Writing a Good Clinical Practice (GCP) Compliant Clinical Trial Protocol

Policy Details	
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Relevant regulations/legislation/guidelines	Statutory Instrument 2004 no 1031 Statutory Instrument 2006 no 1928 (as amended from time to time)

Change History			
Date	Version Number	Change details	Approved by
Oct 10	2.0	Transfer to King's Health Partners Livery, clarification that all study specific procedures must be defined in the trial protocol. Minor amendments to remove duplication in SOP.	Jackie Powell
Oct 12	3.0	Scheduled review and re-branding of JCTO to KHP-CTO.	Jackie Powell
19 Dec 14	4.0	Scheduled review and consistency check.	Jackie Pullen
28 Feb 17	5.0	Scheduled review, glossary update and inclusion of HRA changes.	Jackie Pullen
24 Oct 18	5.1	Minor amendment to include trials managed by KHP-CTO.	Jackie Pullen
24 Feb 2020	6.0	Minor amendment to replace the word subject with participant. Additional text added relating to consent, randomisation and use of CRFs as source data.	Jackie Pullen
01 Jun 2023	7.0	Scheduled review. Updates to protocol content including data confidentiality statement, database lock as EoT definition, IRAS number to be main identifier, removal of lab and site details on the cover page	Kirsty Hough

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1.0 GLOSSARY

Adverse Event (AE) - Any untoward medical occurrence in a participant to whom a medicinal product has been administered, including occurrences which are not necessarily caused by or related to that product.

Chief Investigator (CI) - A Registered Physician, Dentist, Pharmacist or Registered Nurse who has overall responsibility for the conduct of the trial.

Clinical Trial - Any investigation in human participants, other than a non-interventional trial, intended to discover or verify the clinical, pharmacological and/or other pharmacodynamic effects of one or more medicinal product and/or to identify any adverse reactions to one or more such products and/or to study absorption, distribution, metabolism and excretion in one or more such products with the object of ascertaining the safety or efficacy of those products.

Good Clinical Practice (GCP) - as defined in the Regulations.

Health Research Authority (HRA) – An authority in England established in 2011. The authority exercises functions in connection with the facilitation and promotion of research and the establishment of research ethics committees.

Investigational Medicinal Product (IMP) - Means a pharmaceutical form of an active substance or placebo being tested, or used as a reference in a clinical trial. This includes a medicinal product which has a marketing authorisation but is, for the purposes of the trial -

- **(a)** used or assembled (formulated or packaged) in a way different from the form of the product authorised under the authorisation,
- **(b)** used for an indication not included in the summary of product characteristics under the authorisation for that product, or
- **(c)** used to gain further information about the form of that product as authorised under the authorisation

King's Health Partners (KHP) - King's Health Partners Academic Health Science Center is a pioneering collaboration between one of the King's College London (University) and three of London's most successful NHS Foundation Trusts – Guy's & St Thomas', King's College Hospital and the South London & Maudsley.

King's Health Partners Clinical Trials Office (KHP-CTO) - Established in 2006 by King's College London, Guy's & St Thomas' NHS Foundation Trust, South London and Maudsley NHS Foundation Trust and King's College Hospital Foundation Trust to provide a streamlined approach for all aspects of trial administration.

KHP-CTO Quality Team – Comprises the Quality Manager, Clinical Research Associate(s), Clinical Trial Administrator(s), Systems Executive, Training Executive(s) and Training Assistant.

KHP-CTO Standard Operating Procedures (SOPs) - "Detailed, written instructions to achieve uniformity of the performance of a specific function," SOPs are the base on which Quality Systems and Processes are conducted and monitored against.

Medicines & Healthcare products Regulatory Agency (MHRA) - UK competent authority responsible for regulation of clinical trials.

Partner Organisations – King's College London, Guy's & St Thomas' NHS Foundation Trust, King's College Hospital NHS Foundation Trust, South London and Maudsley NHS Foundation Trust and any other Organisations that may join the KHP-CTO Partnership from time to time.

Quality Assurance (QA) - Systems and processes established to ensure that a trial is performed and the data are generated, documented and reported in compliance with GCP and the applicable regulatory requirements.

Quality Control (QC) - The operational techniques and activities undertaken within the quality assurance system to verify that the requirements for quality of the trial-related activities have been fulfilled.

Research & Development Dept (R&D) – NHS department responsible for confirmation of capacity and capability for all clinical research.

Research Ethics Committee (REC) – An independent body in a Member State, consisting of healthcare professionals and non-medical members, whose responsibility is to protect the rights, safety and well-being of human participants involved in a trial and to provide public assurance of that protection by, among other things, expressing an opinion on the trial protocol, the suitability of the investigators and the adequacy of facilities, and on the methods and documents to be used to inform trial participants and obtain their informed consent.

The Regulations - The Medicines for Human Use (Clinical Trials) Regulations 2004, transposed the EU Clinical Trials Directive into UK legislation, as Statutory Instrument 2004 1031. This became effective on the 1st May 2004. An amendment to implement Directive 2005/28/EC was made to the Regulations as Statutory Instrument 2006 no 1928. As amended from time to time.

