STANDARD OPERATING PROCEDURE FOR TRIAL SET-UP IN CLINICAL TRIALS OF INVESTIGATIONAL MEDICINAL PRODUCTS

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1. PURPOSE

This SOP describes the procedures for setting up a Clinical Trial of Investigational Medicinal Product (CTIMP) to ensure compliance with the Medicines for Human Use (Clinical Trials) Regulations 2004 and 2006 (the UK Clinical Trial Regulations) and the principles of Good Clinical Practice (GCP). As part of the set-up process construction of a Trial Master File (TMF) is required which contains the essential trial documents (ICH GCP section 8 and UK CT regulation 31A).

2. SCOPE

Unless otherwise specified in the CTIMP Risk Assessment, this document applies to CTIMPs sponsored or co-sponsored by the University of Dundee (UoD) and NHS Tayside (NHST).

The definition of Sponsor is an individual, company, institution or organisation, which takes responsibility, for the initiation, management and financing (or arranging the financing) of the trial (ICH GCP 1.53 and UK CT regulation 3).

This SOP applies to all staff who have a role or responsibility in CTIMP set-up including those who manage, coordinate or advise on set-up and/or start-up procedures.

This SOP should be read in conjunction with the TASC SOP that describes the Approvals Process for CTIMPs

3. RESPONSIBILITIES

It is a legal requirement for CTIMPs to be set up, and conducted, in accordance with the UK Clinical Trial Regulations. The responsibility for set-up is the Sponsor's, however the performance of specific set-up duties will be delegated by the Sponsor to the Chief Investigator (CI) by way of a delegation agreement between the Sponsor and the CI.

The TMF includes the Case Report Forms (CRFs), the Pharmacy Site File(s) (PSF) and the Sponsor File (SF) (set-up at TASC). For multi-site trials, the TMF also includes the Investigator Site File(s) (ISF).

4. PROCEDURE

4.1 Funding

4.1.1 The CI must secure and administer financial resources to finance the trial.

4.1.2 If the trial is externally funded, the CI must ensure an agreement is in place to confirm financial flow and oversight between the holder (recipient) of the funding and the Sponsor prior to the start of the trial.

4.2 Insurance/Indemnity

4.2.1 TASC must confirm that adequate insurance and/or indemnity arrangements are in place to cover liabilities.

4.2.2 The CI must ensure that evidence of insurance is held in the TMF and ISFs.

4.3 Sponsorship

4.3.1 The CI must ensure that Sponsorship is in place (see TASC SOP for Sponsorship of Clinical Trials).

4.3.2 The CI will be required to sign a Co-Sponsorship Agreement and Chief Investigator Declaration which sets out the duties delegated by the Sponsor to the CI, and the duties retained by the Sponsor, to ensure the set-up and conduct of the trial to the UK Clinical Trial Regulations.

4.3.3 Study Registration:
The CI must ensure that the Trial is registered on an appropriate publicly accessible research register before recruitment of the first participant. See TASC Publication Policy and TASC SOP for Registering and Reporting Research in a Publicly Accessible Database.

4.4 SOPs

4.4.1 The CI must adhere to the pertinent TASC CTIMP SOPs and Policies, designated at Risk Assessment, which are available to read as master versions on the TASC website.

4.4.2 Where the CI wishes to use local SOPs or external SOPs, this must be agreed with the Sponsor at Risk Assessment.

4.4.3 Approval will be given only for local SOPs which are trial or group specific and additional to TASC SOPs.

4.4.4 Approval will be given only for external SOPs where adherence to such a SOP at an external Site is necessary to aid trial conduct and where the SOP is compliant with the equivalent TASC SOP.

4.4.5 An SOP Trial Log (Doc Ref 007) must be maintained in the TMF, PSF and ISF if appropriate.

4.5 Protocol

4.5.1 The CI should write the protocol using the latest version of the Health Research Authority (HRA) Protocol Template on the HRA website, unless previously discussed with the sponsor.

4.5.2 The CI and research team must conduct the trial in compliance with the protocol approved by the Sponsor, Medicines & Healthcare Products Regulatory Agency (MHRA), other regulatory authorities, Research Ethics Committee (REC) and NHS R&D permission.

4.5.3 The CI and research team must not deviate from or amend the protocol without agreement from the Sponsor and subsequent approval from the MHRA, REC and NHS R&D, HRA and other countries regulatory bodies as appropriate (see TASC SOP for CTIMP Amendments).

