IMAGINE

Integrating Medically Actionable Genomics INto Early-phase trials

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This trial will be performed according to the Research Governance Framework for Health and Community Care (Second edition; 2006) and World Medical Association Declaration of Helsinki Ethical Principles for Medical Research Involving Human Subjects 1964 (as amended)

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Trial Summary

Title: **I**ntegrating **M**edically **A**ctionable **G**enomics **IN**to **E**arly-phase trials

Background: We are in an era of precision medicine where we aspire to make treatment decisions for our patients based on the molecular characteristics of their tumour. In current clinical practice, there are some examples where therapy is molecularly guided (e.g. cetuximab in KRAS wild-type colorectal cancer and olaparib for BRCA1/2 mutant ovarian cancer). The molecular information directing therapy is often based on somatic mutations in the diagnostic specimen. There is, however, now strong scientific evidence that in some cases tumour tissue at the point of diagnosis is significantly different than tumour tissue following multiple lines of treatment. This means that for some patients, molecular characterisation of the tumour should be established from a biopsy of the tumour taken after the last line of therapy. Currently there is limited infrastructure in Scotland to support the delivery of molecularly guided cancer therapy. We therefore need to establish mechanisms to take tumour biopsies and process tumour samples for molecular profiling in a clinically useful timeframe (< 6 weeks). The early-phase trials teams in Edinburgh and Glasgow provide eligible patients across Scotland with access to new experimental anti-cancer treatments by running multiple early-phase clinical trials. Patients are referred by their oncologist when they have no remaining standard treatment options. The early-phase trials teams are staffed by consultant oncologists specialising in experimental therapeutics, clinical research fellows and experienced research nurses. Together they provide an excellent environment for establishing molecularly guided therapy. A central focus of the Glasgow Precision Oncology Laboratory (GPOL), based at the Wolfson Wohl Cancer Research Centre (WWCRC) and the Queen Elizabeth University Hospital, is to use the most advanced DNA sequencing techniques to match the right treatment to the right patient. The IMAGINE study will bring together Scotland's expertise in the development of new cancer treatments and DNA sequencing. The

	study will recruit 250 patients and will allow an in-depth analysis of tumours from Scottish patients by the GPOL. The initial aim is that a pathway is developed that allows tumour molecular profile data for our patients to be available quickly enough, to influence the choice of the most appropriate experimental anti-cancer treatment.
Design:	Multi-centre, non-randomised, sample collection, feasibility study.
Primary Objective:	To establish a framework in which tumour samples can be obtained and molecular profiles generated in a clinically useful timeframe (less than 6 weeks).
Secondary Objectives:	To report the complication rate arising from obtaining tumour biopsies suitable for molecular profiling. To report the proportion of patients where biopsy contained adequate tumour. To report the proportion of patients where adequate DNA was isolated from archival tissue or contemporaneous biopsy. To establish a molecular tumour board. To report the proportion of patients where an actionable aberration is identified. To report the proportion of patients where an appropriate therapy was accessible.
Exploratory Objectives:	To obtain blood samples for assessment of circulating biomarkers. To establish a repository of molecular profiles with associated clinical data for further translational research.
Primary Endpoint:	Proportion of patients where molecular profiling was generated in a clinically useful timeframe.
Secondary Endpoints:	Biopsy complication rate Proportion of patients where the biopsy contained adequate tumour Proportion of patients where adequate tumour DNA was isolated (archival tissue or contemporaneous biopsy).

Proportion of patients where an actionable aberration is identified
Proportion of patients where an appropriate therapy was accessible

Population: Patients referred for consideration of early-phase clinical trials who are fit for systemic anti-cancer therapy and are able and potentially willing to have a tumour biopsy or have had prior tumour profiling.

Participating Sites: Beatson West of Scotland Cancer Centre (BWoSCC)
Edinburgh Cancer Centre

Eligibility:

Inclusion Criteria

1. Adult patients aged 16 or over
2. Patients referred for consideration of early-phase clinical trials with histologically confirmed advanced solid tumours
3. Patient meets one of the following criteria:
   a. Available archival tumour sample or willing to have a tumour biopsy
   b. Had prior tumour molecular profiling*
4. Patient deemed a suitable candidate for further systemic anti-cancer therapy
5. Willing and able to provide signed informed consent

Exclusion Criteria

None.

*note these patients will not contribute to primary or secondary objectives, will have no tumour or blood sampling but will contribute data for translational research.

Intervention: Patients referred for consideration of early-phase clinical trials will give written, informed consent.
Archival tumour tissue will be requested.
For patients where a contemporaneous biopsy is of interest (for example suspected actionable resistance mechanism) an attempt will

be made to obtain tumour tissue by imaging-guided (Ultrasound or CT) or other suitable biopsy
Blood will be taken for DNA extraction and to examine circulating tumour markers.
Molecular characteristics of the tumour will be established.
For a sub-set of patients who have successful analysis of biopsy tissue an archival sample will be requested and analysed for comprehensive examination of resistance mechanisms.
Patients who have had prior tumour sequencing will not be asked to contribute archival or blood samples for the study. They will be asked for their clinical and molecular data to be contributed to the study database to facilitate translational research.

Duration: We expect to recruit 50-80 patients per year with an aim of recruiting 250 patients (with molecular profiles) within 4 years.

Statistical Analysis: As this is a feasibility study, we plan to use descriptive statistics to report our experience. We will record the complication rates, the number of cases where samples were not fit-for-purpose (insufficient DNA, inadequate quality of DNA etc.) and the time it takes from consent to obtaining molecular profiles. We will also report on how often actionable aberrations are described and potential therapies available.

