Protocol Development Toolkit

Protocol development is an essential first step in turning your research question into a study. These Protocol Development Steps provide guidance on all elements of Protocol development in addition to practical advice such as how to navigate regulations and guidelines, the importance of community engagement and tips on collaborative writing.

The Global Health Network and European & Developing Countries Clinical Trials Partnership (EDCTP) Editorial Team

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Protocol development - Start

Elements

When do I need a protocol?

Right at the start of your research development. Once the initial question has been set, the process of protocol development can begin to turn the research question into a study. The purpose of the protocol is to document the study plan, ensuring that an accurate answer can be obtaining in a safe, ethical and practicable way in the chosen clinical setting [The Global Health Network Process Map - see 'Develop clinical research protocol'].

Consider what your research involves? Anything which includes a change or addition to standard clinical care practice and requires additional data collection becomes research and therefore requires the development of a protocol.

A good clinical study comes down to setting a single and clear **question**, which is your **primary objective**, and then determining what you are going to measure in order to answer that question, your **primary endpoint**. If you keep this in mind in everything you do then you will run a good study. What is my question? Is what I am doing going to answer that question – accurately?

Develop your research question

In this first step towards developing a clinical research study, you must determine the research question or hypothesis to be tested [The Global Health Network Process Map - see 'Develop research question'].

The research question forms the foundation of any study and is vital to the effectiveness and validity of the research to be carried out. This **short course** is aimed at all those carrying out clinical research and explores the main factors which affect and influence the development of a valid research question.

Researchers need to consider carefully the questions they set and their appropriateness to the local community and the public health gaps in the region. **This article** covers important considerations when formulating a research question.

The PICOT format (Population, Intervention, Comparator, Outcome, Time) is a helpful approach for formulating research questions that explore the effect of therapy. This directs researchers to consider the sample of subjects that a researcher wishes to recruit, the intervention to be provided to participants, what the chosen intervention will be compared with, what will be measured to examine the effectiveness of the intervention and the duration for data collection. [**What is your research question? An introduction to the PICOT format for clinicians**]

What input might be required?

The process of developing a protocol is should be a collaborative one. It might involved many partners for a large multi-centred study and so the number of contributors will vary with the size and complexity of the planned research. Regardless of whether it is a single centre study or an international collaboration, developing the protocol should always involve all the roles and teams who are going to be involved in implementing each step. Therefore, it is important to consider what input might be required from different team members [The Global Health Network Process Map - see 'Develop study protocol'].

It is likely you will need to include:

- The clinical team
- Statistician
- Pharmacist
- Study coordinators
- Data managers
- Laboratory staff
- Community engagement

Consider also consulting other specialists, if your study plans might require other expertise.

Protocol development - Consider

Elements

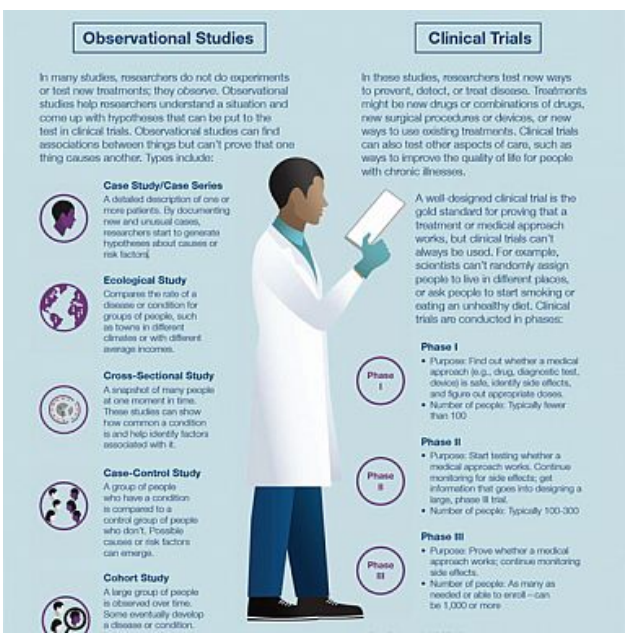
Things to consider

This section focuses on the items to consider prior to starting to develop your protocol. We assume that you already have a research question or hypothesis you plan to test.

