Precision-Panc Master Protocol
Personalising Treatment For Pancreatic Cancer
Version 2: 6th October 2017

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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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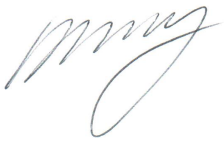
Signature: 

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Trial Summary

Title:	Precision-Panc Master Protocol for patients with pancreatic cancer
Design:	The Precision-Panc Master Protocol is a "portal" protocol for patients with known or suspected pancreatic cancer to be accrued through multiple centres in the UK, with the option of being subsequently enrolled into PRIMUS (**P**ancreatic cance**R** **I**ndividualised **M**ulti-arm **U**mbrella **S**tudy) examining different treatment regimens and/or biomarker development. Eligible patients will undergo tumour biopsy and blood collection prospectively for molecular profiling at a central laboratory and the results may be used to inform enrolment to PRIMUS studies. For details of the platforms and assays being used for molecular profiling, please see Lab Manual.
Duration of Study	5 years
Primary Objective:	To establish a mechanism and framework to recruit and screen patients with pancreatic cancer to perform molecular profiling, evaluation of circulating biomarkers, and enable enrolment to Precision-Panc PRIMUS studies.
Secondary Objectives:	• To assess the overall survival (OS) in patients enrolled in Precision-Panc and relate this to molecular profile information. • To assess the safety of obtaining tumour biopsies suitable for molecular profiling within a standard patient treatment pathway. • To establish a central repository of molecular profiles with accompanying phenotypic data and accompanying biospecimens for further translational research. • To establish a dynamic platform for evaluation of circulating biomarkers to subsequently inform design of subsequent clinical studies.
Exploratory objectives:	To assess the progression-free survival (PFS) in patients enrolled in Precision-Panc and relate this to molecular profile information.
Population:	Patients with pancreatic cancer.
Eligibility:	• Adult patients (age >16 years) **Either:** • Presence of a hypodense pancreatic mass highly suspicious of primary pancreatic cancer with or without distant metastasis as assessed by a Pancreatic Multi-Disciplinary Team (MDT) **Or** • Histologically or cytologically confirmed pancreatic ductal adenocarcinoma and its variants

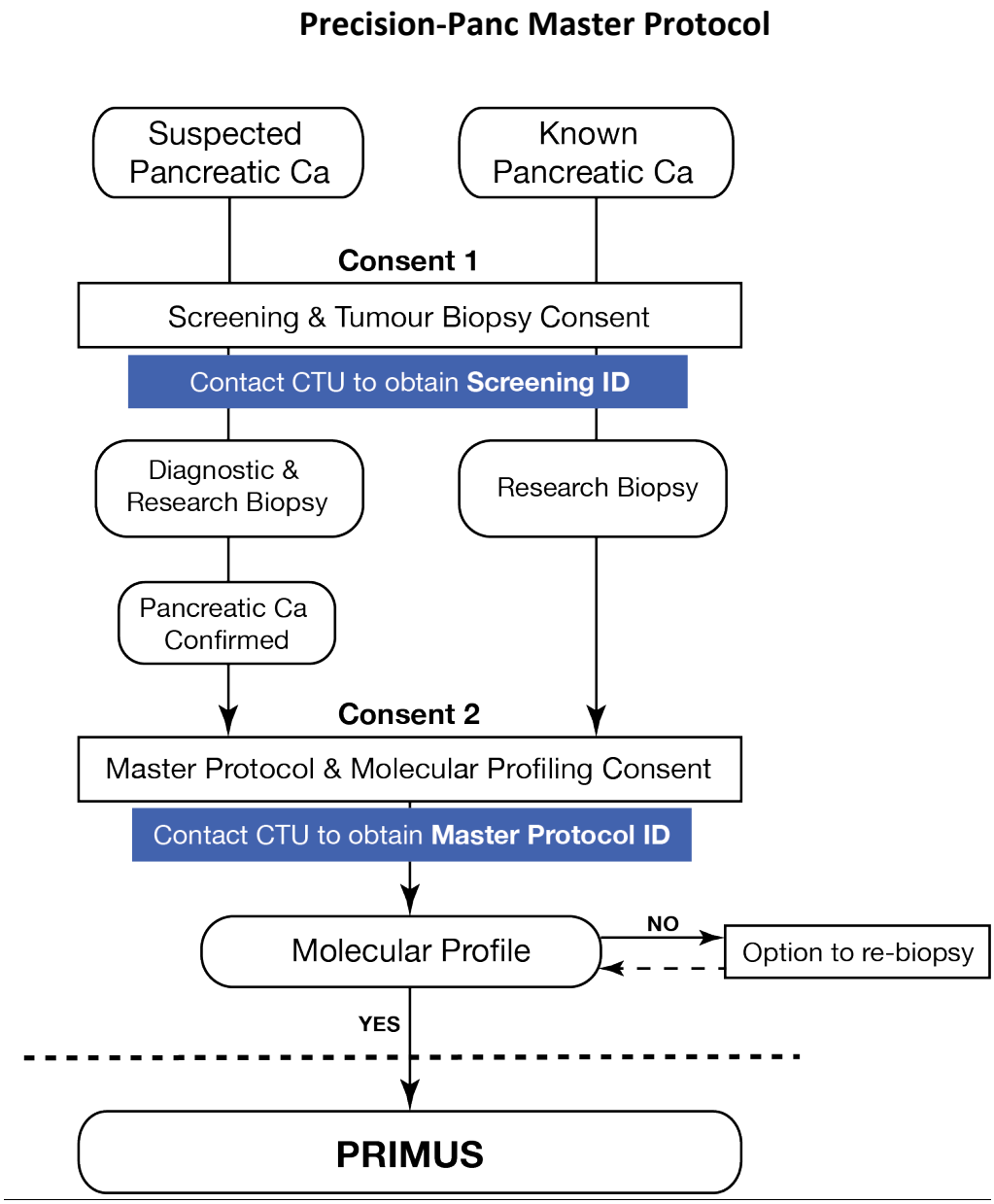
	• Patient is willing and able to undergo tumour biopsy aimed at obtaining sufficient tissue for molecular profiling. • Patient is deemed suitable to receive chemotherapy and/or radiotherapy, and/or surgery pending on stage of disease at presentation • Signed informed consent for Screening research tumour biopsy (Consent 1) • Signed informed consent for Precision Panc Master Protocol molecular profiling (Consent 2).
Statistical Analysis:	The primary objective of this protocol is to provide a "portal" to individual PRIMUS studies, which will be appropriately powered according to their study design and primary end-point. Each of these studies will have their own statistical design and be subject to their own individual regulatory and ethical review. It is intended to correlate OS and PFS data from patients with confirmed pancreatic cancer on this protocol with molecular profile information; this will be achieved using standard techniques such as Cox multiple regression, adjustments for multiple testing and Kaplan-Meier estimates. A detailed analysis plan will be developed for individual projects.