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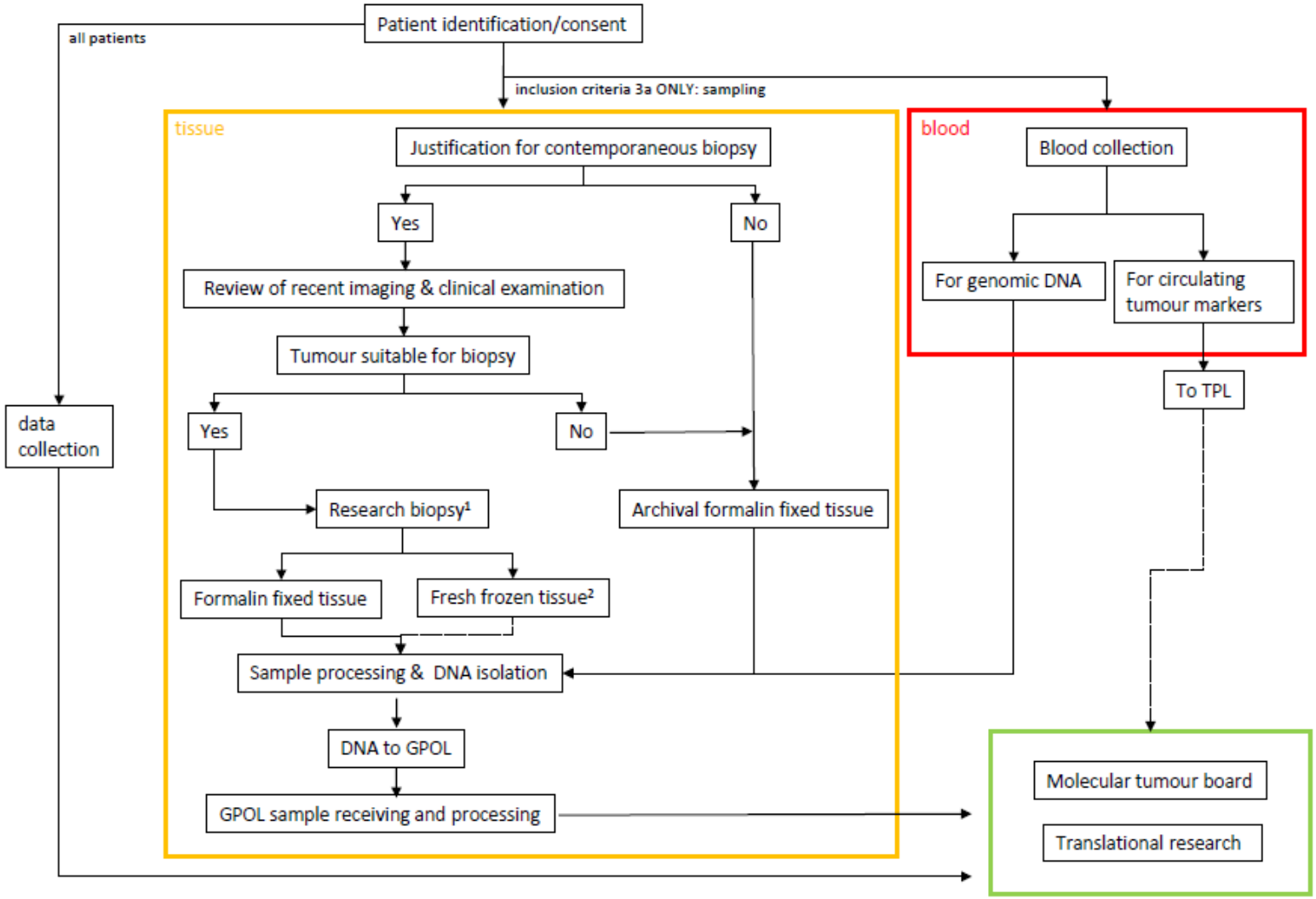
Abbreviations

AE	Adverse Event
BWoSCC	Beatson West of Scotland Cancer Centre
CRUK	Cancer Research United Kingdom
CaCTUS	Cancer Clinical Trials Unit Scotland
CRU	Clinical Research Unit
CTC	Clinical Trial Coordinator
CTU	Clinical Trials Unit
CI	Chief Investigator
CRF	Case Report Form
CTIMP	Clinical Trial of an Investigational Medicinal Product
DNA	Deoxyribonucleic acid
ECMC	Experimental Cancer Medicine Centre
GPOL	Glasgow Precision Oncology Laboratory
HRA	Health Research Authority
IDMC	Independent Data Monitoring Committee
IHC	Immunohistochemistry
NGS	Next Generation Sequencing
PV	Pharmacovigilance
PI	Principal Investigator
PM	Project Manager
PNF	Pregnancy Notification Form
R&D	Research and Development
REC	Research Ethics Committee
RAE	Related Adverse Reaction
SAE	Serious Adverse Event
SRAE	Serious and Related Adverse Event
TPL	Translational Pharmacology Laboratory
TSC	Trial Steering Committee
WWCRC	Wolfson Wohl Cancer Research Centre

Trial Flow Chart



¹Archival formalin fixed tissue also requested for the patients having research biopsy ²Held at site: If formalin fixed tissue yields inadequate tumour, frozen tissue sent for path review. TPL=translational pharmacology lab. GPOL=Glasgow Precision Oncology Laboratory

