Queen's University Belfast

Research and Enterprise

Standard Operating Procedure
Research Governance

Title:	**Development, Review and Amendment: Study Protocol**		
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* For all University sponsored research recorded as risk category level 4, including IMP studies
# For all other University sponsored research involving human participants

Revision Log

Previous Version number	Date of Review/Modification	Reason for Review/Modification	New Version Number
Final v 1.0	10/11/09	Annual Review	Final v 1.0
Final v 1.0	10/11/10	Annual Review/ Update following MHRA GCP Inspection	Final v 2.0
Final v 2.0	17/08/12	Periodic Review	Final v 3.0
Final v 3.0	06/10/14	Periodic Review	Final v 4.0
Final v4.0	19/09/16	Periodic Review	Final v 5.0

1. Purpose

This Standard Operating Procedure (SOP) describes the process for developing, reviewing, and amending a research study protocol. It contains the necessary information to assist researchers to write a protocol in accordance with the ICH Guidelines for Good Clinical Practice (ICH-GCP) standards for clinical trials, that fall under the European Clinical Trials Directive 2001/20/EC and the Medicines for Human Use (Clinical Trials) Amendment Regulations (SI 2006/1929), hereafter referred to as 'The Regulations', that came into force in 2006. It is anticipated that a full review of all Research Governance SOPs will be necessary after the proposal to repeal Directive 2001/20/EC is implemented. This is to ensure that the University conducts Clinical Trials of Investigational Medicinal Products (CTIMPs) in accordance with EC Member State legislative requirements. The primary focus of the SOP is for CTIMPs but it is relevant for any research project involving human participants.

2. Introduction

A research protocol is a legal document. It details the study plan for a research study outlining answers to the components of the research and, in particular, giving careful consideration to the health, safety and welfare of research participants.

The development of a new study is the responsibility of the lead academic and, if necessary, the relevant clinical team from the Health and Social Care (HSC) setting. It is recognised that the lead academic may be a clinical academic and appointed jointly between the University and a HSC Trust.

The Chief Investigator may delegate the responsibility for writing the clinical protocol and its associated documents to a designated qualified individual.

3. Scope

This SOP applies to all members of University staff; both academic and support staff as defined by Statute 1 and including honorary staff and students who are conducting research within or on behalf of the University.

4. Responsibilities

4.1 Chief Investigator

It will be the responsibility of the Chief Investigator (CI), or the appropriate designated person, to involve the suitable expertise of biostatisticians, information technology/database experts, clinicians and relevant other experts as appropriate when drafting the protocol.

He/she must conform to the research governance requirements of the University and, where applicable, the host HSC Trust.

He/she must ensure that all internal and external regulatory authority approvals are in place before the first research participant is recruited.

He/she must register all interventional studies on a publicly accessible database

He/she must ensure that the study is logged onto the Insurance Database and that the correct level of risk is designated to the proposed research. The risk levels are detailed in the below table.

Risk	Descriptor
Level 1	Those projects which although involving human subjects are in no way associated with a medicinal purpose or do not involve issues such as alcohol and illicit drug use or higher risk sexual behaviour. Level 1 projects essentially involve research into, for example, behaviour, attitudes, rights and education issues. These projects do not include an intervention[1].
Level 2	Those projects that have more relevance to healthcare and include, for example, survey work on access to health care or issues such as alcohol and illicit drug use or higher risk sexual behaviour. These projects do not include an intervention.
Level 3	These projects essentially involve research involving collecting data (including risk factor data) in human subjects and correlating this with, for example, health status, and advances in diagnostics. The projects do not involve altering treatment regimens or the standard of routine care that these individuals receive. These projects do not include an intervention.
Level 4	These studies generally either involve an intervention which has the aim of changing health status or behaviour or involve procedures that are generally more invasive in nature, but do not have the attributes/characteristics of Level 4b studies.
Level 4b	These studies involve Clinical trials of Investigational Medicinal Products or clinical trials into medical devices or involve procedures which aim to induce illness or other conditions (eg inflammation) in study subjects for the purpose of testing the efficacy of new treatment approaches.

[1] An intervention is classed as a change directly related to the study that may alter the research subject's health, physically or mentally and includes any potential to alter behaviour as a result of participation.

The Insurance Database will be audited by the University annually and any discrepancies will be reported back.

5. Procedure

5.1 Writing a Clinical Protocol

The CI will determine who is best qualified to write the clinical protocol, a template of which is attached as Appendix 1, and who is required to review and approve the same.

For Phase I and Phase II studies, pharmacological and biological studies the contents will vary, as appropriate.

