CTC Expectations.....2016

Lesley Burgess
On behalf of the Clinical Trial Committee
What are the CTC expectations to be awarded a category 1b/2a ....and what annoys the CTC reviewers.....
# CTC CATEGORIES

<table>
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<td>1A</td>
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<tr>
<td>1B</td>
<td>Approved. Ethics pending</td>
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<td>Not approved. For approval by in house evaluators</td>
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<tr>
<td>2B</td>
<td>Not approved. For approval by the original evaluator and in-house if a need arise</td>
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<tr>
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<td>Not approved. Response to be discussed by the full CTC</td>
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<tr>
<td>4</td>
<td>Not approved – Referral for specialist opinion outside CTC</td>
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<tr>
<td>5</td>
<td>Not approved on scientific grounds</td>
</tr>
<tr>
<td>6</td>
<td>Rejected. Administrative and technical items outstanding</td>
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Meeting CTC Expectations

How to get a positive response from the

Presented by Prof Lesley Burgess
On behalf of the CTC Members

2016 version
ELECTRONIC SUBMISSION OF CLINICAL TRIAL DOCUMENTS (AMENDMENTS, BIOEQUIVALENCE STUDIES, AND RESPONSES)

TO ALL APPLICANTS

The purpose of this document is to notify applicants of the electronic submission process in the Clinical Trials Unit (CTU), Medicines Control Council (MCC), in order to improve the turnaround times of applications. A number of e-mail addresses have been registered to support this initiative. Applicants are requested to use each specific e-mail address exclusively for a specific type of communication.
Summary:

E-mail address for Responses to new Clinical Trial applications and related queries:
CTCResponses@health.gov.za

E-mail address for Protocol amendments, responses to amendments and related queries:
CTCAmendments@health.gov.za

E-mail address for Additional Investigators & Sites, responses to additions and related queries:
CTCInvestigators&sites@health.gov.za

E-mail address for Bioequivalence studies, BE amendments, responses to BE studies and related queries:
CTCBEprotocols@health.gov.za
Communication to the industry

• Applications should be sent to the MCC and followed by electronic submission – attached proof of submission with the electronic submission
• Electronic submission should be complete – include protocol, ICFs, etc
• Password protected documents take longer to process
• Communication lines – communicate directly with the CTU, NOT WITH THE REVIEWERS
Clinical Trials Unit (CTU)

Director: Clinical Evaluations and Trials
Ms P Nkambule
X8126

Deputy-director: Clinical Trials
Dr D Diale
X9467

Medicine Control Officer:
Ms M Ramathe
X8128
(Protocol Amendments, New CTAs)

Medicine Control Officer:
Mr P Mabille X8129
(Additional investigators and sites, New CTAs)

Medicine Control Officer:
Ms D Thosago X8127
(Additional investigators/sites and B/E studies, New CTAs)

Medicine Control Officer:
Ms K Malatji
(Notification studies, Protocol amendments, New CTAs)

Admin officer
Ms Tebogo Lekalakala

PA: Ms S Mashishi
X9470
Answering queries

• Dedicated email address to submit responses: CTCResponses@health.gov.za

• Answer questions directly and in detail with due thought and knowledge...do not rely on junior staff to deal with this task

• Poorly answered questions just raise more queries....

• facetious answers make us mad....
• 8 sites – CTF1 did not indicate dispensers/pharmacists for each site – question raised
• Reply from sponsor: All the information was supplied previously
When do you need to submit a CTF1 form....

Notification versus formal approval depends on:

• Whether of not the research meets the definition of a clinical trial, and

• Whether the trial involves an investigational product
What is a clinical trial?

Any investigation in human subjects intended to discover or verify the clinical, pharmacological and/or pharmacodynamic effects of an investigational product(s), and/or identify any adverse reactions to an investigational product(s), and/or to study absorption, distribution, metabolism and excretion of an investigational product(s) with the objective of ascertaining its safety and/or efficiency.

ICH Glossary 1.12
Investigational product

A pharmaceutical form of an active ingredient or placebo being tested or used as a reference in a clinical trial, including a product with a marketing authorization when used or assembled (formulated or packaged) in a way different from the approved form, or when used for an unapproved indication, or when used to gain further information about an approved use.

