sample
- Core biopsy/ resection specimen
- Archival post-PARPi tumour sample (cohort C only)

Results of Ca125, haematology and biochemistry tests (that are carried out as standard of care for this patient group), will be collected. Samples will be handled as per standard of care.

4.4 Participation in concurrent clinical trials

Since the PAIRS study is a sample collection study, patients can participate simultaneously in another trial provided the Sponsor(s) of both studies approve co-enrolment within their trial. The burden of procedures

within each study will need to be considered carefully to ensure it is not unacceptable. Studies considered acceptable for co-enrolment (from perspective of PAIRS Sponsor) can be agreed at site initiation and co-enrolment will be captured at patient registration.

4.5 Duration of Trial Participation

4.5.1 Duration of Trial

The study will recruit patients over a period of 36 months followed by 6 month follow-up.

4.5.2 Duration of Trial Follow-up

Once patients in cohort A and B have had biopsy/blood sampling at progression there will be no further study procedures. For all patients (cohorts A, B and C), there will be long-term follow-up data collection to capture subsequent therapy, progression free survival on subsequent therapy and survival. For patients who have progressed on PARPi prior to or on study there will be follow up at 6 months post progression. For patients in cohort A who do not progress during the study the final follow up will occur at the end of the study.

5 ASSESSMENT OF SAFETY

In the PAIRS study, we do not intend to collect data on adverse events related to the standard of care systemic anti-cancer therapy that the patients will be receiving at the same time they are participating in the PAIRS study. We ask investigators to report any serious adverse events **related** to the study biopsy that are **serious** and **unexpected**. As is standard of care, adverse events will be captured at routine clinic appointments. If a **serious**, **unexpected** adverse event, **related** to the study biopsy occurs then this will need to be reported as detailed below. CTCAEv5 will be used to determine severity.

6 SAFETY REPORTING

Safety reporting will be performed by the Pharmacovigilance Department of the CRUK Glasgow CTU as delegated by the trial Sponsor

6.1 Safety Reporting for Non CTIMPs

6.1.1 Definitions

The PAIRS study procedures include only blood sampling, which will be taken at the same time as standard of care bloods, and one biopsy procedure. There is no extra risk from the blood sampling and there is only a low risk of the biopsy causing Adverse Events (AEs) or Serious Adverse Events (SAEs). Therefore these definitions apply to all trial participants from the biopsy up to and including 28 days after.

Term	Definition
Adverse Event (AE)	An adverse event (AE) is any untoward medical occurrence in a subject to whom a medicinal product or study intervention is administered, which does not necessarily have a causal relationship with this treatment/intervention.
Related Adverse Event (RAE)	A related adverse event (RAE) is any untoward and unintended occurrence in a subject administered trial treatment/intervention which is thought to be caused by or related to the trial treatment/intervention.
Serious Adverse Event (SAE)	A serious adverse event (SAE) means any untoward medical occurrence that requires the following, whether or not considered related to the study procedure. • Requires inpatient hospitalisation or prolongation of existing hospitalisation* • Results in persistent or significant disability or incapacity • Results in a congenital anomaly/birth defect • Is life-threatening (i.e. at the time of the event)** • Or results in death • Is considered medically significant by the Investigator*** *Requires in-patient hospitalisation should be defined as a hospital admission required for treatment of an AE. No time frame is specified for the duration of the admission. Referral or transfer to hospice care for normal disease management procedures are not considered a hospitalisation. **Life threatening means that the patient was at immediate risk of death from the event as it occurred. It does not include an event that, had it occurred in a more serious form, might have caused death. ***Considered medically significant by the Investigator are events that may not result in death, are not life threatening, or do not require hospitalisation, but may be considered a serious adverse experience when, based upon appropriate medical

	judgement, the event may jeopardise the patient and may require medical or surgical intervention to prevent one of the outcomes listed above. Medical and scientific judgement should be exercised in deciding whether an event is "serious" in accordance with this criterion.

N.B: To avoid confusion or misunderstanding of the difference between the terms "serious" and "severe", the following note of clarification is provided: "Severe" is often used to describe intensity of a specific event (for example CTCAE grade), which may be of relatively minor medical significance. "Seriousness" is the regulatory definition supplied above.

6.1.2 Detecting, Recoding and Reporting of Adverse Events

There is no requirement for sites to record or report any adverse events specifically for the purposes of the PAIRS study. Any adverse events related to standard care systemic anti-cancer therapy will be recorded in the patient notes only.

6.1.4 Reporting of a Serious Adverse Event

Only events that meet the regulatory definition of serious, are related to the biopsy and are not listed as an expected event (see list below), require to be reported as Serious Adverse Events (SAEs).

All SAEs must be coded and graded according to the NCI Common Terminology Criteria for Adverse Events (NCI-CTCAE) Version 5 (Appendix 1). These criteria can be accessed via the National Cancer Institute Website.