In general, the contents of a clinical protocol should include the following subjects:

5.1.1 General Information:

- Protocol title, protocol identifying number and date. Any amendments should also include the amendment number and the dates of amendments.
- Name and address of the Sponsor. Co-sponsor arrangements will be agreed in advance of any submission to the Medicines and Healthcare products Regulatory Authority (MHRA) and ORECNI in collaboration with the Chief Investigator's (CI) employer and the host Trust(s).
- Name and title of the person(s) authorised to sign the protocol and the protocol amendment(s) for the Sponsor.

- Name, title, address and telephone number(s) of the medical expert for the trial, where the CI is not the medical expert.
- Name and title of the investigator(s) responsible for conducting the trial, and the address and telephone number(s) of the trial site.
- Key contact(s) responsible for the ongoing management of the trial.
- Name and address of the clinical laboratory(ies), other medical/technical departments and/or institution(s) involved in the trial.

5.1.2 Background to Protocol:

- Name and description of the investigational product(s).
- A summary of findings from non-clinical studies that potentially have clinical significance and from clinical trials which are relevant to the trial.
- Summary of the known and potential risks and benefits, if any, to human participants, hereinafter referred to as subjects.
- Description of and justification for the route(s) of administration, dosage, regimen, and treatment period(s).
- A statement that the trial will be conducted in compliance with the protocol, Good Clinical Practice (GCP) and the applicable regulatory requirement(s).
- Description of the population to be studied.
- Reference to the literature and date that are relevant to the trial, and that provide background to the trial.

5.1.3 Study Objectives:

- A detailed description of the objectives and purpose of the trial.

5.1.4 Study Design:

A description of the research study should include:

- A statement identifying the primary endpoints and the secondary endpoints, if any, to be measured during the trial.
- A description of the design/type of study to be carried out (e.g. double-blind or placebo-controlled) that includes the procedures and stages to be followed.
- Measures that are taken to minimise and/or avoid bias.
- A description of the study treatment(s), dosage and dosage regimen of the Investigational Medicinal Product (IMP). Dosage form, packaging and labelling of IMP must also be included.
- The expected duration of subject participation, and a description of the sequence and duration of all trial periods, including follow-up, in any.
- A description of the 'stopping rules' or 'discontinuation criteria' for individual subjects, parts of the trial and entire trial.
- Accountability procedures for the IMP(s), including the placebo(s) and comparator(s), if any.
- Maintenance of trial treatment randomisation codes and procedures for breaking codes.
- The identification of any data to be recorded directly on the Case Report Forms (CRFs) (i.e. no prior written or electronic record of data), and to be considered to be source data.

5.1.5 Selection and withdrawal of subjects:

- Subject inclusion criteria.
- Subject exclusion criteria.
- Subject withdrawal criteria (i.e. terminating IMP treatment / trial treatment) and procedures specifying:
  (i) When and how to withdraw subjects from the trial treatment.

(ii) The type and timing of the data to be collected for withdrawn subjects.
(iii) Whether and how subjects are to be replaced.
(iv) The follow-up for subjects withdrawn from IMP treatment/trial treatment.

5.1.6 Treatment of Trial Subjects:

- The treatment(s) to be administered, including the name(s) of all product(s), the dose(s), dosing schedule(s), route / mode(s) of administration, and treatment period(s), including follow-up period(s) for subjects for each IMP treatment / trial treatment group / arm of the trial.
- Medication(s) / treatment(s) permitted (including rescue medication) and not permitted before and/or during the trial.
- Procedures for monitoring subject compliance.
- Methods and timing for assessing, recording, and analysing of efficacy parameters.

5.1.7 Assessment of Safety:

- Which Adverse Events should be recorded?
- Which Serious Adverse should be reported?
- The methods and timing for assessing, recording, and analysing safety parameters.
- Procedures for eliciting reports of and for recording and reporting Adverse Events and inter-current illnesses.
- The type and duration of the follow-up of subjects after Adverse Events.

5.1.8 Statistics:

- A description of the statistical methods to be employed, including timing of any planned interim analysis.
- The number of subjects planned to be enrolled. In multicentre trials, the number of enrolled subjects projected for each trial site should be specified. Reason for choice of sample size, including reflections on (or calculations of) the power of the trial and clinical justification.
- The level of significance to be used.
- Criteria for the termination of the trial.
- Procedure for accounting for missing, unused, and spurious data.
- Procedures for reporting any deviation(s) from the original statistical plan should be described and justified in the protocol and/or in the final report, as appropriate).
- Procedures for reporting.
- The selection of subjects to be included in the analysis (e.g. all randomised subjects, all eligible subjects etc).

5.1.9 Governance Arrangements:

- Details of ethics / regulatory approval.
- Indemnity arrangements.
- Data Handling and Record Keeping.
  (i) Confidentiality.
  (ii) Source documents that contain the source data. Source data has all information, original records of clinical findings, observations, or other activities in a clinical trial necessary for the reconstruction and evaluation of the trial.
  (iii) Case Report Forms – the primary data collection instrument for the study.
  (iv) Record retention.
- Study Monitoring Plan.

