CLINICAL TRIALS

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Good Clinical Practice and Ethical Aspects

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Introduction

Evidence for the usefulness of medical treatments is gained in a variety of ways, the "gold standard" of which is a clinical trial. Clinical trials are the tool used to test the safety and efficacy of most new diagnostic and therapeutic measures in patient populations. Although some medical developments (such as surgical techniques) become accepted as standard practice based on careful clinical observations without a comparative clinical trial, most new therapeutic treatments follow from laboratory experiments performed in tissue culture or in animals. It would be unreliable to translate any of these ideas into medical practice without careful controlled clinical trials. These are phase I–IV clinical trials. The first phase (phase I) is to study, for example, drug delivery and toxicity in healthy volunteers or patients with advanced or incurable diseases. Then in phase II to study drug efficacy and activity in a larger group of patients. Following successful phase I and II studies, a new treatment must be tested against the best existing conventional therapy by means of the phase III study, or randomized controlled trial (RCT). If the new treatment proves superior, it will be submitted to government regulatory authorities for approval, which allows the producers to market the drug and doctors to use it in the treatment of patients. After approval, further trials may be done and ongoing surveillance of treatments is carried out either by individual doctors and institutions auditing results or by reporting of adverse events (phase IV). This article will concentrate on the RCT and, in particular, how this applies to new drug treatments, although it should be borne in mind that these observations apply to any therapeutic intervention.

The Randomized Controlled Clinical Trial

The first clinical trial was ascribed to the British naval surgeon James Lind who wrote in 1753:

> On the 20th of May, 1747, I took twelve patients in the scurvy aboard the Salisbury at sea. Their cases were similar . . . Two of these were ordered a quart of Cyder a day. Two others took twenty five drops of elixir vitriol . . . Two others took two spoonfuls of vinegar . . . Two were put under a course of Seawater. Two others had each 2 oranges and one lemon. Two remaining the bigness of a nutmeg . . . The consequence was the most sudden and visible good were perceived from the use of the oranges and lemons.

In the modern context, the RCT was first developed by RA Fisher in the 1920s for agricultural research, and was introduced some 20 years later into medicine in a trial evaluating antibiotic treatment for tuberculosis. An RCT is a study in which a cohort of subjects with a defined disease is randomly allocated to one or other treatment (which may be an established versus either a new treatment, or using a placebo drug as the control) and their outcomes recorded. The advantages

of an RCT are that randomization avoids the types of bias inherent in observational studies, such as confounding, which may result in apparent differences between treatment groups which do not in fact exist, and that by recruiting large numbers of subjects to a trial the chance that the outcomes between the two arms will differ because of unequal distribution to risk factors becomes small. It is possible to calculate this probability – the *P*-value. If a trial is designed to encompass any patients with a given condition the results can be generalized to the prevention or treatment of the disease as a whole.

The disadvantages of RCT include the randomization process and the difficulties this causes both subjects and researchers, in particular with regard to consent and the effects on the doctor–patient relationship, the concept of equipoise, and the use of a placebo arm in trials. These will be explored in this article.

Design, Conduct, and Review of RCT

An RCT is a carefully designed test to see if one treatment (usually a new one) is superior to an existing treatment. Performing an RCT is a substantial undertaking, requiring cooperation between doctors, scientists, statisticians, and usually a pharmaceutical or biotechnology company (the "sponsor") that has discovered the product to be tested. The first step is to decide how the efficacy of the treatment will be decided (e.g., survival rate of patients with cancer, level of neurological function in patients with multiple sclerosis) and what level of improvement over current treatment the new treatment is expected to produce. For example, if a certain type of cancer has a survival rate of 75% of patients being alive at five years with current treatment, a promising new treatment might be expected to increase this percentage to 85%. The statistician will be able to calculate how many patients will need to be included in the trial to detect this difference reliably if it exists, and how long the patients will need to be followed up. To detect reliably relatively small differences in outcomes, RCTs may involve many hundreds or even thousands of patients.

All RCTs (and indeed all clinical trials of any phase) are set down in detailed written protocols. The protocol is basically an "instruction manual" for undertaking the trial. As well as the prespecified statistics, the protocol will include a list of precisely which patients will be able to enter the trial (called "eligibility criteria"), what treatments they will receive, what tests will be done and when, and what modifications will be made to the treatment if it produces side-effects.

Before the trial can commence, the protocol will be subjected to extensive review by doctors and other experts in the field of medicine relevant to that trial. As well as this, all hospitals and clinics where patients in the trial will be treated must have the trial approved by their ethics committee.

