Writing a Protocol to Good Clinical Practice (GCP)

SOP Reference: JRO/SOP/012

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Effective Date: /18/02/15

Review by: 18/02/17

Author: Nihaad Abbass, Clinical Trial Monitor

Approved by: Gary Roper

Date: 18/02/15

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| Final 7.0 | 18 Feb 2015 | Scheduled Review"
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1. **PURPOSE**

This SOP describes writing a research protocol to Good Clinical Practice (GCP) as required by the Medicines for Human Use (Clinical Trials) Regulations 2004, incorporating GCP amendments (2006). The primary focus of the SOP is clinical trials of investigational medicinal products (CTIMPs) that fall under this legislation. It is also relevant for any project involving humans, their tissue and/or data.

2. **INTRODUCTION**

A research protocol is the *legal* document that outlines the study plan for a clinical trial. The plan must be carefully designed to safeguard the health and safety of the participants, as well as answer specific research questions. A protocol describes who the participants are in the study; the schedule of tests, procedures, medications, and dosages; and the length of the study. While enrolled in a clinical trial, participants following a protocol are seen regularly by the research staff to monitor their health and to determine the safety and effectiveness of their treatment.

It is recommended that the protocol template in Appendix 1 is used for Clinical Trials of Investigational Medicinal Products (CTIMPs). Appendix 2 contains a template protocol for non-CTIMP studies. The procedures described in this SOP will focus mainly on studies of CTIMPs; for all other types of studies, disregard non-applicable sections.

Any amendment to the ethics approved protocol must be reviewed and approved by the Joint Research Compliance Office before the amendment is submitted to the ethics committee and/or MHRA, as changes may affect the terms of sponsorship and insurance cover.

3. **PROCEDURE**

As per International Conference on Harmonisation Good Clinical Practice (ICH GCP), the contents of a CTIMP study protocol should include the following topics:

3.1 **General Information**

- Protocol title, protocol identifying number, and date. Any amendment(s) should also bear the amendment number(s) and date(s).
- Name and address of the sponsor and monitor (if other than the sponsor).
- 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 sponsor’s medical expert (or dentist when appropriate) for the trial.
- Name and title of the investigator(s) who is (are) responsible for conducting the trial, and the address and telephone number(s) of the trial site(s).
- Name, title, address, and telephone number(s) of the qualified physician (or dentist, if applicable), who is responsible for all trial-site related medical (or dental) decisions (if other than investigator).
- Name(s) and address(es) of the clinical laboratory(ies) and other medical and/or technical department(s) and/or institutions involved in the trial.
3.2 Background Information
- 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 subjects.
- Description of and justification for the route of administration, dosage, dosage regimen, and treatment period(s).
- A statement that the trial will be conducted in compliance with the protocol, GCP and the applicable regulatory requirement(s).
- Description of the population to be studied.
- References to literature and data that are relevant to the trial and that provide background for the trial.

3.3 Study Objectives and Purpose
A detailed description of the objectives and the purpose of the study.

3.4 Study Design
The scientific integrity of the trial and the credibility of the data from the trial depend substantially on the trial design. A description of the trial design should include:
- A specific statement of the primary endpoints and the secondary endpoints, if any, to be measured during the trial.
- A description of the type/design of trial to be conducted (e.g. double-blind, placebo-controlled, parallel design) and a schematic diagram of trial design, procedures and stages.
- A description of the measures taken to minimise/avoid bias, including: randomisation and blinding.
- A description of the trial treatment(s) and the dosage and dosage regimen of the investigational product(s). Also include a description of the dosage form, packaging, and labelling of the investigational product(s).
- The expected duration of subject participation, and a description of the sequence and duration of all trial periods, including follow-up, if any.
- A description of the "stopping rules" or "discontinuation criteria" for individual subjects, parts of trial and entire trial.
- Accountability procedures for the investigational product(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 CRFs (i.e. no prior written or electronic record of data), and to be considered to be source data.

3.5 Selection and Withdrawal of Participants
- Subject inclusion criteria.
- Subject exclusion criteria.
- Subject withdrawal criteria (i.e. terminating investigational product treatment/trial treatment) and procedures specifying:
  i. When and how to withdraw subjects from the trial/ investigational product 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 investigational product treatment/trial treatment.

3.6 Treatment of Participants

- The treatment(s) to be administered, including the name(s) of all the product(s), the dose(s), the dosing schedule(s), the route/mode(s) of administration, and the treatment period(s), including the follow-up period(s) for subjects for each investigational product 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.

