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CLINICAL TRIAL: COMPLETE REVIEW

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ABSTRACT

A Clinical trial involves the testing of a new medicine (or other therapy) to evaluate whether it is effective and safe. Clinical trials of drugs can be divided into those assessing the treatment of a disease (e.g. asthma) or those assessing treatments to prevent the occurrence of significant healthcare events in the future (e.g. stroke). Clinical trials provide the qualitative information about the benefits, adverse effects and possible uses of new drugs that allows prescribers and patients to make rational decisions in relation to drug therapy.

KEYWORDS: Approval to begin a clinical trial, Human subject protection, Clinical research (the drug trial process), Regulation of clinical trials, Online clinical trial registers, trial registration, Important of Trial Registration, Organizations with Policies, Funders, Ethics committees, Legal Requirements, National Research Ethics Oversight Agencies, Professional organizations, Publishers, The International Clinical Trials Registry Platform, Clinical Trial Registration, The Universal Trial Number.

CLINICAL TRIALS

WHAT ARE CLINICAL TRIALS?

National institute of Health, USA defines clinical trial as "biomedical or health related research studies that follow a predefined protocol". Clinical trials could be of two types interventional or observational. In the former, any drug or device is tested, while in later, the patients are observed by investigators and health outcome is tested. Trials can be funded by physicians, individuals, organizations medical institutions or federal agencies such as Indian Council of Medical Research in Indian and National Institute of Health in the USA trial can take place in medical colleges, institutions doctors' offices, or community clinics.

Usually, a medicine or a device to be tested is identified and this followed by one or more pilot trials.
New drugs not yet approved by the U.S. FDA (Food and Drug Administration)
New uses of drugs already approved by the FDA,
New ways to give drugs, such as in pill form,
Use of alternative medicines, such as herbs and vitamins,
New tests to find and track disease, and
Drugs or procedures that relieve symptoms.

Clinical trials are carefully designed, reviewed, and completed. The principal investigator is the person in charge of the trial. He or she is a scientist who's an expert in what the clinical trial is about. The principal investigator takes the lead in designing the clinical trial, choosing the research team, and carrying out the study. Often, other scientists, called investigators, are part of the research team.

Clinical trials need to be approved before they can start. Clinical trials need sponsors since they can't be done without money or other support. Sponsors often are government agencies, pharmaceutical (drug) companies, and non-profit organizations. Sponsors of the clinical trial review the research plan (also called protocol). Funding or other support is given by the sponsor once the research plan is approved.

Clinical trials also need approval from an IRB (Institutional Review Board). An IRB is a group of people chosen by the health care center where patients will be enrolled into a clinical trial. Each IRB include five members. These members must include a scientist, someone who's not a scientist, and someone who's not from the health care center. The IRB reviews the research plan to make sure the rights and welfare of patients are protected. After the trial has started, the IRB reviews its progress at least every year.

DSMBs (Data and Safety Monitoring Boards) review the progress of a clinical trial after it has started. Members of DSMBs are experts in clinical trials. They assess if patients are safe, the data is complete, and if the test or treatment is working. Not all clinical trials are reviewed

by DSMBs but only those who the IRB thinks need more review than the IRB does.

What each clinical trial has to offer to patients differs. However, there are four general benefits. First, you'll have access to the most current cancer care. Second, you will be treated by experts. Third, the results of your treatment—both good and bad—are carefully tracked. Fourth, you may help other patients with cancer.

Clinical trials have risks too. Like any test or treatment, there may be side effects. Also, new tests or treatments may not work as good as or better than the one now in use. Another downside may be that paperwork or more trips to the hospital will be needed.

Before doing a clinical trial, investigators conduct preclinical research using human cell cultures or animal models. For example, they might test whether a new medication is toxic to a small sample of human cells in a laboratory.

If the preclinical research is promising, they move forward with a clinical trial to see how well it works in humans. Clinical trials happen in several phases during which different questions are asked. Each phase builds on the results of previous phases.

Types

Clinical trials are classified by the research objective created by the investigators. In an observational study, the investigators observe the subjects and measure their outcomes. The researchers do not actively manage the study. In an interventional study, the investigators give the research subjects an experimental drug, surgical procedure, use of a medical device, diagnostic or other intervention to compare the treated subjects with those receiving no treatment or the standard treatment. Then the researchers assess how the subjects' health changes.

Trials are classified by their purpose. After approval for human research is granted to the trial sponsor, the U.S. Food and Drug Administration (FDA) organizes and monitors the results of trials according to type:

Prevention trials look for ways to prevent disease in people who have never had the disease or to prevent a disease from returning. These approaches may include drugs, vitamins or other micronutrients, vaccines, or lifestyle changes.