Table of Contents

Abbreviations

AE	Adverse Event
CI	Chief Investigator
CRUK	Cancer Research United Kingdom
CTCAE	Common Terminology Criteria for Adverse Events
CTIMP	Clinical Trial of an Investigational Medicinal Product
CRF(s)	Case Report Form(s)
CTU	Clinical Trials Unit
DNA	Deoxyribonucleic Acid
EUS	Endoscopic Ultrasound
eCRF	Electronic Case Report Form
FFPE	Formalin-Fixed Paraffin Embedded
GCP	Good Clinical Practice
GP	General Practitioner
MDT	Multi-Disciplinary Team
NHS	National Health Service
NHS GG&C	NHS Greater Glasgow and Clyde
OS	Overall Survival
PFS	Progression Free Survival
PI	Principal Investigator
PIS	Patient Information Sheet
PRIMUS	**P**ancreatic cance**R** **I**ndividualised **M**ulti-arm **U**mbrella **S**tudy
R&D	Research and Development
RNA	Ribonucleic Acid
REC	Research Ethics Committee
SAE	Serious Adverse Event
SRAE	Serious and Related Adverse Event
SRUE	Serious Related and Unexpected Events
TMF	Trial Master File
UTSC	Umbrella Trial Steering Committee
WGS	Whole Gene Sequencing

Trial Flow Chart



1 INTRODUCTION

1.1 Background

Pancreatic Cancer is the 3rd leading cause of cancer death in Western societies, and is predicted to be the 2nd leading cause within a decade.[1] Despite 50 years of research and therapeutic development, there has been little improvement in patient outcome. The median survival remains 6 months with 90% succumbing within a year of diagnosis. Of those diagnosed with pancreatic cancer in 1970, only 3% survived for five years or more.[2] Today that figure remains largely unchanged and, of the approximately 9,000 people that will be diagnosed with pancreatic cancer in the UK this year, only around 270 will be expected to survive for more than five years.[2]

The majority of patients present with advanced disease, and the standard of care for many years, gemcitabine monotherapy, confers only a marginal survival advantage.[3] Small incremental improvements may be achieved with the addition of erlotinib[4] or capecitabine;[5] however, the incremental survival benefit is in the order of weeks, with the overall median survival still ~6 to 7 months. More recently, encouraging results have emerged for gemcitabine/nab-paclitaxel[6] and FOLFIRINOX[7] combinations, which improve survival by a modest 2 and 4 months respectively. Although these are significant improvements compared to previous progress, they are associated with a significant toxicity profile. The toxicities associated with these new regimens and the modest overall improvement in outcome make them unsuitable for many patients, or mean that patients/clinicians prefer not to use them. This limits their overall impact on patient outcomes. Nevertheless significant durable responses may be present in small subgroups, but these subgroups are yet to be defined. Moreover, while there are a small number of exceptional responders, and occasional cures that have never previously been possible, the majority of patients have disease that is inherently resistant, or rapidly develop resistance on treatment. Therefore, there is an urgent need to both optimise the use of current therapies by identifying responsive (or non-responsive) subgroups and to develop novel therapeutic approaches.

1.2 Rationale and Hypothesis

There is now compelling evidence that the molecular heterogeneity of cancer leads to disparate molecular phenotypes with variable disease outcomes and responses to therapy in histologically indistinguishable cancers.[8-10] Knowledge of the molecular phenotype has the potential to improve therapeutic selection and hence the early delivery of the optimal therapeutic regimen, which would improve overall outcomes, and minimise treatment related morbidity and cost by avoiding ineffective therapies. Some of the recent successes are seen in treating HER2 amplified breast and gastric cancers with trastuzumab, and gastrointestinal stromal tumours with imatinib.