3.7 Assessment of Efficacy

- Specification of the efficacy parameters.
- Methods and timing for assessing, recording, and analysing of efficacy parameters.

3.8 Assessment of Safety

- Specification of safety parameters.
- The methods and timing for assessing, recording, and analysing safety parameters.
- Procedures for eliciting reports of and for recording and reporting adverse event and inter-current illnesses.
- The type and duration of the follow-up of subjects after adverse events.

3.9 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 numbers 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 (any deviation(s) from the original statistical plan should be described and justified in protocol and/or in the final report, as appropriate).
- The selection of subjects to be included in the analyses (e.g. all randomised subjects, all dosed subjects, all eligible subjects, evaluable subjects).

3.10 Direct Access to Source Data/Documents

The Sponsor should ensure that it is specified in the protocol or other written agreement that the investigator(s)/institution(s) will permit trial-related monitoring, audits, IRB/IEC review, and regulatory inspection(s), providing direct access to source data/documents.
3.11 Quality Control and Quality Assurance
Description of procedures to maintain quality control and quality assurance.

3.12 Ethics
Description of ethical considerations relating to the trial.

3.13 Data Handling and Record Keeping
Description of data management procedures.

3.14 Finance and Insurance
Financing and insurance if not addressed in a separate agreement.

3.15 Publication Policy
Publication policy, if not addressed in a separate agreement.

4. REFERENCES
ICH Harmonised Tripartite Guideline for Good Clinical Practice (1996)

5. APPENDICES

5.1 Appendix 1: Template Protocol for CTIMPs

<Study Acronym>

<Full study title>

<Version number and date>

MAIN SPONSOR or co-sponsors: Imperial College London/Imperial College Healthcare NHS Trust (delete as applicable)
FUNDERS: XXX
STUDY COORDINATION CENTRE: XXX

REC reference: XXX
EudraCT reference: XXX

Protocol authorised by:

<table>
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<th>Name &amp; Role</th>
<th>Date</th>
<th>Signature</th>
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</table>

© Imperial College of Science, Technology and Medicine
Study Management Group

Chief Investigator:

Co-investigators:

Statistician:

Trial Management:

Study Coordination Centre

For general queries, supply of trial documentation, and collection of data, please contact:

Study Coordinator:
Address: 
Tel: 
Fax: 

Randomisations:
E-mail: 
Web address: 

Clinical Queries

Clinical queries should be directed to xxx who will direct the query to the appropriate person

Sponsor

Imperial College London/Imperial College Healthcare NHS Trust (delete as applicable) is the main research Sponsor for this study. For further information regarding the sponsorship conditions, please contact the Head of Regulatory Compliance at:

Joint Research Compliance Office
5L10C, 5th Floor Lab Block
Charing Cross Hospital
Fulham Palace Road
London, W6 8RF
Tel: 0203 311 0204
Fax: 0203 311 0203

Funder

[Who is funding the study]
This protocol describes the xxx study and provides information about procedures for entering participants. The protocol should not be used as a guide for the treatment of other participants; every care was taken in its drafting, but corrections or amendments may be necessary. These will be circulated to investigators in the study, but centres entering participants for the first time are advised to contact the trials centre to confirm they have the most recent version. Problems relating to this trial should be referred, in the first instance, to the study coordination centre.

This trial will adhere to the principles outlined in the Medicines for Human Use (Clinical Trials) Regulations 2004 (SI 2004/1031), amended regulations (SI 2006/1928) and the International Conference on Harmonisation Good Clinical Practice (ICH GCP) guidelines. It will be conducted in compliance with the protocol, the Data Protection Act and other regulatory requirements as appropriate.

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APPENDIX 1. EXAMPLE LIST OF EXPECTED TOXICITIES

APPENDIX 2. SUMMARY OF INVESTIGATIONS, TREATMENT AND ASSESSMENTS

GLOSSARY OF ABBREVIATIONS
KEYWORDS
[Insert a list of keywords]

STUDY SUMMARY

TITLE

DESIGN

AIMS

OUTCOME MEASURES

POPULATION

ELIGIBILITY

TREATMENT

DURATION
1. INTRODUCTION

1.1 BACKGROUND
[To include: review of previous studies, disease particulars, incidence, current treatment options, risks and benefits]