Prior to developing your protocol you must consider which regulations and guidelines you need to follow. To ascertain this you will need to:

1. Define what type of study are you planning to conduct?
2. Assess the risk and complexity of your protocol

The same regulations may not apply to a very simple, minimal risk clinical trial or study compared to a higher risk Clinical Trial of an Investigational Medicinal Product (CTIMP).



WHO definition of a clinical trial:
'a clinical trial is any research study that prospectively assigns human participants or groups of humans to one or more health-related interventions to evaluate the effects on health outcomes.

Interventions include but are not restricted to drugs, cells and other biological products, surgical procedures, radiological procedures, devices, behavioural treatments, process-of-care changes, preventive care, etc.' [WHO]

Consider what your research involves? Anything which requires a change to standard clinical care practice and additional data collection becomes research and therefore requires the development of a protocol.

Regulation and guidelines

Clinical trial regulations can be confusing, over recent years there has been a huge increase in regulations applicable to clinical trials. The links below will assist you with identifying those which apply to your research. Also consult your (planned) funder and local research authorities for guidance.

Click here to access NIAID ClinRegs - an online database of country-specific clinical research regulatory information designed to assist in planning and implementing international clinical research.
Click here for a brief overview about clinical trial regulation with links and notes from The Global Health Network
Click here to access the International Ethical Guidelines for Biomedical Research Involving Human Subjects

SPIRIT

The SPIRIT 2013 Statement provides evidence-based recommendations for the minimum content of a clinical trial protocol.

The recommendations are outlined in a 33-item checklist and figure. Important details for each checklist item can be found in the **Explanation & Elaboration paper**.

ICH Good Clinical Practice (GCP)

If you are conducting a clinical trial then you need to follow the principles of **ICH-GCP**. The intention of ICH-GCP is that these principles are adapted to be appropriate for the risk and complexity of your trials – and so it is not necessary to apply ICH—GCP to the letter across your whole trial. The intention is you apply what is relevant and appropriate to assure the quality, safety and ethical conduct of your trials.

There is no legal requirement for other types of research to be conducted in accordance with GCP but the basic principles set out to ensure the data is valid, that the question can be answered by following a robust and appropriate protocol and that the study was conducted ethically and safely. Sound principles for all types of clinical research.

You can take an eLearning course in Good Clinical Practice, available in several languages **here**.
Access the WHO Guidelines for Good Clinical practice **here**.

A note on ICH Good Clinical Practice (GCP)
ICH-GCP draws on the basic principles of the Declaration of Helsinki which states that all research involving human subjects needs to collect reliable and accurate data and protect the rights and the safety of the participants. These principles are of course highly desirable and so surely should be applied to all health related research? However, ICH-GCP guidelines were written for drug and vaccine product development trials and therefore are very difficult to adapt to other forms of clinical trials with different interventions, and non-interventional studies; yet these studies also need to be safe, ethical and accurate. This makes a case for moving away from ICH-GCP and devising new guidelines that assure quality, safety and ethical standards for all studies and be easy to adapt and apply relative to the risk and complexity of the design and context. Appropriate new guidelines such as this would remove the need to differentiate between types of research and thereby remove the barriers to integrated research - so leading to faster and better progress. Surely it is time to do this?

Protocol development - Justify

Elements

Provide justification

The overall aim of the protocol, which is a helpful concept to check along the way, is 'is the protocol answering the question that is set'? Omitting important information on study design can hinder external review. It is important to justify how the proposed study methodology is appropriate for the question posed. Why it is the best approach?

This article is based on HRA guidance entitled '*Specific questions that need answering when considering the design of clinical trials*'. The guidance lays out questions that researchers, sponsors, peer reviewers and ethics committees should ask when planning or reviewing clinical studies.

Will the proposed design answer the research question?

'The research protocol should explain how the proposed study methodology is appropriate for the question posed, demonstrate that the design is likely to answer the research question, and why it is the best approach. The design should be underpinned by a systematic review of the existing evidence, which should be reported in the protocol [8, 9]. Absence of a systematic review raises the question: what is the design based on?