As we gain a deeper understanding of the molecular pathology of pancreatic cancer, we are revealing significant heterogeneity and complexity. Whilst other cancer types have a dominant or highly prevalent molecular subgroup, which is targeted by specific therapies (e.g. oestrogen receptor positivity and anti-oestrogen therapy in breast cancer), pancreatic cancer does not. This may explain why the conventional approach of adding a novel agent to a chemotherapy backbone

either in single-arm non-randomised or in randomised phase II studies with the chemotherapy backbone as the comparator, without any patient selection or enrichment based on molecular profiling, has led us to an impasse for the advancement of pancreatic cancer therapy. This suggests that subgroups of responders do exist, but are not detected as they fall below the threshold of significance in the current unselected clinical trial paradigm. As a consequence, this presents a unique opportunity to test a stratified approach for the treatment of pancreatic cancer through a biomarker driven stratified approach.

The overall framework of Precision-Panc aims to accelerate stratified therapeutic development though co-ordination, data sharing and aligned decision-making. This UK-wide Master Protocol will enable the screening and molecular profiling of patients with pancreatic cancer, embedded within the standard diagnostic pathway to subsequent enrolment in available **P**ancreatic cance**R** **I**ndividualised **M**ulti-arm **U**mbrella **S**tudy (PRIMUS) studies. PRIMUS is the set of clinical trials where patients may be recruited to the most suitable treatment studies based on their molecular phenotype and/or integrated with biomarker discovery and validation approaches. We aim to create a patient-focused environment where attractive trial options are offered to as many patients and their treating clinicians as possible. The aim is to identify the right trial for the patient, rather than current approaches where we search for patients for a specific trial. By offering a range of attractive options for patients and clinicians, we envisage significant increases in recruitment. In addition, Precision-Panc will also provide a platform for drug development in partnership with industry, by screening and identifying subgroup of patients with candidate biomarker of therapeutic responsiveness.

The outcomes of the patients will be recorded on the Master Protocol or the PRIMUS studies. Precision-Panc Master Protocol will serve not only as a molecular profiling platform for PRIMUS clinical trials, but also a translational research platform. The molecular profiling data generated along with the outcome data will be essential in the delineation of molecular mechanisms important in the pathophysiology of pancreatic cancer. This in turn will provide significant opportunities to understand the molecular pathology of pancreatic cancer better, and to identify candidate biomarkers for available therapeutic options and define therapeutic targets for novel drug development.

2 TRIAL OBJECTIVES

2.1 Primary Objective

To establish a mechanism and framework to recruit and screen patients with pancreatic cancer to perform molecular profiling, evaluation of circulating biomarkers, and allow enrolment to Precision-Panc PRIMUS studies.

2.2 Secondary Objective(s)

- To assess the overall survival (OS) in patients enrolled in Precision-Panc and relate this to molecular profile information.

- To assess the safety of obtaining tumour biopsies suitable for molecular profiling within a standard patient treatment pathway.
- To establish a central repository of molecular profiles with accompanying phenotypic data and accompanying biospecimens for further translational research.
- To establish a dynamic platform for evaluation of circulating biomarkers to subsequently inform design of subsequent clinical studies.

2.3 Exploratory Objective(s)

- To assess the progression-free survival (PFS) in patients enrolled in Precision-Panc and relate this to molecular profile information

3 TRIAL DESIGN

The purpose of the Precision-Panc Master Protocol is to define general eligibility criteria for patient recruitment. Eligible patients will be invited to undergo an additional tumour biopsy (either at the time of their diagnostic biopsy [preferable] or at a repeat biopsy, if agreeable). The samples obtained from this biopsy will be subjected to molecular profiling to deliver a molecular profile report based on the analyses of tumour and blood to enable patient enrolment for Precision-Panc PRIMUS studies.

Each of the PRIMUS studies will contain a unique schedule of assessments and eligibility criteria. Once patients have completed participation on a PRIMUS study, they may have the option (based on their longitudinal molecular profiling and fulfillment of eligibility criteria) to enter another PRIMUS study in the Precision-Panc portfolio. Patients will be followed up as part of the individual PRIMUS studies, or if the patients are not suitable for enrolment to recruiting PRIMUS studies, they will be followed up on the Master Protocol.

Patients with a confirmed diagnosis of pancreatic cancer, in whom sufficient tumour material can be obtained to produce a satisfactory molecular profile, will be followed up on the Master Protocol. In addition to the information collected on eCRF by Glasgow CRUK CTU such as adverse events associated with study specific interventions (biopsy, blood sample), and the annual collection of overall survival and anti-cancer treatment, further information will be accessed via routine NHS IT systems, or a periodic data collection exercise performed by site PIs or his/her delegates to facilitate down-stream translational research of Precision-Panc. This will be explained explicitly on the PIS. In addition to the approvals of the relevant governance committees, access to patient data held within the NHS is subject to the provision of consent of patients to share data regarding their treatment and current disease status. The patient information sheet and consent forms associated with the Master Protocol provide the options for patients to opt out of this longer term follow-up data collection.

The Precision-Panc Master Protocol implements a state-of-art molecular screening mechanism for patients with pancreatic cancer to facilitate clinical trial enrollment. Through this process, a wealth

of molecular profiling and phenomic data will also be generated to enable future translational research to identify potential prognostic and predictive biomarkers of therapeutic responsiveness. DNA and RNA sequencing analyses may be evaluated at multiple time points over the course of Precision-Panc participation if necessary, such as re-biopsy and molecular profile on disease progression to enable participation in other PRIMUS studies.