- Screening trials test for ways to identify certain diseases or health conditions.
- Diagnostic trials are conducted to find better tests or procedures for diagnosing a particular disease or condition.
- Treatment trials test experimental drugs, new combinations of drugs, or new approaches to surgery or radiation therapy.
- Quality of life trials (supportive care trials) evaluate how to improve comfort and quality of care for people with a chronic illness.
- Genetic trials are conducted to assess the prediction accuracy of genetic disorders making a person more or less likely to develop a disease.
- Epidemiological trials have the goal of identifying the general causes, patterns or control of diseases in large numbers of people.

Compassionate use trials or expanded access trials provide partially tested, unapproved therapeutics to a small number of patients who have no other realistic options. Usually, this involves a disease for which no effective therapy has been approved, or a patient who has already failed all standard treatments and whose health is too compromised to qualify for participation in randomized clinical trials.[31] Usually, case-by-case approval must be granted by both the FDA and the pharmaceutical company for such exceptions.

Fixed trials consider existing data only during the trial's design, do not modify the trial after it begins, and do not assess the results until the study is completed.

Adaptive clinical trials use existing data to design the trial, and then use interim results to modify the trial as it proceeds. Modifications include dosage, sample size, drug undergoing trial, patient selection criteria and "cocktail" mix.Adaptive trials often employ a Bayesian experimental design to assess the trial's progress. In some cases, trials have become an ongoing process that regularly adds and drops therapies and patient groups as more information is gained.The aim is to more quickly identify drugs that have a therapeutic effect and to zero in on patient populations for whom the drug is appropriate.

Clinical trials are conducted typically in four phases, with each phase using different numbers of subjects and having a different purpose to construct focus on identifying a specific effect.

Phases

Main article: Phases of clinical research

Clinical trials involving new drugs are commonly classified into five phases. Each phase of the drug approval process is treated as a separate clinical trial. The drug development process will normally proceed through phases I–IV over many years, frequently involving a decade or longer. If the drug successfully passes through phases I, II, and III, it will usually be approved by the national regulatory authority for use in the general population.[29] Phase IV trials are performed after the newly approved drug, diagnostic or device is marketed, providing assessment about risks, benefits, or best uses.

Phases [edit]

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Phase	Aim	Notes
Phase 0	Pharmacodynamics and pharmacokinetics in humans	Phase 0 trials are optional first-in-human trials. Single subtherapeutic doses of the study drug or treatment are given to a small number of subjects (typically 10 to 15) to gather preliminary data on the agent's pharmacodynamics (what the drug does to the body) and pharmacokinetics (what the body does to the drugs).[36] For a test drug, the trial documents the absorption, distribution, metabolization, and removal (excretion) of the drug, and the drug's interactions within the body, to confirm that these appear to be as expected.
Phase I	Screening for safety	Often are first-in-person trials. Testing within a small group of people (typically 20–80) to evaluate safety, determine safe dosage ranges, and identify side effects.[29]
Phase II	Establishing the preliminary efficacy of the drug in a "treatment group", usually against a placebo control group	Phase IIa establishes "proof of concept" for efficacy of the drug candidate (in dozens to ~ 100 people with the disease under study),[37] while a Phase IIb trial is a "dose-finding" (or "dose-ranging") study,[37] with a larger treatment group (typically 100–300), to determine efficacy and an optimal dose at which the drug shows therapeutic effect with minimal side effects, combined with further monitoring of safety.[29]
Phase III	Final confirmation of safety and efficacy	Testing with large groups of people (typically 1,000–3,000) to confirm its efficacy, evaluate its effectiveness, monitor side effects, compare it to commonly used treatments, and collect information that will allow it to be used safely.[29]
Phase IV	Safety studies during sales	Postmarketing studies delineate risks, benefits, and optimal use. As such, they are ongoing during the drug's lifetime of active medical use.[29]

Trial design

Clinical study design

A fundamental distinction in evidence-based practice is between observational studies and randomized controlled trials.[38] Types of observational studies in epidemiology, such as the cohort study and the case-control study, provide less compelling evidence than the randomized controlled trial.[38] In observational studies, the investigators retrospectively assess associations between the treatments given to participants and their health status, with potential for considerable errors in design and interpretation.

A randomized controlled trial can provide compelling evidence that the study treatment causes an effect on human health.[38]

Currently, some Phase II and most Phase III drug trials are designed as randomized, double-blind, and placebo-controlled.

Randomized: Each study subject is randomly assigned to receive either the study treatment or a placebo.

Blind: The subjects involved in the study do not know which study treatment they receive. If the study is double-blind, the researchers also do not know which treatment a subject receives. This intent is to prevent researchers from treating the two groups differently. A form of double-blind study called a "double-dummy" design allows additional insurance against bias. In this kind of study, all patients are given both placebo and active doses in alternating periods.

Placebo-controlled: The use of a placebo (fake treatment) allows the researchers to isolate the effect of the study treatment from the placebo effect.