In all clinical trials, patients can only be entered on to the trial after they have provided informed consent. Nearly always, this consent is written and patients are given an information sheet that explains to them the reasons they are being invited to join the trial, what the trial treatments are, and what the potential side-effects and risks are. This written information sheet is also reviewed by the ethics committee to ensure it is sufficiently clear and contains the relevant information. As well as written information, patients will be given a verbal explanation of the trial by the principal investigator, or a member of his/her research staff.

To undertake a study which is not likely to answer the scientific question posed is not only bad science, but also unethical: the patient is being subjected to tests or treatments of which the efficacy cannot be proven in the study. To overcome this, major funding agencies and many ethical committees insist that any proposed research is carefully scrutinized by peer-review processes. When an RCT commences, the sponsor will often set up a committee to review the progress of the trial and assess any problems that may arise. This committee will contain independent medical experts and statisticians who are not involved in the conduct of the trial, and reports regularly to the sponsor. Their recommendations may range from minor matters, such as small changes to the trial treatment and tests done, to recommending the trial be stopped if they think there are new data that may indicate a serious risk to patients.

An example of this "early stopping" happened in May 2002 when an arm of the Women's Health Initiative Study was stopped four years early. In this study, otherwise healthy older women were randomized to receive hormone replacement therapy (HRT) or placebo, the hypothesis being that HRT would prevent a number of diseases, including heart disease. In fact, a little over halfway through follow-up it was found that there was an excess of heart disease (as well as excess breast cancer and stroke, a more expected outcome) and that this very small increase had exceeded the stopping rules. Ethically the trial monitors had to stop the study – it appeared that women in the study had more heart disease, not less, as a result of taking HRT, although there were no excess deaths recorded. However, many clinicians and scientists in the field were disappointed, as stopping the trial early meant that we will never know if taking HRT makes women more or less likely to die

from heart disease, and it is unlikely we will ever again be able to repeat this kind of study.

International Guidelines

The ethics of human experimentation were first widely debated following the disclosure of Nazi practices during World War II. In 1946, at the trial of 23 German doctors charged with "war crimes" and "crimes against humanity" for their experimentation on prisoners of war and civilians, the Nuremberg Code was established. This code aimed to protect the interests of human participants in research. Building upon this, the World Medical Assembly in 1964 adopted the Declaration of Helsinki containing "recommendations guiding physicians in biomedical research involving human subjects." This was most recently adopted at the 52nd World Medical Association General Assembly in 2000.

These guidelines recommend that a patient should firstly be assured of the best proven diagnostic or therapeutic method, and that any new treatment being tested will be at least as advantageous as any other, with a reasonably low chance of side-effects. The patient must be informed of the benefits and hazards of all possible treatments, and must be free to refuse to participate in a trial or withdraw at any time. The physician must also be free to change to another treatment if he/she feels this will benefit the patient. The patient may also anticipate that the doctor/investigator will keep any excess investigations in the trial to a minimum.

A number of other international agencies are involved in research guidelines. The European Directive on Good Clinical Practice in Clinical Trials, published in May 2001 (adopted in the UK in May 2004, administered by the Medicines and Healthcare Regulatory Agency (MHRA)) is one of the most far-reaching of these research guidelines. It stipulates tight control and reporting guidelines for clinical research which may well prove costly and unwieldy in practice – in fact, the UK Medical Research Council (MRC) and main UK cancer charity, Cancer Research UK, have assessed the impact of this on UK research and estimated the added bureaucracy and cost could lead to a fall in research output of 90%.

In the USA, the National Committee for Quality Assurance and the Joint Commission on Accreditation of Healthcare Organizations have collaborated to form the Partnership for Human Research Participation, which accredits institutions, and has a national set of standards and a voluntary oversight process that complements current regulatory efforts. Driven by a number of disasters in research, the American Society of Clinical Oncology has developed policies for conduct of clinical research that aim to enhance public trust in clinical trials by ensuring safety and informed consent, ensuring the integrity of research, encouraging training of researchers, providing accountability and support for the oversight process, and enhancing efficiency and cost-effectiveness of this process. They recommend centralized ethics approvals, education in both science and ethics for researchers, a focus on the process rather than document of consent, federal oversight of research, improved local infrastructures, and avoidance of conflicts of interest.

In the UK, a number of individual medical bodies have also developed guidelines. These include the MRC, the Royal College of Physicians, the King's Fund, the British Medical Association, the Medical Sterile Products Association, and the Association of the British Pharmaceutical Industry (ABPI). There is no statutory legislation on human experimentation (except the Human Fertilization and Embryology Act 1990); however, pharmaceuticals are regulated via the MHRA.