Schedule of Assessments

Time point	Pre-screening	Research unit visit[8]	Biopsy visit [9,10]	Follow-up visit [8,9]	Subsequent lines of Treatment
Scheduled Assessment	**-28 days**				
Standard of care trials-team assessment[1]	**X**				
Informed consent		**X[8]**			
Review of eligibility criteria		**X[8]**			
Clinical examination[2]		**X[2]**			
Adverse events and toxicity assessment[3]				**X**	
Translational Sample Collection					
Formalin fixed block[4]		**X**			
Image guided or other suitable biopsy[5, 6]			**X[10]**		**X**[10]
Translational blood samples[7]		**X**			**X**[11]

Key:

1) Medical history to include demographic details, original cancer details: date of original diagnosis, anatomical location of the primary, original tumour stage, histological sub-type, information regarding known molecular aberrations, time of recurrence and site of metastases. Family history to include history of cancer in first degree relatives. Treatment details to include prior therapies for cancer, including surgery, radiotherapy, chemotherapy and other systemic treatments. Start dates, stop dates and responses and toxicity to be recorded. ECOG performance status.
2) For patients where biopsy is being considered.
3) Adverse event & toxicity assessment according to CTCAE Version 5. Only events relating to image guided biopsy and translational blood samples to be collected. The worst grade experienced should be collected.
4) Formalin fixed block: Tumour tissue taken previously will be retrieved. One block of tissue as free from normal tissue as possible will be requested. The original pathology report must be available. For selected patients where molecular profiling of biopsy tissue identified interesting molecular aberrations, archival block will also be requested.
5) Image guided biopsy: See lab manual for full details of number/ size of cores required and processing details.
6) Other suitable biopsies will be allowed (e.g. skin deposit amenable to punch biopsy). However, this has to be confirmed with the Chief Investigator prior to entering the patient onto the study. Location of biopsied tumour deposit must be recorded in patient notes and CRF. Translational blood sample: to be taken prior to biopsy. See lab manual for details.
7) Visit to be performed when patient attends for standard of care visit.
8) Consent, eligibility review and follow-up may take place remotely.
9) Only to be performed if contemporaneous biopsy felt to be important for patient.
10) Optional image guided or other biopsy in patients who have an exceptional response to treatment or at progression. For patients recruited to a CTIMP, on-treatment and progression biopsies requested in the CTIMP protocol will be accommodated. Where possible IMAGINE biopsy will be combined with biopsies required in CTIMP.
11) Translational blood sample: 10ml blood to be collected for plasma (and buffy coat) storage. To be collected no more than 72 hours prior to administration of anti-cancer therapy

1 INTRODUCTION

1.1 Background

We are now in the era of precision oncology where we aspire to direct cancer treatment based not only on the primary site of disease and histological appearances but also on the molecular characteristics of the tumour. In current clinical practice, there are examples where molecular tumour characteristics are now vital to planning therapy (e.g. KRAS status in colorectal cancer, ALK status in lung cancer and BRCA1/2 status in ovarian cancer). As a result of these successes and progress in the understanding of the molecular biology of cancer there has been a proliferation of molecularly driven clinical trials. However, these late-phase studies continue to restrict eligibility to include only patients with a particular disease site in most cases, with a minority of studies where patients are selected by virtue of a molecular tumour characteristic only in progress [1]. In support of further studies using the latter model, Memorial Sloan Kettering Cancer Centre (MSKCC) reported that a cohort of non-melanoma patients found to have a BRAFV600E mutation and treated with BRAF inhibition had response rates comparable to melanoma patients (~71%)[2].

The Experimental Cancer Medicines Centres in Glasgow and Edinburgh, provide access to experimental treatments for patients who have exhausted the currently approved treatments for their condition. Many of these experimental treatments are targeted therapies, designed to modulate a particular molecular pathway. Furthermore, the ECMC Experimental Cancer Trial Finder Project has recently been initiated. This project is designed to facilitate recruitment to early-phase clinical trials on a network-wide basis by providing a clinical trials database searchable by actionable molecular aberration. This will expand our access to specific targeted agents. The majority of these early-phase studies are not restricted to recruitment of patients with one tumour type in the first instance but rather are selected on the basis of putative biomarkers predictive of response to therapy, which has become a vital component of studies even in the early-phase.

Currently we have no programme of molecular profiling of our phase 1 patient population. Most world leading phase 1 units routinely perform Next Generation Sequencing (NGS) on the tumours from their patients with the aim of appropriately matching patients to therapy and facilitating prompt recruitment to specific clinical trials.

To date, MD Anderson have reported their experience of molecular characterization of tumours to direct the choice of early-phase trial. Their IMPACT program recruited 1436 patients. 1179 (82%)

patients had molecular aberrations within their tumour, 637 (44%) had actionable mutations, 390 (27%) received matched treatment and 247 (17%) did not. Patients who had matched treatment had better response rates, progression free and overall survival [3-6]. This study utilised available surplus archival tumour tissue for genomic analysis.

MSKCC have also recently reported their experience of molecular characterisation of metastatic tumours from 10 000 patients using their MSK-IMPACT panel [2]. Their sequencing programme was not limited to potential early-phase clinical participants. They used a hybridization capture-based NGS panel that can detect protein coding mutations, copy number alterations and selected promoter mutations and structural rearrangements in 341 genes (now 410 genes). The median turnaround time was <21 days. At least one actionable mutation was identified in 36.7% of patients. Their cohort comprised of both primary tumours (57%) and metastatic sites (43%). Of the first 5009 patients, 11% received treatment within a clinical trial based on the actionable mutation found.