Clinical studies having small numbers of subjects may be "sponsored" by single researchers or a small group of researchers, and are designed to test simple questions or feasibility to expand the research for a more comprehensive randomized controlled trial.

Active control studies

In many cases, giving a placebo to a person suffering from a disease may be unethical.[41] To address this, it has become a common practice to conduct "active comparator" (also known as "active control") trials. In trials with an active control group, subjects are given either the experimental treatment or a previously approved treatment with known effectiveness.

Master protocol

In such studies, multiple experimental treatments are tested in a single trial. Genetic testing enables researchers to group patients according to their genetic profile, deliver drugs based on that profile to that group and compare the results. Multiple companies can participate, each bringing a different drug. The first such approach targets squamous cell cancer, which includes varying genetic disruptions from patient to patient. Amgen, AstraZeneca and Pfizer are involved, the first time they have worked together in a late-stage trial. Patients whose genomic profiles do not match any of the trial drugs receive a drug designed to stimulate the immune system to attack cancer.

Clinical trial protocol

Main article: Clinical trial protocol

A clinical trial protocol is a document used to define and manage the trial. It is prepared by a panel of experts. All study investigators are expected to strictly observe the protocol.

The protocol describes the scientific rationale, objective(s), design, methodology, statistical considerations and organization of the planned trial. Details of the trial are provided in documents referenced in the protocol, such as an investigator's brochure.

The protocol contains a precise study plan to assure safety and health of the trial subjects and to provide an exact template for trial conduct by investigators. This allows data to be combined across all investigators/sites. The protocol also informs the study administrators (often a contract research organization).

The format and content of clinical trial protocols sponsored by pharmaceutical, biotechnology or medical device companies in the United States, European Union, or Japan have been standardized to follow Good Clinical Practice guidance issued by the International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH). Regulatory authorities in Canada and Australia also follow ICH guidelines. Journals such as Trials, encourage investigators to publish their protocols.

Design features

Informed consent

Example of informed consent document from the PARAMOUNT trial

Clinical trials recruit study subjects to sign a document representing their "informed consent". The document includes details such as its purpose, duration, required procedures, risks, potential benefits, key contacts and institutional requirements.[46] The participant then decides whether to sign the document. The document is not a contract, as the participant can withdraw at any time without penalty.

Informed consent is a legal process in which a recruit is instructed about key facts before deciding whether to participate. Researchers explain the details of the study in terms the subject can understand. The information is presented in the subject's native language. Generally, children cannot autonomously provide informed consent, but depending on their age and other factors, may be required to provide informed assent.

Statistical power

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In any clinical trial, the number of subjects, also called the sample size, has a large impact on the ability to reliably detect and measure the effects of the intervention. This ability is described as its "power", which must be calculated before initiating a study to figure out if the study is worth its costs. In general, a larger sample size increases the statistical power, also the cost.

The statistical power estimates the ability of a trial to detect a difference of a particular size (or larger) between the treatment and control groups. For example, a trial of a lipid-lowering drug versus placebo with 100 patients in each group might have a power of 0.90 to detect a difference between placebo and trial groups receiving dosage of 10 mg/dL or more, but only 0.70 to detect a difference of 6 mg/dL.

Placebo groups

Main article: Placebo-controlled studies

Merely giving a treatment can have nonspecific effects. These are controlled for by the inclusion of patients who receive only a placebo. Subjects are assigned randomly without informing them to which group they belonged. Many trials are doubled-blinded so that researchers do not know to which group a subject is assigned.

Assigning a subject to a placebo group can pose an ethical problem if it violates his or her right to receive the best available treatment. The Declaration of Helsinki provides guidelines on this issue.

Duration

Timeline of various approval tracks and research phases in the US

Clinical trials are only a small part of the research that goes into developing a new treatment. Potential drugs, for example, first have to be discovered, purified, characterized, and tested in labs (in cell and animal studies) before ever undergoing clinical trials. In all, about 1,000 potential drugs are tested before just one reaches the point of being tested in a clinical trial.For example, a new cancer drug has, on average, six years of research behind it before it even makes it to clinical trials. But the major holdup in making new cancer drugs available is the time it takes to complete clinical trials themselves. On average, about eight years pass from the time a cancer drug enters clinical trials until it receives approval from regulatory agencies for sale to the public.Drugs for other diseases have similar timelines.

Some reasons a clinical trial might last several years:
For chronic conditions such as cancer, it takes months, if not years, to see if a cancer treatment has an effect on a patient.

For drugs that are not expected to have a strong effect (meaning a large number of patients must be recruited to observe 'any' effect), recruiting enough patients to test the drug's effectiveness (i.e., getting statistical power) can take several years.

Only certain people who have the target disease condition are eligible to take part in each clinical trial. Researchers who treat these particular patients must participate in the trial. Then they must identify the

desirable patients and obtain consent from them or their families to take part in the trial.