1.2 RATIONALE FOR CURRENT STUDY
[To include: research question and hypothesis, as well as potential risks and benefits]

2. STUDY OBJECTIVES
[List the primary, secondary and other study objectives]

3. STUDY DESIGN
[Type of study: eg randomised double-blind placebo controlled etc.]  
[Duration: ie what constitutes the treatment phase and the follow-up phase of the study]  
[Number and type of subjects to be recruited: eg 800 participants, 400 of which healthy]

3.1 STUDY OUTCOME MEASURES
What are the endpoints of the study?[eg: disease-free survival, toxicity etc]

4. PARTICIPANT ENTRY

4.1 PRE-RANDOMISATION EVALUATIONS
[What tests need to be included before a participant can enter the study? Eg, FBC, LFT, biopsy, CT scan. All screening procedures should be included]

4.2 INCLUSION CRITERIA
[Include justifications, if necessary]
4.3 EXCLUSION CRITERIA
[Include justifications, if necessary]

4.4 WITHDRAWAL CRITERIA
[Describe procedures for stopping early]
[Describe procedures for participants should they wish to withdraw their consent, ie will all data to date be held, will all data be destroyed]

5. RANDOMISATION AND ENROLMENT PROCEDURE

5.1 RANDOMISATION OR REGISTRATION PRACTICALITIES
[Describe procedures enrolling participants and what needs to be completed prior to randomisation. Give numbers to ring for randomisation]

5.2 UNBLINDING
[unblinding is discouraged during the study unless required to by urgent safety measures. Give details on how this will be done (if applicable). Please see safety reporting SOP for further details]

6. TREATMENTS

6.1 TREATMENT ARMS
[Mention dosage, route of administration, labelling, packaging, where study drugs will come from, whether a supply will be delivered to pharmacy at randomisation/registration, if study drug is free.]

6.2 DOSE MODIFICATIONS FOR TOXICITY
[Tables are especially useful to demonstrate what dose reductions should be taken in the event of toxicity]

6.3 PREMEDICATION
[Drugs should be listed if they are to be prescribed before or during trial treatment, eg antibiotics]

6.4 INTERACTION WITH OTHER DRUGS
[Are there any medications that the participant should avoid?]

6.5 DISPENSING AND ACCOUNTABILITY
[Procedures for pharmacy]

7. PHARMACOVIGILANCE

7.1 DEFINITIONS
Adverse Event (AE): any untoward medical occurrence in a patient or clinical trial subject administered a medicinal product and which does not necessarily have a causal relationship with this treatment. An AE can therefore be any unfavourable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporarily associated with the use of an investigational medicinal product (IMP), whether or not considered related to the IMP.
Adverse Reaction (AR): all untoward and unintended responses to an IMP related to any dose administered. All AEs judged by either the reporting investigator or the sponsor as having reasonable causal relationship to a medicinal product qualify as adverse reactions. The expression reasonable causal relationship means to convey in general that there is evidence or argument to suggest a causal relationship.

Unexpected Adverse Reaction: an AR, the nature or severity of which is not consistent with the applicable product information (e.g., investigator’s brochure for an unapproved investigational product or summary of product characteristics (SmPC) for an authorised product). When the outcome of the adverse reaction is not consistent with the applicable product information this adverse reaction should be considered as unexpected. Side effects documented in the SmPC which occur in a more severe form than anticipated are also considered to be unexpected.

Serious Adverse Event (SAE) or Serious Adverse Reaction: any untoward medical occurrence or effect that at any dose:

- Results in death.
- Is life-threatening – refers to an event in which the subject 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 hospitalisation, or prolongation of existing inpatients’ hospitalisation.
- Results in persistent or significant disability or incapacity.
- Is a congenital anomaly or birth defect.

Medical judgement should be exercised in deciding whether an AE/AR is serious in other situations. Important AEs that are not immediately life-threatening or do not result in death or hospitalisation but may jeopardise the subject or may require intervention to prevent one of the other outcomes listed in the definition above, should also be considered serious.

Suspected Unexpected Serious Adverse Reaction (SUSAR): any suspected adverse reaction related to an IMP that is both unexpected and serious.

7.2 CAUSALITY
Most adverse events and adverse drug reactions that occur in this study, whether they are serious or not, will be expected treatment-related toxicities due to the drugs used in this study. The assignment of the causality should be made by the investigator responsible for the care of the participant using the definitions in the table below.