Other centres have reported studies where molecular profiling has directed treatment choice but in smaller cohorts and not within an early-phase clinical trial population. One of the earliest studies reported was from Von Hoff *et al* who reported on 86 patients who had molecular tumour profiling. 84 tumours had aberrations and 66 patients received matched treatment. In 27% of patients who received matched treatment PFS was longer on the matched treatment than the PFS following the prior therapy [10]. More recently a group of 8 academic centres in France reported the results of the SHIVA trial. This was a multi-centre, open label, proof-of-concept, randomized, controlled phase 2 trial where advanced cancer patients, in whom standard of care had failed, had molecular profiling of their tumour. Patients with tumours with an alteration in either the hormone receptor pathway, PI3K/AKT/mTOR pathway or the RAF/MEK pathway were included. Patients were then randomized to 'matched' treatment or physician's choice. 741 patients were screened and 293 (40%) patients had an aberration. 99 patients were randomized to the experimental group and 96 to the control group. The median PFS was 2.3 months in the experimental group versus 2 months in the control group (HR 0.88, 95% CI 0.65-1.19, P=0.41) [11, 12]. The University of California, San Diego Moores Cancer Centre reported on their PREDICT program where 347 patients had NGS of their tumour. 87 patients received matched therapy and 93 unmatched. More patients in the matched group had a response to treatment (35.5% vs 16.1%, p=0.02) and PFS was longer in the matched group (4 vs 3 months, p=0.039) [13, 14]. Finally, The Princess Margaret Cancer Centre in Toronto have reported their experience of molecular profiling of tumour tissue to guide treatment. In this study, archival tumour tissue was tested using a targeted NGS panel. Somatic mutations were classified according to clinical actionability. 1640 tumours were tested. 15% of the patients were treated in clinical trials

with 84 patients being in 'genotype matched' trials. The response rate was higher in patients treated on 'genotype matched' trials (19% vs 9%)[15].

While widely variable rates of successfully matching patients to therapy, based on molecular profiling, have been reported (25%-77%) studies appear to suggest that when patients can be molecularly matched to therapy, response rates, progression free and overall survival improve. Furthermore, it is generally accepted that patients treated in a trials active centre have improved outcomes regardless of whether they themselves reach study entry [16].

Even in the absence of detecting an actionable mutation there is much to gain from sequencing data generated from our early-phase clinical trial population. In the era of precision medicine and in an environment where approximately three quarters of our clinical trial portfolio comprises of commercial studies, it is an important step forward for us to demonstrate our capabilities to molecularly profile our phase I population. This would help to attract further studies and thus ensure that our portfolio includes a wide variety of targeted agents consequently improving our ability to molecularly match patients to therapy and ultimately improve clinical outcome. Additionally, it provides the opportunity for translational research, facilitated by our molecular profiling program, to lead to investigator initiated studies.

1.2 Trial Rationale and Hypothesis

Where clinical trials allow recruitment of patients across several tumour sites, patients are currently matched to a clinical trial based on their clinical characteristics. Scotland's ECMCs aspire to establish a mechanism in which tumours can be molecularly profiled to aid patient selection for specific clinical trials.

The first vital step in the pathway to obtaining molecular profiling for our early-phase trials participants is accessing tumour tissue. Secondly, tissue samples need to be processed and molecular profiles generated using NGS. Thirdly, we will develop a process for interpretation of results and consideration of the clinical impact of findings.
Alongside profiling of tumour, blood samples will be taken to develop non-invasive methods of tumour profiling by examining circulating tumour markers.

This study aims to test the feasibility of obtaining molecular profiles in a clinically useful timeframe (<6 weeks).

The molecular profiles generated from the trial participants' archival tumour/ recurrent/metastatic disease and circulating tumour markers will form part of a translational research program to understand cancer evolution and treatment resistance. Since patients are sometimes referred to the early-phase trials unit who have had tumour profiling through a commercial vendor we plan to ask these patients to consent to their molecular profiling and clinical data to be captured through eIMAGINE .

In the early stages of this study the molecular profiling results generated were not intended to inform treatment decisions as the assay used was not approved for clinical use, however the assay is now validated within the NHS so treatment may be directed by this tumour profile information for a proportion of patients recruited.

2 STUDY OBJECTIVES

This is a multi-centre, non-randomised sample collection, feasibility study.

2.1 Primary Objective

To establish a mechanism and framework in which tumour samples can be obtained and molecular profiles generated in a clinically useful timeframe (<6 weeks).

2.2 Secondary Objectives

- To report the complication rate arising from obtaining tumour biopsies suitable for molecular profiling.
- To report the proportion of patients where biopsy contained adequate tumour.
- To report the proportion of patients where adequate DNA was isolated from archival tissue or contemporaneous biopsy.
- Establish a molecular tumour board.
- To report the proportion of patients where an actionable aberration is identified.
- To report the proportion of patients where an appropriate therapy was accessible.

2.3 Exploratory Objectives:

- To obtain blood samples for assessment of circulating biomarkers.
- To establish a repository of molecular profiles with associated clinical data for further translational research.

3 TRIAL DESIGN

This multi-centre, non-randomised, sample collection, feasibility study will be performed according to the Research Governance Framework for Health and Community Care (Second edition, 2006).