A clinical trial might also include an extended post-study follow-up period from months to years for people who have participated in the trial, a so-called "extension phase", which aims to identify long-term impact of the treatment.

The biggest barrier to completing studies is the shortage of people who take part. All drug and many device trials target a subset of the population, meaning not everyone can participate. Some drug trials require patients to have unusual combinations of disease characteristics. It is a challenge to find the appropriate patients and obtain their consent, especially when they may receive no direct benefit (because they are not paid, the study drug is not yet proven to work, or the patient may receive a placebo). In the case of cancer patients, fewer than 5% of adults with cancer will participate in drug trials. According to the Pharmaceutical Research and Manufacturers of America (PhRMA), about 400 cancer medicines were being tested in clinical trials in 2005. Not all of these will prove to be useful, but those that are may be delayed in getting approved because the number of participants is so low.

For clinical trials involving potential for seasonal influences (such as airborne allergies, seasonal affective disorder, influenza, and skin diseases), the study may be done during a limited part of the year (such as spring for pollen allergies), when the drug can be tested.

Clinical trials that do not involve a new drug usually have a much shorter duration. (Exceptions are epidemiological studies, such as the Nurses' Health Study).

What are the phases of a clinical trial?

Clinical trials are broken down into phases, with each phase having a different purpose within the trial. Phase I trials involve a small group of people (20-80) and are concerned with determining a safe dose of the drug being studied as well as its potential side effects. In Phase II, the treatment or drug is tested in more people (100-300) for further evaluation - this time, determining the time of the drug or treatment's effectiveness against the disease for which the patient is being treated. Even more people (1,000-3,000) are participants in Phase III of a trial, when the intervention is compared to standard treatments and further information is collected about safety and side effects. In Phase IV trials, conducted after a treatment has been approved for specific indicated conditions by the FDA, post-marketing studies are carried out to collect more information about the optimal use of the drug or treatment and to further evaluate its side effects.

Clinical trials may be carried out in different locations, including hospitals, clinics, individual physician practices, university health centers, or community health centers.

How can one find out what clinical trials are currently being conducted?

The web site http://clinicaltrials.gov is a searchable database of federally and privately funded clinical trials being conducted in the U.S. and around the world. Your doctor or health-care team may also offer information about clinical trials that are currently under way for your specific condition.

How is a clinical trial performed, and what sort of preparation is needed?

Before a clinical trial can be carried out, thorough preparation is necessary, including extensive reviews of the proposed trial, its methodology, and the goals of the trial. An Institutional Review Board (IRB) consisting of physicians, statisticians, researchers, patient advocates, and others must pre-approve every clinical trial in the U.S. The job of the IRB is to ensure that the trial is ethical, legal, and that the rights of those participating are fully protected. For example, individual participants' names are kept secret and not included in the results or publicly available information about a trial.

Every clinical trial has a strictly defined protocol that is approved by the IRB. A protocol describes what types of people may participate in the trial; outlines the exact the schedule of tests, procedures, medications, and/or dosages involved in the trial; and specifies the length of the study. Generally, doctors check the patient thoroughly at the start of the trial, provide instructions and directions for participation in the trial, monitor the patient during the actual trial, and remain in contact, sometimes with further monitoring after the trial is completed.

In many clinical trials, patients will be randomly assigned to a test group or a control group. The control group receives the standard and accepted treatment for a given condition, while the test group receives the experimental medication or treatment to be evaluated. When a trial is "double-blinded," neither the participants nor the treating doctors know if an individual patient is receiving the standard treatment versus the experimental treatment. Double-blinded trials offer the advantage of allowing the treating health-care team and the patient to make unbiased observations about patient progress and the effectiveness of the treatment being evaluated. A double-blind study is also referred to as a double-masked study. Results obtained from a randomized, double blind clinical trial are considered the most accurate and reliable types of results, and help those conducting the trial to draw the most accurate conclusions.

What is informed consent?

Informed consent is giving your consent to participate in the clinical trial after having learned about the trial and

having had the opportunity to ask questions. You should be fully aware of all the details, risks vs. benefits, and expectations of the trial before agreeing to participate. When you give informed consent, you sign a document - which should be in a language that you understand - that describes the rights of the participants as well as gives details of the study and names of the investigators who are conducting the study and contact information for these people.

Is patient privacy maintained in a clinical trial?
Clinical trials are required to maintain strict patient privacy. Your name will not be published anywhere that data about the trial are published or included in any publicly available information. Some clinical trials may require that you be seen and examined by a larger treatment team than would typical medical care. For example, this may include research nurses who only see patients enrolled on clinical trials.

