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SOP 320
Developing a Research Protocol

For Use in:	Research
By:	All staff
For:	All staff involved in the conduct of research
Division responsible for document:	Research & Development
Key words:	Research Protocol
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Version and Document Control:

Version No:	Date of update	QPulse Change Request reference (CR no.)	Change Description	Author
3	October 2023	CR 214	Process of protocol approval to include review and approval by the Sponsor. Protocol structure reviewed against guidance available on HRA website. Referencing CTIMP Protocol Development Tool, CIP reference, New flowchart appendix 4, removal of reference to EudraCT number	Basia Brown, Ania Spurdens, Michael Sheridan, Juliet High

This Standard Operating Procedure (SOP) is available on the Research & Development pages on the NNUH website

Copies downloaded from the website are only valid on the day of downloading.

1. Contents

2. Definitions of Terms Used / Glossary

CI	Chief Investigator
CTA	Clinical Trials Agreement
CTIMP	Clinical Trial of an Investigational Medicinal Product
CTU	Clinical Trials Unit
EU	European Union
GCP	Good Clinical Practice
HRA	Health Research Authority
NNUHFT	Norfolk and Norwich University Hospitals NHS Foundation Trust
R&D	Research and Development
SOP	Standard Operating Procedure
UEA	University of East Anglia

3. Objectives

To describe the process for writing health care research proposals and protocols.

4. Scope

To describe the process for researchers at Norwich CTU, UEA and NNUHFT.

5. Purpose

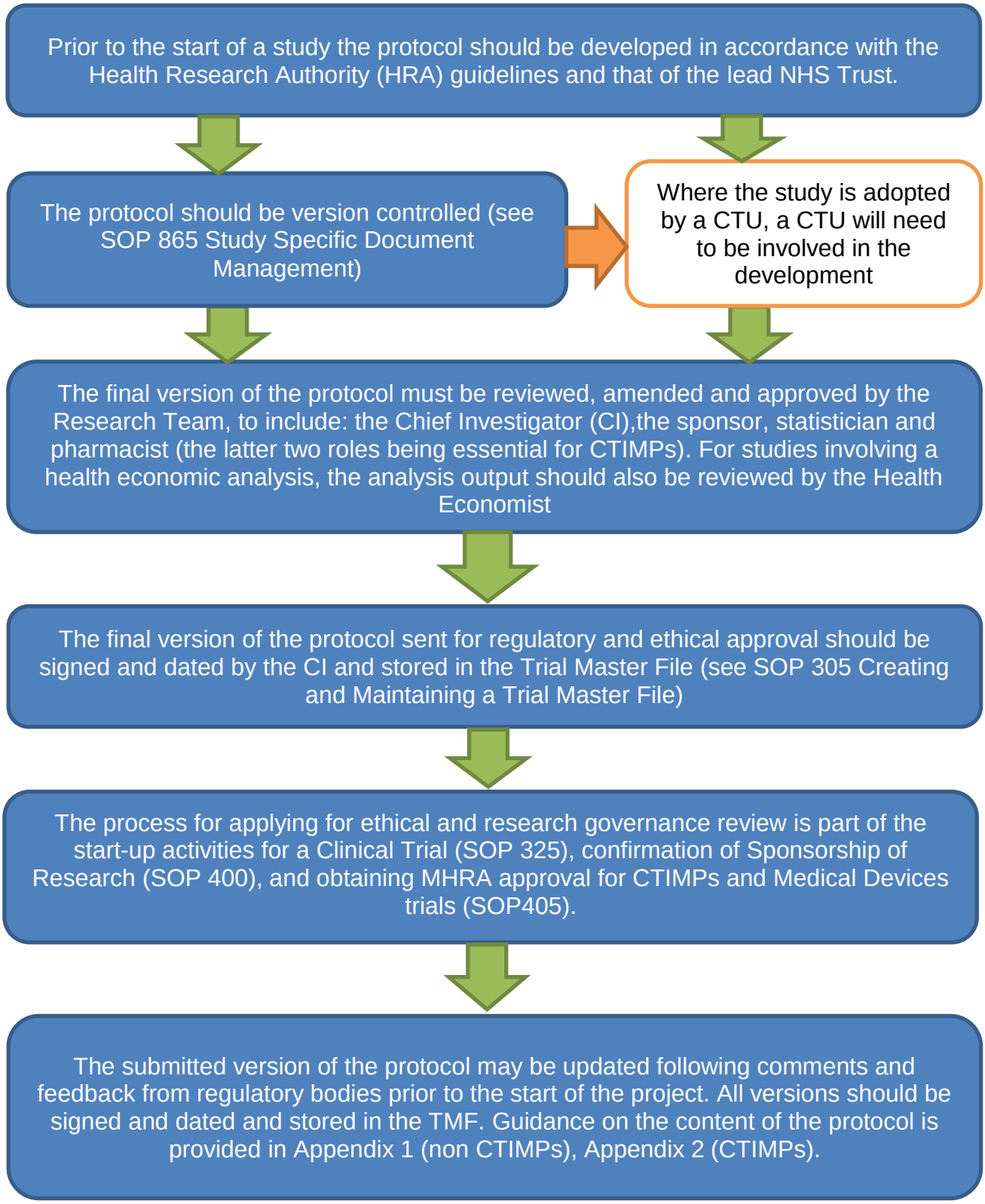
This process aims to ensure the research team has the correct guidance to enable production of protocols for research studies. Research is carefully designed to safeguard the health and safety of the participants in compliance with the conditions and principles of Good Clinical Practice (GCP) and the applicable UK guidelines and regulations.