3.1 Trial Population

Patients referred for early-phase clinical trials who are fit for systemic anti-cancer therapy and are able and potentially willing to have a tumour biopsy or have had prior tumour profiling will be enrolled. We expect to recruit 250 patients in a four year recruitment period.

3.2 Inclusion Criteria

1. Adult patients aged 16 or over
2. Patients referred for early-phase clinical trials with histologically confirmed advanced solid tumours
3. Patient meets one of the following criteria:
    a. Available archival tumour sample or willing to have a tumour biopsy
    b. Had prior tumour molecular profiling*
4. Patient deemed a suitable candidate for further systemic anti-cancer therapy
5. Willing and able to provide signed informed consent

3.3 Exclusion Criteria

None.

*note these patients will not contribute to primary or secondary objectives, will have no tumour or blood sampling but will contribute data for translational research.

There will be no exception to the eligibility requirements at the time of registration. Queries in relation to the eligibility criteria should be addressed to the Chief Investigator. Patients are eligible for the trial if all of the inclusion criteria are met.

3.4 Identification of participants and consent

Patients referred for consideration of early-phase clinical trials at Glasgow or Edinburgh ECMC will be assessed in a new patient consultation as is standard practice. Those patients who are deemed as being potential early-phase clinical trial participants will be given a patient information sheet regarding this trial and will be given the opportunity to consent to trial participation (a minimum of

24 hours from the initial consultation for patients undergoing an additional biopsy). All efforts will be made to ensure patients understand the commitment required to fulfil the trial requirements. In addition, patients should be made aware that participation is voluntary and they can withdraw from the trial at any time without their standard care being affected. No screening activities related to the trial may be undertaken until consent has been obtained.

3.5 Registration

Patients cannot be screened or 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 at the following contact details:

Registration Service:

Registration to the trial can be performed by either telephone or email:

Telephone Number: 0141 301 7201
Email: ggc-recruitment.crukglasgowctu@nhs.scot

Registration Service: Monday - Thursday 08:30-17:00, Friday 08:30-16:30
Emails received outside office hours will be actioned the next working day

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 trial intervention.

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.
- Any other relevant reason in the opinion of the investigator.

If the patient withdraws from the trial it should be clearly documented in the patient's notes what they are withdrawing from (consent to use any past data, consent to use any samples collected or consent for further data collection from the date of consent withdrawal).

If the 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.

4 TRIAL PROCEDURES

4.1 Trial Endpoints

4.1.1 Primary Endpoints

- Proportion of patients where molecular profiling was generated in a clinically useful timeframe

4.1.2 Secondary Endpoints

- Biopsy complication rate
- Proportion of patients where the biopsy contained adequate tumour
- Proportion of patients where adequate tumour DNA was isolated (archival tissue or contemporaneous biopsy).
- Proportion of patients where an actionable aberration is identified
- Proportion of patients where an appropriate therapy was accessible

4.2 Trial Schedule

Patients referred for consideration of early-phase clinical trials in Glasgow or Edinburgh ECMC will be assessed in a new patient consultation as is standard practice. Those patients who are assessed as being potential early-phase clinical trial participants will be given a patient information sheet regarding this study and will be given the opportunity to consent to study participation. After written informed consent has been obtained, an archival tumour sample will be requested for analysis. For some patients where contemporaneous biopsy is thought to be of value (i.e. suspected targetable resistance mechanism) image-guided/other suitable biopsies will be performed according to local standard management where possible. Since patients referred for consideration of early phase clinical trials are not restricted to defined tumour sites, biopsies may be obtained from a variety of anatomical locations. The biopsy location will be determined by radiology review of recent imaging. Tumour areas where there is a risk of damage to blood vessels or lung tissue will not be biopsied.

Blood samples will be taken for isolation of DNA and to examine circulating tumour markers. Tumour samples will be processed according to the study lab manual. As per standard practice, patients will be added to the early-phase trial waiting list and offered participation in a CTIMP based on their clinical characteristics and any already known genetic information. Patient investigations and evaluation as well as assessments during treatment, will be unaffected by participation in this trial and will be performed according to the early-phase clinical trial protocol. When molecular profile results become available the phase 1 team will come together to discuss any potential clinical impact of the results. The results will be communicated to the patient if the patient remains fit for systemic anti-cancer treatment and is continuing to attend the research unit.

eIMAGINE is the database that has been developed to capture the molecular and clinical data generated in the IMAGINE study. The database will be the platform used for the interpretation of results and consideration of the clinical impact of findings. In addition, it will form a resource for translational research aiming to identify biomarkers of response and treatment resistance. Patients who are referred to the early-phase trials unit who have already had tumour sequencing performed via a commercial vendor (and are not fit/willing to have a research biopsy) will be able to contribute their clinical and sequencing data to eIMAGINE via eligibility criteria 3b. Although these patients will not contribute to the primary or secondary objectives their clinical and sequencing data will make a valuable contribution to translation research studies examining associations between molecular aberrations and response and resistance. Patients who enter the study under inclusion criteria 3b will not be asked to provide tumour or blood samples.

4.2.1 Screening Assessments

Trial consent and procedures can take place remotely where possible if the patient has been assessed by the ECMC team and judged a suitable early-phase clinical trial participant (see 11.2 for detail on consent process).

