PARADIGM (BR32)

OlaPArib And RADiotherapy In newly-diagnosed GlioblastoMa:

Short-course radiotherapy plus olaparib for newly diagnosed glioblastoma in patients unsuitable for radical chemoradiation: a randomised phase II clinical trial preceded by a lead-in phase I dose escalation study.

PHASE I INITIATION SLIDES

(VERSION 2, 09 MAR 2016)

TRIAL DETAILS

- The trial is being co-ordinated by CRUK via the Cancer Research UK Clinical Trials Unit, Glasgow (CRUK CTU)
- Co-sponsors of the trial are Greater Glasgow & Clyde Health Board (GG&CHB) and University of Glasgow (GU)
- Chief Investigator is Professor Anthony Chalmers
- The trial has been endorsed by Cancer Research UK and will be funded by AstraZeneca under the terms of their collaboration with the National Cancer Research Network.

Please note this presentation has been prepared as part of your site initiation. These slides are a complement to the protocol. All site staff must have read and understood the protocol and the trial requirements prior to signing off the initiation acknowledgment sheet.

- The trial will be conducted according to ICH GCP guidelines

- The trial will be conducted in accordance with the EU Directive 2001/20/EC
- The trial will be carried out in accordance with the World Medical Association Declaration of Helsinki (1964) and the Tokyo (1975), Venice (1983), Hong Kong (1989), South Africa (1996), Edinburgh (2000), Washington (2002), Tokyo (2004), Seoul (2008) amendments

TRIAL TEAM

• Chief Investigator :	Professor Anthony Chalmers
• Trial Statisticians:	Caroline Bray/Jamie Stobo
• Project Manager:	Anna Morris
• Sponsor Pharmacist:	Dr Samantha Carmichael
• Pharmacovigilance Manager:	Lindsey Connery
• Clinical Trial Coordinator:	Susan Dillon
• Trial Monitor:	Michaela Rodger
• Co-Sponsor Representative:	Paul Dearie

TRIAL DESIGN AND PHASE I OBJECTIVES

This trial is a multi-centre, two-stage, clinical trial of olaparib in combination with radiotherapy. Phase I is a dose escalation trial of olaparib in combination with short course radiotherapy and will follow a 3+3 cohort design. The starting dose of olaparib will be 50mg once daily and the planned escalation dose levels are 100mg once daily, 100mg twice daily and 200mg twice daily. This will be followed by a randomised, placebo controlled, double-blind phase II trial of radiotherapy plus placebo versus radiotherapy plus olaparib (at the dose determined in phase I).

Primary objective (Phase I):

- To identify a recommended dose of olaparib to be administered in combination with radiotherapy.

PHASE I COMPONENT

Patients will be recruited into the phase I component in cohorts of 3-6 patients. There are four dose levels to be explored. There will be no dose reduction permitted if the starting dose is not tolerated. Patients who do not tolerate the starting dose must be removed from the trial.

Dose Level	Olaparib Dose PO (starting 3 days prior to radiotherapy)
Cohort -1	There will be no dose reduction permitted if the starting dose is not tolerated. Subjects who do not tolerate the starting dose must be removed from the study.
Cohort 1	50mg once daily
Cohort 2	100mg once daily
Cohort 3	100mg twice daily
Cohort 4	200mg twice daily

Each cohort will consist of a minimum of 3 patients

- Treatment within a new cohort will only commence once the 3rd patient from the previous cohort becomes evaluable and there are no DLTs in that cohort
- If one patient among the first 3 cohort patients experiences a DLT, then the dose level will be expanded to include 6 evaluable patients
- If only one patient among the first 6 patients in any given cohort experiences a DLT, treatment within the next cohort may commence
- If 2 or more patients among the first 3-6 patients experience DLTs, then that dose will be considered intolerable. Previous cohort dose will be considered as MTD and taken forward into phase II

DOSE LIMITING TOXICITIES (DLTs)

Dose Limiting Toxicities will be defined as:

- Failure to complete radiotherapy because of toxicity, as considered by the investigator in consultation with the safety review committee (SRC) (i.e. with no evidence of tumour progression).
- Any grade ≥3 toxicity (CTCAE 4.0) that was not present prior to commencing olaparib and which, in the opinion of the investigator in consultation with the SRC, is due to olaparib or the combination of olaparib and radiotherapy. Such toxicities will be classed as a DLT from start of olaparib treatment until end of olaparib treatment (i.e. 4 weeks after end of radiotherapy treatment).