6. Rules

A research protocol is an essential document which provides the research team with a plan for undertaking the study

- A protocol is a legal document that, once approved by regulatory and ethical bodies, all parties and organisations involved in the study agree to comply with
- Investigators should sign and date the signature page of the current protocol and organisations should refer to the protocol in their agreements about the study
- The protocol must be written by the Research Team prior to applying for any approval and prior to starting the study

7. Procedure for Research Protocol Development



Please refer to Appendix 4 for a visual guidance on milestones in study development.

The final draft protocol and other essential study documents, including the IRAS form, participant information sheet (PIS) and informed consent form (ICF) will be reviewed by the sponsor prior to submission. The Sponsor Representative will confirm review of these documents by electronically authorising the IRAS form submission.

Once regulatory approvals have been issued for a study, any changes to the protocol will need to be submitted formally for review as an amendment. The process for seeking approval for amendments to the research protocol is detailed in:

- SOP 215 (Research Study Amendments)
- SOP 405 (Obtaining and Maintaining Medicines and Healthcare Products Regulatory Approvals Agency (MHRA) Approval for a Clinical Trial).

8. UEA and NCTU Procedure

The procedure will be as defined in the local working practice documentation.

Where a CTU has been delegated responsibility for developing the research protocol, the CTU's research protocol template may be used with Sponsor approval.

9. Appendix 1 Guidance for protocol structure for non CTIMPs

Protocol Identification, reference numbers, version numbers, dates and signatures

Protocol reference numbers

- A protocol reference number is unique for each study and required on each protocol
- The Sponsor must have input into the reference number used

Protocol version number and dates

- Allocate version numbers and dates to protocols during the drafting process
- The final protocol that is submitted to the ethics committee should be numbered as version 1.0 and dated with the date of finalisation
- If protocol amendments are made, the protocol version number and date must be updated

Protocol signature

- The protocol and amendments must be reviewed and signed by the Sponsor
- Provide name and title of person(s) authorised to sign the protocol and a signature and date block

Protocol requirements:

a) Title:

The title clearly identifies the study and contains a brief description of the study design and objectives.

b) Investigators:

List everyone who has made a material contribution to the design of at least one component of the study.

Include name and contact details.

c) Abstract/Summary:

Summarise the objectives of the study.
Give a brief outline of the design and methods.

d) Introduction:

Outline the background to the research; include a critical review of the current knowledge or literature, including published and unpublished work in the area.

Gaps in the evidence should be identified; as should the potential value of furthering knowledge in this field, such as theoretical or practice-based applications of the potential research outcomes.