Unfortunately, our and other research has found that study protocols often lack important information on study design, which hinders external review [2, 3, 7, 12]. The HRA guidance therefore encourages researchers to explain:

- *how the proposed research method is appropriate for the question posed*
- *the reasoning behind the choice of any treatment difference sought, as well as the other parameters used in the determination of the sample size*
- *how the relevant successes and failures of previous studies have been taken into account in the design of the planned trial*
- *the reason for the choice of comparators*
- *the randomisation and blinding methods*
- *the suitability of the statistical tests*
- *how the sample to be studied is representative and thus, generalisable to the wider group of patients*

Trial design

There are many ways to design a clinical trial and using the most efficient and appropriate design approach is important. Applying the right design will give you the best chance of answering the question that you set. The most appropriate design will allow you to use the minimum number of subject to answer the question.

Consider an adaptive trial design. Flexible, agile trial designs are more efficient and allow for various options to be built in to the design of the trial. Adaptive design is particularly useful when there is minimal information available on which to base the sample size calculation. Therefore, having an adaptive design allows the protocol to be adjusted within the same study as more data is gained. This is ethical and efficient and allows for growing evidence to guide the study.
Click here for a paper on adaptive trial design.

Systematic review

Item number 6a in the SPIRIT Statement Checklist requires: '*Description of research question and justification for undertaking the trial, including summary of relevant studies (published and unpublished) examining benefits and harms for each intervention.*' To place the trial in the context of available evidence, the explanation and elaboration document strongly recommends an up-to-date systematic review of relevant studies be summarised and cited in the protocol.

Click here to access the Cochrane group interactive learning modules on conducting systematic reviews.

Statisticians should be involved, if possible and if you need them, at an early stage of development. They provide input on the study design, outcomes measures, sample size, randomisation and analysis and these factors will influence all your subsequent steps.

Sample size calculation

It is an important to get sample size calculation right, if the sample size is too small it will not be able to answer the question posed, and would be a waste of time and money (and unethical). All study protocols should provide information on sample size with solid reasoning behind the calculations and how they have been determined. The justification should be a concise summary of how the assumptions used in the calculation were chosen and why they are considered plausible for the planned study. Assumptions should take account data from previous studies and any systematic review of existing relevant evidence [**Noclor Research Support Statistical Considerations**].

Click here for the ICH Topic E 9 Statistical Principles for Clinical Trials
Click here for the CREDO statistics training module which provides a background of statistical principles relevant to clinical research and trial design

Protocol development - Plan

Elements

Planning

Before putting pen to paper it is important to research and plan properly. Successful trials often share similar characteristics. They are:

- Conceptually simple and tailored to the patient group and the reality of the context in which they are treated (high dependency ward or a community health centre?)
- Address questions of clinical relevance where genuine uncertainties exist
- Avoid unnecessarily complex/restrictive entry criteria to ensure generalisability, where appropriate
- Avoid unnecessarily complex data requirements (resulting from a careful justification of each data point to be collected)
- Ensure the most appropriate choice of control arm (where appropriate)
- Ensure robust allocation concealment (where possible)
- Ensure robust blinding of intervention or appropriately blinded outcome assessments (where appropriate). [**Clinical Trials Toolkit Trial Planning and Design**]

Therefore, time invested in generating a robust, feasible protocol at the development stage can influence the success of your trial.

SEPTRE (SPIRIT Electronic Protocol Tool and Resource) is an innovative, web-based software solution that makes it easier to create, manage, and register high-quality protocols for clinical trials.

The Global Health Network **Resources Gateway** links to a wealth of useful resources which will assist you with considering data management, safety reporting, ethics and community engagement.

The **Practihc Trial Protocol Tool** provides templates and detailed information on what should be included in each section of the Protocol under the 'What should be in a good protocol' option.

CONSISE has developed standardised research protocols for Influenza, MERS-CoV and Zika Virus (ZIKV) which have all been developed with large numbers of technical experts, including WHO and incorporate knowledge and experience learned from conducting epidemiologic studies all over the world.

