Ministry of Health and Sports

Reviewing Clinical Trials

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Clinical Trials

For the purposes of registration, 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

The research protocol must be submitted for consideration, comment, guidance and approval to a research ethics committee before the trial begins. This committee must be independent of the researcher, the sponsor and any other undue influence.

It must take into consideration the laws and regulations of the country or countries in which the research is to be performed as well as applicable international norms and standards but these must not be allowed to reduce or eliminate any of the protections for research participants set forth in this Declaration

Declaration of Helsinki

A trial should be conducted in compliance with the protocol that has received prior institutional review board (IRB)/independent ethics committee (IEC) approval/favourable opinion

ICH-GCP

Players in Clinical Trials

1. Drug Regulatory Body
2. Sponsor
3. Investigators
4. IRB
5. Trial Participants
6. Clinical Trial Services Provider
7. Site Supporting Organisations
8. Data Safety and Monitoring Committee

- James Lind is seen as the father of clinical trials. As the first to introduce control groups in 1747, he documented that citrus fruits in diet could prevent scurvy.

- Placebos were first used in 1863.
- The idea of randomisation was introduced in 1923.
- The first trial using properly randomised treatment and control groups was carried out in 1948 by the Medical Research Council, UK. This trial also adopted blind assessment enabling unbiased analysis of the results.
- The three cornerstones of clinical trial design are still *controls, randomisation and blinding*

Type of control

- Placebo
- No treatment
- Different dose or regimen of the trial test treatment
- Standard treatment

The benefits, risks, burdens and effectiveness of a new intervention must be tested against those of the best current proven intervention, except in the following circumstances: The use of placebo, or no treatment, is acceptable in studies where no current proven intervention exists; or where for compelling and scientifically sound methodological reasons the use of placebo is necessary to determine the efficacy or safety of an intervention and the participants who receive placebo or no treatment will not be subject to any risk of serious or irreversible harm. Extreme care must be taken to avoid abuse of this option (DOH)

Pre-clinical stage

Develop a pharmacological profile of the drug.

Determine the acute toxicity of the drug in at least two species of animals.

Conduct short-term toxicity studies ranging from 2 weeks to 3 months, depending on the proposed duration of use of the substance in the proposed clinical trials.

Investigational New Drug Application (IND)

Phase I Clinical Trial (Human Pharmacology)

- phase I trials are generally associated with a higher risk of harm than any other trial
- *first-into-man trials and dose escalating trials.*
- *usually conducted on small populations of healthy humans* to specifically determine a *drug's toxicity, absorption, distribution, metabolism, excretion, duration of action, drug-to-drug interaction and drug-to-food interaction*
- often conducted in a dedicated inpatient clinic, where the participant can be observed by full-time staff, usually until several half-lives of the drug have passed
- Some are conducted in patients (test drug are too toxic for the healthy person) eg. Anticancer drugs

Phase II Clinical Trials (Therapeutic Exploratory)

- Safety and efficacy
- Larger population of individuals afflicted with the disease or condition for which the drug was developed.
- Require close monitoring of each participant
- Estimate proper dosage

Phase III Clinical Trials (Therapeutic Confirmatory)

- Compare with current standard treatments for the relevant conditions
- Large trials
- Demonstrate of confirm the therapeutic benefit

Phase IV Clinical Trials (Therapeutic Use)

- Post marketing surveillance
- Safety surveillance (pharmacovigilance)
- Study the effectiveness of the treatment after approval
- Usually required by regulatory authority
- May be carried out by sponsor voluntarily

Scientific evaluation of clinical trial protocol

Third party review: Have any regulatory or scientific bodies reviewed and formally accepted the current version of the protocol? Have any other ECs reviewed the protocol?

Protocol development: Are the names of the persons involved in the protocol development, their qualifications and responsibilities provided?

Pre-clinical information: What is the safety and efficacy profile of the test article?

Test article manufacturing: Is the product evidently manufactured according to GMP?

Study objective: What is the scientific rationale behind the study?

Clinical rationale: What is (are) the expected benefit(s) of the test article in normal clinical care?

Study design – treatment: If placebo comparison is used rather than the best standard treatment, what is the justification?

Study design – outcome: Is the study exploratory or confirmatory in nature? Is the primary outcome of the trial a clinical outcome or a surrogate outcome? Is the outcome the current and most valid internationally accepted outcome? Does the trial use the best possible comparison groups for its purpose?

Study design – randomisation: Does the trial use randomisation to treatment groups? If randomised, how will this be performed?