An explanation of the reasons for undertaking the work should be included in this section, incorporating a reflective stance whereby the researcher/s reflect upon their reasons for undertaking the research and interest in the field.

e) Objectives:

Outline broad objectives that should follow on from the identified gaps in the literature and rationale for the study.

Stated objectives should allow for unexpected emergent findings to be incorporated as part of the research findings.

f) Study Design:

Provide summary of study design which will answer the research question.

g) Location of study:

What is the location of the study and any specific tasks.

h) Participants:

Information regarding participants should be provided:

- Expected study population, including a rationale of why they are relevant to your research question(s).
- Methods by which participants will be identified and recruited and what criteria will be used for deciding whether or not individuals are eligible to participate.
- Expected sample size and justification.
- Nature of expected adverse events along with the reporting procedures that will be used.
- Assessment and follow up requirements
- End of the study schedule and requirements
- Consent process and relevant timelines
- Issues such as the potential transferability of results to alternative populations.

i) Sampling methods:

Sampling methods and justifications may be framed in terms of gaining access to particular populations, or in terms of fit with the research design.

j) Methods of data collection:

- What data will be collected
- Reason for data collection
- Method of collection
- Schedule for collection

k) Data Management & Analysis

- Method of data recording
- Collection
- Management and access
- Statistical Analysis Plan (SAP) including assumptions of analysis
- Data analysis package
- Reporting of data and statistical analysis results
- Electronic data capture, analysis and reporting

l) Study Administration & Ethical Issues

- Arrangements for the day-to-day management of the study.
- Methods by which the participants' interests will be safeguarded. For example; the process of risk limitation; how you will maintain confidentiality or anonymise participants' data and how you will deal with any apparent psychological harm
- State whether there has been user involvement in design of the study, and whether user involvement will be incorporated as an ongoing aspect of the research.
- State whether you have adhered to any set of ethical guidelines
- Any proposal should clearly state who is funding the research study and what interest they have in its outcome.
- Confirm the sponsorship arrangements for the study.

m) Resource Requirements:

- Resource implications to the host organisation
- Other departments
- Outline the timetable/schedule of the research and costs.

n) Study Plan:

A study plan or flow chart showing a brief summary of the order, site and timing of all procedures may be included.

o) Definition of End of Study

A definition of what is considered the end of study should be documented in the protocol. This will be the time point at which an end of study declaration should be submitted to the regulatory bodies (see SOP 335 Project Closure).

For most studies this will be the date of the last visit of the last participant. It may also be the completion of any follow-up monitoring and data collection, as described in the protocol.

p) Supervision for student projects:

The protocol should name any individual(s) who will supervise the research project and the intended arrangements for the supervision.

q) Dissemination & Outcome (SOP 340 Clinical Trial reporting):

Reporting of study findings:

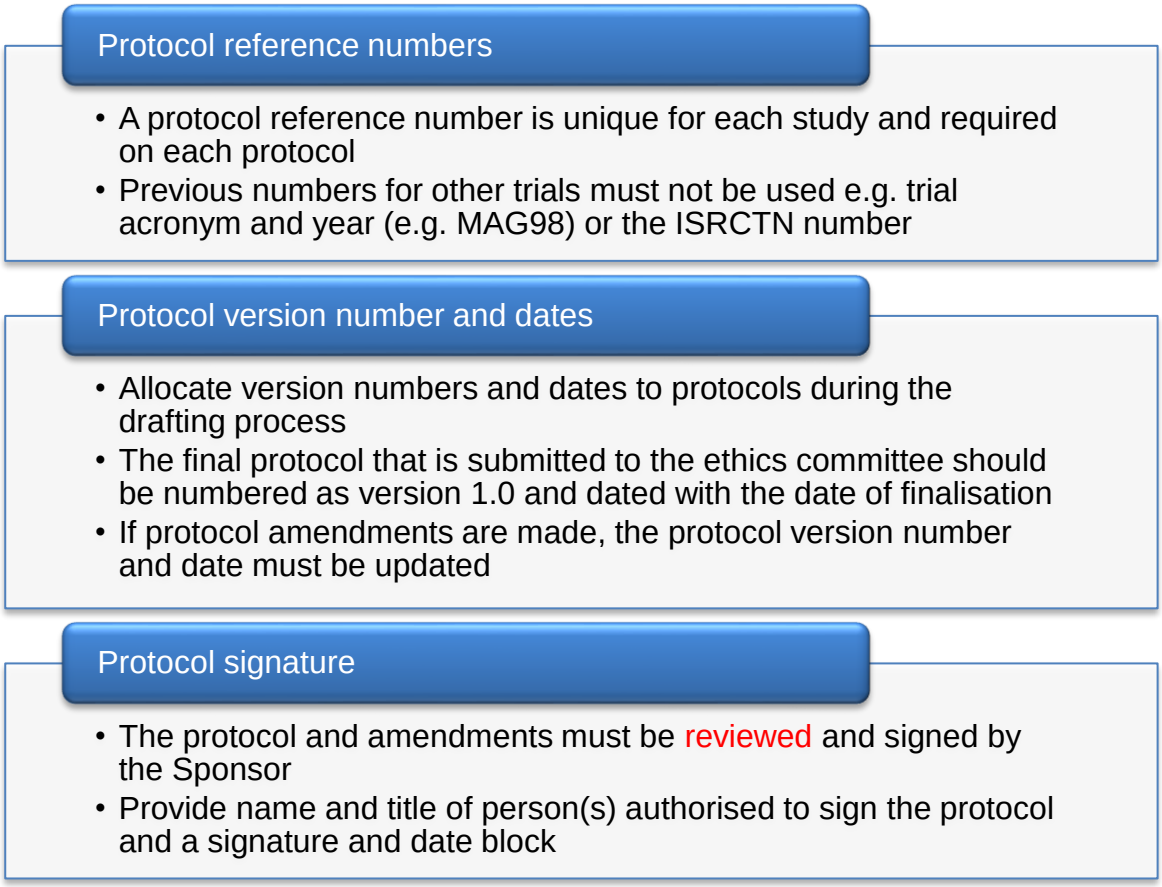
- Publish or present the findings including any report of findings to the participants.
- Any implications for future practice and theoretical knowledge advancement should also be suggested.

r) Archiving of study records and data (SOP 900 Archiving, retrieval and destruction of Research Documents):

- Location of archive for principal location, vendor and site locations
- Period of archiving

10. Appendix 2 Requirements for a protocol structure for CTIMPs and Further Guidance

Protocol Identification, reference numbers, version numbers, dates and signatures



The CTIMP Protocol Development Tool is available at
https://www.hra.nhs.uk/documents/323/ctimp-protocol-development-tool.docx

Further Guidance:

a) General Information:

- Provide names & addresses of key study personnel
- Provide names & addresses of clinical laboratories, drug supply organizations and any other institutions involved in the trial.

b) Other guidance for good protocol development:

Include the Risk Assessment for the study (SOP 700 Risk Assessment and SOP 725 Capacity, Capability and Risk Assessment).

c) Safety Reporting:

ICH GCP requires that both investigators and sponsors follow specific procedures when reporting adverse events/reactions in clinical trials involving IMPs. These procedures should be described un-ambiguously in the safety section of the protocol and may require additional documents that should be referred to in this section e.g.:

- The trial safety management plan (SmPC)
- Reference Safety Information (RSI)
- The Sponsor is responsible for providing this information for this section.

See SOP 205 Adverse Events: Identifying, Recording and Reporting for CTIMPs and Device Trials.

d) Protocol amendments:

See SOP 215 Research Study Amendments.

11. Appendix 3 Requirements for a Clinical Investigation Plan (CIP) for Medical Device Trials

From Guidance_for_mfrs_-_compiling_a_submission_to_MHRA_-_May_2021.pdf (publishing.service.gov.uk)

A copy of the clinical investigation plan must be provided, which should be in line with

ISO14155:2020.

The following information should either be included in the Clinical Investigation Plan or within other documents submitted to MHRA

Name(s), address(es) of the institution(s) in which the clinical investigation will be conducted

A signed copy of the signature page for the Clinical Investigation Plan signed by all UK investigators

Description of intended purpose and mode of action of device

Investigation parameters and design

Aims and objectives of clinical investigation (bearing in mind which essential requirements or general safety and performance requirements are being addressed by the Clinical Investigation in question).