EVALUABLE PATIENTS FOR PHASE I

All patients receiving at least one fraction of radiotherapy with concomitant olaparib will be evaluable for safety decisions.

The following patients will not be evaluable (unless they experience a DLT):

- Patients who have missed two or more fractions of radiotherapy, two or more days of olaparib during the radiotherapy treatment, or seven or more days of olaparib during the post-radiotherapy period for reasons other than a DLT (or dose interruption due to toxicity) will not be evaluable for dose escalation decisions and will be replaced.
- Any patient who has dose modifications not permitted by the trial protocol.

Non-evaluable patients will be replaced unless 2 or more DLTs have already been observed in that cohort.

DOSE ESCALATION DECISION

The decision to escalate to the next dose cohort will be made by a safety review committee with clinical representation from each of the participating phase I sites.

When the criteria to stop dose escalation are met, the information will be communicated to all participating sites by email correspondence from the trial team at the CRUK CTU to the trial CI, all PIs and main contacts for each phase I site so that no patients are further exposed to dosages above the maximum tolerated dose (MTD).

SLOT REQUESTS AND SLOT ALLOCATION

Each cohort has an initial 3 places which should be filled using the slot request system. Ethically we cannot refuse treatment to an eligible patient that has consented to a trial so each site must ensure that they have a slot on the cohort before the patient has been approached with the patient information.

SLOT ALLOCATION

- CRUK CTU will provide a slot request form for the site that should be completed and returned to the CRUK CTU in order for a slot to be allocated.
- Upon receipt of the slot request form CRUK CTU will process the form and allocate the slot if there is one available.

- Upon confirmation of the slot allocation the site can approach the patient with the patient information, consent (if patient agrees) and begin the screening process.
- For patients that decline participation or fail to meet the eligibility criteria please contact the CRUK CTU asap in-order to re-allocate the slot.

For slot allocations and requests:

Susan Dillon
Tel: 0141 301 7232
Fax: 0141 301 7228
Email: susan.dillon@glasgow.ac.uk

INFORMED CONSENT PROCESS

Informed consent process:

- Two original Consent Forms must be completed by a clinician (or deputy listed on delegation log)
- Two originals signed and completed by the patient
- Date must be prior to registration
- Make one photocopy
  - Original to be filed in Investigator File
  - Original to be given to patient (+PIS)
  - Photocopy to be filed in hospital notes
- Consent Form must not be sent to your coordinating trials office

FOR ERRORS NOTED AFTER CONSENT

- Add explanatory note/file note
- New version of Patient Information Sheet must be provided to patients consented with previous version. This must be given to all patients regardless of treatment stage, during next possible clinic visit.
- Patients who are still on active treatment will be required to repeat the consent process using the updated form. If it is not appropriate to re-consent patient (i.e. patient terminally ill) please make a note regarding this in the patients case notes and on re-consent log which is filed in your study sitefile.

CONSENT WITHDRAWAL

When the patient specifically asks to withdraw their consent at any point in the trial. If this occurs:

- Document clearly in the patient notes that the patient has withdrawn consent, the level of consent withdrawal and the reason (if the patient has given any)
- Complete the consent withdrawal notification form
- Send the consent withdrawal notification form to the CRUK CTU
- No further follow-up should be collected on the patient from that point onwards.

REGISTRATION FOR TRIAL TREATMENT (PHASE I)

Prior to commencing any trial related procedures, all participants will be fully informed about the risks, benefits and procedures involved in trial participation, and will sign a consent form confirming this process. All patients will then undergo a period of screening during the 28 days prior to initiation of trial treatment. All patients must be registered onto the trial prior to commencement of any treatment.

Screening evaluations (within 28 days of registration) will consist of:

- Demographic details
- Medical history
- Pregnancy test
- MRI of the brain - *Must be reported as per protocol. This involves using RANO Criteria.*

Screening evaluations (within 7 days of registration) will consist of:

- Physical examination
- WHO performance status
- Review of medications

- Vital signs
- Pregnancy test
- Full neurological examination
- Full blood count
- Serum biochemistry

→ Check that patient fulfils eligibility criteria as per trial protocol section 3.2 and 3.3 -*There will be no exceptions to the eligibility requirements at the time of registration. Queries in relation to the eligibility criteria should be addressed prior to calling for registration. Patients are eligible for the trial if all the inclusion are met and none of the exclusion criteria applies.*
→ Check that patient has given written informed consent as per the informed consent process.
→ Complete Registration Form.