- Informed consent
- Review of eligibility criteria
- Demographic details
- Medical history to include original cancer details: Date of original diagnosis, anatomical location of the primary, original tumour stage, histological sub-type and information regarding known molecular aberrations, date of recurrence, sites of metastases
- Family History to include family history of cancer in first degree relatives

- Treatment details to include full details of all prior therapies for cancer, including surgery, chemotherapy and other systemic treatments, and radiotherapy. Dates of treatment, dose prescribed, response and toxicity to treatment should be included
- ECOG Performance Status
  Clinical Examination (for patients where biopsy is being considered)

5 TRANSLATIONAL RESEARCH SAMPLE COLLECTION (INCLUSION CRITERIA 3A ONLY)

5.1 Translational Research

The tumour samples and blood samples collected as part of this study will undergo molecular profiling including but not limited to panel sequencing. Details of sample collection and plans for translational research analysis will be outlined in the laboratory manual.

5.2 Formalin fixed blocks

Tumour tissue taken previously will be retrieved. One block of tissue (or slides/curls) as free from normal tissue as possible will be requested. The corresponding pathology report must be available.

5.3 Imaging-guided tumour biopsies

Confirmation should be sought from the Principal Investigator if a biopsy is considered of added value. Where possible, cores of tissue as free from normal tissue as feasible will be obtained. After review of recent imaging, the radiology and clinical team will plan the safest anatomical location to biopsy.

Full details on number/size of cores, fixatives and sample handling are contained in the laboratory manual. Following the procedure the patient will be observed in a clinical area to ensure recovery from the procedure before discharge. On discharge, contact details for the research unit will be provided for use if the patient develops symptoms of concern.

Location of biopsied tumour deposit must be recorded in CRF.

Biopsies will be obtained when feasible. If no site is deemed safe for biopsy an archival sample will be requested. An optional second biopsy may be performed where patients have had an exceptional response or at progression.

5.4 Other suitable biopsies

Other suitable biopsies will be allowed (e.g. skin deposit amenable to punch biopsy). However, this has to be confirmed with the Chief Investigator prior to entering the patient onto the study. Location of biopsied tumour deposit must be recorded in CRF.

5.5 Blood samples

After informed consent has been obtained and the patient has been registered, 10 ml blood will be collected, centrifuged and plasma (with buffy coat) stored. In addition, up to 20ml whole blood will be collected and stored. Ideally this should be taken at the same time as the plasma sample, but can be taken at any point following patient registration. Details are outlined in the laboratory manual.

DNA isolated from whole blood will be matched with DNA isolated from tumour to allow tumour: normal analysis of DNA. Some DNA from whole blood will be retained so that in the event of identification of a previously undiagnosed germline mutation this DNA can be used for formal genomic analysis. When a germline mutation is identified patients will be referred to a clinical geneticist. As the study progresses, we may move to tumour only analysis of DNA. In the event of this occurring the sample of whole blood will be retained so that if there is suspicion of a germline aberration from sequencing of the tumour the DNA can be isolated and used for confirmatory testing by clinical genetics.

If the patient then participates in an early-phase clinical trial assessing an experimental anti-cancer treatment, a further 10 ml blood will be collected for plasma (and buffy coat) storage, prior to both first and second cycles of anti-cancer therapy. Samples should be collected no more than 72h prior to administration of anti-cancer therapy. The collection of these blood samples is optional and this will be stated in the consent form.

5.6 Sample Handling and Storage

All biopsy samples and archival tumour samples will be processed according to the lab manual. DNA will be isolated and sent to GPOL who will be responsible for analysis.

Standard operating procedures according to Good Clinical Practice for Clinical Laboratories will be used where applicable.

Blood samples for isolation of DNA will be sent to the molecular genetics laboratory at Queen Elizabeth University Hospital. Blood samples for analysis of circulating biomarkers will be transferred

to and stored in the Translational Pharmacology Lab, Institute of Cancer Sciences, University of Glasgow.

For long term storage, biopsy material or blood samples may be transferred to NHS GGC biorepository.

A laboratory manual will be provided with further details of these processes.

5.7 Duration of Trial Participation

5.7.1 Duration of Trial Follow-up

Patients will be followed up for response to subsequent therapies and to assess survival outcomes. The maximum length of follow-up is 8 months following the last patient recruited.

6 SAFETY REPORTING

Safety reporting will be performed by the Pharmacovigilance Department of the CRUK Glasgow CTU as delegated by the trial Sponsor. Safety reporting will meet the HRA requirements for safety reporting in research other than CTIMPs.

6.1 Safety Reporting for Non CTIMPs

6.1.1 Definitions

These definitions apply to all trial participants from the first trial intervention or procedure (biopsy/blood sampling) up to and including 30 days after the last procedure.

Term	Definition
Adverse Event (AE)	An adverse event is any untoward medical occurrence in a subject to whom a trial treatment or intervention has been administered, including occurrences which are not necessarily caused by or related to that treatment or 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)	In research other than CTIMPs, a Serious Adverse Event is defined as an untoward occurrence that:

	• 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. **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

6.1.2.1 Detection of Adverse Events

Participants will be asked at each trial visit about the occurrence of AEs since their last visit.

AEs will be recorded, notified, assessed, reported, analysed and managed in accordance with the HRA requirements. AEs must be recorded as they are reported, whether spontaneously volunteered or in response to questioning about well-being at trial visits. The questioning about AEs will cover the current visit as well as the period of time between the previous and the current visit. All AEs

must be documented in full in the patient's medical records whether they are required to be recorded in the CRF or not.