Patients who complete all the screening procedures and assessments on this Master Protocol may be candidates for enrolment into PRIMUS studies, wherein they will receive treatment. A high level summary of the molecular profile report (marked "Research Use Only") will be returned to Precision-Panc participating sites from the central reference laboratory (Glasgow Personalised Oncology Laboratory). The assignment of patients to an available PRIMUS study will be based on a shared decision-making process between the patient and the treating clinicians in accordance with the eligibility criteria specific to each of the PRIMUS studies.

3.1 Trial Population

The Precision-Panc Master Protocol aims to recruit, consent and screen a minimum of 2,500, and a maximum of 5,000 patients with pancreatic cancer, over a period of 5 years

3.2 Inclusion Criteria

- Adult patients (age >16 years).
- **Either:**
    - Presence of a hypodense pancreatic mass highly suspicious of primary pancreatic cancer with or without distant metastasis as assessed by a Pancreatic Multi-Disciplinary Team (MDT).

  Or
    - Histologically or cytologically confirmed pancreatic ductal adenocarcinoma and its variants.
- Patient is willing and able to undergo tumour biopsy aimed at obtaining sufficient tissue for molecular profiling.
- Patient is deemed suitable to receive chemotherapy and/or radiotherapy, and/or surgery pending stage of disease at presentation.
- Signed informed consent for screening research tumour biopsy (Consent 1).
- Signed informed consent for Precision-Panc Master Protocol molecular profiling (Consent 2).

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

3.3 Identification of participants and consent

Patients may be identified in a number of ways:

a) Through the regional Pancreatic MDTs that are recruiting patients for Precision-Panc

b) Via direct approach to study researchers (for example through the study website or through Pancreatic Cancer UK who are strategic partners for the study).

However, study researchers will refer patients to their local Pancreatic MDT for assessment.

Through a face-to-face meeting, the study will be fully explained to potential participants by a member of the research team and they will be given adequate time to consider potential participation and all efforts will be made to ensure patients understand the commitment required to fulfil the trial requirements. In addition, patients will be made aware that participation is voluntary and they may withdraw at any time without their standard care being affected. No screening activities related to the trial will be undertaken until informed consent has been obtained. A medical practitioner will confirm eligibility.

When obtaining consent the following steps will be followed:

- A detailed discussion will be held between the patient and a member of the study team knowledgeable about the research and the risks & benefits to the patient.
- Potential participants will be able to ask any questions that they wish in the meeting mentioned above, but will also be given details of study research nurse/coordinator, so that they may raise questions with them directly at any time before, during or after the study complete.
- Patients will be familiarised with the methods for study withdrawal and the fact that they may withdraw at any time without explanation and without compromising their on-going medical care.
- Consent will only be obtained from those patients capable of providing their own consent.
- A copy of the patient information sheet and signed consent forms will be given to the patient to take away to read and keep.

3.4 **Registration**

To register a patient on the trial and/or to obtain either a screening number or a Master Protocol ID, contact the CRUK Clinical Trials Unit, Glasgow. Registration to the trial can be performed by either telephone or fax on the following numbers:

Telephone Number: 0141 301 7195
Fax Number: 0141 301 7946

The patient's eligibility criteria will be reviewed and confirmation given that the consent for research biopsy (Consent 1) has been obtained before an initial **screening ID** will be allocated.

Once cancer is confirmed and the patient gives consent for Master Protocol molecular profiling (Consent 2) the Glasgow CRUK CTU will be contacted a second time and a Precision-Panc **Master Protocol ID** will be generated

All patients must be screened and registered onto the Master Protocol prior to commencement of any study procedure. With the patient's consent the participant's GP will be informed of their involvement in the trial.

3.5 **Withdrawal**

In consenting to the Precision-Panc Master Protocol Molecular Profiling (Consent 2), patients are consented to molecular profiling under the Precision-Panc Master Protocol, follow-up and data collection. A separate consent will be obtained for any subsequent PRIMUS study that the patient may choose to enroll on to. However, patients may voluntarily discontinue from the Precision-Panc Master Protocol at any time for any reason without prejudice.

Patients will be discontinued from the Precision-Panc Master Protocol for the following reasons:

- Termination of the study by the sponsor
- Voluntary withdrawal from study by patient.

Patients have the right to withdraw from Precision-Panc Master Protocol at any point for any reason and without explanation. Similarly, the investigator may withdraw patients from the Master Protocol prior to biopsy in the event of intra-current illness, or any other relevant reasons. If the patient withdraws consent from Master Protocol participation no further analysis of their samples will be undertaken and their samples will be returned to the biorepository to be placed into long-term storage or destroyed completely according to the wishes of the patient. However, where patient samples have a completed molecular profile available, they should be followed up as per Master Protocol schedule, unless consent has been withdrawn from all further follow-up procedures. However, where a participant withdraws consent due to an adverse event, this does not preclude the reporting of Adverse Events (AEs), Serious Adverse Events (SAEs) and serious, related and unexpected events related to tumour biopsy, which are required to be reported according to the protocol for regulatory purpose.