If any doubt about the causality exists the local investigator should inform the study coordination centre who will notify the Chief Investigators. The pharmaceutical companies and/or other clinicians may be asked to advise in some cases.

In the case of discrepant views on causality between the investigator and others, all parties will discuss the case. In the event that no agreement is made, the MHRA will be informed of both points of view.

<table>
<thead>
<tr>
<th>Relationship</th>
<th>Description</th>
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<tr>
<td>Unrelated</td>
<td>There is no evidence of any causal relationship</td>
</tr>
<tr>
<td>Unlikely</td>
<td>There is little evidence to suggest there is a causal relationship (e.g. the event did not occur within a reasonable time after administration of the trial medication). There is another reasonable explanation for the event (e.g. the participant’s clinical condition, other concomitant treatment).</td>
</tr>
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</table>
Possible | There is some evidence to suggest a causal relationship (e.g. because the event occurs within a reasonable time after administration of the trial medication). However, the influence of other factors may have contributed to the event (e.g. the participant’s clinical condition, other concomitant treatments).

Probable | There is evidence to suggest a causal relationship and the influence of other factors is unlikely.

Definitely | There is clear evidence to suggest a causal relationship and other possible contributing factors can be ruled out.

Not assessable | There is insufficient or incomplete evidence to make a clinical judgement of the causal relationship.

7.3 REPORTING PROCEDURES
All adverse events should be reported. Depending on the nature of the event the reporting procedures below should be followed. Any questions concerning adverse event reporting should be directed to the study coordination centre in the first instance. A flowchart is given below to aid in the reporting procedures.

7.3.1 Non serious AR/AEs
All such toxicities, whether expected or not, should be recorded in the toxicity section of the relevant case report form and sent to the study coordination centre within one month of the form being due.

7.3.2 Serious AR/AEs
Fatal or life threatening SAEs and SUSARs should be reported on the day that the local site is aware of the event. The SAE form asks for nature of event, date of onset, severity, corrective therapies given, outcome and causality (i.e. unrelated, unlikely, possible, probably, definitely). The responsible investigator should sign the causality of the event. Additional information should be sent within 5 days if the reaction has not resolved at the time of reporting.

SAEs
An SAE form should be completed and faxed to the study coordination centre for all SAEs within 24 hours. However, relapse and death due to <condition>, and hospitalisations for elective treatment of a pre-existing condition do not need reporting as SAEs.

SUSARs
In the case of suspected unexpected serious adverse reactions, the staff at the site should:

Complete the SAE case report form & send it immediately (within 24 hours, preferably by fax), signed and dated to the study coordination centre together with relevant treatment forms and anonymised copies of all relevant investigations.

Or

Contact the study coordination centre by phone and then send the completed SAE form to the study coordination centre within the following 24 hours as above.

The study coordination centre will notify the MHRA, REC and the Sponsor of all SUSARs occurring during the study according to the following timelines; fatal and life-threatening within 7 days of notification and non-life threatening within 15 days. All investigators will be informed of all SUSARs occurring throughout the study.
Local investigators should report any SUSARs and/or SAEs as required by their Local Research Ethics Committee and/or Research & Development Office.

Contact details for reporting SAEs and SUSARs
Fax: xxx, attention xxx
Please send SAE forms to: xxx
Tel: xxx (Mon to Fri 09.00 – 17.00)

8. ASSESSMENT AND FOLLOW-UP

[How long will the participant be followed up for? When and what will their assessments consist of? Efficacy assessments should also be included]

8.1 LOSS TO FOLLOW-UP

[list procedures for participants lost to f/up, eg if flagging through ONS]
8.2 TRIAL CLOSURE
[ ]
[Definition of end of trial]

9. STATISTICS AND DATA ANALYSIS
[Statistical plan, eg sample size calculation and data analysis, methods of randomisation.]
[Describe interim analyses, if planned]

Data and all appropriate documentation will be stored for a minimum of 10 years after the completion of the study, including the follow-up period.

10. MONITORING

10.1 RISK ASSESSMENT
[Describe the risk assessment that has taken place for the study. Is the study considered high, medium or low risk? How does this justify level of monitoring provided?]