Who can participate in a clinical trial?
Each trial has specific inclusion and exclusion criteria to determine the exact patient populations that may participate. Individuals who fit the predefined and preapproved inclusion criteria for a trial may participate if the trial is currently accepting participants. Inclusion criteria are based on factors such as patient age, gender, the type and stage of a disease, previous treatment history, and other medical conditions. Some clinical trials seek participants with illnesses or conditions to be studied in the clinical trial, while others need healthy participants.

Are people paid for participating in clinical trials?
Some clinical trials offer monetary compensation for participants. Other trials may offer their participants free health care that is related to the condition being studied, or screening examinations. There are no requirements for those who sponsor clinical trials to pay or otherwise compensate participants.

What are the pros and cons of participating in a clinical trial?
The benefits of clinical trials are many and range from taking an active role in the management of one's own health care, helping others by aiding the process of knowledge acquisition and development of enhanced treatments, being cared for by - or in accordance with the protocol which has been developed by - leading health care teams in a given field, and in some cases, receiving access to new treatments before they are approved. However, there are also risks, including side effects of drugs and risks of any procedures that may be performed. In some cases, clinical-trial participation may require more frequent doctor visits or hospitalizations than standard care, and you may have to travel to a study site that is farther away than your local health-care practitioner's office.

Some questions you may want to ask before participating in a clinical trial include the following:

- What is the purpose of the trial?
- Is a new type of treatment being tested? How does this differ from the accepted or standard therapy for my condition?
- Has the drug or treatment ever been tested before?
- How will participation impact my daily life and schedule? Will it be necessary to be in the hospital?
- What are the risks and possible side effects of the treatment?
- Who will pay for the treatments? Will I receive reimbursement or any type of compensation for my time or expenses?
- How long is the trial expected to last?
- How will I receive results of the trial, and how will I know if the treatment is successful?

Can a person leave a clinical trial once it has started?
An informed consent document is not a legal contract that requires participation in a study for the length of a study. A participant is free to leave a clinical trial at any time without prejudice to their ongoing medical care. They will not have access to the experimental medicine being studied if they leave the trial.

Who sponsors clinical trials?
Clinical trials can be sponsored or funded by a variety of organizations or individuals. Federal agencies such as the National Institutes of Health (NIH), the Department of Defense (DOD), and the Department of Veteran's Affairs (VA) frequently fund and sponsor clinical trials. Additionally, clinical trials may be sponsored by medical institutions, charitable foundations, advocacy groups, physicians, and/or biotechnology or pharmaceutical companies.

What happens after a clinical trial is completed? Is there follow-up care?
The researchers in the trial will stay in contact with participants and inform them of the conclusions of the trial. In some cases, you may be asked to provide long-term follow-up in the form of patient surveys or periodic health examinations. Since most clinical trials provide short-term treatments related to a specific condition, they are not a substitute for primary health care. Your regular health-care provider should be aware of the trial and will work with the researchers during the trial. When the trial is over, you will continue to receive care through your primary care provider and any other practitioners required for your condition.

Clinical Trial Registration
What is trial registration?
WHO regards trial registration as the publication of an internationally-agreed set of information about the design, conduct and administration of clinical trials. These details are published on a publicly-accessible website managed by a registry conforming to WHO standards.

Why is Trial Registration Important?

The registration of all interventional trials is considered to be a scientific, ethical and moral responsibility because:

There is a need to ensure that decisions about health care are informed by all of the available evidence

It is difficult to make informed decisions if publication bias and selective reporting are present.

The Declaration of Helsinki states that "Every clinical trial must be registered in a publicly accessible database before recruitment of the first subject".

Improving awareness of similar or identical trials will make it possible for researchers and funding agencies to avoid unnecessary duplication.

Describing clinical trials in progress can make it easier to identify gaps in clinical trials research

Making researchers and potential participants aware of recruiting trials may facilitate recruitment

Enabling researchers and health care practitioners to identify trials in which they may have an interest could result in more effective collaboration among researchers. The type of collaboration may include prospective meta-analysis.

Registries checking data as part of the registration process may lead to improvements in the quality of clinical trials by making it possible to identify potential problems (such as problematic randomization methods) early in the research process.

You cannot register a trial with WHO. The WHO ICTRP is not a clinical trials registry.

To register a trial, submit the details directly to any one of the Primary Registries in the WHO Registry Network or an ICMJE approved registry.

To meet the requirements of the International Committee of Medical Journal Editors (ICMJE) you can register your trial with any Primary Registry in the WHO Registry Network or an ICMJE approved registry.

To meet WHO requirements for transparency and publication, it is only necessary for your trial to be registered once, in either a Primary Registry in the WHO Registry Network or an ICMJE approved registry.

NOTE: Regulatory, legal, ethical, funding and other requirements for oversight and conduct of clinical trials differ from country to country. It is recommended that those responsible for conducting a clinical trial check to make sure they are complying with the specific requirements of each country.

