**Form FHS015hlp: Preparing the Research Protocol Section C - Pointers for Researchers**

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| Instructions |
| * Forms to be downloaded from the Administrative Forms web page at

<http://www.health.uct.ac.za/fhs/research/humanethics/forms> * All researchers must complete Section C.
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Introduction

A protocol is the formal design or detailed plan of a study. It explains what will be done, when, where, how, and why. A departmental research committee or equivalent body with relevant methodological expertise must review the scientific merit of the protocol before submission to the Human Research Ethics Committee (HREC).

Although most protocols include a dedicated ‘ethics’ section, for each section researchers should determine if there are specific ethical issues and indicate how they will be justified and managed. Making ethical issues more explicit and transparent in the protocol will assist and focus the HREC review process. The research must comply with the Helsinki Declaration of 2013 which addresses important ethical issues in research: <http://www.health.uct.ac.za/sites/default/files/image_tool/images/116/Helsinki%202013.pdf>

Researchers should consider, where appropriate, the following criteria when preparing a research proposal for submission to the HREC:

Aims, Background and Significance

* Are the study aims and objectives clearly specified?
* Are there adequate preliminary data to justify the research?
* What are the gaps and uncertainties in the field?
* Is the literature review adequate, current and relevant (wherever possible, the literature review must include pertinent references to **local research** in the proposed field of study)?
* Does the current state of the science warrant including human participants?
* Are further bench, animal or modelling studies needed?
* In the context of previous studies, what is the contribution of the present research?
* Is the question worth asking? Is the hypothesis worth testing?
* Why is it worth doing in this particular setting?

Scientific Design

* What is the role of the principal investigator in designing the study?
* Is the scientific design adequate to answer the study’s questions?
* Is the scientific design adequately described and justified?
* Does the study involve a placebo?
* If so, why is a placebo needed?
* Could the study be done without a placebo?
* Does the study include a drug wash-out phase?
* If so, why is it necessary and where will it take place?
* Does the study require blinding? If so:
* How exactly will one arm’s intervention be made to look like the other arm’s intervention?
* Who will prepare the blinded agents?
* What are the procedures for breaking the blind, e.g. for medically indicated reasons?
* When will the blind be broken for data analysis?
* What plans are in place to reduce the risk of blinds being broken by participants communicating with each other?
* Are study aims and objectives achievable in the given time frame?
* Are the proposed tests or measurements appropriate, valid and reliable to answer the scientific question in the local context?
* Does the protocol have scientific merit?
* Do the principal and co-investigators have adequate experience to conduct the study?

Study Population

* How many participants will be included at the study site?
* If a multicentre study, how many participants will be included in the entire project?
* What are the medical, demographic and psychosocial characteristics of the local study population?
* In the case of special populations such as children, persons highly dependent on medical care, or psychiatric patients, is it essential to include them in the research? Is the research important to their health and wellbeing?

Inclusion and Exclusion Criteria

* Are inclusion and exclusion criteria clearly stated and reasonable?
* Are any individuals inappropriately included as participants?
* Are any individuals inappropriately excluded as participants?
* Does the study include vulnerable groups such as children, prisoners, psychiatric patients, individuals with impaired decision-making capacity? If yes, are adequate safeguards included to protect their rights and welfare?
* Is the inclusion of vulnerable populations justified?
* Can the study be done without involving vulnerable populations?
* Will the study target or exclude a particular ethnic or language group?
* Who, in the research team, will decide if an individual participant is eligible?
* Is the selection of participants appropriate for the question being asked?
* Are laboratory parameters appropriate?

Recruitment and Enrolment

* Are recruitment methods well-defined?
* How will individuals be identified for recruitment into the study?
* Who will be responsible for recruitment and what are their qualifications?
* Is the individual responsible for recruitment suitable for the task?
* Is the location, setting, and timing of recruitment acceptable?
* Are all recruitment materials submitted and acceptable, e.g. flyers, posters, advertisements, radio announcements?
* Are procedures for screening participants prior to recruitment acceptable?
* If recruitment will occur during a critical or stressful period, what precautions are in place to assist voluntary decision-making?