- Financing, if not addressed in a separate agreement.
- Conflict of Interest(s).
- Publication and reporting of the trial, if not addressed in a separate agreement.

5.2 Review and Approval of a Clinical Protocol

5.2.1 The CI or designated individual will circulate the draft protocol to previously identified persons who are relevant experts to ensure that the proposed clinical protocol has been developed to conduct scientifically robust research.

5.2.2 The designated persons will ensure that the proposed protocol meets the applicable regulations and guidelines and is ethically sound.

5.2.3 The CI or designated individual will address any comments raised by designated persons, and will repeat the process until all the points are addressed.

5.2.4 The final draft protocol will be reviewed and approved by all previously designated persons by the CI.

5.2.5 Once internally approved, the CI will give the protocol a version number and approval date.

5.2.6 The protocol will be peer reviewed in accordance with the University's Regulations for Research Involving Human Participants.

5.2.7 Further changes will be made, if required, following the peer review process. In the event of changes, sequential version numbers from the original should be used.

5.2.8 The CI will include the protocol version number and effective date in the protocol.

5.2.9 The CI will liaise with the University's Research Governance Team and if appropriate the Trust Research Office, to ensure that the appropriate procedures are followed and in turn, that the necessary regulatory authorities are informed and authorise the protocol.

5.2.10 The CI must retain a copy of the appropriate regulatory and site specific authorisations within their Trial Master File.

5.3 Amendments to a Clinical Protocol

5.3.1 The CI may make any editorial or typographical changes to the protocol.

5.3.2 Any changes that relate to the study, for example inclusion/exclusion criteria, age of participants, numbers to be recruited etc are considered significant and must be resubmitted to all the appropriate internal and external regulatory authorities for their authorisation.

5.3.3 The funding body must also be kept informed of any proposed changes.

5.3.4 The CI will retain approved clinical protocols and their attachments, as well as subsequent revisions and any associated correspondence with regulatory authorities.

5.4 Protocol Deviation

5.4.1 The sponsor and CI are allowed to deviate from the authorised protocol in order to take the appropriate safety measures to protect trial subjects against any immediate hazard to their health or safety.

5.4.2 The CI must inform the sponsor immediately, who in turn will ensure that the appropriate regulatory authorities, such as the MHRA and Ethics Committee, of the measures taken and explain the need for them.

6. References

International Conference on Harmonisation (ICH) Harmonisation Tripartite Guideline: Guideline for Good Clinical Practice E6 (R1).
http://www.ich.org/products/guidelines.html (last accessed 19 September 2016).
University College London, Standard Operating Procedure, Writing a Protocol to Good Clinical Practice (GCP).

7. Appendices

Appendix 1: Protocol Template

Queen's University Belfast

Study Title: insert full title including brief reference to the design, disease or condition being studied, and primary objective

Internal Reference No: This should be assigned by the investigator/department

Ethics Ref: Insert

Date and Version No: Insert

Chief Investigator:	Insert name and contact details
Investigators:	Insert names of key collaborators
Sponsor:	
Funder (if applicable):	Insert details of organisation providing funding
Signatures:	The approved protocol should be signed by author(s) and/or person(s) authorised to sign the protocol

Include other relevant information as necessary e.g. name of Contract Research Organisation, Medical/Safety Monitor.

TABLE OF CONTENTS

- **AMENDMENT HISTORY**

Amendment No.	Protocol Version No.	Date issued	Author(s) of changes	Details of Changes made

List details of all protocol amendments here whenever a new version of the protocol is produced.

- **SYNOPSIS**

It may be useful to include a synopsis of the study for quick reference. Delete or alter as appropriate/required.

Study Title	
Internal ref. no.	
Study Design	
Study Participants	
Planned Sample Size	
Follow-up duration	
Planned Study Period	
Primary Objective	
Secondary Objectives	
Primary Endpoint	
Secondary Endpoints	
Intervention (s)	

- **BACKGROUND AND RATIONALE**

Outline the scientific justification for the research. Give an outline of the background to the study, with references to literature and other relevant research.

Give an outline of the main research questions. Give a brief outline of the intervention (if applicable) and summary of findings from previous studies (if relevant) that potentially have clinical significance.

Provide summary of the known and potential risks and benefits of any of the study procedures (where applicable)

Describe the population to be studied.

- **OBJECTIVES**

There is usually only one primary objective, the rest are secondary objectives.

The wording of the objectives should be clear, unambiguous and as specific as possible.

- **4.1 Primary Objective**

Insert primary objective

- **4.2 Secondary Objectives**

Insert secondary objectives

- **STUDY DESIGN**

5.1 Summary of Study Design

Describe the overall study design e.g., double-blind, sham-controlled, parallel design, open labelled, observational.