Organizations with Policies

The organizations listed below have policies on clinical trial registration. If you know of an organization that could be added to this list, please contact us.

Codes of Research Practice

Guidelines for the Conduct of Research in the Intramural Research Program at NIH

NHMRC, Australian Code for the Responsible Conduct of Research

UK Research Integrity Office, Code of Practice for Research (3.7.13)

Funders

Canadian Institutes of Health Research (CIHR)

National Institute of Allergy and Infectious Diseases

National Institutes of Health (NIH), United States of America

Well come Trust

Ethics Committees

Mc Master University

Health Research Authority (HRA), UK

The Royal Children's Hospital Melbourne

Legal Requirement

Agência Nacional de Vigilância Sanitária (ANVISA), Brazil

Drugs Controller General, India

European Commission

Food and Drug Administration (FDA) Amendment Act 2007

Ministerio de Salud, Argentina

Ministry of Health, Israel: Guidelines for Clinical Trials In Human Subjects

Department of Health, South Africa

National Health Act of 2004

South African Good Clinical Practice Guidelines - 2006

Swiss National Clinical Trials Portal (SNCTP/Kofam)

National Research Ethics Oversight Agencies

National Statement on Ethical Conduct in Human Research (2007), Australia

Tri-Council Policy Statement: Ethical Conduct for Research Involving Humans (TCPS), Canada

Professional Organizations

American Medical Assocation

European Medical Research Councils / European Science Foundation

FairDrugs.org: Call for Ethical Clinical Trials in Developing Countries

National Health and Medical Research Council: Australian Code for the Responsible Conduct of Research

Pan American Health Organization

Red Latinoamericana de Ética y Medicamentos (RELEM): The Buenos Aires Declaration on the Ethics of Clinical Trials

The Association for Research in Vision and Ophthalmology

The Society for Clinical Trials
World Medical Association: Declaration of Helsinki

Publishers
British Medical Journal (BMJ)
Council of Science Editors (CSE)
Pan American Journal of Public Health
International Committee of Medical Journal Editors (ICMJE)
SciELO (Scientific Electronic Library Online)
Statement on Publishing Clinical Trials in Indian Biomedical Journals. Indian J Med Res 127, February 2008, pp 104-105
Joint Statement of Establishing Chinese Clinical Trial Registration and Publication System. Chinese Clinical Trial Registration and Publication Collaboration
World Association of Medical Journal Editors (WAME)

Universities
Boston University Medical Campus
Imperial College London
University of Oxford

The Universal Trial Number (UTN)
The aim of the Universal Trial Number (UTN) is to facilitate the unambiguous identification of clinical trials. The UTN is not a registration number.

The UTN is a number that should be obtained early in the history of the trial. The UTN should:
- Become permanently attached to the trial
- Be used whenever information about the trial is communicated
- Become part of the trial's identity
- Be documented in the trial protocol
- Be submitted every time the trial is registered.

It is recognized that some UTNs will be attached to trials that do not progress; that is, trials that never become fully developed protocols and that never recruit participants. Some UTNs will therefore never appear attached to a registered trial.

When should a UTN be obtained?
It is recommended that the UTN be obtained as soon as the first draft of the protocol has been compiled, although it can be obtained either sooner or later. For example:
- As soon as an investigator has an ideaas soon.
- As the idea becomes a research proposalat the time the first draft of the protocol is compiled.
- At the time the first meeting is held to discuss the protocol.
- At the time the first meeting of potential investigators is held.

A UTN may be obtained later in the trial's history (e.g. at the time of submission to the first ethics committee, or at the time of submission to a funding agency). It is likely to be more effective in unambiguously identifying a trial, though, if it is obtained early.

How can we obtain a UTN?
The process of obtaining a UTN involves 2 stages:
- Applying for and obtaining a security code
- Applying for and obtaining the UTN

To apply for the security code, the applicant will need to provide:
- The name of the individual submitting the request (Requestor)
- The email address of the individual submitting the request
- The Requestor's organization

An email containing a secure hyperlink will then be sent to the email address entered. You should click on the hyperlink which will take you to the 'Get UTN' web site, where you should click on 'Get UTN'. The UTN will then be sent to you in an email.

Who should obtain the UTN?
The Sponsor, the Principal Investigator or other appropriate person (for example, the administrator of a collaborative trials group) should obtain a UTN for each trial.
How many UTNs should a trial have?
One only.

What should we do with the UTN?
You should use it every time you need to identify the trial. The UTN should be submitted whenever the trial is registered. It may be entered into a field dedicated specifically to the UTN, or it may be entered into the secondary identifier field.

Is the UTN mandatory?
No, the UTN is not currently mandatory, although some registries may choose to make providing the UTN mandatory in order to register a trial on their registry.

What should we do if a trial registry does not have a separate field for the UTN?