Research Procedures

* Are the rationale and details of research procedures adequately described and acceptable?
* Is there a clear differentiation between research procedures and standard of care?
* Does the protocol (and consent form) spell out how frequently participants will visit the study site, how long each visit will last and what will happen at each visit? This is particularly important when already over-burdened health care workers are part of the study sample.
* Are there adequate plans to inform participants about specific research results, e.g. incidental findings, clinically relevant findings?
* Are there adequate plans to inform participants about specific research results that might affect their decision to continue participation?
* Are individuals who are performing procedures adequately trained?
* Could the same results be achieved with less risky interventions? What are the trade-offs?
* Is the location of the study adequate to assure participants’ safety and comfort (e.g. appropriate equipment for monitoring and emergencies, a child-friendly setting for paediatric research)?
* Is the location of the study adequate to assure researchers’ safety?

Drug, Device and Biologics Considerations

* Is the status of the drug or device adequately described?
* If necessary, is the supporting documentation from the sponsor included with the submission; for example, investigator’s brochure, package inserts/ labelling, SAHPRA approval?
* Do preclinical or initial clinical data indicate that the risks associated with the proposed use of the drug or device are acceptable?
* Are the drug dose and route of administration appropriate?
* If more than one drug is used, have the drugs been used in combination before? Is there a possibility of adverse drug interactions? If so, does the protocol include relevant warnings or exclusions?
* Is the investigational product thought to be immunogenic?
* Is there evidence to suggest toxicities may be clinically significant including carcinogenesis and teratogenesis?
* Are contraceptive or barrier precautions necessary?
* Will participants be allowed to take therapy for treatment of other conditions during the study? If not, why not?
* How will compliance with treatment be determined? What happens if a participant does not comply?
* Does the control treatment arm accord with current standards of patient care?
* Where relevant, is there adequate justification for hybrid study designs such as Phase 1/2 or Phase 3/4 studies?
* What is required of a participant to have a device inserted, e.g. anaesthesia?
* Will a device need to be serviced or replaced? If so, who is responsible, where will this happen? Who will cover the costs?
* What is expected of the participant who suspects a device is unsatisfactory?
* Are the drug or device safety data sufficient to warrant the proposed phase of testing?
* If the study involves a marketed drug or device for an unapproved or off-label indication is SAHPRA approval necessary?
* Does the protocol describe acceptable measures for storage, access and control of the drugs, devices or biologics?
* Does the protocol clearly and consistently identify if the drug is SAHPRA approved, a new use for an approved drug or investigational?

Risks and Benefits

* Are risks and benefits adequately identified, evaluated and described, including physical, psychological, social, and economic?
* Are there risks to the community or a particular group of individuals, e.g. stigmatisation?
* Do risks stated in the protocol match the risks described in the informed consent form?
* Are risks reasonable in relation to anticipated benefits?
* Are risks reasonable in relation importance of knowledge to be gained?
* Are risks minimised to extent possible? For example, where possible, study procedures are already being performed on participants for diagnostic or treatment purposes.

Process of Obtaining Informed Consent and Assent

* Is the process well-defined?
* Does the process minimise the possibility of undue influence?
* Does the process provide sufficient time, privacy and an adequate setting for participants to decide?
* Who will obtain consent or assent? Is the individual obtaining consent or assent adequately trained?
* What is the relationship between the investigator and the participant? If the investigator is also the participant’s treating physician, could this pressurise participants to enrol?
* Is the setting where individuals are being recruited or would report for research-related activities the same as where they are seen for clinical care? If so, this may cause confusion about what is research activity and what is standard care.
* Are issues relating to participants’ comprehension considered?
* How will a researcher decide if a participant has decision-making capacity to choose to enrol in a study?
* Is the language used in the consent form appropriate for participants’ level of understanding?
* Are terms such as ‘randomisation’ clearly defined and illustrated (e.g. like flipping a coin)?
* Will an interpreter be necessary to obtain consent?
* Will consent forms need translation? Participants are entitled to information in the language of their choice.
* Will informed consent be ongoing through-out the study?
* What procedures will be followed for participants who want to withdraw during the study?
* Do consent forms include all the elements needed to comply with regulatory and ethical standards? See Standard Operating Procedure on Informed Consent.
* What is the study about? What will happen to me in the study?
* Why is the study being done?
* Where will the study take place? Why have I been selected?
* When will the study begin and possibly finish?
* Who will lead the study?
* Does the information in the consent/ assent forms coincide with information in the scientific protocol?
* In the case of clinical trials, does the information sheet or consent document contain appropriate information about possible side effects, possible drug interactions, administration, dosage and timing, whether the medication may cause drowsiness, what to do if a dose is missed and important toxicological findings?
* Does the consent form state that participants can contact the HREC if they have a complaint or questions about their rights and welfare as research subjects?