ISARIC is a community of research networks and individuals collaborating to provide a platform through which global, patient-oriented clinical studies can be developed, executed and shared. Protocols, Informed Consent Forms, Case Report Forms, Standard Operating Procedures, training materials and other research tools are available to support implementation of the research.

The **SPIRIT 2013 Statement** provides evidence-based recommendations for the minimum content of a clinical trial protocol. The recommendations are outlined in a 33-item checklist; the minimum list of items is by no means exhaustive*:

ADMINISTRATIVE INFORMATION
1. Title
2. Trial registration
3. Protocol version
4. Funding
5. Roles and responsibilities

INTRODUCTION
6. Background and rationale
7. Objectives
8. Trial design

METHODS
9. Study setting
10. Eligibility criteria
11. Interventions
12. Outcomes
13. Participant timeline
14. Sample size
15. Recruitment
16. Allocation
17. Blinding (masking)
18. Data collection
19. Data management
20. Statistical methods
21. Data monitoring
22. Safety/harms
23. Auditing

ETHICS AND DISSEMINATION
24. Research ethics approval
25. Protocol amendments
26. Informed consent process
27. Confidentiality
28. Declaration of interests
29. Access to data
30. Ancillary and post-trial care
31. Dissemination policy

APPENDICES
32. Informed consent materials
33. Biological specimens

*Community engagement

Community engagement is not specified in this list but is a very important and often overlooked step.

Early engagement with the community will help identify relevant local partners and inform decisions about ethical trial design in a LMIC setting.

This engagement can help inform:

- protocol development
- approaches to seeking and documenting consent
- conducting the research, e.g. employing or training community members
- reimbursing the community for additional costs or use of resources, e.g. researcher accommodation, water, power, etc. (where appropriate)
- access to data and samples resulting from the trial
- understanding how best to disseminate research findings to maximise the benefit to the community [**MRC GUIDELINES FOR MANAGEMENT OF GLOBAL HEALTH TRIALS**]

For further information on community engagement consult **MESH**: This member site is a collaborative open-access web space for people involved in community engagement with health research in LMICs. It provides an online meeting place where community engagement practitioners, researchers, health workers and others can network, share resources and discuss good practice.

Click here for a paper called '**Moving targets: The challenges of studying infectious diseases among pregnant women in resource limited settings**' which highlights the importance of community engagement and **here** for a webinar on community engagement in clinical research.

Lessons learned

Looking at published protocols, reading articles about trial success factors and lessons learned pieces can help you with developing your protocol. Some examples are below and others can be found on the External Resources tab.

Factors associated with trial success
Increasing protocol suitability for clinical trials in sub-Saharan Africa: a mixed methods study

Example protocols:
This toolkit from the **Children's Hospital of Philadelphia Research Institute** has example protocols for both descriptive and observational trials.
The **Practihc Trial Protocol Tool** has examples of protocols under the 'Protocol Library' section.

Protocol development - Write

Elements

Where to start

The SPIRIT 2013 Statement provides evidence-based recommendations for the minimum content of a clinical trial protocol. The recommendations are outlined in a 33-item checklist and figure and important details for each checklist item can be found in the **Explanation & Elaboration paper**.

The SPIRIT 2013 Explanation and Elaboration paper provides a description and examples of what should be included for each SPIRIT checklist item.

'This SPIRIT 2013 Explanation and Elaboration paper provides important information to promote full understanding of the [SPIRIT] checklist recommendations. For each checklist item, we provide a rationale and detailed description; a model example from an actual protocol; and relevant references supporting its importance. We strongly recommend that this explanatory paper be used in conjunction with the SPIRIT Statement. A website of resources is also available (www.spirit-statement.org). The SPIRIT 2013 Explanation and Elaboration paper, together with the Statement, should help with the drafting of trial protocols. Complete documentation of key trial elements can facilitate transparency and protocol review for the benefit of all stakeholders.'

Toolkits and Guidance

There are several websites available where you can explore information and templates to get a fuller picture of what you might need to include in your protocol. See our **External Resources** page for a searchable list or try the links below.