Site staff must contact the CRUK CTU to register the patient for trial treatment, this can be done by either telephone or fax on the following numbers:

Tel no: 0141 301 7232
Fax no: 0141 301 7228*
08.30-17.00 Mon-Thurs and 08.30-16.30 Friday, except public holidays
* **Faxes received outside of office hours will be processed the next working day**

✓ Each patient will be allocated a unique sequential patient ID number(6 digit number) for the trial.
✓ Dose level of trial drug will be provided dependent on the dose cohort the patient is being registered onto.

TREATMENT AND DURATION (PHASE I)

- Hypofractionated, short-course radiotherapy (40 Gray in 15 fractions) over 19 – 21 days
- Olaparib will be commenced 3 days prior to radiation and will continue throughout radiotherapy treatment and for a further four weeks for a total of 50 - 52 days.
- If there are delays in radiotherapy, olaparib dosing should continue on those days which may result in a total number of treatment days of >52 days.
- The dose of olaparib will be according to the current dose cohort that they are taking part in.
- The planned dose escalation levels for olaparib to be explored are:
  - 50mg once daily
  - 100mg once daily
  - 100mg twice daily
  - 200mg twice daily

RADIOTHERAPY INFORMATION

Please refer to section 5.3 of the trial protocol for full details on radiotherapy treatment.

- Radiotherapy treatment should start within 6 weeks of surgery. An additional week will be allowed if required.
- The use of CT planning is mandatory.

- Radiotherapy will be delivered to a total dose of 40.05 Gy in 3 weeks, in a once daily schedule of 2.67 Gy per fraction, five days per week for a total of 15 fractions.

- Delays of up to 7 days are permitted once the patient has started radiotherapy. This includes breaks in treatment caused by public holidays, transport failure, machine breakdown, intercurrent illness and other potential factors. In the case of delays, dose compensation for any associated increase in overall treatment time is not required.

- Radiotherapy Quality Assurance will be conducted through the UK RTTQA team. Pre-trial Facility Questionnaires will be sent to all participating sites, to collect contact, equipment and delivery technique details. Each site will be required to submit a 'Dummy Run' case, comprising a case chosen by the site that has been outlined and planned according to the PARADIGM protocol. The RTTQA team will undertake review of volumes and dose distribution and must approve the Dummy Run case before sites can open the trial.

SUPPLY OF TRIAL DRUG

Olaparib

Olaparib will be provided free of charge by AstraZeneca to sites for use of patients in the PARADIGM trial and will be trial specific investigational medicinal product trial stock.

- Olaparib is considered IMP for the purpose of this trial

- Olaparib is supplied as a green, film-coated tablet containing 25mg or 100mg drug substance

- Olaparib should be stored at ambient temperature below 30$_0$C, must be stored in its original bottle with the cap on tightly and must not be refrigerated

Full instructions regarding management, labelling and accountability the trial drug is given in a separate IMP Management Document for the trial.

PREPARATION, ADMINISTRATION AND DOSE GUIDELINES

The investigator or a delegated individual (e.g. pharmacist) must ensure that the trial drug is dispensed in accordance with the protocol, local standard operating procedures and applicable regulatory requirements.

- The bottle number, batch number, dose prescribed, quantity and expiry of the olaparib supplied must be recorded in the accountability logs. Both bulk stock and individual patient accountability logs must be completed.

- Tablets will be dispensed in two instalments:
    1. to cover the prescribed dose for the radiotherapy dosing period
    2. to cover the prescribed dose for 4 weeks after radiotherapy.

- Patients will be required to return all bottles (including empty bottles) of trial medication at the 2nd dispensing visit and again upon the completion of treatment. Any remaining tablets must be documented in the accountability logs. Any evidence of non-compliance with the prescribed dosing must be reported to the local PI.

Patients should be instructed to take olaparib no sooner than one hour after food, and then refrain from eating for a further two hours due to potential effect of food on absorption. The olaparib tablets should be swallowed whole and not chewed, crushed, dissolved or divided. If vomiting occurs shortly after the olaparib tablets are swallowed, the dose should only be replaced if all of the intact tablets can be seen and counted. Should any patient miss a scheduled dose for whatever reason (e.g., as a result of forgetting to take the tablets or vomiting), the patient will be allowed to take the scheduled dose up to a maximum of two hours after that scheduled dose time. If greater than two hours after the scheduled dose time, the missed dose is not to be taken and the patient should take their allotted dose at the next scheduled time.