Privacy and Confidentiality

Privacy refers to persons and to their interest in controlling access of others to themselves. Confidentiality refers to data.

* Are provisions to protect participants’ privacy adequate? If participants will be contacted in person, it should be by someone who has reason to know their confidential information.
* Is the phone number that potential participants call in response to an advertisement only used by the research team?
* If a member of the research team does not cover this phone line on a 24-hour basis, are potential participants directed to leave their name and contact details?
* If personal information is left on a message machine, how is it protected and who collects it?
* How are prospective participants contacted if they leave a call back message?
* Are provisions to protect confidentiality of data during and after research adequate, in particular where data or specimens are identifiable or coded (e.g. locked filing cabinet, password-protected computer files)?
* Are provisions for storage, coding and use of identifiers adequate?
* Is it clear how data will be collected and stored?
* Will data be anonymous, i.e. the identity of the individual cannot be determined, no links exist between the data and the individual about whom the data are collected?
* Will data be de-identified, i.e. identifiers have been removed, links exist between the data and the individual about whom the data are recorded but are not readily accessible to the researcher?
* Will data be coded, i.e. identifiers have been removed but can readily be replaced through the use of a master list which is accessible to the researcher?
* Are data identifiable, i.e. the identity of the individual is recorded, linked or associated with the data?
* If the data are not going to be destroyed, who will be responsible for maintaining confidentiality and security over time?
* What will happen to data if a PI/researcher for any reason leaves the study?
* Is there a plan for handling unexpected or incidental findings?
* Will the information be given only to the participant?
* If the participant is minor, will information be provided to both or only to the parent?
* Who will convey the information and in what form (oral or written)?
* Does the participant want to be contacted about clinically relevant findings after a study has ended? Would this be feasible? How will a participant’s privacy be protected?
* Is there a plan regarding what information will be given to participants?
* In the case of focus groups, are participants told that confidentiality cannot be guaranteed as group members may disclose what was discussed when they leave the research setting?
* If audio or videotaping is used, how will tapes be stored and for how long?
* All transcripts should identify interviewees by a code rather than a name.
* Do participants know who will carry out the transcription?
* Ask interviewees not to name third parties on audio-recordings (without their consent), especially if comments are offensive or insulting.
* If recordings will be archived, specific consent is required.
* In research using small numbers of participants, will their responses be identifiable?
* Are participants told to whom and under what circumstances information will be conveyed to third parties? Participants need to know that no guarantee of absolute confidentiality is possible as there will always be a theoretical possibility of an accidental breach.
* Where researchers have to disclose legally-mandated information gathered during research, is this made clear in the consent or assent forms? If observed or disclosed during a research study, researchers have a legal obligation to report child physical or sexual abuse or deliberate neglect, family violence, notifiable diseases such as tuberculosis, information sought under a warrant or subpoena or in FDA-related research, incidents involving medical devices [21 CFR 803].

Storage of Biological Specimens

* Will biological specimens be stored for future use?
* Do the protocol and the consent form address possible future use of specimens?
* In the case of uniquely identified specimens, especially those containing genetic material, do the participant and family understand where and how their genetic material will be stored and protected and who will have access to it and why?
* How will this understanding be verified, and what will be done if a participant withholds or withdraws consent for such a donation?