2.0 BACKGROUND AND PURPOSE

The Medicines for Human Use (Clinical Trials) Regulations 2004 transposed the European Union Directive 2001/20/EC into UK Law effective from the 1st May 2004 (and as amended from time to time). The Regulations state that the protocol is a document that describes the objective(s), design, methodology, inclusion and exclusion criteria of participants participating in a trial, monitoring, publication policy, statistical considerations and organisation of a trial. The term protocol refers to the protocol, successive versions of the protocol and protocol amendments.

This SOP describes the format for writing a research protocol to Good Clinical Practice (GCP) as required by the Regulations. The primary focus of this SOP is CTIMPs that fall within the Regulations; however, it is may also be relevant for any project involving humans, their tissue and/or data.

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 to answer specific research questions. A protocol fully describes who the participants are in the study; the schedule of tests, defines all study 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 related Protocol Template (see Section 5.1) is used for clinical trials of Investigational Medicinal Products (CTIMPs). The procedures described in this SOP and in the protocol template focus on CTIMPs, however both can be adapted for all clinical research. For non-CTIMP research studies non-applicable sections may be deleted.

3.0 SCOPE

All CTIMPs sponsored by one or more of King's Health Partner Organisations, or clinical trials where the sponsor responsibilities are managed by the KHP-CTO.

Although only a legal requirement for trials that fall within the Regulations, all other clinical research protocols should be compliant with the Principles and Conditions of GCP. Therefore, the scope of this SOP may be extended to all clinical research projects conducted by the Partner Organisations.

4.0 PROCEDURE

4.1 Responsibility

It is the responsibility of the Chief Investigator to supervise the writing of the trial protocol. This may be done in conjunction with collaborators and will undergo detailed peer review. It is the responsibility of the Sponsor to ensure adequate peer review has been conducted.

4.2 General Information

All trial procedures and processes will be defined in the main text of the protocol thereby negating the requirement for trial specific SOPs. The contents of a CTIMP protocol will include, but is not limited to, the following:-

4.2.1 Header & Footer

- IRAS number, date and document version control, protocol identifying code or number.

4.2.2 Cover Page

- Protocol title and Trial Identifiers (EudraCT number *if applicable*, ISRCTN *if applicable)*, IRAS number.
- Name, address and contact details for the Sponsor.
- Name, address, contact details and title of the Chief Investigator and any collaborators.
- Table of Contents.

4.2.3 Protocol Synopsis

4.2.4 Background and Rationale

- A brief description of the proposed trial and a description of the population and disease that is to be investigated.
- Name and description of the investigational product(s), device(s) or radiation exposure.
- A summary of findings from non-clinical studies that potentially have clinical significance, and from previous clinical trials which are relevant to the trial.
- A summary of the known and potential risks and benefits to human participants should be presented, together with a justification for the choice of route of administration, dosage, dosage regimen, and treatment period(s). This should be supported by appropriate references to the published literature on the disease or condition, its treatment and the use of the study drug for the indication.
- Data from previous studies as well as any other information that provides background for the trial should be cited.

4.2.5 Trial Objectives and Design

- A description of the design of trial.
- Specific statements of the purpose (i.e. aims and objectives) of the trial, together with a definition of the primary (and secondary) endpoints.
- A time/event matrix (flow chart) of trial procedures to determine activities involved during each clinic visit (e.g. blood tests).

4.2.6 Trial Medications

- Provide a description of the trial treatment; specify the brand or manufacturer of IMP & supplier, including placebo doses.
- Provide a description of the dosage forms, packaging, and labelling of the product(s) that will be given.
- Specify the route of administration, dosage and dosage regimen of all medicinal products (or devices) under investigation.
- It is necessary to define the expected duration of IMP administration, and to describe the sequence and duration of all trial periods (e.g. “wash-out”, “treatment”, “follow-up” etc.).

- Define any special dietary or “life-style” requirements that will be imposed (e.g. contraceptive requirements, no smoking or no alcohol to be drunk within a specified time prior to, and until a specified time after, each dose; a low fat or high fat diet, a specified interval of starvation between doses etc.).
- Specify the method to be used for drug accountability and where IMPs will be stored prior to dispensing/administration.
- State how participant compliance will be determined.
- Specify whether concomitant mediation is permitted and whether this is to be recorded.

4.2.7 Selection and Withdrawal of Participants

A simple list format is the preferred style: -

- ***Inclusion criteria -*** details of age, sex, disease, prior treatment constraints etc., under which a participant is deemed to be suitable (eligible) to participate in the trial. This will include healthy volunteers and any “control” groups that may be required. Each such “group” will be defined separately. Informed consent to participate (written) must be stated as an inclusion criterion**.**
- ***Exclusion criteria -*** details of age, sex, disease, prior treatment constraints or any other reason under which a participant is considered to be unsuitable for inclusion into the study population. This should not merely be corollary of the inclusion criteria.
- ***Selection of Participants -*** state where participants will be recruited from, i.e. from clinic or referred from GP surgeries/other hospitals etc.
- ***Consent Procedures –*** provide details of the consent procedure for participants.
- ***Randomisation Procedure/Code Break -*** provide details of the randomisation procedure to be used for each participant and details of the code break procedure and the conditions in which it is intended to be used, if necessary.
- ***Participant withdrawal criteria -*** explain the circumstances under which investigational product treatment/trial treatment will be terminated and the procedures specifying exactly when and how to withdraw participants from the investigational product treatment and or trial. Detail the type and timing of the data to be collected for withdrawn participants, whether and how participants are to be replaced and the follow-up for participants withdrawn from investigational product treatment/trial treatment.
- ***Expected duration of trial -*** detail the expected duration of clinical participation and define the end of the trial – this is often database lock.