Full instructions regarding management, labelling and accountability the trial drug is given in a separate IMP Management Document for the trial.

PRESCRIPTION ARRANGEMENTS

Trial prescriptions must be used, but will not be supplied by the sponsor. Sites are responsible for devising their own prescription form. Prescriptions should include the following information in addition to standard prescribing details;

- Clearly identify that patients are in the PARADIGM trial
- PARADIGM patient trial number

Alternatively, electronic prescribing systems can be used. Whichever method of prescribing is used it must be clear the IMPs are being prescribed as part of the PARADIGM Trial. Prescriptions must either be version controlled or subject to a validation process. Wherever possible the original prescription should be retained within the pharmacy file but where this is not possible a copy of the prescription must be retained in the pharmacy file and a copy accessible by the investigator.

Full instructions regarding management, labelling and accountability the trial drug is given in a separate IMP Management Document for the trial.

PATIENT TABLET RETURNS AND DESTRUCTION

Patient returns:

- Tablet counts for olaparib should be documented on each **PARADIGM (Phase I) Patient Specific Accountability Log - OLAPARIB**

Destruction:

- Destruction must be recorded using the **Olaparib Destruction of Clinical Trials Supplies Log**.
- Patient returns can be destroyed once accountability is completed and provided that any discrepancies are resolved.
- Expired or unused stock must have written permission from Sponsor prior to destruction.

DOSE MODIFICATIONS FOR OLAPARIB

No dose modifications will be allowed
If patients experience dose limiting toxicities while taking olaparib, the drug should be discontinued.

DOSE DELAYS FOR OLAPARIB

No dose delays will be allowed
If patients experience dose limiting toxicities while taking olaparib, the drug should be discontinued.

Delays of up to 7 days in radiotherapy are permitted once the patient has started radiotherapy. Patients should continue taking olaparib until radiotherapy is completed and for four weeks after completion of radiotherapy, unless the cause of the delay is thought to be related to olaparib or olaparib/radiotherapy combination.

CONCOMITANT THERAPIES

All concomitant therapy taken at any point from 4 weeks before registration up to and including the end of treatment

visit will be documented in the appropriate section of the trial CRFs and in the patient's medical records along with dose, frequency and therapeutic indication.

Please refer to section 5.10 of the trial protocol for guidance on prohibited therapies.

The following potent inhibitors of CYP3A must not be used for any patient receiving olaparib

- Ketoconazole, itraconazole, ritonavir, indinavir, saquinavir, telithromycin, clarithromycin and nelfinavir

(wash-out period 1 week)

Whilst this is not an exhaustive list, it covers the known potent inhibitors that have most often previously been reported to be associated with clinically significant drug interactions.

In addition, to avoid potential reductions in exposure due to drug interactions and, therefore, a potential reduction in efficacy, the following CYP3A4 inducers are excluded unless a washout period occurs before administration of IMP:

- Phenytoin, rifampicin, rifapentin, rifabutin, carbamazepine, phenobarbitone, nevirapine, modafinil and St John's Wort (Hypericum perforatum)
- Wash-out period for phenobarbitone: 5 weeks
- Wash-out period for any of the others: 3 weeks

TRANSLATIONAL RESEARCH

Patients must consent to participate in the translational studies

Tissue collection:

- Patients will be asked to consent to use of residual tumour tissue that was removed at the time of their original neurosurgical operation and was not needed for routine diagnosis and treatment for research purposes.
- If consent is obtained, residual tumour tissue will be collected and stored by the Glasgow Biorepository and will be used after the trial is complete for translational research projects aimed at identifying which patients benefit from addition of olaparib to radiotherapy.

Blood samples:

Additional blood samples will be taken as per the schedule of assessments and used specifically for translational research purposes.

- Blood samples will be collected locally then transferred to Glasgow Analytical Services Unit, which is part of the Glasgow Experimental Cancer Medicine Centre (ECMC).
- Researchers will apply to the ECMC Steering Committee to gain access to the blood samples.

Aims:

The main aims of the translational research projects will be to identify molecular biomarkers that have potential to predict which glioblastoma patients will benefit from the addition of olaparib to radiotherapy, and to investigate whether olaparib has any protective effects on the normal brain. Blood tests will be analysed to look for circulating cells or DNA that has come from the tumour, which can sometimes be used to obtain information about the tumour.