Type of investigation. A clear description of the type of study design (e.g. single-arm or controlled, parallel group or crossover) and purpose of the study (feasibility vs confirmatory).

If applicable, details of the type of randomisation to be used (e.g. simple, block, stratified, minimisation). If stratified randomisation or minimisation is used, the stratification/minimisation variables should be listed.

If applicable, the study classification e.g. a superiority trial (to show that the test device is superior to the comparator), an equivalence trial (aiming to show that two treatment arms only differ by an amount which is clinically unimportant), or a non-inferiority trial (to demonstrate that the test device is not clinically inferior to the comparator).

If applicable, details of the approach to blinding (double-blind, single-blind or open label with justification).

Sample size (with justification) - see section 1.2 of the MHRA guidance on statistical considerations. Even in a first-in-human or pilot/feasibility study which does not propose to test a formal hypothesis it should be justified that the proposed sample size is suitable for the purpose of the study.

Number of centres participating in the study with justification.

Duration of study with start and finish dates and proposed follow-up period, (with justification).

Criteria for patient selection including: Inclusion and exclusion criteria (with justification and any age limits specified), Criteria for withdrawal.

Description of the generally recognised methods of diagnosis or treatment of the medical condition for which the investigational testing is being proposed.

Where applicable, details of any proposed post-market clinical follow-up plan and provision of long-term safety and performance data of the device under investigation

Consideration should be given to adding a section on how the study will be conducted during a global pandemic/regional epidemic or natural disaster

Data collection/analysis/statistics

Description of end points (primary and secondary) and the data recorded to achieve the end points, method of patient follow-up, assessment and monitoring during investigation.

The analysis populations to be used.

The hypotheses which are to be tested and/or the device performance characteristics which are to be estimated in order to satisfy the objectives of the clinical investigation. The statistical methods to be used to accomplish these tasks should be described for the primary (and preferably the secondary) variables.

The significance level to be used for any statistical tests, and whether this is 2-sided or 1-sided.

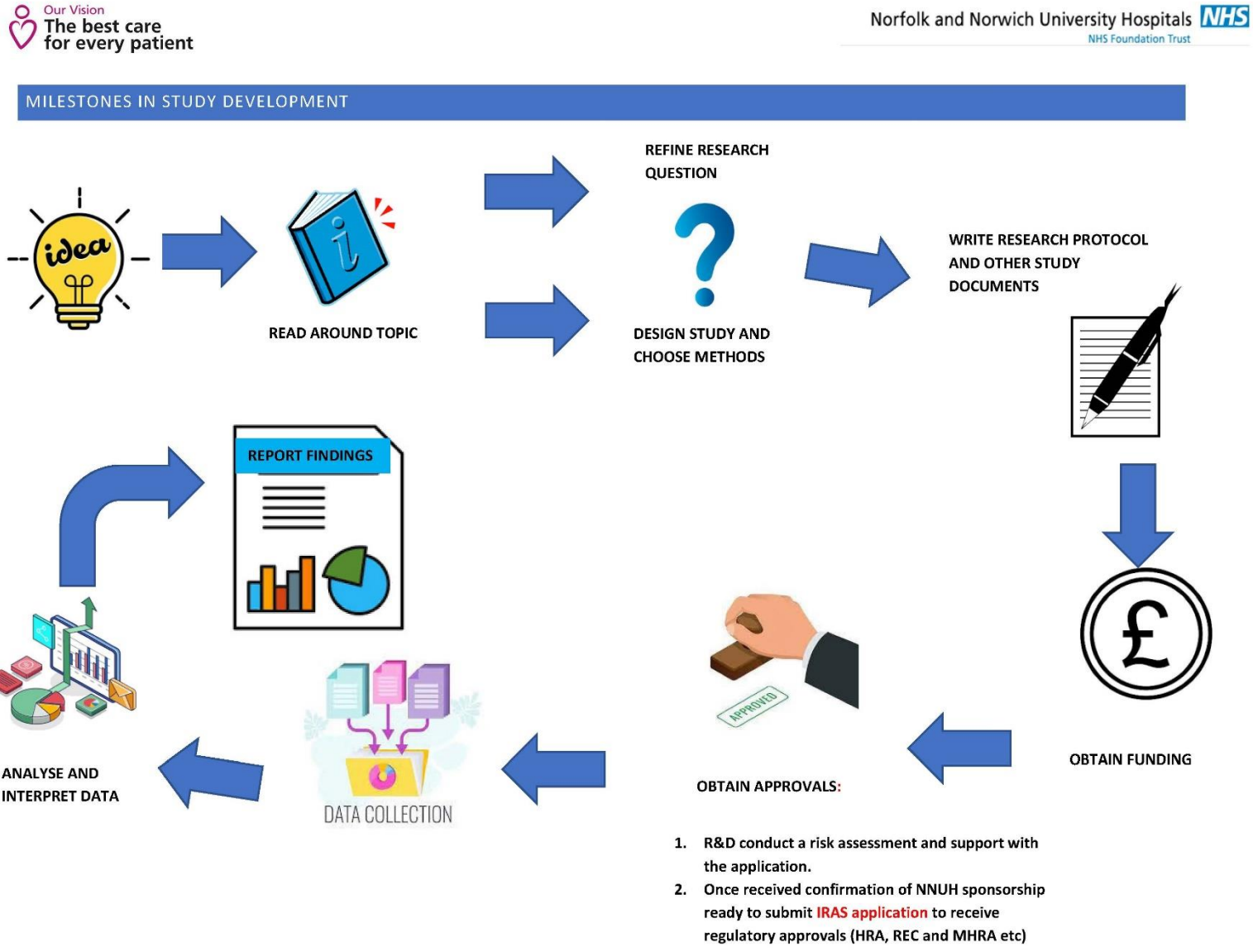
Methods for handling missing data should be stated, with sensitivity analyses to assess the impact of missing data, if appropriate.