SAEs must be assessed for seriousness, causality and severity. This assessment is the responsibility of the Investigator (or doctor designee)

Investigators must consider if there is a reasonable possibility of establishing a causal relationship between the SAE and the study biopsy on their analysis of all the available evidence. The assessment must be made on the basis of anticipated effects of the biopsy as specified in the protocol, or if related to the patient's disease, either the disease under investigation or a concurrent illness.

Investigators must, whenever possible, provide a causality assessment for SAEs based on the information available at reporting, any temporal information and their knowledge of the disease and the study procedure. The causality assessment provided by an Investigator shall not be downgraded, but may be upgraded, by the CI.

Investigators should report these to the Pharmacovigilance Department, CRUK Glasgow CTU immediately and under no circumstances should this exceed 24 hours following first awareness of the event by the Investigator or site staff.

SAEs must be reported by submitting the SAE eForm on the MACRO database. A paper back up form will be made available and can be used if there are issues reporting on MACRO. Any SAEs reported on paper must be added to MACRO as soon as possible.

Email: mvls-ctu-pv@glasgow.ac.uk
Telephone: 0141 211 3567/0203/3968 or 232 2068

The purpose of this obligation is to ensure the CI, on behalf of the Sponsor, has the necessary information to continuously assess the benefit-risk balance of the clinical trial.

All initial SAE reports will have a SAE reference number generated for the report and will be acknowledged by the Pharmacovigilance Department. If no acknowledgement is received within 48 hours sites are required to contact the Pharmacovigilance Department to check the report has been successfully submitted and received.

For guidance on submitting and completing the initial and follow up SAE forms please refer to the SAE Completion Guidelines, which will be provided by the Pharmacovigilance Department, CRUK Glasgow CTU. The CI will be notified by e-mail of all SAEs received.

SAEs must be reported locally by the PI at each site in accordance with the local practice at their site.

A follow-up report must be submitted when the SAE resolves, is unlikely to change, or when additional information becomes available. If the SAE meets the criteria for expedited reporting to the REC, then follow up information must be provided as quickly as possible and in the timeframe requested by the CRUK Glasgow CTU and CI. A follow up report should also be submitted if additional SAEs occur or new information becomes available about previously reported SAEs.

SAEs are required to be reported from the first trial biopsy for up to 28 days after. Any event that meets the criteria for a SAE (including events that the Investigator thinks are medically important but maybe do not require hospitalisation or are fatal etc.) that occur after 28 days post intervention are also required to be reported if the Investigator thinks that the SAE is related to the trial intervention and unexpected. The

Investigator must report such SAEs to the CRUK Glasgow CTU Pharmacovigilance Department without undue delay, again within 24 hours of first knowledge of the event.

Investigators must follow up serious, related and unexpected events, by providing follow-up SAE reports until the event has completely resolved or will never resolve.

For any questions relating to SAE reporting, please contact the Pharmacovigilance Department:

Pharmacovigilance Department, CRUK Glasgow CTU

Email: mvls-ctu-pv@glasgow.ac.uk

Telephone: 0141 211 3567/0203/3968 or 232 2068

Contact details are also provided at the front of the protocol and in the SAE completion guidelines.

6.1.5 Expected Events

The following is a list of events that are expected as a result of the trial biopsy:

1. Minor bleeding
2. Haematoma
3. Pain
4. Bleeding requiring blood transfusion
5. Bleeding requiring intervention (radiological or surgical)
6. Infection at the site of biopsy
7. Pneumothorax
8. Damage to adjacent organ (colon/solid organ)

If the biopsy is CT guided, there will be additional expected events including:

- Induction of another cancer many years after the exposure (the risk of death from such a cancer is thought to be 0.1%)
- Allergy to CT contrast
- Renal impairment secondary to contrast

6.1.6 Identifying Events for Expedited Reporting

The assessment of SAEs for expedited reporting will be undertaken by the CTU and CI based on the list of expected events for biopsy at the time the SAE occurs.

6.1.7 Expedited Reports

CRUK Glasgow CTU on behalf of the (co) Sponsor is responsible for the expedited reporting of all serious, related and unexpected events to the REC, Sponsor and PIs and trial sites. The CI (or CI designee) is responsible for deciding if an event is unexpected and requires expedited reporting. The requirement for expedited reporting starts with the first REC approval of the trial. It ends with the completion of the trial for all patients recruited.

SAEs will be reported to the REC where in the opinion of the CI and/or the Reporting Investigator the event was:

- Related – that is, it resulted from administration of any of the research procedures

and is

- Unexpected – that is, the type of event is not listed in the protocol as an expected event

Reports of related and unexpected SAEs will be generated from the trial database and signed by the CI. The report will then be submitted within 15 days of the CRUK Glasgow Clinical Trials Unit becoming aware of the event, using the 'Report of Serious Adverse Event form' for non-CTIMPs published by the Health Research Authority (HRA). If the assessment of causality provided by the Investigator differs from that of the CI (assessment is made on behalf of the Sponsor), the opinion of both the Investigator and CI will be provided in the expedited report.