6.1.2.2 Recording of Adverse Events

Full details of AEs including the nature of the event, start and stop dates, severity (CTCAE grade), seriousness and causality (relationship of the AE to the trial intervention) and outcome will be recorded in the patient's medical records and on the study case report form as required. AEs must be reported from the first trial intervention (biopsy/blood sampling) and followed until:

- They resolve
- If present at pre-trial intervention, until the AE returns to the CTCAE grade observed at pre-intervention/procedure
- The AE is confirmed as unlikely to ever resolve

If none of the criteria above are met by 30 days after the last trial procedure (post biopsy or blood sampling), the AE no longer requires to be followed up. Perceived lack of efficacy is not an AE.

An exacerbation of a pre-existing condition is an AE.

The Investigator does not need to actively monitor patients for AEs once the trial has ended.

6.1.3 Assessment of Adverse Events

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

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

In determining whether an AE is an adverse reaction, Investigators must consider if there is a reasonable possibility of establishing a causal relationship between the event and the trial procedure (biopsy/blood sampling) based on their analysis of all the available evidence. The assessment must be made on the basis of anticipated effects of a biopsy or blood sampling as specified below in the protocol, or related to the patient's disease, either the disease under investigation or a concurrent illness.

The investigator must, whenever possible, provide a causality assessment for AEs based on the information available at reporting and their knowledge of the disease and potential effects of biopsies or blood sampling procedures. The causality assessment provided by an Investigator shall not be downgraded by the CI.

6.1.4 Reporting of a Serious Adverse Event

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

Investigators must report Serious Adverse Events (SAEs) to the Pharmacovigilance Office, 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.

Email: mvls-ctu-pv@glasgow.ac.uk
Telephone: 0141 211 3567/0203/3969 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.

For guidance on submitting and completing initial and follow up SAE forms please refer to the SAE Completion Guidelines, which will be provided by the Pharmacovigilance Office, CRUK Glasgow CTU. The CI will receive notification, by email, of all SAEs received.

SAEs must be reported locally by Investigators in accordance with the local practice (e.g. R&D Office).

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. All follow-up information is required to be reported promptly and follow up reports must be submitted until all AEs listed on the initial SAE report resolve or will never resolve. A follow up report should also be submitted if additional AEs occur or new information becomes available about previously reported AEs.

SAEs are required to be reported from the first trial procedure (biopsy/blood sampling) for up to 30 days after the last trial procedure.

Investigators must follow-up serious and related 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 team:

Pharmacovigilance Office, CRUK Glasgow CTU
Email: mvls-ctu-pv@glasgow.ac.uk
Telephone: 0141 211 3567/0203/3969 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:

- Minor bleeding
- Haematoma
- Pain
- Bleeding requiring blood transfusion
- Bleeding requiring intervention (radiological or surgical)
- Infection at the site of biopsy
- Pneumothorax
- 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 about 1 in 1500)
- Allergy to CT contrast
- Renal impairment secondary to contrast

The expected events as a result of blood sampling include:

- Minor bleeding
- Haematoma
- Pain

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 above list of expected events for biopsy and blood sampling at the time the SAE report is received.

When deciding if an event is unexpected consideration will be made by the CI as to whether the event adds significant information on the specificity, increase of occurrence or severity of a known, serious and related event that is already recognised and documented in the protocol.

6.1.7 Expedited Reports

CRUK Glasgow CTU on behalf of the 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 within the EU. It ends with the completion of the trial for all patients recruited (from the EU).

SAEs will be reported to the REC where in the opinion of the CI 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 CTU 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 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. If the risk-benefit of participation is adversely affected, appropriate prompt action will be decided upon by the CI, Sponsor and Trial Steering Group 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.

7 STATISTICS AND DATA ANALYSIS

As this is a feasibility study we plan to use descriptive statistics to report our experience. The following will be summarised along with appropriate 95% confidence intervals:

Primary Endpoints

- Proportion of patients where molecular profiling was generated in a clinically useful timeframe

Secondary Endpoints

- Biopsy complication rate
- Proportion of patients where the biopsy contained adequate tumour
- Proportion of patients where adequate tumour DNA was isolated (archival tissue or contemporaneous biopsy).
- Proportion of patients where an actionable aberration is identified
- Proportion of patients where an appropriate therapy was accessible

8 TRIAL CLOSURE/DEFINITION OF END OF TRIAL

The trial will end when the Trial Management Committee agrees that there is insufficient funding to support further recruitment and no reasonable prospect of additional support being obtained. It is estimated that current funding will support recruitment of 250 patients.

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

End of trial notification will be submitted to the Research Ethics Committee (REC) within 90 days using the 'Declaration of the end of a study, form. However, if the trial is terminated either (1) before the date for the conclusion of the trial specified in the protocol for that trial or (2) before the number of events required by the trial has occurred, the REC will be notified in writing of the termination of the trial within 15 days of the date of termination with a clear explanation of reasons and details of follow-up measures, if any, taken for safety reasons.

8.2 Clinical Trial Summary Report

The clinical trial summary report should be submitted to the REC within one year of submitting the end of trial notification. The CI in association with CRUK Glasgow CTU is responsible for compiling and submitting the final report to both sponsor and the REC.

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. 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.

9 DATA HANDLING

All patients should be registered on study at the Cancer Research UK Glasgow Clinical Trials Unit, The Beatson West of Scotland Cancer Centre, Glasgow. Registration must take place prior to any study specific procedures being performed.

Please refer to section 3.5 for Registration Details.