- The Global Health Network Process Map
- CHOP Research Institute Writing a Protocol Guidelines
- Increasing Protocol Suitability for Clinical Trials in Sub-Saharan Africa
- Five questions that need answering when considering the design of clinical trials
- Field Trials of Health Interventions: A Toolbox P. G. Smith et. al.
- Practihc Trial Protocol Tool
- WHO recommended format for a clinical trial Protocol

Writing skills

Even with the assistance of a great template writing a research protocol can be a challenging and difficult task. The links below offer guidance and support on writing and publication skills to assist you.

AuthorAID is a free pioneering global network that provides support for researchers in low and middle income countries.

The development process is a cycle of review and modification by contributors and reviewers so input may be required several times before the protocol is finalised.

Collaborative writing and version control

If you have multiple contributors working on your protocol it may be useful to learn more about collaborative writing. Collaborative writing has many benefits, but it requires coordination planning and communication to be successful. Consult the resources below for further guidance on writing collaboratively and version control.

Click here for an example guideline on document version control from the Spirit Statement.
Click here for an overview of a collaborative writing process.

Protocol development - Tools

About

CONCEPT PROTOCOL

Once a research question has been set the next step is to consider the methods to answer it. At this stage, it is useful to write **a brief concept protocol**. This document can be helpful in introducing the idea to all the groups that are likely to be approached for approvals.
A short one or two page concept proposal can be discussed with all potentially interested parties at an early stage. When working with external sponsors or developing multi-centre studies it is common practice to hold protocol development meetings to encourage contribution to setting the question and designing the protocol.

The **Concept Protocol Crowd Review tool** available here on the EDCTP Knowledge Hub embraces the crowdsourcing model. If you are embarking on a health research study and would like feedback on your concept protocol from the EDCTP Knowledge Hub and The Global Health Network community, please do submit it online **here**.

SEPTRE

SEPTRE (SPIRIT Electronic Protocol Tool and Resource) is an innovative, web-based software solution that makes it easier to create, manage, and register high-quality protocols for clinical trials. The Global Health Network is partnering with the team who developed the tool at the Women's College Hospital, University of Toronto to promote this tool to those researchers who might otherwise be unable to.

Click here for more information about the SEPTRE Tool.

SEPTRE
SPIRIT Electronic Protocol Tool & Resource

Access

For our registered users we will be offering an opportunity to have free access to this tool to users in low resource settings. The SEPTRE group will make a needs assessment of the request and if granted users will be able to utilise the system without cost. For organisations or individuals based in higher income countries or institutions we request you apply via the main **SEPTRE request form** via the SEPTRE website.

Registered users please go to **SEPTRE Electronic Protocol Tool** to apply for access.

Organisations or individuals based in higher income countries or institutions please apply via the main **SEPTRE request form** via the SEPTRE website

Protocol development - Review

Elements

Review process

Your protocol will be reviewed several times during development, both as part of the collaborative writing process and when seeking funding/regulatory approval.

Any research into human subjects needs to be approved by whatever committees are required by:

1. Your country's legal requirements
2. Your institutional requirements
3. Your funder's requirements
4. Your collaborator requirements

[**The Global Health Network Process Map** - see **'Submit to Institutional Review Board(s)'**]

Peer review

A peer review may be performed as a necessary part of a funding proposal; however, even if it isn't specified as a necessity by the funder, peer review can be sought for further guidance and as additional good practice step [**The Global Health Network Process Map** - see 'Peer review'].

Peer-review and publication of research protocols offer several advantages to all parties involved. Among these are the following opportunities for authors:

- external expert opinion on the methods
- demonstration to funding agencies of prior expert review of the protocol
- proof of priority of ideas and methods
- solicitation of potential collaborators [**G. Eysenbach**]

For an example checklist of the items which might be reviewed during a peer review **click here**

'Research ethics committees review proposed studies with human participants to ensure that they conform to internationally and locally accepted ethical guidelines, monitor studies once they have begun and, where relevant, take part in follow-up action and surveillance after the end of the research. Committees have the authority to approve, reject or stop studies or require modifications to research protocols.' **World Health Organisation: Research ethics committees Basic concepts for capacity-building**

Ethics review

To adhere to international guidelines and legal requirements research involving human subjects requires independent ethics committee review. These committees are known as Institutional Review Boards (IRBs) or Research Ethics Committees (RECs). Your protocol is one of several documents which must be submitted for review.