ICH 1.33
Trial objectives..... investigation of the brain and behavioural effect of a single dose of intranasal oxytocin using neuroimaging.....in human subjects with and without post-traumatic stress disorder

“As such, no therapeutic outcomes will be investigated. Therefore, it is not a clinical study.....”
CTC must approve all trials involving:

- Use of an unregistered drug
- Use of a South African registered drug (and the drug is being sourced locally) when
  - New dose
  - New route of administration
  - New indication (i.e. not already included in the South African package insert)
  - Associated with increased risk
For a notification, need to submit:

- Cover letter
- Protocol
- South African approved Package Inserts
- Patient Information leaflet and Informed Consent Form
- Curriculum Vitae in MCC format
- Declaration(s)
- Valid malpractice insurance
- Valid GCP training certificate
- Registration with statutory bodies
- Questionnaires
- Ethics Committee(s) approval or copy of the submission to Ethics
- NHREC Registration
- 6 monthly progress reports
- Notification of additional sites
- CD
- Insurance

Can be submitted on an ad hoc basis
• Not required for single site studies

• For multi-site studies, the National PI must be involved in the trial

E. JOINT DECLARATION BY SPONSOR (OR REPRESENTATIVE) AND PRINCIPAL INVESTIGATOR (OR NATIONAL PRINCIPAL INVESTIGATOR) CONCERNING SUFFICIENT FUNDS TO COMPLETE STUDY*

Title:

Protocol:

I, <full name>, representing <sponsor or representative>

And

I, <full name>, Principal Investigator/National Principal Investigator

Hereby declare that sufficient funds have been made available to complete the above-identified study.
Staff resources

• Appropriate and sufficient staffing per study
• Pharmacist/dispensing doctor must be clearly indicated
  – Nurses may not dispense in the clinical trial field
  – If you only have 1 dispenser/pharmacist, what is the site’s back-up plan
• Subinvestigators who are actually participating in clinical trials and not just window-dressing
• Staff that are conducting clinical procedures need to be appropriately trained and registered with a professional body
• Field of expertise
Clinical associates

GOVERNMENT NOTICE

DEPARTMENT OF HEALTH

No. R. 433

25 May 2015

HEALTH PROFESSIONS ACT, 1974 (ACT NO.56 OF 1974)

REGULATIONS DEFINING THE SCOPE OF PRACTICE OF CLINICAL ASSOCIATES
Suggestions

• Applicant should review this form prior to submission to CTC

• Workloads must appear within the CTF1 application form and not merely be referred to as an attachment
Capacity-building

- Previously disadvantaged researchers and research staff
- Academic sites
- Ways in which capacity is being developed within these groups
If this definition is not met, why?

• Include names of previously disadvantaged researchers and academic centres approached

• Reason for non-participation
  – Turned study down due to lack of time/resources/suitable participants etc
What does not fall into definition of capacity of building:

- Social development programmes of sponsors/CROs
- Promises by sponsors/CROs to provide GCP training for research staff
- Descriptions on how researchers/CRAs will benefit by being exposed to new drugs
- Sites responding that they will consider previous disadvantaged employees in future
- Sites responding that they would like to employ a previously disadvantaged staff member but none applied
- Training the receptionist to be a study coordinator
- Community initiatives, service and location
- “A large pool of patients will have access to a novel form of treatment for.....”
- Building relationships with private practices
But we are not looking for reckless capacity-building....

• Proposal of a previously disadvantaged PI with no previous clinical trial experience (only academic research)
• Backed up by 2 subinvestigators....workloads indicated that they were both extremely busy...1 had more than 800 participants on trials
Now we also want to see......
Investigator workloads

- We are looking for evidence that the investigator has sufficient time to conduct (yet another) clinical trial.
- If necessary, add an explanation.....provide supporting detail...
- Needs to be completed accurately and account for 168 hours per week (that is 24 hours x 7 days)....very few investigators only sleep for 25 hours per week.
- If all workloads for a site are the same, we will question it.....
- If workloads do not appear to correlate with the number of trials conducted, we will question....
- We will look for evidence that all the investigators duties are accounted for.....teaching duties, private practice, etc.
GCP Training

• Course must be accredited by the HPCSA
• Basic course must be by attendance
• 3-yearly refresher course
• Refresher course may be online course....but must be a South African based course (SAGCP)
• If GCP lapses >6 months, must repeat basic course
• Does not include GCP course done
  – As part of multinational clinical trial “official training”
  – As part of an investigator meeting
  – For NIH/other international funder
Updated SAGCP

- Still following the 2006 version
- Currently undergoing a rewrite and has been forwarded for consultation...
Trial remuneration

• Investigator remuneration
  – Need details of payment to site
  – Not sufficient to just state “Not applicable as the investigator is paid on a monthly salary”

• Participant remuneration
  – Should be in keeping with NHREC requirements: time, inconvenience, expenses
  – R150 does not cover a participant requiring caregivers/parents/legal guardians etc to accompany them.....nor does it take into account inflation since this fee was first
  – We are looking for minimum reimbursements of R250-R300...more if the study population requires caretakers/parents/legal guardians to accompany the participant.....
PAYMENT OF TRIAL PARTICIPANTS IN SOUTH AFRICA:

ETHICAL CONSIDERATIONS

FOR RESEARCH ETHICS COMMITTEES

Suggested citation: NHREC (2012). Payment of trial participants in South Africa: Ethical considerations for Research Ethics Committees (RECs). NHREC.