4.6 Establishing a TMF or ISF

4.6.1 The CI or delegate is responsible for establishing a TMF (see the TASC SOP for Establishing a TMF and ISF).

4.6.2 The Principal Investigator (PI), or delegate, at external Sites is responsible for establishing an ISF and PSF

4.6.3 It is the responsibility of the CI and PI(s) or delegates to ensure that all essential documents, as described in the TASC TMF/ISF Index, are filed in the TMF and ISF as appropriate. (Doc Ref 018 Trial Master File Index and Doc Ref 019 Investigator Site File Index).

4.6.4 All trial-related documents, including the TMF, PSF and ISF, should be stored securely and in a manner that protects confidentiality.

4.6.5 The TMF, PSF and ISF should be maintained in a ready-state manner to allow for inspection, audit or monitoring on request.

4.7 Establishing a Pharmacy Site File (PSF)

4.7.1 The CI should contact NHST Clinical Trial Pharmacy at the earliest opportunity to discuss trial set-up. Clinical Trial Pharmacy will establish an Investigational Medicinal Product (IMP) Handling Guideline, which should be filed in the SF, TMF, PSF and ISF.

4.7.2 The CI, or PI at external Sites, should ensure that the Summary of Product Characteristics (SmPC) or Investigators Brochure (IB) is supplied to the NHST Clinical Trial Pharmacy and each Site Pharmacy if being utilised for the study. Where changes to the Reference Safety Information (RSI) necessitate a substantial amendment, the amended version of the SmPC or IB must be supplied to all Site Pharmacies in a timely manner. The updated SmPC or IB must also be provided to the Sponsor, as part of the amendment, for the SF and retained in the TMF and ISF(s).

4.7.3 The CI, or PI at external Sites, should ensure that current versions of the fully approved Protocol are supplied to each Site Pharmacy and that any amended, fully approved versions of the Protocol are supplied in a timely manner.

4.7.4 The CI should provide the NHST Clinical Trial Pharmacy with the Sponsor Letter, REC favourable opinion letter, MHRA Clinical Trial Authorisation/Notification (CTA/CTN), HRA approval and NHST R&D permission letter. For multi-Site trials, the CI should provide PIs with these letters.

4.7.5 The CI should ensure that an IMP Handling Guideline is in place with each Site Pharmacy and that the trial is registered with each Pharmacy as per local requirements.

4.8 Third Party Agreements

4.8.1 The CI must ensure that Agreements (contracts) or Statements of Services with third party organisations providing services such as (but not limited to); IMP supply, laboratory work, statistics, supply of equipment, trial management, data management, are approved by the TASC Legal Team and signed off by the TASC R&D Director or delegate.

4.8.2 All agreements must be instructed by the Research Governance Manager or the TASC Legal Team and the Sponsor must be a signatory to these contracts/agreements.

4.8.3 The Legal Team must be notified of any changes to any agreements and all changes must be approved by the TASC Legal Team and signed off by the TASC R&D Director or delegate.

4.8.4 The CI must ensure that all staff appointed to work on the trial and who are not employees of the Sponsor (contracted staff) have appropriate employment contracts and hold substantial or NHS honorary contracts/letters of access as appropriate.

4.9 Material Transfer Agreement (MTA) and Tissue

4.9.1 The CI must ensure that where required a Material Transfer Agreement (MTA) is in place for the transfer and storage of human tissue prior to any

participant being enrolled in the trial. MTAs must be approved by the TASC Legal Team and signed off by the TASC R&D Director or delegate.

4.9.2 The CI must be aware of, and adhere to, all obligations and requirements for the storage and transfer of tissue.

4.9.3 The CI, or PIs at external Sites, must obtain agreement from NHS labs, UoD labs and any others for any processing, storage and handling of tissue and bloods prior to recruiting the first participant.

4.9.4 Any central labs used in the research must hold the necessary licence/accreditation, a copy of this should be stored within the TMF/ISF.

4.9.5 The CI must ensure that clear instructions are given to each participating site in the MTA Protocol.

4.10 Approvals

4.10.1 The CI must ensure that the following approvals have been obtained prior to any screening procedure for the trial and prior to the first participant being consented and entered into the trial (refer to the TASC SOP for Approval for Amendments):

- Sponsor Approval.
- Sponsor Regulatory Green Light
- MHRA clinical trial authorisation or clinical trial notification acknowledgment. Equivalent authorisation should be obtained for non-UK participating countries.
- REC favourable opinion Equivalent authorisation should be obtained for non-UK participating countries.
- Scotland - NHS R&D management approval. England – Healthcare Research Authority approval and NHS confirmation of capacity and capability. Wales - Healthcare Research Wales approval and NHS confirmation of capacity and capability Northern Ireland – Health and Social Care Trust Research Management Permission. Equivalent authorisation should be obtained for non-UK participating countries.
- Any other necessary approvals.