Further details regarding sample handling and sample shipping will be provided by CRUK CTU in due course.

ASSESSMENT AND FOLLOW-UP

Evaluations during radiotherapy treatment

During radiotherapy treatment all patients should be seen once a week and the following assessments performed:

- Review of adverse events
- Review of medications, including steroid dose if applicable
- WHO performance status
- Blood sample for haematology and biochemistry
- Blood sample for research purposes

Evaluations during additional olaparib treatment

Patients will be seen after 2 weeks of the additional 4 week olaparib treatment period (2 weeks after the end of radiotherapy), and the following assessments performed:

- WHO performance status
- Review of adverse events
- Review of medications, including steroid dose if applicable
- Vital signs
- Blood sample for research purposes

Evaluations after completion of trial treatment

Patients should be seen in clinic on completion of olaparib treatment and at 4 and 8 weeks after completion of olaparib treatment and the following assessments performed:

- Physical examination including full neurological examination
- Review of medications, including steroid dose if applicable
- Review of adverse events
- WHO performance status
- Blood samples for haematology and biochemistry (week 4 only unless CTC >1 toxicity in which case repeat until resolved)
- Blood samples for research purposes
- Mini Mental Status examination and Quality of Life questionnaires
- MRI brain for disease assessment (week 8 only, reported using RANO criteria)

ASSESSMENT AND FOLLOW-UP (continued)

Evaluations during follow-up

Once patients have completed assessment at 8 weeks they will enter follow-up and should be assessed every 2 months or until clinical or radiological disease progression. Regular MRI scans are not required and patients should undergo MRI examination if there are symptoms or signs of disease progression, according to local policies. At each visit the following assessments should be performed:

- Physical examination including full neurological examination
- Review of medications, including steroid dose if applicable
- Review of adverse events
- WHO performance status
- Mini Mental Status examination
- Quality of Life questionnaires

Follow-up after clinical or radiological progression

Once a date of progression has been recorded, patients should be followed up according to local practice until death. Assessments should be as per local practice. Survival data should be collected either directly or by contacting the patient's GP.

SITE SET UP

CTU GLASGOW

Main REC approval - MHRA approval - Site Initiation Slides
- Investigator Site File - Pharmacy Site File

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SITE

Delegation and Study Specific Training Log – SSI – R&D Approval
– Clinical Trial Agreement – Investigator and Lead Pharmacist CVs
- GCP Certificates for PIs – PIS/CF, GP Letter etc. on Trust headed paper
- Lab normal ranges and accreditation certificates (haem and biochem)

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INITIATION PROCESS

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DRUG SUPPLY

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SITE ACTIVATED

CRFs and CRF COMPLETION

CRFs for the trial:

- Registration Form
- Pre-Treatment form
- Treatment Form
- End of Treatment Form
- Follow–Up Form
- Concomitant Medication Form
- Consent Withdrawal Notification Form
- Pregnancy Notification Form
- SAE Form *Please note the SAE form is faxed to Pharmacovigilance at the CRUK CTU and the original SAE report is kept at site.*

CRF completion:

- CRF completion guidelines for the trial are currently being developed and will provided to sites when available
- Entries to the CRFs will be made in black ball-point pen and must be legible. Correction fluid etc. must not be used
- Any errors must be crossed out with a single stroke, correction inserted and change initialled and dated. An explanation can be written next to amendment if necessary
- Please ensure all data submitted on the CRFs is verifiable in source documents
- Take photocopy of all completed CRFs. Originals to be sent to CRUK CTU Glasgow

CRF completion timelines:

- Data entry – within 4 weeks of the patient visit
- Resolution of queries – within 4 weeks of receipt
- All data should be returned to CRUK CTU within 1 week of sign off

PHARMACOVIGILANCE

Clinical Trial Regulations require:

- Investigators document Adverse Events (AEs) in patient notes and the CRF as required
- Investigators report Serious Adverse Events (SAEs) immediately to the CRUK CTU
- The CRUK CTU (on behalf of the Sponsor) will make expedited reports of SAEs that meet the criteria for SUSARs to the Regulatory Authority (MHRA), REC, Sponsor and AstraZeneca
- The CRUK CTU will produce Development Safety Update Reports in conjunction with the Chief Investigator