1. PURPOSE

The purpose of this document is to propose to Research Ethics Committees (RECs) certain considerations for payment of clinical trial participants in South Africa.
Emergency trolleys

• Each unit must have its own resuscitation trolley ON SITE and be responsible therefore. Cannot rely on hospital which is only 2 km down the road.
– Cannot rely on hospital casualty
– Cannot rely on another site

• Needs to be complete
– Minimum lists are being compiled
– Emergency drugs and apparatus, oxygen, defibrillator

• Needs to be checked regularly

• Each site must keep “log book” of all emergencies

Can request waiver under certain conditions – e.g. a trial using a topical cream which is not absorbed
HIV

• “Known or suspected HIV” as an exclusion criteria
  – HIV testing necessary, especially in trials involving IP which affects participant’s immunity
  – Long-term trials,...will HIV testing be repeated during course of trial...what if participant test positive during course of trial
  – Necessary consent forms
  – Trained personnel to give counselling

• Related hepatitis B, etc
## Clinical Trial Agreement

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<th>Contract Number</th>
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<th>Indemnity (#5.2.2)</th>
<th>Statement in ICF that ABPI will be followed (#5.2.3)</th>
<th>Sponsor liable for costs of medical care (#5.2.5.1)</th>
<th>Obligation of sponsor to report findings that may affect participant safety / influence study conduct (#5.2.5.2)</th>
<th>Obligation of sponsor to send data and safety monitoring reports (#5.2.5.3)</th>
<th>Obligation of sponsor to communicate study results (#5.2.5.4)</th>
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Participant insurance

• SA GCP: Trial sponsor must ensure that the participants of a clinical trial are covered by comprehensive insurance in the event of physical (bodily) harm or injury, including death

• This means that the insurance company will compensate a participant for medical expenses which may have resulted directly from their participation in a particular clinical trial (either from using the medicine in question or participating in the required procedures).
Basic Principles

• Should be paid when participants suffer bodily injury (including death)...

• .....when, on the balance of probabilities, the injury was attributable to the administration of a IP under trial or any clinical intervention or procedure provided for by the protocol that would not have occurred but for the inclusion of the patient in the trial....

• ...regardless of whether the adverse reaction causing the injury was foreseeable or predictable, or the fact that the patient has freely consented (whether in writing or otherwise) to participate in the trial

• .... should be paid regardless of whether the patient is able to prove that the company has been negligent in relation to research or development of the medicinal product under trial or that the product is defective
No compensation should be paid

- for the **failure of a medicinal product to have its intended effect or to provide any other benefit to the patient**.
- for **injury caused by other licensed medicinal products** administered to the patient as a comparator.
- to patients receiving **placebo** in consideration of its **failure to provide a therapeutic benefit**.
- to the extent that the injury has arisen:
  - through **significant protocol deviation**
  - through the **wrongful act or default of a third party**, including a doctor’s failure to deal adequately with an adverse reaction
  - through **contributory negligence by the patient**.
Assessment of Compensation

• The amount of compensation paid should be appropriate to the nature, severity and persistence of the injury and should in general terms be consistent with the quantum of damages commonly awarded for similar injuries by an English Court in cases where legal liability is admitted.

• …where the company concedes that a payment should be made to a patient but there exists a difference of opinion between company and patient as to the appropriate level of compensation, it is recommended that the company agrees to seek at its own cost (and make available to the patient) the opinion of a mutually acceptable independent expert.
Miscellaneous

- The undertaking given by a company extends to injury arising (at whatever time) from all administrations, clinical interventions or procedures occurring during the course of the trial but not to treatment extended beyond the end of the trial at the instigation of the investigator.

- Adherence to these Guidelines does not affect the right of a patient to pursue a legal remedy in respect of injury alleged to have been suffered as a result of participation.