A Patient's Journey through a Clinical Trial

The clinical trial process is described in Figure 1.

Ethical Dilemmas in Clinical Trials

RCTs provoke ethical controversy for several reasons. One of the main reasons is that, in an RCT, the treatment a patient receives will be determined by random allocation rather than directly by the doctor and patient themselves. This is contrary to the usual model of medical care where treatment decisions are made by the doctor advising the patient of his/her recommendation and what alternatives there are. In an RCT, both the doctor and the patient must be comfortable with the process of randomization.

An RCT is aiming to test whether a new treatment is better than the "best" current treatment. The concept of "equipoise" has been used to describe the situation where the doctor believes that the patient's best interests would be equally served regardless of which treatment he/she was randomized to. In that circumstance, deciding treatment by random allocation is ethical. However, if the doctor honestly believes that, for an individual patient, one of the treatments in the trial is likely to be less effective or more risky than another treatment, then the doctor is not in equipoise and should not recommend that patient enter the trial.

Equipoise has also been extended beyond the individual doctor to encompass the body of expert

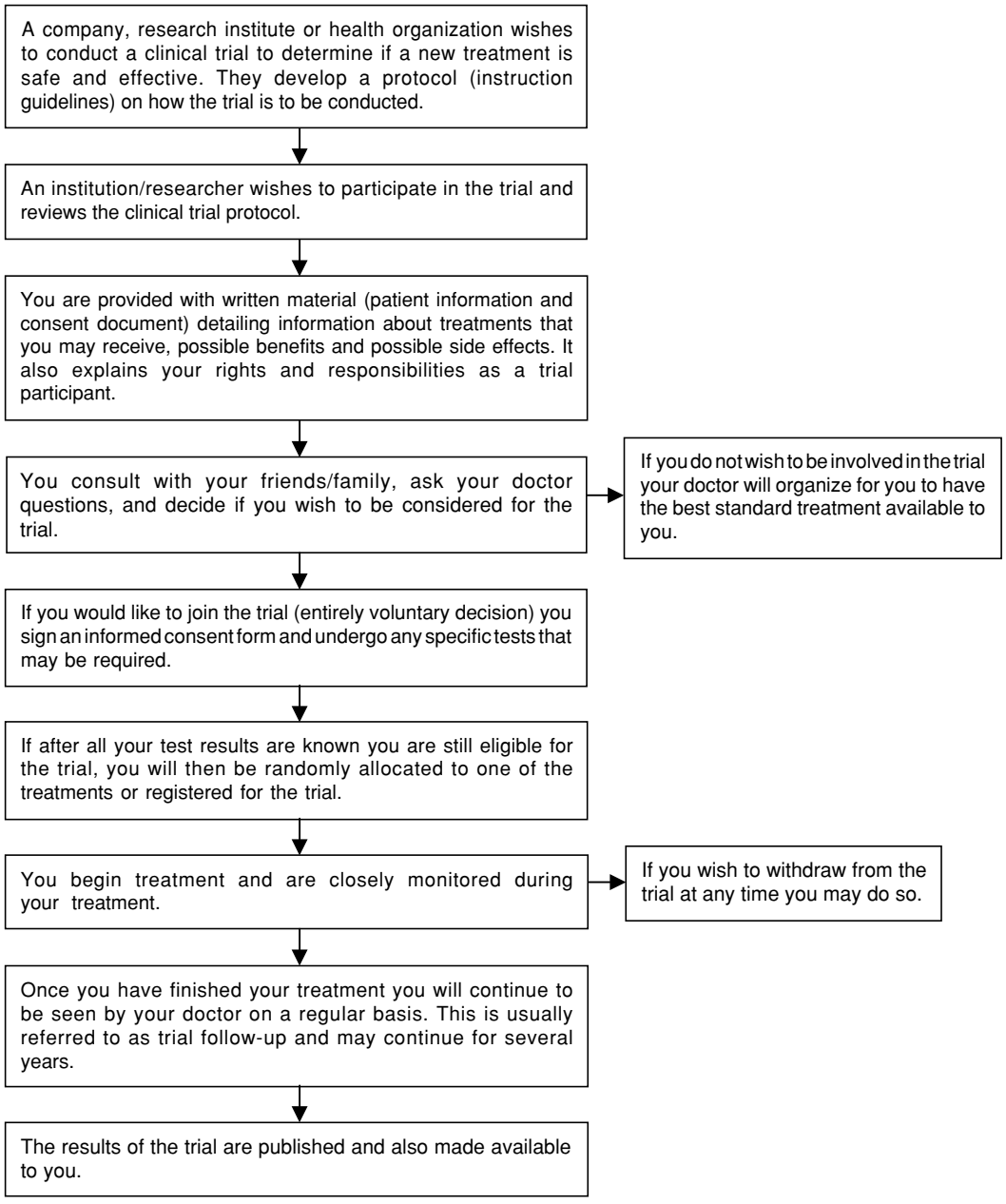

Figure 1 The clinical trial process.