4.2.8 Treatment Procedures by Visit

- Describe the sequence of procedures to be performed at each visit as detailed in the time/event flowchart in the protocol synopsis (section 4.2.3).
- Define the procedure to be followed for participants in the event of early withdrawal from the trial.
- Include any laboratory measurements.

4.2.9 Assessment of Efficacy and Safety

- List the primary and secondary efficacy parameters.
- Describe the primary and secondary measures that will be used to determine the efficacy of treatment (e.g. glucose, blood pressure, tumour reduction etc).
- Describe the measures that will be used to determine participant safety during the trial.

4.2.10 Procedures for Recording and Reporting Adverse Events

- Include definitions of Adverse Events as defined in the Regulations.
- Detail pharmacovigilance reporting requirements and processes in place for the trial.
- Define any adverse events that may be expected or are a trial outcome and therefore do not require reporting. For trials where the IMP is licensed, it is permissible to state that events or reactions listed in the SmPC do not need to be reported.

4.2.11 Treatment Stopping Rules

- Define the treatment stopping rules for individual participants and for groups (if applicable).

4.2.12 Trial Statistics

- A description of the statistical methods to be employed, including timing of any planned interim analyses will also be provided.
- The number of participants to be enrolled will be stated, together with the rationale for the sample size (the “power calculation”). The level of significance that is to be used in each trial analysis must be stipulated, together with the procedure(s) for accounting for any missing, unused, and spurious data.
- The data set for any analysis must be clearly stipulated (e.g. “all participants”, “randomised participants”, “intent to treat”) and the population(s) clearly defined.

4.2.13 Trial Steering Committee

- Detail the composition and function of the Committee (if used/applicable). The Committee Chair should be independent (i.e. not a Co-Investigator). Lay members or patient population representative are desirable.

4.2.14 Data Monitoring Committee

- Detail the composition and function of the Committee (if used/applicable) (i.e. - to assess trial progress, occurrence of adverse events and all other aspects). Define how often the committee will meet.

4.2.15 Direct Access to Source Data and Documents

- Include a statement that the Investigator(s) and the institution(s) will permit trial-related monitoring, audits, REC review, and regulatory inspections (where appropriate) by

providing direct access to source data and other documents (i.e. patients' medical records, participants' case record forms, blood test reports, X-ray reports, histology reports etc.).
- Inclusion of a statement on Data Protection and Participant Confidentiality

4.2.16 Ethics & Regulatory Approvals

- The inclusion of a statement that the trial will be conducted in compliance with the principles of the Declaration of Helsinki (specifying which amendment), the Principles and Conditions of GCP and all of the applicable regulatory requirements (specify current legislation) is required.
- Statement that recruitment will not commence at any site until relevant REC, HRA and Regulatory Authorities approvals are in place including local site approval. Include a statement confirming that any subsequent protocol amendments will be submitted to the REC, HRA and Regulatory Authorities for approval, and that the trial will be conducted according to the Regulations and GCP, particularly specifying Pharmacovigilance reporting, submitting annual safety reports, progress reports and the clinical trial summary report including trial registry reporting requirements.

4.2.17 Quality Control and Quality Assurance

- Describe the procedures to ensure quality control and quality assurance (i.e. all sites will be monitored). Oversight of this will be maintained by the KHP-CTO Quality Team.
- Describe how the data will be handled – e.g. anonymised / pseudo-anonymised.
- Define how long the data will be stored for and how it will be archived.

4.2.18 Data Management

- State whether electronic or paper CRF will be used and describe the type of database.
- Describe how the data will be handled and analysed.
- Describe in detail if the CRF will be used as source e.g. participant questionnaires and how this data will be controlled and overseen by the PI

4.2.19 Publication Policy

- State where and how the trial results will be made public (e.g. poster presentation at conferences, publication in mainstream journal, publicly assessable database etc.).

4.2.20 Finance

- Describe how the trial is being funded.

4.2.21 Insurance and Indemnity

- Describe the insurance and/or indemnity that will be in place for the trial.

4.2.22 Signature(s)

- Signed and dated by the Chief Investigator *(minimum)* and Statistician if applicable.

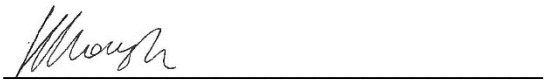
5.0 RELATED TEMPLATES

5.1 GCP Clinical Trials Protocol Template

6.0 RELATED DOCUMENTS

None

7.0 APPROVAL and SIGNATURE



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01 JUNE 2023
Date