- A company sponsoring a trial should encourage the investigator to make clear to participating patients that the trial is being conducted subject to the ABPI Guidelines relating to compensation for injury arising in the course of clinical trials and have available copies of the Guidelines should they be requested.
Venter vs Roche (2014)

Costs must be reasonable and \textbf{does not include} costs for, for example, a loss of income, compensation for pain or emotional suffering. This was recently confirmed in the decision by the Western Cape High Court in the matter of \textit{Venter v Roche}. Guideline 4.11 of the SA GCP 2006 states that the sponsor of a study should pay the costs for the medical treatment of any bodily injury \textit{without} the participant having to prove that the sponsor was at fault.
Osteoarthritis case

- Participants receiving a monoclonal antibody for osteoarthritis and 12/25 experienced worsening osteoarthritis of which 4 had probable avascular necrosis (no biopsy done)
- Study was closed by FDA due to incidence of avascular necrosis
- American CRO/sponsor initially refused to pay out as site could not prove study drug was the probable cause
- Eventually settled – sponsor paid for 4 hip replacements and 8 prosthesis, on condition a non-disclosure form was signed
What are we looking for?

• Proof that ABPI is being followed
• Insurance company must be locally based / have local representative
• Appropriate insurance cover for the trial risk and patient numbers
  – R1 million is not sufficient per case when there is a risk for ICU stay etc
• Must cover duration of trial or statement that insurance will be renewed annually
• Must not require legal action for access
• Indemnification of investigators
Recruitment advertisements

- Print advertisements
- Social media (Facebook, Twitter)
- Need ethics approval
Informed consent of trial participants

• Availability of suitable forms
• Unacceptable statements, usually related to medical-care and/or insurance in the event of a research-related injury
• Special populations may require special consideration
  – Minors
  – Emergency Research

Provide the SOPs for obtaining informed consent under these conditions
Post-trial access

• If the study involves chronic diseases for which there is no readily available alternative treatment and/or they benefit from the medication and where withdrawal is likely to lead to deterioration of their health status, post-trial access is mandatory...UNTIL THE DRUG BECOMES AVAILABLE IN THE PUBLIC HEALTH SECTOR
  – Cerebral palsy
  – Primary pulmonary hypertension
  – Thrombo-embolic pulmonary hypertension
• Provide details in the CTF1
• Recommended: a roll-over protocol to be approved by CTC together with the original clinical trial
• Amendments providing for a roll-over are less satisfactory
• Approval of a roll-over trial protocol after the trial is over is possible but not recommended
• Care must be taken to prevent gaps in patient treatment between the original and roll-over protocols
Incomplete/shoddily completed CTF1 applications

- CTF1 provided in PDF format or with tracked changes
- CTF1 password protected… and no password provided
- Reference to attachments/other documents instead of completing all sections as requested within the CTF1
- No/poor justifications for objectives, hypotheses, eligibility criteria, etc
- Mindless “cut and paste”
  - CTF1 submissions >200 pages long
  - Preclinical information
  - Previous clinical experience
  - Statistics
  - Stock sponsor responses: safety, publication policies, etc
4. Background information (summarised – essential points that apply to this trial) [1-2 sentences max for each point]:
Disease / problem
South African context (e.g. local epidemiology)
Properties of Drug / Entity; hypotheses about mechanism of action, etc.
Pre-clinical findings: (e.g. laboratory / animal / toxicity / mutagenicity)
Clinical findings (e.g. phases; PK; PD; dose-finding; ADRs, NNT/NNH, other)
Systematic review(s) and/or citations per year-group on a Medline search
• Discrepancies in information
• “Error! Source Reference not found!”
• Clear that CTF1 has been completed by non-medical / junior sponsor/CRO employee
  – Requires a knowledge of research
  – Requires a knowledge of the disease profile
  – Requires a knowledge of statistics
• Clear that CTF1 has never been proof-read
  – Suggest that the national PI read this document prior to submission
  – Number of sites do not correlate with submission documents
• Disease prevalence/incidence rates provided are either outdated and/or not related to South Africa
• Calculation of required amount of IP for which exemption is required – generally accept 20% overage
• Avoid and/or explain any apparent conflict of interests
  – Be transparent
• Give an overview of the monitoring process
• Explain DSMB activity – charter, membership, etc
• Give reasons why a host country is not being included
• Explain any potential ethical dilemmas
• Ethics committee
  – Provide explanation if the “usual” ethics committee is not being used
Suggestions

• Get a senior “scientific” employee of the CRO/sponsor to review the CTF1

• Consult a statistician

• Involve the national PI in the scientific aspects of the submission
Problems associated with amendments

• Now a dedicated email address for submission of amendments: CTCAmendments@health.gov.za
• Not completing and/or attaching the CTF2 – especially when the applicant thinks that the amendment is only administrative with no risk to patient safety
• Not completing the summary of changes with the rationale
• Not highlighting or deleting the actual changes between the “old” and “new” texts but underlining the entire text
• Not indicating the study tracking number of the CTF2