10.2 MONITORING AT STUDY COORDINATION CENTRE
[EG data entry checks, double data entry, consent form checks, missing or unusual data values]

10.3 MONITORING AT LOCAL SITE
[based on risk assessment, how many site visits, what level of source data verification]

11. REGULATORY ISSUES

11.1 CTA
This study has Clinical Trials Authorisation from the UK Competent Authority; MHRA. Reference: XXX

[this will change if the study is conducted overseas, include other competent authorities as required]

11.2 ETHICS APPROVAL
The Study Coordination Centre has obtained approval from the XXX Research Ethics Committee. The study must be submitted for Site Specific Assessment (SSA) at each participating NHS Trust. The Study Coordination Centre will require a copy of the Trust R&D approval letter before accepting participants into the study. The study will be conducted in accordance with the recommendations for physicians involved in research on human subjects adopted by the 18th World Medical Assembly, Helsinki 1964 and later revisions.

11.3 CONSENT
Consent to enter the study must be sought from each participant only after a full explanation has been given, an information leaflet offered and time allowed for consideration. Signed participant consent should be obtained. The right of the participant to refuse to participate without giving
reasons must be respected. After the participant has entered the trial the clinician remains free to give alternative treatment to that specified in the protocol at any stage if he/she feels it is in the participant’s best interest, but the reasons for doing so should be recorded. In these cases the participants remain within the study for the purposes of follow-up and data analysis. All participants are free to withdraw at any time from the protocol treatment without giving reasons and without prejudicing further treatment.

11.4 CONFIDENTIALITY
Participants’ identification data will be required for the registration process. The Study Coordination Centre will preserve the confidentiality of participants taking part in the study and is registered under the Data Protection Act.

11.5 INDEMNITY
Imperial College London holds negligent harm and non-negligent harm insurance policies which apply to this study/ Imperial College Healthcare NHS Trust holds standard NHS Hospital Indemnity and insurance cover with NHS Litigation Authority for NHS Trusts in England, which apply to this study (delete as applicable)

11.6 SPONSOR
Imperial College London/Imperial College Healthcare NHS Trust (delete as applicable) will act as the main Sponsor for this study. Delegated responsibilities will be assigned to the NHS trusts taking part in this study.

11.7 FUNDING
xxx are funding this study. [Any per patient payments, investigator payments should be detailed here]

11.8 AUDITS AND INSPECTIONS
The study may be subject to inspection and audit by Imperial College London/Imperial College Healthcare NHS Trust (delete as applicable) under their remit as Sponsor, the Study Coordination Centre and other regulatory bodies to ensure adherence to GCP.

12. TRIAL MANAGEMENT
A Trial Management Group (TMG) will be appointed and will be responsible for overseeing the progress of the trial. The day-to-day management of the trial will be co-ordinated through the xxx Study Coordination Centre. [Describe whether a Trial Steering Committee or Data Monitoring Committee will be convened]

13. PUBLICATION POLICY
The study’s publication policy should be described in full. Below is an example paragraph. All publications and presentations relating to the study will be authorised by the Trial Management Group. The first publication of the trial results will be in the name of the Trial Management Group, if this does not conflict with the journal’s policy. If there are named authors, these will include at least the trial’s Chief Investigator, Statistician and Trial Coordinator. Members of the TMG and the Data Monitoring Committee will be listed and contributors will be cited by name if published in a journal where this does not conflict with the journal’s policy. Authorship of parallel studies initiated outside of the Trial Management Group will be according to the individuals involved in the project.
but must acknowledge the contribution of the Trial Management Group and the Study Coordination Centre.

14. REFERENCES
[List of useful and relevant references for the study]

EXAMPLE APPENDICES
Appendices should be additional information to the protocol and can consist of:
- Common Terminology Criteria for Adverse Events (NCI CTC).
- RECIST criteria.
- WHO / ECOG Performance status.
- Drug information from SmPC.
- PIS, Consent form, GP letter (although may be more practical to have them separate).
- Summary of dose modifications.
- Expected side effects.
- Schedule of events table.

Appendix 1. Example List of Expected toxicities

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<tr>
<th>Toxicity</th>
<th>Drug A</th>
<th>Drug B</th>
</tr>
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<tr>
<td><strong>Haematopoietic:</strong></td>
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<tr>
<td>Anaemia</td>
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<tr>
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<td></td>
<td>✔</td>
</tr>
<tr>
<td>Neutropenia</td>
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<td></td>
</tr>
<tr>
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<td><strong>Gastrointestinal:</strong></td>
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<td>Abdominal pain</td>
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Appendix 2. Summary of investigations, treatment and assessments

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<td>FBC, U&amp;E, LFT</td>
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<tr>
<td>Informed consent</td>
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</table>