If a trial registry does not have a specific field for the UTN, enter it in the secondary identifier field.

How will the UTN work?
The UTN will be one of many identifiers that a trial may have, just as a driving license number may be one of many identifiers that an individual human has. Even though a single object has multiple identifiers, each one may play a role in helping to identify the object. When an individual applies for a passport, for example, they may be required to show 3 forms of identification (such as driving license number, a credit card number, a utilities bill number) to verify that an individual exists. Similarly, when a trial is registered, multiple identifiers may be able to help us to verify that a trial exists.

The UTN will help us to unambiguously identify a trial by enabling us to link (or "bridge") multiple records on the same trial together on the ICTRP search portal.

What if my trial was registered before the UTN?

We recognize that in some circumstances, a trial registered prior to the inception of the UTN may request retrospective assignment. UTN numbers may be issued for previously registered trials.

In order to avoid duplication of records and permit accurate record bridging on the ICTRP, it is strongly suggested that only the coordinating centre apply for the UTN. Once the UTN has been assigned, the coordinating centre should update all records within primary registers and on all other documentation (e.g., ethical review committee submissions, letters, etc) to reflect the UTN.

Remember a trial, no matter how many sites should have only one UTN.

Circumstances where retrospective UTN applications may be considered are:

- Proposal, registered (not yet enrolling
- Trial registered and enrolment terminate
- Trial registered, still enrolling, no new sites
- Trial registered, still enrolling, adding a new site

As the primary purpose of the UTN is to identify a trial through stages of a clinical trial (including registration, approvals, trial recruitment, and participant follow up), the utility of a UTN following trial completion and/or publication is currently limited. While it is possible to apply for a UTN, it is again strongly suggested that this be a centralized process and that all documentation be linked to the UTN, retrospectively.

ICTRP

Introduction

The International Clinical Trials Registry Platform (ICTRP) is a global initiative that aims to make information about all clinical trials involving human beings publicly available. It was established in 2006 in response to demand from countries through the World Health Assembly for:

"a voluntary platform to link clinical trials registers in order to ensure a single point of access and the unambiguous identification of trials with a view to enhancing access to information by patients, families, patient groups and others"{World Health Assembly, 2005 16 /id}

The Secretariat of the ICTRP is housed by the World Health Organization in its headquarters in Geneva and:

- Publishes the ICTRP Search Portal: a web site and database that makes it is possible for anyone in the world to search, for free, data provided by clinical trial registries around the world that meet WHO criteria for content and quality. Data on the portal is updated weekly.
- Supports the WHO Registry Network: a forum for Registries to exchange information and work together to establish best practice for clinical trial registration and the collection of high quality data
- Supports countries and regions: wanting to establish clinical trial registries or policies on trial registration. In some cases, these registries will be a catalyst for other capacity-building activity in clinical trial conduct and oversight -particularly ethical and regulatory oversight.

Any registry that enters clinical trials into its database prospectively (that is, before the first participant is recruited) and meets the WHO Registry Criteria, or that is working with ICTRP towards meeting these criteria, can be part of the WHO Registry Network. The WHO Registry Criteria have been categorized into six main areas:

- Content
- Quality and Validity
- Accessibility
- Unambiguous Identification
- Technical Capacity
- Administration and Governance

Primary Registries in the WHO Registry Network are those that meet all WHO Registry Criteria. Primary Registries meet the requirements of the International Committee of Medical Journal Editors (ICMJE). Partner Registries in the WHO Registry Network must meet most, but not all, of the criteria. Specifically, they are not required to have a national mandate, and they can be limited in scope (for example, to trials in a particular disease or intervention).Data Providers are responsible for a database that is used by one or more registries.

- Data Providers provide data to WHO for inclusion in the ICTRP Search Portal.
- The ICTRP will accept trial records from Data Providers if it is satisfied that those trial records have been created and managed in a manner that is consistent with the WHO Registry Criteria.

Why standards are necessary

The registries in the WHO Registry Network are disparate in remit and functionality. In order to promote harmonisation in the way in which data are collected and validated by these registries and thus ensure a baseline level of data quality, minimum standards need to be determined and implemented. In doing so, participating registries will improve the usability of the World Health Organization's (WHO) International Clinical Trials Registry Platform (ICTRP) Search Portal and ultimately benefit all those looking for and using information about clinical trials. How these standards will be use by the ICTRP. The standards contained in this document are based on the criteria clinical trial registries must attain in order to be recognised as a Primary Registry in the WHO Registry Network, and must maintain in order to retain

that recognition. They are minimum standards and individual registries may choose to impose stricter requirements than those defined in this document. In some instances, ideal standards have also been suggested. All registries in the WHO Registry Network, and registries applying for Primary or Partner Registry status, must be able to demonstrate that they comply with the standards by:

1. Having documented, registry-specific Standard Operating Procedures (SOPs) in place and
2. Providing a written commitment to comply with the standards; and
3. Updating that commitment on an annual basis along with an update of the WHO Registry Profile; and
4. Agreeing to site visits and random audits by the ICTRP Secretariat and/or delegated auditors.