- For an example of the ethics review process at the WHO please **click here**.
- Access the Global Health Network Global Health **Bioethics, Research Ethics and Review** an online community for all those interested in global health bioethics and research ethics and **TREAD** the Research Ethics Application Database.

Protocol development - Implement

Elements

Trial registration

All research should be registered in a publicly accessible database and many funders expect all researchers, research sponsors and others to meet this fundamental best practice standard. For clinical trials, it is a condition of a favourable ethical opinion to do so. For all other studies, it is a good practice expectation. [**HRA Research registration and research project identifiers**].

Your protocol will form the basis of the information you are required to enter to register your trial.

ClinicalTrials.gov run by the United States National Library of Medicine (NLM) was the first online registry for clinical trials and is the largest and most widely used today.

Similar clinical trial databases now exist all over the world: The **WHO's trial registry** is globally applicable. African trials can be registered in the **Pan African Clinical Trial Registry (PACTR)**, Australia and New Zealand share the same clinical trial registry, known as the **Australia and New Zealand Clinical Trial Registry** (ANZCTR). Clinical Trial registry exists in other countries such as India, China, Brazil, Sri Lanka, Japan etc.

An introduction to the 'study walk-through' method:
The study walk-through is a method to ensure that every step in a study protocol is carefully considered in its operational context, and that those responsible for undertaking the step are tasked with overseeing it appropriately.

The entire study team is gathered as early as possible in the planning of the study
An overview of the study protocol is presented, focusing on the primary endpoints and how these will be measured.
One team member then leads the process of describing the study step-by-step, as it would be operated at the study centres.
Each team member is encouraged to imagine each step from the participant's perspective.
The process covers steps from community engagement and recruitment, through each visit, until the end of the study.
The processes and data collected are discussed in the context of actions that relate specifically to the patients, e.g. clinical assessments.
The coordinator leads the discussion of each study step, which is recorded as the discussion flows.

Standard Operating Procedures (SOPs)

SOPs translate the protocol into the real steps and activities needed to run the study in the specific setting where it is to be undertaken. Therefore, SOPs need to be developed by all those in the study team who will be tasked with delivering each of these steps. SOPs should never be written remotely by a distant sponsor or other stakeholder, such as a CRO and simply given to a research site to implement. The whole point is to reflect who, why and how each step will be implemented (see the 'study walk-though method' above for ideas on how to liaise with the entire study team to generate SOPs).

There are many examples of SOPs available online - some examples are below and others can be located in 'External resources':

For downloadable templates and tools for clinical research, including SOPs, consult the Global Health Trials' **Tools and Templates Library**

The **CHAIN Network, Study Resources** section has example SOPs and other useful tools and template.

Click here for example Standard Operating Procedures (SOPs) for clinical trials that meet NIH requirements. DGHI is pleased to share these documents with others who are working in resource-limited locations. Although most of these SOPs were developed for AIDS clinical trials, many of these documents can be modified and extrapolated to meet your specific project needs.

Click here for resources guidelines and templates for writing clinical research SOPs.

Assemble essential documents in Trial Master File (TMF)

The TMF is a file which contains all the documents for a study, it may be held in different formats e.g. paper and/or electronic and can be inspected by auditors and regulatory bodies. It is set up at the start of a study, with documentation added throughout the trial and is then archived at the end of the study. The TMF contains the trial's essential documents and should include your protocol and any amendments.

A commonly used framework for essential documents is described in **ICH GCP E6 Section 8** and guidance on the TMF and Archiving is provided in **Eudralex Volume 10** (EU Clinical Trial Guidelines).

ICH GCP definition of Essential Documents:
Essential Documents are those documents which individually and collectively permit evaluation of the conduct of a trial and the quality of the data produced. These documents serve to demonstrate the compliance of the investigator, sponsor and monitor with the standards of Good Clinical Practice and with all applicable regulatory requirements. [**ICH GCP**]