SOP Ref: JRCO/SOP/012
Final 7.018/02/15
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5.2 Appendix 2: Template Protocol for non-CTIMPs

<Study Acronym>

<Full study title>

<Version number and date>

MAIN SPONSOR: Imperial College London/Imperial College Healthcare NHS Trust (delete as applicable)
FUNDERS: xxx
STUDY COORDINATION CENTRE: xxx
NRES reference: xxx

Protocol authorised by:

Name & Role       Date       Signature
Study Management Group

Chief Investigator:

Co-investigators:

Statistician:

Study Management:

Study Coordination Centre (may not be applicable)

For general queries, supply of study documentation, and collection of data, please contact:

Study Coordinator:
Address: Registration:
Tel: E-mail:
Fax: Web address:

Clinical Queries

Clinical queries should be directed to XXX who will direct the query to the appropriate person

Sponsor

Imperial College London/Imperial College Healthcare NHS Trust (delete as applicable) is the main research Sponsor for this study. For further information regarding the sponsorship conditions, please contact the Head of Regulatory Compliance at:

Joint Research Compliance Office
5L10C, 5th Floor Lab Block
Charing Cross HospitalFulham Palace Road
London W6 8RF
Tel: 0203 311 0204
Fax: 0203 311 0203

Funder

[Who is funding the study]

This protocol describes the XXX study and provides information about procedures for entering participants. Every care was taken in its drafting, but corrections or amendments may be necessary. These will be
circulated to investigators in the study. Problems relating to this study should be referred, in the first instance, to the Chief Investigator.

This study will adhere to the principles outlined in the NHS Research Governance Framework for Health and Social Care (2\textsuperscript{nd} edition). It will be conducted in compliance with the protocol, the Data Protection Act and other regulatory requirements as appropriate.

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3. STUDY DESIGN
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9. STUDY MANAGEMENT
11. PUBLICATION POLICY
12. REFERENCES
EXAMPLE APPENDICES
APPENDIX 1. SUMMARY OF INVESTIGATIONS, TREATMENT AND ASSESSMENTS

GLOSSARY OF ABBREVIATIONS
KEYWORDS
[Insert a list of keywords]
STUDY SUMMARY

TITLE
DESIGN
AIMS
OUTCOME MEASURES
POPULATION
ELIGIBILITY
DURATION

REFERENCE DIAGRAM

[if appropriate]
1. INTRODUCTION

1.1 BACKGROUND
[To include: review of previous studies, disease particulars, incidence, current treatment options, risks and benefits]

1.2 RATIONALE FOR CURRENT STUDY
[To include: research question and hypothesis]

2. STUDY OBJECTIVES

[List the primary, secondary and other study objectives]

3. STUDY DESIGN

[Type of study: eg tissue collection, physiological, epidemiological etc]
[Duration]
[Number and type of subjects]

3.1 STUDY OUTCOME MEASURES
[Are there endpoints to the study?]

4. PARTICIPANT ENTRY

4.1 PRE-REGISTRATION EVALUATIONS
[What tests need to be included before a participant can enter the study? Eg, FBC, LFT, biopsy, CT scan. All screening procedures should be included]

4.2 INCLUSION CRITERIA
[Include justifications, if necessary]

4.3 EXCLUSION CRITERIA
[Include justifications, if necessary]

4.4 WITHDRAWAL CRITERIA
[Describe procedures for stopping early]

5. ADVERSE EVENTS

5.1 DEFINITIONS
Adverse Event (AE): any untoward medical occurrence in a patient or clinical study subject.

Serious Adverse Event (SAE): any untoward and unexpected medical occurrence or effect that:
• Results in death
• Is life-threatening – refers to an event in which the subject 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 hospitalisation, or prolongation of existing inpatients’ hospitalisation
• Results in persistent or significant disability or incapacity
• Is a congenital anomaly or birth defect

Medical judgement should be exercised in deciding whether an AE is serious in other situations. Important AEs that are not immediately life-threatening or do not result in death or hospitalisation but may jeopardise the subject or may require intervention to prevent one of the other outcomes listed in the definition above, should also be considered serious.

5.3 REPORTING PROCEDURES
All adverse events should be reported. Depending on the nature of the event the reporting procedures below should be followed. Any questions concerning adverse event reporting should be directed to the Chief Investigator in the first instance.