4.11 Training

4.11.1 The CI must ensure that all Site PIs and other research staff are fully trained on the protocol and trial procedures prior to involvement in the trial. Training may be given during pre-trial and during the course of the trial and should include but is not limited to:

- The protocol and any amendments.
- CRF (refer to TASC SOP).
- The informed consent procedure (refer to TASC SOP), consent form, participant information sheet and other trial documents.
- Adverse event reporting (refer to TASC SOP).

- Prescribing procedures.
- Completion of source documents particularly participant's hospital or GP medical records/case notes.
- Breaking the randomisation code for a participant for safety reasons if the trial is blind (refer to TASC SOP).
- Responsibility to report serious breaches (refer to TASC SOP).

4.11.2 The CI must keep a record of training to confirm that members of the research team are trained.

4.11.3 The CI must ensure all research staff are GCP trained in a timely manner at trial set-up/start-up. Refer to TASC Policy on GCP Training.

4.11.4 The CI must ensure that the TMF, PSF or ISF contains up-to-date GCP certificates and CVs (signed and dated) for all research staff involved with the trial. If held separately, the location should be File Noted in the TMF, PSF or ISF.

4.12 Trial delegation and signature log

4.12.1 The CI or PI is responsible for the completion and maintenance of the TASC Delegation Log (Doc Ref 057) in the TMF, PSF or ISF, prior to and during the trial. The Log should confirm all research staff involved with the trial and their duties which have been delegated to them by the CI or PI.

4.12.2 All significant duties or tasks such as taking consent, assessing eligibility, prescribing or dispensing IMP, physical examinations etc. can be delegated by the CI, or PI, to those who have the necessary education, training and experience. If the CI or PI delegates tasks to other team members, the CI and PI still retains responsibility for the trial at Site.

The following duties can only be delegated on the delegation log to a trial clinician:

- assess the eligibility of trial participants
- perform medical examinations
- sign-off completed SAE forms
- review safety information such as line listings or SUSARs
- review clinical information such as NHS labs, ECG and imaging
- respond to medical queries
- approve IMP prescriptions.

4.12.3 The CI and PI must ensure that no staff member is added to the Delegation Log without appropriate training.

4.12.4 The Delegation Log must contain the signature and initials of trial staff to ensure they can then be identified on trial documents such as CRFs, case notes, and prescriptions.

4.13 Participant Screening Log and Participant Randomisation Log

4.13.1 The CI (or delegate) is responsible for keeping a confidential list of names of all participants consenting to the trial (ICH GCP 8.3.21), see Doc Ref 076 (Screening Log). This is the only place where the full name, CHI/hospital number and contact details (optional) of trial participants are documented and allows the CI to reveal the identity of participants if necessary.

4.13.2 The CI or delegate is also responsible for keeping a list of all participants that were randomised, see Doc Ref 071 (Randomisation Log) and ICH GCP (8.3.20 & 8.3.22). Participants should be referred to by initials and/or trial number only.

4.13.3 Aside from the screening log, prescriptions or IMP request forms, participants should only be referred to by their initials and/or trial number on CRFs or elsewhere.

4.13.4 The CI or delegate must notify a TASC trial monitor of the trial start date. The trial start date will be the date when the first participant signs an Informed Consent Form.

4.14 Trial equipment

4.14.1 The CI or PI is responsible for the proper maintenance of all equipment used in the trial. This may include fridges, freezers, centrifuges, weighing scales and equipment used for medical procedures.

4.14.2 The CI is responsible for ensuring that appropriate indemnity arrangements are in place for any equipment loaned for use in the trial. The CI should seek advice regarding indemnity from the TASC Legal Office.

4.15 Trial meetings

4.15.1 A Trial Management Group (TMG) should be established and regular meetings should be held. Meetings should be minuted or notes made of all significant decisions and follow-up actions. Copies of minutes or notes must be kept in the TMF.