Give the expected duration of participant participation, number of visits, and a description of the sequence and duration of all study periods.

- **5.2 Primary and Secondary Endpoints/Outcome Measures**

Describe the end-points/outcome measures and how/when they will be measured during the study.

Endpoints/outcome measures should reflect the objectives. It is important that only one primary endpoint/outcome measure is selected as it will be used to decide the overall results or 'success' of the study. The primary endpoint/outcome measure should be measurable, clinically relevant to participants and widely accepted by the scientific and medical community.

5.3 Study Participants

- **5.3.1 Overall Description of Study Participants**

Give an overall description of the study participants.

Example:

Participants with <<medical condition>> of *xyz* severity and <<*other symptoms/disease specific criteria*> or healthy adults aged <<insert age>>.

- **5.3.2 Inclusion Criteria**

Example criteria (amend as appropriate):

Participant is willing and able to give informed consent for participation in the study.
Male or Female, aged 18 years or above.
Diagnosed with required disease/severity/symptoms, any specific assessment criteria for these)
Additional criteria as required

5.3.3 Exclusion Criteria

The participant may not enter the study if ANY of the following apply:

Specify any diseases/disorders/ conditions that would preclude entry into the study
Additional criteria as required

1.4 Study Procedures

Describe all study procedures and assessments in detail. Add visit numbers as appropriate. Add schedule of procedures as an appendix if appropriate.

5.4.1 Informed Consent

It should be specified who will take informed consent and how and when it will be taken. Informed consent should be obtained prior to any study related procedures being undertaken.

5.4.2 Study Assessments

List and describe each assessment specifying time points. Include screening and eligibility assessment, baseline and subsequent assessments.

- **5.5 Definition of End of Study**

The definition of end of study must be provided. In most cases the end of study will be the date of the last visit of the last participant. Any exceptions should be justified.

Example:

The end of study is the date of the last <<visit/ telephone follow up/ home visit>>of the last participant.

- **INTERVENTIONS**

Describe interventions (if applicable) including the name(s) of procedure/device, intervention schedule(s), treatment period(s), if applicable

- **SAFETY REPORTING (IF APPLICABLE)**

- **7.1 Definition of Serious Adverse Events**

Example:

A serious adverse event is any untoward medical occurrence that:

- Results in death,

- Is life-threatening,

NOTE: The term "life-threatening" in the definition of "serious" refers to an event in which the participant was at risk of death at the time of the event; it does not refer to an event which hypothetically might have caused death if it were more severe.

- Requires inpatient hospitalisation or prolongation of existing hospitalisation,
- Results in persistent or significant disability/incapacity, or
- Is a congenital anomaly/birth defect.
- Other important medical events*

*Other events that may not result in death, are not life threatening, or do not require hospitalisation, may be considered a serious adverse event when, based upon appropriate medical judgement, the event may jeopardise the participant and may require medical or surgical intervention to prevent one of the outcomes listed above.

- **7.2 Reporting Procedures for Serious Adverse Events**

- A serious adverse event (SAE) occurring to participant should be reported to the REC that gave a favourable opinion of the study where in the opinion of the Chief Investigator the event was: 'related' – that is, it resulted from administration of any of the research procedures; and 'unexpected' – that is, the type of event is not listed in the protocol as an expected occurrence. Reports of related and unexpected SAEs should be submitted within 15 days of the Chief Investigator becoming aware of the event, using the NRES report of serious adverse event form (see NRES website**).**

- **STATISITICS**

- **8.1 The Number of Participants**

State the approximate number of participants required with justification.

- **8.2 Analysis of Endpoints**

Describe analysis of primary and secondary endpoints.

- **ETHICS**

Describe ethical considerations relating to the study. Include general and study specific ethical considerations.

- **9.1 Participant Confidentiality**

Example:
The study staff will ensure that the participants' anonymity is maintained. The participants will be identified only by initials and a participants ID number on the CRF and any electronic database. All documents will be stored securely and only accessible by study staff and authorised personnel. The

study will comply with the Data Protection Act which requires data to be anonymised as soon as it is practical to do so.

9.2 Other Ethical Considerations

Include any other ethical considerations specific to the study e.g. involvement of vulnerable participants, participants who are unable to consent for themselves.

- **DATA HANDLING AND RECORD KEEPING**

Describe method of data entry/management

Example:
All study data will be entered on a <<quote software and validation procedure>>. The participants will be identified by a study specific participants number and/or code in any database. The name and any other identifying detail will NOT be included in any study data electronic file.

- **FINANCING AND INSURANCE**

Describe financing and insurance arrangements.

- **REFERENCES**

Insert references used in text.