Investigators will receive all expedited reports.

The CI will assess if the risk-benefit assessment has been affected by each serious, related and unexpected event they identify and that is reported. If the risk-benefit of participation is adversely affected, appropriate prompt action will be decided upon by the CI, Sponsor and if required the Umbrella Trial Steering Committee and implemented by the Trial Management Group.

6.1.8 Annual progress report

An annual progress report, including information on the safety of trial participants if relevant, will be prepared by the Project Manager and submitted to the REC.

6.1.9 Reporting to the Medicines and Healthcare Products Regulatory Agency (MHRA)

There is no statutory requirement to report SAEs to the MHRA for clinical research which does not fall under the requirements of the Medicines for Human Use (Clinical Trials) Regulations such as non-CTIMPs.

6.1.10 Safety Data Handling

SAEs will be reported by completing and submitting an eForm on MACRO.

The Pharmacovigilance Department will review all SAE data and generate data queries for any missing or inconsistent information. Site staff are required to review and respond to data queries within 7 days. It is the responsibility of the PI to ensure SAEs and data queries are submitted in a timely manner (SAE's within 24 hour of occurrence and queries within 7 days of receipt). A data rulings document will be provided for Investigators recording any minor corrections to the SAE data that may be made by the Pharmacovigilance Department.

A data escalation process will be in place for any issues with SAE data return/quality/response to requests. The following process will be followed:

Step 1: E-mail letter to site main contact and copy in site PI

Step 2: E-mail letter direct to site PI and copy in site main contact

Step 3: E-mail letter to CRN Research Delivery Manager (or equivalent) /R&D and copy in site PI and main contact

Step 4: Discuss suspension of recruitment at site until data issues resolved

7 STATISTICS AND DATA ANALYSIS

7.1 Trial Design and Sample Size

PAIRS is a multi-centre, non-randomised, sample collection study which aims to collect paired (pre and post-PARPi treatment) tumour samples from 200 patients with HGOC from around 260 patients recruited. The sample size of 200 has been selected since it would be feasible and allow proportions of resistance mechanisms as low as 5% to be reported with 5% precision as detailed below.

196 samples allow the exact 95% confidence interval for a proportion of 15% with a given resistance mechanism to be estimated with 5% precision (which is equivalent to estimating a proportion of 15% or lower with a maximum standard error of approximately 2.6% or any proportion with a maximum standard error of approximately 3.6%).

Looking at a range of possible proportions:

- If 15% of patients have the resistance mechanism then the true value lies between 10 and 20% 95% of the time
- If 10% of patients have the resistance mechanism then the true value lies between 5.8 and 14.2% 95% of the time
- If 5% of patients have the resistance mechanism then the true value lies between 1.9 and 8.1% 95% of the time

Some of the mechanisms of resistance which we hope to detect may be exclusive to the BRCA1/2 mutant (BRCA1/2m) context. We estimate that in a population of 200 patients with PARPi progression tumour samples, approximately 15% of these patients could have a BRCA1m (based on incident rate of approximately 10% and enrichment for BRCAm patients in a population on PARPi) [Rust, 2018 #2430]. For populations of 30, 40 and 50 BRCA1m patients, the table below indicates how often a particular resistance mechanism would be observed for a range of "true" values (estimated via simulations).

sample size: BRCA1m patients	n (%; [95% CI]) mechanism of interest	true value 15%	true value 20%	true value 25%
30	≤2 (7% [1%-22%])	15%	4%	1%
30	≤3 (10% [2%-27%])	32%	12%	4%
30	≤4 (13% [4%-31%])	52%	26%	10%
30	≤5 (17% [6%-35%])	71%	43%	20%
30	≤6 (20% [8%-39%])	85%	61%	35%
30	≤7 (23% [10%-42%])	93%	76%	51%
40	≤3 (8% [2%-20%])	13%	3%	>1%
40	≤4 (10% [3%-24%])	26%	8%	2%
40	≤5 (13% [4%-27%])	43%	16%	4%
40	≤6 (15% [6%-30%)	61%	29%	10%
40	≤7 (18% [7%-33%])	76%	44%	18%
40	≤8 (20% [9%-36%])	86%	59%	30%
40	≤9 (23% [11%-38%])	93%	73%	44%
50	≤4 (8% [2%-19%])	11%	2%	>1%
50	≤5 (10% [3%-22%)	22%	5%	>1%
50	≤6 (12% [5%-24%])	36%	10%	2%
50	≤7 (14% [6%-27%])	52%	19%	5%

50	≤8 (16% [7%-29%])	67%	31%	9%
50	≤9 (18% [9%-31%])	79%	44%	16%
50	≤10 (20% [10%-34%])	88%	58%	26%
50	≤11 (22% [12%-36%])	94%	71%	38%

95% exact confidence intervals

For example, in a sample size of 30 BRCA1m patients:

- if the true value is 15%, we'd observe 6 or fewer patients with the mechanism 85% of the time
- if the true value is 20%, we'd observe 4 or fewer patients with the mechanism 26% of the time
- if the true value is ≥25%, we'd observe 4 or fewer patients with the mechanism ≤10% of the time

Any resistance mechanism identified may be a useful biomarker for use in the clinical development of novel agents targeting the mechanism, where the incidence of the occurrence of the biomarker will be required to inform if a biomarker selection should be used in the early clinical development of the novel agent or not. For example, if a cut-off of 20% was deemed appropriate not to pursue a biomarker driven trial, in a sample size of 30 patients, if 7 or more patients with the mechanism were observed, the biomarker selection may not be recommended given the low likelihood of the true rate being ≤15%. Conversely, 4 patients or less were observed with shieldin loss, the biomarker selection may be recommended given the low likelihood of the true rate being ≥20%. There is an area of uncertainty in-between these scenarios, but the final decision could be informed by confidence intervals such as those provided in the table.

Increasing the sample size from the anticipated 30 (which could be achieved by increasing the number of patients recruited to Cohorts B and C) is of modest benefit, however the additional information may be beneficial if the observed proportion was in an area of uncertainty. For this reason we intend to keep the proportion of patients recruited with BRCA1/2m tumours under review at our Trial Management Group.

7.2 Analysis Plan

7.2.1 Primary Analysis

Analysis will be performed by the research teams in the University of Glasgow and Edinburgh. Overall responsibility for analysis will be that of the Chief Investigator. The first aim of PAIRS is to build a cohort of 200 paired tumour samples from women with HGOC. We will use descriptive statistical analyses to record the number of cases where samples were not fit-for-purpose (for example, insufficient DNA obtained, DNA of inadequate quality).

7.2.2 Safety Analysis

If any serious, unexpected AEs related to the biopsy are reported, descriptive statistics will be used to report their incidence.

7.2.3 Exploratory Analysis

Status of HRR genes, homologous recombination status and methylation status of HHR genes in tumour samples pre and post-PARPi will be described.

Descriptive statistics will be used to report the proportion of patients with each resistance mechanism, the proportion of patients where the resistance mechanism can be identified in ctDNA and the proportion of patients where resistance mechanism can be identified in ctDNA prior to detection of disease progression by standard clinical assessments (including Ca125). In ctDNA analysis, TP53 mutation allele fraction will be used as a control for tumour DNA and the dynamics of changes in TP53 allele fraction and detection of resistance mechanisms will be examined.

Identified resistance mechanisms will be correlated with clinical and pathological characteristics. The appropriate statistical method for correlation will depend on the incidence of the resistance mechanism.

The University of Edinburgh will receive samples from sites, process and transfer for analysis, as required for exploratory analysis described, to Sponsor nominated laboratories.

7.3 Interim Analysis

There are no planned interim analyses.

8 TRIAL CLOSURE/DEFINITION OF END OF TRIAL

The trial will end when the Trial Management Group agrees that one or more of the following situations apply:

- The end of the trial definition will be the date of last data capture. Date of last data capture will be met when all outstanding data has been returned from all sites, all required data queries have been resolve and the database is finalised to allow analysis to take place to answer all protocol endpoints.
- There are safety concerns
- There is insufficient funding to support further recruitment and no reasonable prospect of additional support being obtained

- Recruitment is so poor that completion of the trial cannot reasonably be anticipated

8.1 End of Trial Notification/Declaration of the End of a Study Form

The Declaration of the end of a Study form should be completed within 90 days of end of study, or within 15 days if terminated early.

8.2 Clinical Trial Summary Report

The REC and Sponsor will receive a copy of the final study report.

8.3 Temporary Halt of a trial

If recruitment to the trial needs to be temporarily halted for reasons not specified in the protocol the Sponsor will inform the REC immediately and at the latest within 15 days from when the trial is temporarily halted. This includes trials where the stoppage was not envisaged in the approved protocol and where there is an intention to resume it. It does not include trials where recruitment may be temporarily halted for logistical reasons such as trial team availability. The notification will be made as a substantial amendment and will clearly state what activities have been halted and the reasons for this. To restart a trial that has been temporarily halted the Sponsor will make a request as a substantial amendment providing evidence that it is safe to restart the trial. If the Sponsor decides not to recommence the trial the REC will be notified in writing within 15 days of the decision, using the end-of-trial declaration form.

8.4 Early Termination of a Trial

In the case of early termination the Sponsor will notify the end of a trial to the REC immediately and at the latest within 15 days after the trial is halted, explaining the reasons and describing the follow-up measures, if any, to be taken for safety reasons. This does not include trials that complete early because full recruitment has been achieved.

9 DATA HANDLING

9.1 CRFs

The CRFs for this trial will be completed using the electronic remote data capture (eRDC) system, MACRO®. Prior to recruitment beginning at each site, the MACRO® User Guide will be sent to sites.
In the event the electronic data capture system (MACRO) is not ready when the study commences, paper CRFs/data collection tools and paper SAE forms will be provided to the sites to use initially.