ADVERSE EVENT REPORTING

- All AEs must be followed;
  - until resolution,
  - or for at least 30 days after discontinuation of trial medication,
  - or until toxicity has resolved to baseline,
  - or < Grade 1,
  - or until toxicity is considered to be irreversible

- All AE and toxicities must be graded according to the NCI-CTCAE Version 4.0

- An exacerbation of pre-existing condition is an AE

- All AEs must be recorded in full in the patient's notes with details of the nature of the event, start and stop dates, severity (the CTCAE grade), seriousness (if the AE is considered serious or non-serious) and causality to olaparib and radiotherapy and outcome

DEFINITION OF A SERIOUS ADVERSE EVENT

A Serious Adverse Event (SAE) is defined as any untoward medical occurrence that is not necessarily related to protocol treatment 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 or birth defect
- Is considered medically significant by the Investigator

Life threatening:

- The patient is 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.

Requires in-patient hospitalisation:

- Is a hospital admission required for treatment of an adverse event even when the adverse event is not related to the protocol treatment.

REPORTING SAEs

- Serious Adverse Events (SAEs) must be reported immediately (within 24 hours of knowledge of the event)
- SAEs are reported using the CTU SAE report form for the PARADIGM trial
- Sites must complete the SAE report form and fax the report to Pharmacovigilance at the CRUK CTU Glasgow fax number **0141 301 7213**
- The CRUK CTU will create a SAE reference number and will send an acknowledgement fax to confirm receipt
- The CRUK CTU will request additional information if the event is unexpected
- CRUK CTU will raise queries for any inconsistent or missing information
- SAEs must be reported locally by the PI at each site in accordance with the local practice at their site (i.e. Ethics Committee, R&D Office)
- SAEs are required to be reported for up to 30 days after discontinuation of trial treatment
- Any SAE that occurs after 30 days post treatment is also required to be reported if the PI thinks that the SAE is related to the protocol treatment, and is medically important

PROCEDURE FOR REPORTING SAEs AND SAE REPORT PROCESSING

PROCEDURE FOR IDENTIFYING UNEXPECTED AND RELATED EVENTS

EXPEDITED REPORTING

SAEs that meet the criteria for SUSARs will be reported to the MHRA, REC, Sponsor and AstraZeneca where in the opinion of the Chief Investigator the event was:

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

AND

- Unexpected – that is the type of event not listed as an expected occurrence in the Reference Safety Information (RSI). The RSI is section 5.4 of the Investigator Brochure that has regulatory approval to assess the expectedness of SAEs

OR

- Is an interaction between olaparib and the radiotherapy treatment

CRUK CTU on behalf of the Sponsor is responsible for the expedited reporting of all SUSARs to the required Regulatory Authorities, Research Ethics Committee (REC), PI at trial sites and the trial Sponsor(s) as well as AZ.

- Fatal or life threatening SUSARs will be reported within 7 days of the CRUK CTU receiving the first notification of the unexpected event. Any additional information will be reported within eight days of sending the initial report
- All other SUSARs will be reported within 15 days of the CRUK CTU receiving the first notification of the unexpected reaction.

PHARMACOVIGILANCE DOCUMENTATION

The Pharmacovigilance section of the site file must be maintained and contain the following documentation:

- Copy of all SUSAR and DSUR reports
- All SAE reports that have been submitted by the site (these may be filed with the CRFs if a file note produced by your site, recording the location of SAE reports, is filed in the site file)
- Copies of the current and previous RSI (Investigator Brochures for olaparib) with other related documentation such as the front sheet document
- All other correspondence from Pharmacovigilance

MONITORING (1)

Central Monitoring

Trial sites will be monitored centrally by checking incoming forms for compliance with the protocol, data consistency, missing data and timing. Trial staff will be in regular contact with site personnel (by phone/fax/email/letter) to check on progress and deal with any queries that they may have.

On-site and Remote Telephone Monitoring

The 1st visit will take the form of a remote telephone monitoring visit:

- The time & date will be agreed with a member of the Site Trial Team & a separate time & date agreed with a member of the Clinical Trials Pharmacy Department
- A pro forma covering the questions which will be covered during the telephone monitoring visit will be sent with confirmation of the confirmation of the agreed date
- Please set aside 50 to 70 minutes for this call.