4.15.2 For large multi-centre trials, trial oversight committees should also be set up e.g. a Data Monitoring Committee (DMC) and Trial Steering Committee (TSC), in order to review trial data and oversee trial management at regular pre-defined intervals during the trial. Minutes of all meetings should be maintained in the TMF.

4.16 Pharmacy responsibilities

4.16.1 The Clinical Trials Pharmacist (or delegate), at each Site is responsible for setting up and maintaining the PSF and PSF Index.

4.16.2 The PSF contains original and confidential documents and must be kept in a secure location with restricted access for the duration of the trial.

4.16.3 The Clinical Trials Pharmacist (or delegate) is responsible for preparing the Dispensing Procedure prior to the first participant entering the trial.

4.16.4 Where the trial pharmacy is not an NHS Pharmacy, the Sponsor will approve the use of such a pharmacy and it will be subject to audit by the NHS Tayside Clinical Trials Pharmacist (or delegate).

4.17 Sponsor responsibilities

4.17.1 TASC is responsible for setting up and maintaining the SF in accordance with the SF Index (Doc Ref 096).

4.17.2 The SF contains confidential documents and is kept in TASC in a locked room with restricted access.

4.17.3 All pertinent correspondence concerning the trial is filed in the SF including monitoring visit reports and action lists from monitoring.

5. ABBREVIATIONS & DEFINITIONS

CI	Chief Investigator
CRF	Case Report Forms
CTA	Clinical Trial Authorisation
CTIMP	Clinical Trial of Investigational Medicinal Product
CTN	Clinical Trial Notification
DMC	Data Monitoring Committee
GCP	Good Clinical Practice
HRA	Health Research Authority
IB	Investigators Brochure
IMP	Investigational Medicinal Product
ISF	Investigator Site File
MHRA	Medicines & Healthcare Products Regulatory Agency
MTA	Material Transfer Agreement
NHST	NHS Tayside (Tayside Health Board)
PI	Principal Investigator
PSF	Pharmacy Site File
REC	Research Ethics Committee
RSI	Reference Safety Information
SF	Sponsor File
SmPC	Summary of Product Characteristics
TASC	Tayside Medical Sciences Centre
TMF	Trial Master File
TMG	Trial Management Group
TSC	Trial Steering Committee
UoD	University of Dundee

6. ASSOCIATED DOCUMENTS & REFERENCES

Doc Ref 007 SOP Trial Log
Doc Ref 018 Trial Master File index
Doc Ref 019 Investigator Site File Index
Doc Ref 057 Delegation Log
Doc Ref 071 Randomisation Log
Doc Ref 076 Screening Log
Doc Ref 096 Sponsor File Index

WORLD MEDICAL ASSOCIATION DECLARATION OF HELSINKI Ethical Principles for Medical Research Involving Human Subjects.

Medicines for Human Use (Clinical Trials) Regulations 2004. *It is assumed that by referencing the principal regulations, all subsequent amendments made to the principal regulations are included in this citation.*

7. DOCUMENT HISTORY

Version Number:	Reviewed By (Job Title)	Effective Date:	Details of editions made:
1.0	Patricia Burns, (Clinical Trials Supervisor) Catrina Forde, (Senior Research Governance Manager)	01/11/2009	New
2.0	Catrina Forde (RGM)	01/05/2012	Updated in line with current practice.
3.0	Catrina Forde (SRGM)	23/09/2014	Updated in line with current practice.
4.0	Catrina Forde (SRGM)	23/09/2016	Scheduled review. Addition of a new numbered section (4.8.3) for changes to agreements.
5.0	Margaret Band (Senior Trial Manager)	23/09/2018	New TASC SOP format implemented. Minor changes to text.
6.0	Margaret Band (Senior Trial Manager)	26/11/2018	Reference to TASC SOP on Sponsor Regulatory Green Light and associated Checklist (Doc Ref 116) and CTIMP Protocol Template (Doc Ref 054) removed. Now use HRA Protocol template. Change of reference from TASC SOP for Approvals for CTIMPs to SOP for Sponsorship of Clinical Trials. Reference to TASC SOP for Registering and Reporting

			Research in a Publicly Accessible Database added.

8. APPROVALS

Sign		Date
APPROVED BY:	Professor Jacob George, R&D Director, NHS Tayside	
Signature		16 NOV 2018
APPROVED BY:	Dr Valerie Godfrey, TASC QA Manager, Chair of Clinical Research Guidelines Committee	
Signature	Valerie Godfrey	16 Nov 2018