Access to the MACRO database is restricted by role and functionality is dependent on this:

- The Sponsor do not have access to the database and as such have no direct access to the clinical data.

- CRUK Glasgow CTU staff access is managed by the MACRO Administrator (IT team in CRUK Glasgow CTU). Regardless of role, no CRUK Glasgow CTU staff are not authorised to input or change any clinical data on the database (CRUK Glasgow CTU staff have access to amend the database as outlined in Section 9.2).
- Participating site staff access is managed by the trial team within the CRUK Glasgow CTU following submission of the appropriate documentation. Sites will only have access to the patients recruited within their site. Only site staff are authorised to input or change the clinical data.

At the end of the trial, sites will be provided with the final clean dataset of all their patients electronically following the CRUK Glasgow CTU SOPs.

It is the responsibility of the Principal Investigator to ensure eForms are completed in a timely manner (within 4-6 weeks of the study visit) and to review and approve all data captured on the eForms. **Please ensure that all data submitted on eForms are verifiable in the source documentation or that any discrepancies are recorded and explained.**

In addition to completing the MACRO® database there will be some paper CRFs, the registration form should be completed on the paper form prior to emailing or calling CRUK Glasgow CTU.

Please refer to the data completion guideline document in the Investigator Site File (ISF). Please also note that some study forms must be signed by the PI or another clinician delegated to do so on the delegation log. These forms will be defined in the completion guidelines.

Other essential documents, including source data, consent forms, and regulatory documentation, will be archived by, or for the Investigator, in an appropriate archive facility in line with current regulatory requirements and made available for monitoring, audit and regulatory inspection as required.

9.2 Central Review of Data

CRUK Glasgow CTU will regularly review the data for compliance with the protocol, and for inconsistent or missing data. Should any missing data or data anomalies be found within the eForms upon CRUK Glasgow CTU review, queries will be generated within the MACRO® study database for the site to access and resolve. Sites are expected to review and respond to queries within the database in a timely manner (within 4-6 weeks). Any issues identified at sites in relation to poor data/slow response to data queries will be managed as per the data escalation process below.

Any amendments made to the database by the CRUK Glasgow CTU during the course of the study will be detailed in a Data Rulings Document which will be circulated to all sites for information. Examples of these may include, but are not limited to:

- Marking fields/eforms as not applicable/not available
- Clearing DCFs which have been raised to site and are no longer applicable
- Clearing warnings when sites have responded satisfactorily to the query

All data will be managed as per the CRUK Glasgow CTU SOPs.

9.3 Data Escalation Processes

Where issues with data return/quality/response to requests are identified at sites, the following process will be followed:

Step 1: E-mail letter to site main contact and copy in site PI
Step 2: E-mail letter direct to site PI and copy in site main contact
Step 3 E-mail letter to CRN Research Delivery Manager (or equivalent) and copy in site PI and main contact
Step 4: Discuss suspension of recruitment at site until data issues resolved. These discussions will take place within the Trial Management Group (including the Chief Investigator and Sponsor)

9.4 Record Retention and archiving

Archiving of the trial essential documents should be performed by both the participating trial site and Sponsor/CRUK Glasgow CTU.

Participating sites are responsible for archiving their trial related documentation and should follow the requirements of their R&D Office in conjunction with advice from the CRUK Glasgow CTU and Sponsor regarding the duration of document retention. Sites should not archive their trial documentation until they have been instructed by the CRUK Glasgow CTU or Sponsor that they are able to do so. Where possible, at the time of archiving, sites will be notified of the archiving retention period. If this is not confirmed at the time of archiving, sites should not destroy archived documentation until authorisation is given from the Sponsor.

The Sponsor and CRUK Glasgow CTU will be responsible for archiving the Trial Master File (TMF) and all other essential trial documentation that is not held at participating trial sites as per their applicable SOPs.

In the event that a patient's care is transferred to another hospital (who are also participating in this study) a Patient Transfer Form must be completed by the original recruiting site (or the current site responsible for the patient) to request that the transfer is performed within the CRUK Glasgow CTU and MACRO® system. The original recruiting site will be recognised with the recruitment of the patient. The original (or current) site will be responsible for ensuring all is up-to-date prior to the transfer of the patient on the MACRO® system. Once the transfer has been processed, the new site will be responsible for returning all outstanding trial documents from that point onwards including any outstanding data prior to the date of transfer.

10 TRIAL MANAGEMENT

10.1 Trial Start Up

Sites wishing to participate in the trial should contact CRUK Glasgow CTU. A PI must lead the trial at each site and they will be responsible for providing CRUK Glasgow CTU with all core documentation. Protocol training will be given to sites via initiation slides that will be provided to sites prior to the trial opening at that site. Once all the documentation is received at CRUK Glasgow CTU an initiation call will be performed and after this the site will be contacted by email when they are activated and are able to recruit patients to the trial.