However, any coded samples, cells, and data derived from the patient's tissues that have already been sent to other researchers or placed into the research databases before they indicate their desire to withdraw from the study, may not be removed or destroyed. This information will be clearly stated in the patient information and consent form(s).

If the patient withdraws from the Precision-Panc Master Protocol, 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 a patient withdraws their consent from the trial the site must document this is the study electronic Case Report Form (eCRF).

In addition to the scenario where an individual patient may voluntary withdraw from Precision-Panc Master Protocol, the study team may also withdraw patient from Precision-Panc in the rare incidents that sufficient tumour material cannot be obtained to produce a satisfactory molecular

profile, even through multiple attempts, especially if further biopsy attempt is deemed harmful. This is explained explicitly in the PIS.

4 TRIAL PROCEDURES

4.1 Trial Schedule

4.1.1 Visit 1: Initial Biopsy Consent and Tissue Sample Collection (Consent 1)

Following confirmation of potential eligibility (please refer to Section 3.2), patients will be asked to provide written informed consent to undergo a Precision-Panc screening research biopsy (Consent 1) at, or subsequent to, the time of their diagnostic biopsy.

The site will then contact CRUK CTU Glasgow to obtain a screening number prior to the biopsy being undertaken.

Patients will then undergo a core biopsy procedure of the primary tumour and/or metastatic lesion(s). This can be done either through a EUS procedure or percutaneously by interventional radiology pending local expertise and clinical staging of disease.

For EUS biopsy (sites collecting fresh frozen samples)

Core Biopsy Number	**Processing Details**	**Purpose**
1 - 3	FFPE, once diagnosis is made, ship diagnostic block to NHS GG&C Biorepository	Diagnostic purposes, then Genomic analysis (targeted gene panel sequencing), +/- transcriptomic analysis (RNAseq), and IHC analyses if necessary
4 - 5	Fresh frozen, shipped to NHS GG&C Biorepository	Genomic analyses (WGS) +/- transcriptomic analysis (RNAseq)

For EUS biopsy (sites not collecting fresh frozen samples)

Core Biopsy Number	**Processing Details**	**Purpose**
1 - 4	FFPE, once diagnosis is made,	Diagnostic purposes, then Genomic analysis

	ship diagnostic block to NHS GG&C Biorepository	(targeted gene panel sequencing), +/- transcriptomic analysis (RNAseq), and IHC analyses if necessary

For percutaneous IR biopsy (sites collecting fresh frozen samples)

Core Biopsy Number	**Processing Details**	**Purpose**
1 - 2	FFPE, once diagnosis is made, ship diagnostic block to NHS GG&C Biorepository (≥ 1cm tumour per core)	Diagnostic purposes, then Genomic analysis (targeted gene panel sequencing), +/- transcriptomic analysis (RNAseq), and IHC analyses if necessary
3	Fresh frozen, shipped to NHS GG&C Biorepository (≥ 1cm tumour per core)	Genomic analyses (WGS) +/- transcriptomic analysis (RNAseq)

For percutaneous IR biopsy (sites not collecting fresh frozen samples)

Core Biopsy Number	**Processing Details**	**Purpose**
1 - 2	FFPE, once diagnosis is made, ship diagnostic block to NHS GG&C Biorepository (≥ 1cm tumour per core)	Diagnostic purposes, then Genomic analysis (targeted gene panel sequencing), +/- transcriptomic analysis (RNAseq), and IHC analyses if necessary

FFPE = formalin fixed and paraffin embedded; NHS GG&C = NHS Greater Glasgow and Clyde; WGS = whole genome sequencing

4.1.2 Visit 2: Molecular Profile Consent and Screening Assessment (Consent 2)

1. Once a diagnosis of pancreatic cancer is established and research tumour biopsies have been obtained, patients must give additional, separate, written informed consent for Precision-Panc Master Protocol molecular phenotyping of their biopsy sample (Consent 2).

2. Eligibility assessment: as per Section 3.2.
3. The site will then contact CRUK CTU Glasgow to obtain a Master Protocol ID.
4. Demographics data, medical, family, and cancer history: medical history is obtained and documented including prior diagnosis, prior treatment and concomitant diseases.
5. Whole blood sample for germline and circulating biomarker analysis will be taken (for more details, please refer to Master Protocol lab manual).
6. The research biopsies should then be sent to Glasgow Bio-repository for where they will be logged and processed. Some samples will be extracted at the Wolfson Wohl Cancer Research Centre. Analyses of the materials and generation of the molecular profile will also take place at the WWCRC (please see lab manual for full details regarding shipping).

4.2 Laboratory Tests

All tissue samples collected will be transported to their local NHS Biorepository in the format as outlined in the Lab manual before transported to NHS GG&C Biorepository and Laboratory Genetics Department where they will be logged and the sample quality reviewed. Please refer to the lab manual for details on the logistics of tissue sample handling, shipping, processing, and the types of molecular analyses to be performed.

4.3 Duration of Trial Participation and Master Protocol Follow-up

Patients recruited on the Master Protocol who have pancreatic cancer, and sufficient tumour material to produce a satisfactory molecular profile, will be followed up until death. In addition to the information collected on eCRF by Glasgow CRUK CTU such as adverse events associated with study specific interventions (biopsy, blood sample), and the annual collection of overall survival and anti-cancer treatment, further information will be accessed via routine NHS IT systems, or a periodic data collection exercise performed by site PIs or his/her delegates to facilitate down-stream translational research of Precision-Panc.