5.3.1 Non serious AEs
All such events, whether expected or not, should be recorded.

5.3.2 Serious AEs
An SAE form should be completed and faxed to the Chief Investigator within 24 hours. However, relapse and death due to <condition>, and hospitalisations for elective treatment of a pre-existing condition do not need reporting as SAEs.

All SAEs should be reported to the <name of REC> where in the opinion of the Chief Investigator, the event was:
• ‘related’, ie resulted from the administration of any of the research procedures; and
• ‘unexpected’, ie an event that 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 SAE form for non-IMP studies. The Chief Investigator must also notify the Sponsor of all SAEs.

Local investigators should report any SAEs as required by their Local Research Ethics Committee, Sponsor and/or Research & Development Office.

Contact details for reporting SAEs
Fax: xxx, attention xxx
Please send SAE forms to: xxx
Tel: xxx (Mon to Fri 09.00 – 17.00)

6. ASSESSMENT AND FOLLOW-UP
[Will there be a follow up? When and what will their assessments consist of? Efficacy assessments, if applicable, should be included]

[Definition of end of study]

7. STATISTICS AND DATA ANALYSIS
[Statistical plan, eg sample size calculation and data analysis.]

Data and all appropriate documentation will be stored for a minimum of 10 years after the completion of the study, including the follow-up period.

8. REGULATORY ISSUES

8.1 ETHICS APPROVAL
The Chief Investigator has obtained approval from the xxx Research Ethics Committee. The study must be submitted for Site Specific Assessment (SSA) at each participating NHS Trust. The Chief Investigator will require a copy of the Trust R&D approval letter before accepting participants into the study. The study will be conducted in accordance with the recommendations for physicians involved in research on human subjects adopted by the 18th World Medical Assembly, Helsinki 1964 and later revisions.

8.2 CONSENT
[If using anonymised tissue samples only, this section will not be relevant]
Consent to enter the study must be sought from each participant only after a full explanation has been given, an information leaflet offered and time allowed for consideration. Signed participant consent should be obtained. The right of the participant to refuse to participate without giving reasons must be respected. After the participant has entered the study the clinician remains free to give alternative treatment to that specified in the protocol at any stage if he/she feels it is in the participant’s best interest, but the reasons for doing so should be recorded. In these cases the participants remain within the study for the purposes of follow-up and data analysis. All participants are free to withdraw at any time from the protocol treatment without giving reasons and without prejudicing further treatment.

8.3 CONFIDENTIALITY
The Chief Investigator will preserve the confidentiality of participants taking part in the study and is registered under the Data Protection Act.

8.4 INDEMNITY
Imperial College London holds negligent harm and non-negligent harm insurance policies which apply to this study/ Imperial College Healthcare NHS Trust holds standard NHS Hospital Indemnity and insurance cover with NHS Litigation Authority for NHS Trusts in England, which apply to this study (delete as applicable)

8.5 SPONSOR
Imperial College London/Imperial College Healthcare NHS Trust (delete as applicable) will act as the main Sponsor for this study. Delegated responsibilities will be assigned to the NHS trusts taking part in this study.

8.6 FUNDING
xxx are funding this study. [Any per participant payments, investigator payments should be detailed here]

8.7 AUDITS
The study may be subject to inspection and audit by Imperial College London under their remit as sponsor and other regulatory bodies to ensure adherence to GCP and the NHS Research Governance Framework for Health and Social Care (2nd edition).
9. **STUDY MANAGEMENT**

The day-to-day management of the study will be co-ordinated through xxx.

10. **PUBLICATION POLICY**

[The study's publication policy should be described in full]

10. **REFERENCES**

[List of useful and relevant references for the study]

**EXAMPLE APPENDICES**

Appendices should be additional information to the protocol and can consist of:

- Common Terminology Criteria for Adverse Events (NCI CTC)
- RECIST criteria
- WHO / ECOG Performance status
- PIS, Consent form, GP letter (although may be more practical to have them separate)
- Expected side effects
- Schedule of events table

**Appendix 1. Summary of investigations, treatment and assessments**

<table>
<thead>
<tr>
<th>Exam</th>
<th>Week of Treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Pre-treatment</td>
</tr>
<tr>
<td>MRI</td>
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</tr>
<tr>
<td>Chest x-ray</td>
<td>X</td>
</tr>
<tr>
<td>History, physical exam</td>
<td>X</td>
</tr>
<tr>
<td>ECG</td>
<td>X</td>
</tr>
<tr>
<td>WHO performance status</td>
<td>X</td>
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