10.2 Core Documents

The core documents may include and are not limited to:

- Local R&D approval/local capacity and capability approval/HRA approval
- Signed Clinical Trial Agreement
- Delegation and study specific training log, please note that updated delegation logs must be submitted on a 6 monthly basis to CRUK Glasgow CTU
- CVs and GCPs for PI
- Lab accreditation certificates (if applicable)
- PIS and GP letter on local headed paper
- Initiation acknowledgements
- Site initiation/accreditation checklist
- MACRO User Request Form

10.3 Management of protocol deviations and violations

Deviations

Organisations must notify the Sponsor (via CRUK CTU) of all deviations from the protocol or GCP immediately. The Sponsor requires a report on the incident(s) and a deviation form will be provided to site for completion. This should be completed by site as soon as possible and returned to the PM or CTM. If site staff are unsure whether a certain occurrence constitutes a deviation from the protocol or GCP, the CRUK Glasgow CTU trial team and Sponsor can be contacted immediately to discuss. The Sponsor will assess all incidents with respect to the criteria of a "serious breach".

Serious Breach

Events that match the criteria of a "serious breach" will be reported to the REC within 7 days of the matter coming to the attention of the Sponsor.

The HRA Standard Operation Procedures for Research Ethics Committees (version 7, June 2019) defines a serious breach as a breach of the protocol or of the conditions or principles of Good Clinical Practice (or equivalent standards of conduct of non-CTIMPs) which is likely to affect to a significant degree the safety or physical or mental integrity of trial subjects or the scientific value of the research.

The report should include details of when the breach occurred, the location, who was involved, the outcome and any information given to the participants. The REC should also be informed of any further corrective or preventative action the Sponsor plan to take

10.4 Trial Management Group (TMG)

The trial will be coordinated from CRUK Glasgow CTU by the TMG. The TMG normally includes those individuals responsible for the day-to-day management of the trial. Members of the TMG include the CI, Co Investigators, Project Manager, Trial Statistician, Pharmacovigilance CTC, Sponsor Representative, Patient Representative, and Laboratory Representative. The role of the group is to monitor all aspects of the conduct and progress of the trial, ensure that the protocol is adhered to and take appropriate action to safeguard participants and the quality of the trial itself

10.5 Umbrella Trial Steering Committee (UTSC)

The role of the Umbrella TSC is to provide overall supervision of the trial and ensure that it is being conducted in accordance with the principles of GCP and the relevant regulations. The UTSC should agree any major trial modifications, provide advice to the investigators on all aspects of the trial and have members who are independent of the investigators, in particular an independent chairperson.

Decisions about continuation or termination of the trial are usually the responsibility of the UTSC in consultation with funders and the Sponsor.

11 REGULATORY ISSUES

11.1 Ethics Approval

The trial will be carried out in accordance with the World Medical Association Declaration of Helsinki (1964) and its revisions (Tokyo [1975], Venice [1983], Hong Kong [1989], South Africa [1996] and Edinburgh [2000]). Favourable ethical opinion will be sought from the West of Scotland Research Ethics Committee 5 before patients are entered onto this clinical trial. The CI will be responsible for updating the ethics committee of any new information related to the trial.

11.2 Consent

Consent to enter the trial must be sought from each participant only after full explanation has been given, an information sheet offered and time allowed for consideration. Signed participant consent must be obtained, the consent forms should also be signed by the person carrying out the consent procedure at site, who must be detailed on the study specific delegation and training log as having authorisation. The PI is responsible for ensuring if the taking of consent is delegated to a designee, the designee is suitably qualified by training or experience to take informed consent.

The right of the participant to refuse to participate without giving reasons must be respected. After the participant has entered the trial the clinician remains free to give alternative treatment to that specified in the protocol at any stage if he/she feels it is in the best interests of the participant, but the reasons for doing so must be recorded. In these cases the participants remain within the trial for the purposes of follow-up and data analysis. All participants are free to withdraw at any time from the trial without giving reasons and without prejudicing further treatment.

An original completed consent form must be retained at each site in the appropriate section of the Investigator Site File, and a photocopy placed in the patient's medical records. All patients must be given either an original or a copy (as per local site practice) of the signed patient information sheet and consent form for their records. Consent forms must be retained on site and not submitted to the CRUK Glasgow CTU. Remote consent is permitted within this study.

Some patients who are no longer alive may be registered to cohort C if local regulations allow access to samples and data in an anonymised form for research purposes (for example if samples were collected under a generic research consent).

In the event that new patient information sheets/consent forms are produced throughout the duration of the trial, it maybe that patients already participating in the trial should be re-consented to the updated version of the patient information sheet. However, if the Principal Investigator decides that this is not in the best interests of the patient re-consent is not required. Decisions not to re-consent patients must be documented in the patient's medical records. Remote re-consent is permitted within this study.

11.2.1 Remote Consent

Remote consent is permitted within this study.