Study design – blinding: Are the investigator, participants and the trial outcome evaluator blinded? If blinding is utilised, how is this ensured?

Study design – sample size: Has a proper sample size calculation been made? Who calculated the sample size? What were the assumptions behind the sample size calculation?

Participant availability: Are there enough participants available? What is the anticipated duration of patient recruitment? Are there other clinics or hospitals available to secure the anticipated sample size?

Resources: Are enough financial and manpower resources available for completion of the trial?

Risk Benefit Balance

- *In medical research involving human subjects, the well-being of the individual research subject must take precedence over all other interests.*
- *Medical research involving human subjects may only be conducted if the importance of the objective outweighs the inherent risks and burdens to the research subjects (DOH)*

The benefit is not strictly related to the participants, but in fact it is more related to the benefit of society, i.e., accumulation of new knowledge and the advancement of science

Informed Consent

The Investigator should have the EC' s written approval of the written informed consent document, and any other written information to be provided to participants; any revised written informed consent document and written information should receive the EC' s approval in advance of use; it should not contain language that causes the participant to waive any legal rights, or release the investigator, institution or sponsor from liability for negligence; and language used during the informed consent process should be as non-technical as practical. Prior to participation in a trial , the written informed consent document should be signed and personally dated by the participant, or their legally acceptable representative, and also by whoever conducted the informed consent discussion.

The study team should also continue to provide updates to the participants when new information arises that may influence their participation

EC has the right to conduct site visits and audits

EC should be informed continuously about any SAEs identified at any sites involved in a specific trial.

EC has only partial oversight of the informed consent process and is only able to ensure that the written information provided to participants is correct and to some extent appropriately updated

Secondary Analysis of the Clinical Database

- Use in research of data contained in previously created dataset
- Participants have not been given their consent for such use
- Analysis of clinical databases for hospital administrative purposes does usually not require any EC review or approval.
- However, as a requirement for publication in many international biomedical journals, an EC must review and accept secondary analysis of clinical database studies
- Depend on the nature of the research question and sensitivity of the data, EC decide whether each participant should be contacted to get consent for the usage of data

Vulnerable participants

"Individuals whose willingness to volunteer in a clinical trial may be unduly influenced by the expectation, whether justified or not, of benefits associated with participation, or of a retaliatory response from senior members of a hierarchy in case of refusal to participate"

- Diminished metal capacity to give consent
- Diminished capacity to provide consent

Conflict : Currently, the regulatory authorities want both to protect and include vulnerable participants in clinical trials

Privacy and Confidentiality

Privacy encompasses being free from interference by others – especially in relation to personal information, thoughts and opinions, and personal communications with others.

Confidentiality includes the responsibility to protect such personal information from unauthorised access, use, disclosure, modification, loss or theft

Safety Monitoring

EC must ensure that a clinical trial incorporates a plan to assess the safety of participants

"An independent data-monitoring committee (Data safety and Monitoring Committee DSMC)that may be established by the sponsor to assess at intervals he progress of a clinical trial, the safety data, and the critical efficacy endpoints, and to recommend to the sponsor whether to continue, modify or stop a trial"

A DSMC must be autonomous in the trial, and the EC should receive copies of all DSMC reports and recommendations

Participant Recruitment Procedure

Recruitment of participants for a trial can take place

- through the patient pool at the study site
- referral of participants from other clinics
- by advertisement
- directly approaching and screening the public

These information should be clearly defined

Finder fees ?? Referral Fees ??

Qualification of Investigators and Research Staff

"The investigator(s) should be qualified by education, training and experience to assume responsibility for the proper conduct of the trial, should meet all the qualifications specified by the applicable regulatory requirement(s), and should provide evidence of such qualifications through up-to-date curriculum vitae and/or other relevant documentation requested by the sponsor, the IRB/IEC, and/or the regulatory authority(ies)"

Conflict of Interest

- A conflict of interest can be defined as any situation in which an individual or corporation is in a position where personal or corporate interests could interfere with a professional obligation.
- The existence of a conflict of interest is not evidence of wrongdoing
- Not inherently negative
- How it is handled makes the difference

Dissemination of Trial Result

The sponsor, investigator and institution have an ethical responsibility to make reasonable efforts to publicly disseminate the results of clinical research in a timely manner.

However, it has to be accepted that negative research results are less often submitted and accepted for publication in international medical journals.