9.1 Data Collection

The eIMAGINE database has been developed for collection of the IMAGINE study dataset.
The purpose of the database is two-fold. First, it has to provide a platform that allows us to have clinical and genomic data in one place to facilitate conducting a molecular multidisciplinary meeting. Second, the database will provide a translational research resource that can be used by the study team to examine relationships between genomic aberrations and patient outcome. The database will be held securely on NHS systems and accessible only to specific study team members.
When data are being used for the translational research component of the study it will be identifiable only by study ID. Access to the data for future research projects will be subject to future ethical approval.

The following information will be collected;

Baseline:

- Demographic data: Patient's initials, date of birth, and clinician.
- Clinical details: Performance status
- Family history of cancer in first degree relatives
- Original cancer details: Date of original diagnosis, anatomical location of the primary, original tumour stage, histological sub-type and information regarding known molecular aberrations, date of recurrence, site of metastases
- Treatment details: All prior therapies for cancer, including surgery, chemotherapy and other systemic treatments, and date of last treatment. For chemotherapy; number of prior regimes, names and doses of prior chemotherapy drugs; radiological and biochemical responses to prior chemotherapy (where appropriate); date(s) of radiological progression following prior chemotherapy, previous toxicity
- Imaging-guided/ other suitable biopsy: date of biopsy, anatomical location of deposit that was biopsied.

- Adverse events following biopsy. Adverse events to be graded according to CTCAE v5 and assigned causality in relation to study procedures.
- Sample receipt, processing, % tumour, cellularity, pathology information, molecular genetics QC data and processing information
- Actionable aberration identified

Progression:

Early-phase-trial ID, target, date treatment started, number of cycles, best response and date, toxicity and date of progression

For patients who do not enter CTIMP: subsequent therapy, date treatment started, number of cycles, best response and date, toxicity and date of progression

Overall Survival:

- Date of death will be collected

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 site and they will be responsible for providing CRUK Glasgow CTU with all core documentation. Protocol training will be provided to site prior to the trial opening at that site. Once all the documentation is received at CRUK Glasgow CTU the site will be contacted by email when they are activated and are able to recruit patients to the trial.

10.2 Core Documents

- 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
- CV and GCP Certificate for PI
- PIS and GP letter on local headed paper
- Training acknowledgement for each member of study team
- Site initiation/accreditation checklist

10.3 Management of protocol deviations and violations

Deviations

Organisations must notify the Sponsor 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 CRUK Glasgow CTU. 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.

National Research Ethics Service SOP for Research Ethics Committees (version 6.1, January 2015) 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)

A TMG will oversee the running of the trial and normally includes those individuals responsible for the day-to-day management of the trial. Members of the TMG include the CI, Co Investigators, CTU Project Manager, Pharmacovigilance Manager, Study Statistician, Sponsor Representative, Pathology, Radiology and Lab Representatives.

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.

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 before patients are entered onto this clinical trial. The CI will be responsible for updating the REC 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. Consent can be completed in a face to face consultation or remotely (via video or telephone consultation). Where remote consent is undertaken, the participant will be provided with the consent form prior to the consultation. At the remote consultation the participant should initial, sign and date the consent form and the investigator should document the consent process in the patient record. The paper copy of consent completed by the participant should be brought to site at the participant's next visit. Regardless of the mode of consent, the consent forms should be signed by the participant and 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 protocol treatment without giving reasons and without prejudicing further treatment.

An original completed consent form (with participant and investigator signatures) 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.

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.

11.3 Confidentiality

All information collected during the course of the trial will be kept strictly confidential.
Information will be held securely on paper and electronically. All aspects of the 2018 Data Protection Act will be complied with and operationally this will include:

- Consent from participants to record personal details including initials, date of birth, CHI number, hospital number, GP name and address.
- Appropriate storage, restricted access and disposal arrangements for patient's personal and clinical details
- Consent from participants for access to their medical records by delegated 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 anonymization of documentation is required, site is responsible for ensuring only the instructed identifiers are present before sending to the appropriate person
- If a participant withdraws consent from 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.

NHS Greater Glasgow & Clyde (as the Health Board participating in clinical trial) is responsible for the following:

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

11.5 Sponsor

NHS Greater Glasgow and Clyde will act as the main sponsor for this trial. Minimal delegated activities will be assigned to the CRUK Glasgow CTU and the participating sites taking part in this trial.

11.6 Funding

The trial is funded by a grant from, University of Glasgow Medical, Veterinary and Life Sciences, Medical Fund, and APACT Fund, CRUK Glasgow Centre and from Edinburgh ECMC and CRUK Edinburgh Centre.

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 REC 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 office.

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. Any Sponsor's responsibilities that have been delegated to the CI will be documented within the 'Responsibilities delegated to the Chief Investigator' form. Some of these duties will be performed via the CRUK Glasgow CTU as the co-ordinating centre for the trial.

11.8.2 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.
- Data quality.

11.8.3 CRUK Glasgow Clinical Trials Unit (CTU)

The CRUK Glasgow CTU provides support for all regulatory submissions (ethics, HRA, R&D) and any amendments, all administration relating to the submissions and any amendments and management of safety reporting. The CI is responsible for data quality and safety.

11.8.4 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 any monitoring or audit as identified in the trial protocol and also for inspection purposes.

11.8.5 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.

12 PUBLICATION POLICY

The IMAGINE 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 without prior approval of the TMG.

The data arising from IMAGINE will belong to the trial Sponsor NHS GGC. The TMG shall act as custodian of this data.

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