- patients will be provided with patient information sheet via email or letter (or in person if attending clinic)
- Patients will be provided with an appointment for consultation by phone or video consultation to discuss the information (after having had at least 24 hours to consider).
- If the patient is interested in participating in the study, the consent process can take place over the phone or video. Patient agreement that consent can take place remotely will be documented.
- If the patient wants to proceed. The patient will sign and date the consent during the consultation.
- The consent process will be documented in source documentation
- The patient will be asked to return the patient information sheet/consent to site at a subsequent face to face consultation.
- Once the patient information sheet/consent (signed and dated by the patient) is received by site it will be signed and dated by the investigator.
- A copy will be taken and sent to the patient for their record. It will be documented in source that this happened. Copy to be kept in source and original in site file as per standard of care process.

11.3 Confidentiality

All information collected during the course of the trial will be kept strictly confidential, and only information that is directly relevant to the objectives and outcome measures detailed in the protocol will be collected. The collection of additional data not so specified is not permissible.

Information will be held securely on paper and electronically at the CRUK Glasgow CTU. The CRUK Glasgow CTU will comply with all aspects of the 2018 Data Protection Act and operationally this will include:

- Consent from participants to record personal details including initials, year of birth, and sex at birth.

- Appropriate storage, restricted access and disposal arrangements for patient's personal and clinical details
- Consent from participants for access to their medical records by responsible individuals from the research staff or from regulatory authorities, where it is relevant to trial participation
- Consent from participants for the data collected for the trial to be used to evaluate safety and develop new research.
- Where central monitoring of source documents by CRUK CTU (or copies of source documents) are required (such as scans or local blood results), the patient's name must be obliterated by site before sending.
- Where anonymisation of documentation is required, sites are responsible for ensuring only the instructed identifiers are present before sending to CRUK Glasgow CTU.
- Note that trials involving tissue collection where potentially genomic analysis will be performed details on ethnicity will be collected to complement this analysis.

If a participant withdraws consent from further trial treatment and / or further collection of data their samples will remain on file and will be included in the final trial analysis unless they specifically withdraw consent for this.

11.4 Liability, Indemnity and Insurance

No special insurance is in place for patients in this trial other than standard NHS liability insurance providing indemnity against clinical negligence. This does not provide cover for non-negligence e.g. harm caused by an unexpected side effect of participating in a trial. The sponsors have responsibility for ensuring that financial cover for damages or compensation arising from no fault harm is available to patients, where applicable. Cover for this clinical trial has been agreed under the current policy.

The Hospital Trust/Health Board at each participating site is responsible for the following:

1. Acts and omissions of its own staff and others engaged by it, including the Clinical Trials Unit and PI;
2. Ensuring the appropriate insurance administered by the National Health Service Litigation Authority is in place;
3. Ensuring any non-NHS employees involved in the clinical trial have Honorary Contracts with the Trust/Board to cover access to patients and liability arrangements.

These responsibilities are outlined and agreed within the Clinical Trial Agreement.

11.5 Sponsor(s)

NHS Greater Glasgow and Clyde will act as the main sponsor for this trial. Delegated activities will be assigned to the CRUK Glasgow CTU and NHS Trusts/Boards taking part in this trial. Details of responsibilities will be outlined in the clinical trial agreement that should be signed prior to site initiation.

11.6 Funding

This study is being funded by a grant from Wellbeing of Women and supported by Artios Pharma Limited.

11.7 Protocol Amendments

Any change to the trial protocol will require an amendment. Any proposed, non-administrative, protocol amendments will be initiated by the CI following discussion with the TMG and any required amendment forms will be submitted to the ethics committee and Sponsor. The CI and the TMG will liaise with trial Sponsor to determine whether an amendment is non-substantial or substantial. All amended versions of the protocol will be signed by the CI, Lead Statistician and Sponsor representative. Before the amended protocol can be implemented favourable approval must be sought from the original reviewing REC, trial Sponsor, and participating site R&D offices.

11.8 Allocation of Trial Responsibilities

11.8.1 Sponsor Responsibilities (NHS GG&C)

The Sponsor is responsible for confirming there are proper arrangements for the initiation and management of the trial. **Chief Investigator (CI)**

The CI is directly responsible for:

- Ensuring the protocol and any amendments are in place.
- Clinical oversight of the safety of patients participating in the trial, including the ongoing review of the risk/benefit.
- For review of SAEs and determination if SAEs meet the criteria for expedited reporting within 24 hours.
- Providing advice and recommendations on medical issues that arise involving the management of the patients on the trial.

At the outset of the trial development period, the CI will sign the CRUK Glasgow CTU Memorandum of Understanding (MoU) document which details the key responsibilities of the CI and CRUK Glasgow CTU, where applicable giving indicative timelines for completion.

From the perspective of the Sponsor and for ethics purposes, the CI for the trial will be Dr Patricia Roxburgh.