How Registries will use these standards

These standards outline the broad criteria Primary Registries in the WHO Registry Network must fulfil in six main areas: content, quality and validity, accessibility, unambiguous identification, technical capacity and administration and governance. Primary and Partner Registries in the WHO Registry Network must adapt these broad standards into registry-specific SOPs which detail the way in which each of these standards are operationalized within each registry.

Translation of these standards

These standards have been developed, and will be maintained, in English. Registries may choose to translate these standards into the language/s used by registry staff; however the registry must take responsibility for any translation, and ensure that at least two (2) people have checked and confirmed the accuracy of the translation.

Updating these standards

The intention is to update this standards document in 2013. Individual standards may be updated on ad hoc basis, depending on need. Any proposed modifications, revisions or additions made in the interim will be posted to and discussed on the WHO Registry Network Share point. Once a new or modified standard is agreed it will be posted to the ICTRP's web site. Registries are advised to regularly check the Share point and ICTRP web site to make sure they are part of the discussion around new standards and are using current information.

Other standards

Several other organizations have developed standards that relate either directly or indirectly to those contained in this document. These include the International Committee of Medical Journal Editors (ICMJE) updated statement on trial registration requirements (see: www.icmje.org/update_june07.html); the Ottawa Statement (see: http://ottawagroup.ohri.ca/); and data interchange standards initiatives such as CDISC (see: www.cdisc.org), HL7 (see: www.hl7.org) and others. The standards contained in this document are in accordance with the ICMJE requirements for trial registration.

Responsibilities

Minimum international standards defined in this document.

There are several parties which have responsibilities in ensuring that we all have access to complete and meaningful information about clinical trials being conducted throughout the world. Responsibilities of the RegistryA registry accepting trials for registration must make all reasonable efforts to ensure that an individual who is submitting a trial for registration (known as the Responsible Registrant)

i) is a real person
ii) is the appropriate person to be registering the trial, and
iii) provides complete, accurate and meaningful data for each item in the WHO

Trial Registration Data Set at the time of initial registration Registration Data Set.Registries are also responsible for ensuring they have quality control processes and procedures in place to ensure compliance with all of the

Responsibilities of the Responsible Registrant

The Responsible Registrant is an appropriate representative of the trial's primary Sponsor. The Responsible Registrant is responsible for making sure that the data submitted for each item in the WHO Trial Registration Data Set for a trial is complete, accurate and meaningful at the time the trial is initially registered. They are also responsible for keeping that data up-to-date.

The Responsible Registrant will make every reasonable effort to ensure that a trial is registered once, and only once in any one register, and that the trial is registered in the fewest number of registers necessary to meet applicable regulations. If a trial is, by necessity, registered in more than one registry then the Responsible Registrant is responsible for ensuring that all known identifiers for the trial are included in each registry's record as Secondary Identifiers to facilitate unambiguous identification of the trial.

Other stakeholders with responsibilities

Comprehensive prospective trial registration is a global effort that requires the assistance of more parties that just Responsible Registrants and the Registries to which they submit their data. Journal editors, ethics committees / institutional review boards (IRBs), regulatory authorities and funding agencies can all play a major role in ensuring complete research transparency by requiring trials under their auspices to be prospectively registered. In this way we can achieve the goal of ensuring that all involved in research in humans accept that the registration of all interventional trials is a scientific, ethical and moral responsibility.

The Standards

The minimum standards which must be attained to satisfactorily meet the requirements of a Primary Registry in the WHO Registry are defined in this document. To apply for, and retain, status as a Primary or Partner Registry in the WHO Registry Network, Registries must fulfil allof the minimum standards.Unless otherwise stated, the terms "registry" or "registries" refers to Primary Registries in the WHO Registry Network throughout this document.

CONCLUSION

In view of the above facts, we have learned that the Clinical Trial help find new ways to prevent, detect, or treat diseases that are safe and effective. Each clinical trial has criteria describing who can join. Children as well as adults, healthy volunteers and patients, and people of a diverse range of ethnic and racial backgrounds can and are encouraged to participate in clinical trials. Clinical trials offer hope for many people, while giving researchers a chance to find treatments that could benefit patients in the future. Healthy volunteers say they take part to help others and contribute to moving science forward. People with an illness or disease may take part to help others, but also to have a chance to receive the newest treatment and get added care and attention from the clinical trial staff. Clinical trials may involve risk, as can routine medical care and the activities of daily living. When weighing the risks of clinical trials, consider the possible harms that could result from taking part in the study, the level of harm, and the chance of any harm occurring.

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