The investigators must anyhow submit a final report of the trial to the EC for review and approval, providing details about major outcomes of the trial

Case Scenarios

Dr. Kristianna Haugen ~ consultant oncologist ~ has been approached by a research organisation that is handling a phase I clinical trial of a novel drug for the treatment of acute small cell carcinoma of the lung for a multinational pharmaceutical company based in the US. The drug under evaluation will be tested in a small group of patients with late stage cancer and requires the investigator to draw regular quantities of blood amounting to no more than 800 ml in total over a two-week period, so that a full range of haematological, biochemical, pharmacokinetic and pharmacodynamic parameters can be assessed. The size of the tumour will also be measured. Dr. Haugen has background pre-clinical information concerning the drug from some publications she read several months ago, and thinks the new drug being evaluated will be a breakthrough in the treatment of cancer. She is naturally very keen to be an investigator for the trial and duly submits an application to her hospital's EC for consideration.

The EC chair was surprised when he read the protocol, i.e., that as much as 800 ml of blood would be drawn from terminally ill cancer patients. Being a specialist in haematology, he knows that a normal blood donation of healthy individuals varies from 200 to 550 ml, depending on the country, and a full blood donation should in principle not be repeated over an eight-week period. The chair noted that the protocol had listed a well-known medical university in the United Kingdom as a potential trial site, so he simply sent an email to the EC chair at that university and asked for comments on the protocol in question. It took just a few hours before the email reply: "*No, we did not accept the protocol, since it is harmful and unethical to collect 800 ml in terminally ill patients – no gain, just pain for very sick participants.*" The EC chair could not disapprove the protocol, since that can only be done by during a full EC review meeting.

Note: This scenario in fact represents a true case; sponsors may assume that even if one EC does not accept a protocol, maybe another will. Consulting other ECs involved in the review of the same protocol is in fact good practice and should be encouraged

Dr. Jacqueline Dupont, an oncologist, wishes to be the investigator of a phase I trial to assess the pharmacodynamic and pharmacokinetic properties of a new drug for the treatment of terminally ill patients with small cell carcinoma of the lung. Pre-clinical trials of the new drug have proven to be very effective in animal studies conducted by the company developing the drug, but the company has little information about how it is metabolised, and the safe dosage to use in humans. As this is a phase I trial of a new drug, it is extremely important that all samples of blood drawn from each of the trial participants are taken at specific time intervals so that various parameters can be calculated accurately. This being the case, it has been estimated by the sponsor that approximately 300 ml of blood would be required from each subject over a two-week period.

The protocol and participant information sheet for the trial are clearly written and, in lay terms, point out to the trial participants what will happen to them during their participation in the trial. The sponsor has provided Dr. Dupont with the trial protocol, the investigator's brochure outlining all the pre-clinical data and studies conducted in animals to date, the informed consent form and insurance documentation. The sponsor has also signed the hospital indemnity documentation and furthermore provided the necessary equipment to conduct the trial. Dr. Dupont therefore submits an application to her hospital EC to conduct the trial.

Dr. Dupont, an oncologist, plans to act as the investigator of a phase I trial of a new drug for the treatment of terminally ill patients with small cell carcinoma of the lung. Although the trial population is vulnerable because the patients are terminally ill, the EC review concludes that it is important to allow terminally ill patients to participate in relevant clinical trials, even though the possibility of receiving curative treatment is zero, or close to zero. The scientific rationale behind this trial is seen as acceptable, since the cancer drugs are too toxic to be given to healthy volunteers; there is no other option to advance our knowledge in finding better treatments for future cancer patients.

Note: Vulnerable populations should not automatically be omitted from being invited to participate in a clinical trial. The final decision will always rest with the participant and in this scenario, also with the parent(s) or legally authorised representative.

Do you have Influenza

If your answer is "*YES*" *you may be considered an eligible participant for* entry into a clinical trial of a promising new drug for the treatment of influenza. By participating in the trial, you will receive the following benefits:

- Free medication.
- Free medical examinations by a qualified physician.
- Reimbursement of travel costs to and from the hospital.

For further information contact: Dr. Kim ~ telephone 2020 2345

EC informs Dr. Kim by email that she is not allowed to use a phrase like "*a promising new drug" in an advertisement for trial participant recruitment. Wording such as "promising" or "new" is not permitted, since it is a test article. It is not known* if the drug will be "*promising," and it is not "new" until it has been approved* by the regulatory authority. The EC chair also writes that he has no further comments about the contents of the advertisement and that he will be happy to expedite the review after Dr. Kim submits an appropriate advertisement.

Note: This advertisement tries to gain the attention of potential participants by using unsuitable and inaccurate phrasing such as - *"a promising new drug."*

Questions, Comments and Suggestions would be greatly appreciated !