Data Analysis and Monitoring

* Does the study include a named monitor or contract research organisation (CRO)?
* Does the protocol include a well-formulated plan for interpretation of data and statistical analysis?
* Is the rationale for the proposed number of participants reasonable?
* Are the plans for data and statistical analysis defined and justified, e.g. stopping rules, end points?
* Are there adequate plans for monitoring data?
* Is a data safety monitoring board part of the study? If so, where is the board located, who are its members, and how will the principal investigator communicate with the board? Is the DSMB independent?
* In the case of non-interventional or qualitative research is there a mechanism, such as a reference or event monitoring group, to provide ongoing oversight and impartial analysis of unanticipated incidents?
* Who will be responsible for follow-up of participants suffering a serious adverse event during and after a study has ended?
* Are there any safety concerns to suggest special monitoring?

Resources

* Are the resources to conduct the study appropriate and sufficient (equipment, staff, space, funding)?
* Will counselling or support services be available for participants, if required?
* Will debriefing be available for researchers, if required?
* Will these support strategies (counselling and debriefing) be available at the point of disengagement and termination of the research, if required?

Reimbursement

* Is the compensation to participants reasonable?
* Are there adequate plans to avoid out-of-pocket expenses and costs incurred by participants (e.g. travel expenses, parking costs, refreshments, childminding and lost wages)?
* If the participant does not complete the study, will compensation be pro-rated?
* Is reimbursement in the form of cash, vouchers or gifts? Is this stated in the consent/ assent form?
* If children or adolescents are involved, who receives the compensation?
* Does compensation cover extra costs when parents or caretakers are expected to accompany participants on research visits?

Insurance

* Is there provision for insurance for research-related injuries, if applicable?
* In the case of commercially-sponsored research, does it comply with ABPI Guidelines? Note: all language in consent forms suggesting that participants’ medical aid or medical insurance will incur research-related costs must be removed.
* In the case of investigator-initiated research, is there cover in terms of UCT’s no-fault insurance policy?

What Happens at the End of the Study?

* In the case of Phase III safety and efficacy trials, will the investigational drug, if proven safe and efficacious, be offered to participants at the end of the study and under what conditions; for example, until the drug is licensed in South Africa or for a specified period? If a sponsor does not intend to provide post-trial access, the informed consent document must spell out **in bold lettering:**
* That even if a participant’s condition improves on the study drug it will no longer be provided by the sponsor at the end of the study.
* How participants/patients will be managed at the end of a clinical trial, for example will they resume their previous treatment regimen?
* Will the study offer long-term benefits to the community in the form of capacity building and/or medical or research infrastructure?
* If proven safe and efficacious, is it likely that the investigational drug will be available in an open-label extension study?
* How will participants be informed of important findings?
* How will findings be disseminated to the wider population and research community?
* In the case qualitative research, will participants have any influence about the dissemination of results?

Stakeholder Participation

* Who are the major stakeholders in the research? Describe how those affected by the study can express their views, clarify their needs and contribute to the research.

Conflicts of Interest

* Will any research staff receive incentives for recruiting participants or for any other purpose directly related to the study?
* Do any personnel involved in the design, conduct or analysis of the research have any proprietary interests (e.g. board membership, royalties, patents, trademarks, copyrights or licensing agreements) involving any agent, device or software being evaluated in the study?

Authorship

* Is there a plan to determine authorship?

Ethical and Regulatory Compliance

* Does the protocol state that it complies with:
* The latest version of the Declaration of Helsinki (2013)?
* The Department of Health: Ethics in Health Research: Principles Structures and Processes, 2004?
* Guidelines for Good Clinical Practice in the Conduct of Clinical Trials in Human Participants in South Africa. Second Edition, 2006 (where appropriate)?
* Does the study require approval by the Medicines Control Council?
* Does the study require approval or clearance from hospital or health facility management, school principals or governing bodies, or the Research Committee of the Provincial Government of the Western Cape?

General Presentation

* Is there a table of contents for long protocols so that submissions are easier to read and review?
* Are pages numbered consecutively?
* Has someone proofread the proposal and performed a spell-check?
* Are acronyms and abbreviations explained and defined in the protocol?