MONITORING (2)

The 2nd visit will take the form of an on site monitoring visit:

- Investigators and site staff will be notified in advance about forthcoming pre arranged monitoring visits
- All patient source documentation should be made available to enable Source Document Verification by the Clinical Trial Monitor
- A full working day is required for on-site visits & arrangements should be in place to facilitate the monitor access on the agreed date
- If sites are able to provide printed results/reports these must be filed in the source documents
- If a site is using electronic data reporting systems or electronic records & hard copies are not available the clinical trial monitor must be permitted access to the system either by being issued with a temporary login or a member of staff available for the duration of the visit to facilitate electronic access to authorised reports/results

- The pharmacy department responsible for the trial will be visited to allow monitoring of the pharmacy site file and review of security, storage and accountability of trial drugs.
- All findings will be discussed at an end of visit and any unresolved issues raised as Action Points
- Action Points will be followed up by the monitor until resolved

INVESTIGATOR RESPONSIBILITIES (1)

The following principles are from ICH GCP Topic E6 and apply to clinical trials of Investigational Medicinal Products:

Qualifications & Agreements:

- The Investigator should be qualified by education, training & experience.
- Thoroughly familiar with protocol & medicinal products.
- Comply with GCP and applicable regulations.
- Permit – monitoring and audit by the sponsor and inspection by regulatory authorities.
- Maintain a delegation log of staff involved in the clinical trial at the trial site.
- Ensure that all persons assisting with the trial are adequately informed about the protocol, IMP and their duties and functions.

Resources:

- The Investigator should have sufficient time to properly conduct and complete the trial within the agreed period.
- Have available adequate facilities and qualified staff to conduct the trial properly and safely.

Medical Care of Trial Subjects:

- A qualified physician who is an Investigator (or co-investigator) should be responsible for all trial related medical decisions.
- During and following participation the Investigator should ensure adequate medical care for any adverse events (AEs).
- The Investigator should make as reasonable effort to ascertain reasons for withdrawal from the trial (although a subject is not obliged to give reasons)

INVESTIGATOR RESPONSIBILITIES (2)

Ethics:

- Before initiating the trial there should be written and dated approval/favourable opinion from the Ethics Committee for the protocol, patient information sheet/consent form and any amendments.

Compliance with Protocol:

- The Investigator should conduct the trial in compliance with the protocol.
- Not implement any deviation from the protocol without prior approval/favourable opinion of the IEC and the sponsor.
- The Investigator should document and explain any deviation from the protocol.

The IMP :

- Investigator has responsibility for IMP accountability at trial site
- Some/all IMP duties at the trial site may be assigned to suitably qualified pharmacist.
- Records must be maintained: delivery, inventory, use and destruction
- Storage of the IMP should be as specified by the sponsor/regulatory requirements.

- The IMP should only be used in accordance with the protocol.
- The Investigator (or designee) should explain the correct use of the IMP to each patient.

Registration :

- The Investigator should follow the trial's registration procedures as detailed in the protocol.

INVESTIGATOR RESPONSIBILITIES (3)

Informed consent:

- In obtaining and documenting informed consent, the investigator should comply with the applicable regulatory requirement (s), and should adhere to GCP and to the ethical principles that have their origin in the Declaration of Helsinki.

Reports & records

- The investigator is responsible for accuracy, completeness, legibility and timeliness of the data reported to the sponsor.
- Data reported on CRFs, from source documents should be consistent with source documents or discrepancies explained.
- Corrections should be : dated, initialled, explained (if necessary) and should not obscure the original entry.
- All trial documents should be maintained as specified in ICH GCP E6, Section 8 (Essential documents for the conduct of a clinical trial).

Safety reporting:

- Investigators are responsible for the safety of patients recruited to the trial from their trial site.
- Investigators must report Serious Adverse Events to the sponsor as soon as they become aware of the event.
- Investigators must ensure that follow-up SAE reports are provided until the SAE resolves.
- Investigators must respond to data queries raised on SAE reports within 7 days.
- Investigators must provide information on any potential SUSARs as quickly as possible.

OTHER STAFF

The Principal Investigator has overall responsibility for the conduct of the clinical trial at the trial site.

BUT

• All staff must comply with GCP
• Staff should only perform tasks delegated to them on the delegation log

• Staff should have the appropriate trial related training on the trial protocol
• Staff should ensure that their details are available to the Investigator
• Staff should maintain appropriate confidentiality at all times

CONTACT DETAILS FOR CTU, GLASGOW

Anna Morris
Project Manager
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