5 SAFETY REPORTING

Study-related complications will be monitored on an on-going basis throughout the Study.

5.1 Definitions

These definitions apply to all study participants from consent (Consent 1) to participate in the study.

Term	Definition
Adverse Event (AE)	An adverse event (AE) is any untoward medical occurrence in a subject to whom a medicinal product is administered, which does not necessarily have a causal relationship with this treatment/intervention.

Related Adverse Event (RAE)	A related adverse event (RAE) is any untoward and unintended occurrence in a subject administered trial treatment/intervention which is thought to be caused by or related to the trial treatment/intervention.
Serious Adverse Event (SAE)	A serious adverse event (SAE) means any untoward medical occurrence that at any dose requires the following, whether or not considered related to the trial treatment. • 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.
Serious and Related Adverse Event (SRAE)	A serious and related adverse event (SRAE) is a SAE that may be related to trial treatment/intervention. The assessment of "relatedness" is primarily the responsibility of the Principal Investigator (PI) at site or agreed designee. SAEs will be considered related if the SAE is documented as possibly, probably or definitely related to protocol treatment. The assessment of relatedness is made using

<table>
<tr><td></td><td>the following:

<table><tr><th>Relationship</th><th>Description</th></tr><tr><td>Unrelated</td><td>There is no evidence of any causal relationship.</td></tr><tr><td>Possible</td><td>There is some evidence to suggest a causal relationship (e, g. the event occurs within a reasonable time after administration of the trial treatment/intervention). However the influence of other factors may have contributed to the event (e.g. the patient’s clinical condition, other concomitant treatments).</td></tr><tr><td>Probable</td><td>There is evidence to suggest a causal relationship and the influence of other factors in unlikely.</td></tr><tr><td>Definitely</td><td>There is clear evidence to suggest a causal relationship and other possible contributing factors can be ruled out.</td></tr></table></td></tr>
<tr><td>Serious Related and Unexpected Events (SRUE)</td><td>A serious, related and unexpected Event (SRUE) is any serious and related event, which is unexpected. Unexpected is any event that is not listed in the protocol as an expected event.</td></tr>
</table>

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.

5.2 Detecting, Recoding and Reporting of Adverse Events

Investigators must record all AEs in the patient notes whether they are required to be recorded in other trial documentation or not.

5.2.1 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 Health Research Authority (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.

5.2.2 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. AEs must be reported from consent and followed until resolution, or for at least 30 days after the last protocol related procedure is performed, whichever comes first or until toxicity has resolved to baseline or ≤ grade 1, or until the toxicity is considered to be irreversible. 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.

5.2.3 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 4.03. These criteria can be accessed via the National Cancer Institute Website.

The assessment of AEs is the responsibility of the Investigator (or designee). In determining whether an AE is related to trial participation, Investigators must consider if there is a reasonable possibility of establishing a causal relationship between the event and the protocol related procedures based on their analysis of all the available evidence. The assessment must be made on the basis of anticipated effects of the protocol related procedures as specified below, 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 the trial procedures. The CI shall not downgrade the causality assessment provided by an Investigator.

Although Investigators must record all AEs in the patient notes they are only required to record AEs on the eCRF for the following events if they are a result of a tumour biopsy (percutaneous or endoscopic) or other protocol related procedure:

- Post procedure pain not controlled with simple analgesia
- Pancreatitis
- Post procedure haemorrhage
- Wound infection
- Perforation
- Pneumothorax
- Anaphylactic reaction to local anaesthetic or sedation agents
- Death following complications from biopsy procedure

5.2.4 Reporting of a Serious Adverse Event

Events are only required to be reported as SAEs if they are a result of a tumour biopsy (percutaneous or endoscopic) or other protocol related procedure and meet the regulatory

definition of serious (see section 5.1 Definitions). Investigators must report all SAEs by completing and submitting a SAE report form to the Pharmacovigilance Office, CRUK CTU. SAE reports must be submitted immediately and under no circumstances should this exceed 24 hours following first awareness of the event by the Investigator or site staff.

Pharmacovigilance Office, CRUK CTU, Glasgow
Fax no: +44 (0) 141 232 2157
Tel no: +44 (0) 141 232 2068
+44 (0) 141 211 3567/3968/0203/0352
Email: mvls-ctu-pv@glasgow.ac.uk

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 the initial and follow up SAE forms please refer to the SAE Completion Guidelines, which will be provided by the Pharmacovigilance Office, CRUK CTU, Glasgow. The CI will receive notification, by email, of all SAEs received. SAEs must be reported locally by the PI at each site in accordance with the local practice at their site (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 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 consent for up to 30 days after the end of the final protocol related procedure. Any event that meets the criteria of a SAE (including events that the Investigator thinks are medically important but maybe do not require hospitalisation or are fatal etc.) that occur after 30 days post procedure are also required to be reported if the Investigator thinks that the SAE is related to a trial procedure. The Investigator must report such SAEs to the CRUK CTU Pharmacovigilance Office again without undue delay

Serious and related events, whether they are expected or not, must be followed up for at least 30 days or longer in the case of pancreatitis by providing follow-up SAE reports until the reaction has completely resolved or will never resolve.