11.8.2 CRUK Glasgow Clinical Trials Unit (CTU)

CRUK Glasgow Clinical Trials Unit is a collaboration between the University and NHS Greater Glasgow and Clyde, with staff being employed by both organisations. All activities performed by the CRUK Glasgow CTU for the Trial are delegated and overseen by the trial sponsor.

11.8.3 Participating Site

The Participating Site is solely responsible for the management of the trial within their site. This includes ensuring local management approval has been given, ensuring the trial is conducted according to GCP requirements, and ensuring the appropriate insurance or indemnity is in place. The Participating Site is also responsible for arranging access for on-site monitoring and auditing as identified in the trial protocol and also for regulatory inspections.

11.8.4 Principal Investigator (PI)

The PI is responsible for:

- The delegation of trial activities within their site and ensuring all personnel are adequately trained and qualified to carry out their responsibilities.
- Providing evidence of GCP training (usually a certificate) or undergo the required GCP training.
- The safety and wellbeing of trial patients,
- Reporting any deviations from the protocol to CRUK Glasgow CTU
- Reporting any SAEs or safety issues within 24 hours of becoming aware of the event, including using medical judgement in assigning seriousness and causality.

Full details of the responsibilities of the PI are outlined in the Clinical Trial Agreement. Two original copies of this will be held – one with the Sponsor(s) and the other at the participating site. A photocopy of the signed agreement will also be held at the coordinating trial office.

12 QUALITY ASSURANCE

12.1 Audits and Inspections

Trial Investigators must permit trial related monitoring, audits, REC review and regulatory inspections as required, by providing direct access to source data, CRFs and other documents (patient's medical records, investigator site file, and other pertinent data).

The trial may be subject to inspection and audit by NHS Greater Glasgow and Clyde as Sponsor), the CRUK Glasgow CTU and other regulatory bodies as applicable. If an inspection is scheduled at any participating site, the site must notify the Sponsor at the earliest opportunity.

It is the Sponsor's responsibility to inform the investigators of all intended audits and regulatory inspections involving the participating site. It is the investigator's responsibility to ensure appropriate resources at site and that the inspector(s) have access to all source data.

12.2 On Site and Telephone Monitoring

No routine monitoring will be undertaken for this study. Monitoring may be conducted on a for-cause basis where a need arises. Where monitoring is indicated, this may be conducted by telephone, remotely or by site visit.

Where monitoring is indicated, the PI will allow the Clinical Trial Monitor access to source documents as requested. Investigators and site staff will be notified in advance about forthcoming monitoring visits. On occasion, members of the CRUK Glasgow CTU monitoring team may be accompanied by other staff from the unit for training purposes. Where a participating site is using electronic data reporting systems or electronic patient records and hard copies are not available, the CRUK Glasgow CTU monitor will require access to a computer for the duration of the visit in order to verify all relevant source data against the case report forms. This may involve being given a temporary log-in. If this is not permitted by local policy, there must be a member of site staff available to provide access to the monitor.

12.3 Protocol non-compliance

Protocol non-compliances must be reported by the site study team to the CRUK Glasgow CTU as soon as they are identified. Non-compliances may also be identified by the Clinical Trial Monitor, and the site staff and CRUK Glasgow CTU staff will work together to complete a protocol deviation form and put corrective and preventive actions in place to avoid repeated non-compliance. Where the deviation is of a more serious nature, the Sponsor may be required to report a serious breach of protocol or Good Clinical Practice to the REC. The Sponsor reserves the right to suspend recruitment at a site until an investigation has taken place and corrective and preventive measures have been put in place to ensure future patient safety and/or data integrity.

14 PUBLICATION POLICY

The PAIRS TMG is responsible for approving the content and dissemination of all publications, abstracts and presentations arising from the trial and for assuring the confidentiality and integrity of the trial. It will provide collaborators the International Committee of Medical Journal Editors (ICMJE) criteria (http://www.icmje.org/icmje-recommendations.pdf) will be used to ensure all those who have contributed to the study are appropriately acknowledged.

No site or individual will publish data generated in the PAIRS study without prior approval of the TMG.

The data arising from PAIRS will belong to the trial Sponsor NHS Greater Glasgow and Clyde. The TMG shall act as custodian of this data.

15 REFERENCES

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APPENDIX 1: COMMON TERMINOLOGY CRITERIA FOR ADVERSE EVENTS (CTCAE) VERSION 5.0

https://ctep.cancer.gov/protocoldevelopment/electronic_applications/docs/ctcae_v5_quick_reference_5x7.pdf

APPENDIX 2: ECOG Performance Status

Appendix II: ECOG Performance Status Grade	ECOG
0	Fully active, able to carry on all pre-disease performance without restriction
1	Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature, e.g., light house work, office work
2	Ambulatory and capable of all selfcare but unable to carry out any work activities. Up and about more than 50% of waking hours
3	Capable of only limited selfcare, confined to bed or chair more than 50% of waking hours
4	Completely disabled. Cannot carry on any selfcare. Totally confined to bed or chair
5	Dead