Description of all interim analyses planned and their timing and purpose (e.g. stopping for futility or efficacy). Details of the statistical analysis of the interim data, along with precise rules for which actions will be taken and the results that would lead to those actions (e.g. the trial will be stopped for efficacy if 2-sided $p<0.001$ at the interim analysis). Details of how the type I error of the final analysis will be adjusted to account for the interim analysis. In the case of unblinded interim analyses, details of how dissemination of the results will be restricted to preserve the integrity of the trial.

Description of procedures and details of data to record and report serious adverse events and adverse device related incidents (in line with requirements in MEDDEV 2.7/3 or MDCG 2020-10/1).

lease also refer to MHRA guidance on statistical considerations for further details

12. Appendix 4 – Milestones in study development



13. References and Related Documents

References	
ICH GCP E6 / SI 2004/1041	
Guidance_for_mfrs_-_compiling_a_submission_to_MHRA_-_May_2021.pdf (publishing.service.gov.uk)	
SOP No.	**SOP Title**
SOP 001	Production, Review, Approval and Control of SOPs Related to Research Activities
SOP 215	Research Study Amendments
SOP 305	Creating and Maintaining a Trial Master File
SOP 325	Study Start Up Activities
SOP 335	Project Closure
SOP 340	Clinical Trial reporting
SOP 400	Joint Arrangements for Research Sponsorship
SOP 405	Obtaining and Maintaining Medicines and Healthcare Products Regulatory Approvals Agency (MHRA) Approval for a Clinical Trial
SOP 700	Risk Assessment and SOP 725 Capacity, Capability and Risk Assessment
SOP 865	Study Specific Document Management
SOP 900	Archiving, retrieval and destruction of Research Documents

14. Approval

Author	Basia Brown
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Approved & Authorised NNUH	Julie Dawson
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Date	18 January 2024 | 6:50 GMT
Approved & Authorised UEA	Sarah Ruthven
Role	Research Manager
Signature	DocuSigned by: Sarah Ruthven 50D5F3BEE2F04C1...
Date	18 January 2024 | 8:31 GMT

15. Training Implication

Training Implication	**Yes**
Actions required	• Additional training may be required • Matrix to be updated