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

Pharmacovigilance Office, CRUK CTU, Glasgow
Email: mvls-ctu-pv@glasgow.ac.uk

Telephone: 0141 301 7945/7209/7211/7953

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

5.3 Expected Events

The following is a list of events that are expected as a result of the trial intervention.

- Pain
- Bleeding
- Infection at biopsy site
- Bruising
- Sore throat
- Pancreatitis
- Perforated viscus
- Pneumothorax

5.4 Identifying Events for Expedited Reporting

The assessment of SAEs for expedited reporting will be undertaken by the CTU and CI based on the list of expected events noted above. When deciding if an event is unexpected, the CI should 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.

5.4.1 Expedited Reports

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

SAEs will be reported to the REC where in the opinion of the CI 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 Clinical Trials Unit, Glasgow becoming aware of the event, using the 'Report of Serious Adverse Event form' for non-CTIMPs published by the HRA. If the assessment of causality provided by the investigator differs from that of the CI (assessment is made on behalf of the sponsor), the opinion of both the investigator and CI will be provided in the expedited report.

Investigators will receive all expedited reports. The CI will assess if the risk-benefit assessment has been affected by each serious, related and unexpected event they identify. 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.

5.5 Annual Progress Report

The CI and/or Precision-Panc Project Manager will submit an annual progress report including information on any unexpected events, which are a result of participation in the trial, to the REC.

6 STATISTICS AND DATA ANALYSIS

6.1 Trial Design and Sample Size

This is a prospective screening Master Protocol to provide molecular profiling of patients with pancreatic cancer to subsequent PRIMUS studies and an overall sample size calculation is not appropriate. Individual PRIMUS studies will be appropriately powered according to their study design and primary end-point.

6.2 Analysis Plan

It is intended to correlate OS and PFS data with molecular profile information; this will be done using standard techniques such as Cox multiple regression, adjustments for multiple testing and Kaplan-Meier estimates. A detailed analysis plan will be drawn up for individual projects including consideration of study power.

7 TRIAL CLOSURE/DEFINITION OF END OF TRIAL

No patients will be recruited to the Precision-Panc Master Protocol after 5 years unless additional funding and approval is secured and appropriate protocol amendments are in place. Patients registered to the Precision-Panc Master Protocol will continue to be followed up until death via access to routine NHS systems and the study eCRF.

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

Declaration of the end of a Study form will be submitted to the ethics committee within 90 days of the last patient being registered. However if the trial is terminated before the date for the conclusion of the trial specified in the protocol for that trial the ethics committee 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.

7.2 Clinical Trial Summary Report

The final clinical trial summary report should be submitted to the ethics committee within one year of the study closing. The CI is responsible for compiling and submitting the final report to both sponsor and the REC.

8 DATA HANDLING

8.1 eCRFs

The CRFs for this trial will be completed using the electronic remote data capture (eRDC) system, MACRO®. Prior to recruitment beginning at each site, training will be provided on the MACRO® system.

It is the responsibility of the Principal Investigator to ensure eCRFs are completed in a timeous manner and to review and approve all data captured on the eCRF. **Please ensure that all data submitted on eCRFs are verifiable in the source documentation or that any discrepancies are recorded and explained.**

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

8.2 Central Review of Data

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

To minimise the number of data queries being sent to sites, the CRUK CTU will develop a data rulings document and resolve as many self-evident queries as possible in-house.

8.3 Data Escalation Process

Where issues with data return/quality/response to requests are identified at sites, the following process will be followed:
Step 1: E-mail letter to site main contact and copy in site PI
Step 2: E-mail letter direct to site PI and copy in site main contact
Step 3: E-mail letter to Network Coordinator and copy in site PI and main contact
Step 4: Discuss suspension of recruitment at site until data issues resolve

8.4 Record Retention and archiving

Both the participating trial site Sponsor and CRUK CTU should perform archiving of the trial essential documents as appropriate.

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

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

9 TRIAL MANAGEMENT

9.1 Trial Start Up

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

9.2 Core Documents

The core documents required from each individual participating site for this trial are as follows:
Local R&D approval/HRA approval
Signed Clinical Trial Agreement
Delegation and study specific training log
CVs and GCPs for PI
PIS and GP letter on local headed paper
Initiation acknowledgements
Site initiation/accreditation checklist

9.3 Management of protocol deviations and violations

9.3.1 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 form will be provided during site initiation. If site staff are unsure whether a certain occurrence constitutes a deviation from the protocol or GCP, the Sponsor can be contacted immediately to discuss. The Sponsor will assess all incidents with respect to the criteria of a “serious breach”.

9.3.2 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 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

9.4 Trial Management Group (TMG)

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

9.5 Umbrella Trial Steering Committee (UTSC)

The role of the UTSC is to provide overall supervision of the trial and ensure that it is being conducted in accordance with the principles of GCP and the relevant regulations. The UTSC should agree any significant protocol amendments, provide advice to the investigators on all aspects of the trial and have members who are independent of the investigators, in particular an independent chairperson. Decisions about continuation or termination of the trial or substantial amendments to the protocol are usually the responsibility of the UTSC.

10 REGULATORY ISSUES

10.1 Ethics Approval

Ethical approval for the master protocol will be applied for from the West of Scotland Ethics Committee. Each site wishing to take part in the Precision-Panc platform must have local approval for this prior to registering any patients onto the master protocol. The CI will be responsible for updating the ethics committee of any new information related to the trial.

The trial will be carried out in accordance with the World Medical Association Declaration of Helsinki (1964) and its revisions (Toyoko [1975], Venice [1983], Hong Kong [1989], South Africa [1996] and Edinburgh [2000]).

10.2 Consent

There is a 2-stage process to obtain consent for the Precision-Panc Master Protocol.

Consent 1: Screening and research biopsy consent

After potentially eligible patients are identified, a consent for Precision-Panc screening and research tumour biopsy is obtained for tumour tissue acquisition at the time of diagnostic biopsy (for patients who have not had a cancer diagnosis yet), or for a research biopsy (for patients who already have a histological/cytological cancer diagnosis).

Consent 2: Master Protocol Molecular Profiling consent

After tumour biopsy is performed, and a cancer diagnosis is established, patients will be required to give informed consent for molecular profiling to be performed on tumour tissue (with or without germline analysis), and to be enrolled on to Precision-Panc Master Protocol. Peripheral blood will also be drawn at this time to be used as a source of normal genomic DNA for molecular profiling.

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

The right of the participant to refuse to participate without giving reasons must be respected. 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 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 Precision-Panc team. Each site shall confirm to the CRUK Glasgow CTU that consent has been obtained. The CRUK Glasgow Centre in turn shall notify the CI/WWCRC Project Manager of this consent status.

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 to not re-consent patients must be documented in the patient's medical records.

10.3 **Confidentiality**

All information collected during the course of the trial will be kept strictly confidential.

Information will be held securely on paper and electronically either within the NHS, CRUK CTU or at the WWCRC who will comply with all aspects of the 1998 Data Protection Act and operationally this will include:

- Consent from participants to record personal details including initials, date of birth, CHI/NHS 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 responsible individuals from the research staff or from regulatory authorities, where it is relevant to trial participation
- Consent from participants for the data collected for the trial to be used to evaluate safety and develop new research.
- Where central monitoring of source documents is required (such as scans or local blood results), the patient's name must be obliterated by site before sending.
- Where anonymisation of documentation is required, sites are responsible for ensuring only the instructed identifiers are present before sending to the WWCRC.

If a participant withdraws consent from further trial treatment and / or further collection of Data, existing data generated from their samples will remain on file and will be included in the final trial analysis unless they specifically withdraw consent for this. Upon removal of consent, samples will either be returned to the bio-repository to be placed into long-term storage or destroyed completely according to the wishes of the patient.

10.4 **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

The Hospital Trust/Health Board at each participating site 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 Trust/Board to cover access to patients and liability arrangements.

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

10.5 Sponsor

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

10.6 Funding

A range of stakeholders, including CRUK and Celgene fund the Precision-Panc platform. Additional funding is provided in the form of grant awards directly to Prof Andrew Biankin that support the operational requirements of the Glasgow Precision Oncology Laboratory (GPOL) at the WWCRC. If there are any per patient payments/investigator payments refer to the contract that will provide full information on per patient payments]

10.7 Protocol Amendments

Any change to the trial protocol will require an amendment. Following discussion with the TMG, any proposed protocol amendments will be initiated by the CI and Sponsor. Any required amendment forms will be submitted to the ethics committee. All amended versions of the protocol will be signed by the CI and sponsor representative. Before the amended protocol can be implemented favourable approval must be sought from the original reviewing REC, trial Sponsor and participating site R&D offices.

10.8 Allocation of Trial Responsibilities

10.8.1 Sponsor Responsibilities

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.

10.8.2 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
- Providing advice and recommendations on medical issues that arise involving the management of the patients on the trial.

At the outset of the trial development period, the CI will sign the Sponsor Responsibilities Agreement.

From the perspective of the Sponsor and for ethics purposes, the CIs for the trial will be Juan Valle and David Chang.

10.8.3 Participating Site

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

10.8.4 Principal Investigator (PI)

The PI is responsible for:

- The delegation of trial activities within their site and ensuring all personnel are adequately trained and qualified to carry out their responsibilities.
- Providing evidence of GCP training (usually a certificate) or undergo the required GCP training.
- The safety and wellbeing of trial patients,
- Reporting any deviations from the protocol to the coordinating trial office
- Reporting any SAEs or safety issues within 24 hours of becoming aware of the event.

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

11 QUALITY ASSURANCE

11.1 Audits and Inspections

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

The trial may be subject to inspection and audit by NHS Greater Glasgow and Clyde as Sponsor, to ensure adherence to GCP. If an inspection is scheduled at any participating site, the site must notify the Sponsor at the earliest opportunity.

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

11.2 Central Monitoring

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

11.3 Protocol non-compliance

The site study team must report protocol non-compliances to the Precision-Panc or CRUK Glasgow CTU team as soon as they are identified. The site staff may also identify non-compliances. Sponsor and site staff will work together to complete a protocol deviation form and put corrective and preventive actions in place to avoid repeated non-compliance. The Sponsor reserves the right to suspend recruitment at a site until an investigation has taken place and corrective and preventive measures have been put in place to ensure future patient safety and/or data integrity.

12 PUBLICATION POLICY

The Precision-Panc Steering Committee 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[11] 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 Steering Committee.

The data arising from Precision-Panc Master Protocol will belong to the trial Sponsor NHS Greater Glasgow and Clyde. The Steering Committee shall act as custodian of this data.

For detailed publication policy, please refer to Appendix XX.

13 REFERENCES

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