medical opinion about the best treatment for a disease. Suppose there are two ways of treating that condition and among the medical community some doctors always use method A, some always use method B, and others use either A or B depending on individual circumstances. In this scenario, there is "professional equipoise," even though some individual doctors honestly believe A or B is the best treatment. It is ethical to perform an RCT that determines exactly which is the best treatment and all doctors could ethically participate, although many of the "committed" ones may not wish to do so.

Another ethical dilemma in RCTs involves the use of placebos. A placebo is an inactive inert substance with no therapeutic effect, made to look like the treatment being tested (e.g., a pill of the same color). In an RCT involving a placebo, the patient and often the doctor will not be told if the pill the patient is taking is the active treatment or the placebo. Some patients who are treated with placebo report that their symptoms do improve (placebo effect), probably as a result of the positive psychological effect associated with receiving "treatment." However, placebos cannot be ethically used if there is a proven effective

treatment for that condition. The only time it is ethical for patients to receive the placebo treatment is where there is genuinely no other treatment or (rarely) where the disease is so mild that no treatment is required at that time.

The placebo issue has recently come into focus again because some placebo trials have been carried out in developing countries for conditions such as human immunodeficiency virus (HIV) where there is proven effective treatment in the developed world. Some researchers have argued that such trials are ethical because the effective treatment is not available to these patients because of their cost and thus there is really "no effective treatment" for them. Thus they could not be worse off by receiving a placebo. However, others have argued that performing such trials only exploits already suffering populations deprived of healthcare by using them to gain knowledge that is primarily intended to benefit developed world patients.

Consent in Clinical Trials

To allow a patient to make an autonomous decision to enter a trial, he/she must be fully informed about his/her disease and its treatment. This will include details of the clinical trial the patient is being requested to join, along with the risks and benefits of all possible treatments (of course, a patient outside a trial should also be informed of all possible treatments and not simply the one he/she is offered). If the patient then consents to the treatment or trial then there is informed consent.

But we may be faced with another dilemma: although it is ethically imperative to obtain a patient's fully informed consent before initiating any treatment within a clinical trial, there may be situations in which full disclosure is harmful to the doctor–patient relationship, in particular if the doctor is no longer viewed as offering the patient the "best" individualized treatment, but instead acting as researcher with treatment allocated "randomly". This predicament has been shown to be a major factor in poor accrual rates into clinical trials as the clinical researcher needs to spend considerable effort to explain the trials process to a patient.

The Incompetent Patient

Clinical trials generally require patients to be competent to make informed decisions on whether to enter the trial or not. However in some areas of medicine patients may not be competent to make such decisions. New treatments for childhood diseases must be performed in children below the age of legal consent. Their parent or guardian is able to consent on their behalf, although for older children the doctor will normally give some explanation to the child, and aim to get an understanding if the child at least assents to the trial treatment. Adolescents just below the legal age of consent (18 years in most countries) may formally sign a consent form with their parent/guardian.

Other situations where issues of competency arise are in trials for patients with head injuries, for patients in intensive care units, and for patients with Alzheimer or similar diseases. International guidelines provide some direction on when it is permissible to enroll such patients in trials, and what safeguards need to be in place.

Some writers have suggested that all patients with serious illnesses are incapable of giving fully informed consent to enter trials, as their judgment is clouded by the possibility of death or serious disability. However, serious illness *per se* is not considered sufficient to make a patient incompetent to make other important decisions such as making a will, appointing a power-of-attorney, or deciding to refuse treatment, so it is unlikely that a patient would become incompetent to decide on participation in a trial.

Industry-Sponsored Trials

Development of any new medical product, in particular a new drug, takes at least a decade and many millions of dollars. The final pathway in such drug development is the RCT, thus many are sponsored and run by pharmaceutical companies anxious to prove the worth of their investment. To run such trials requires close cooperation with clinicans who have access to the appropriate patient population and are willing to participate. By necessity there is a cost to this and the pharmaceutical company must recompense the clinical research team. This is often over and above the actual cost of running the trial, with the excess going to fund other research of the team. However, the clinical researcher must walk a fine ethical line in order not to be coerced by financial gain into participation in a trial which does not meet the ethical requirements outlined above. Equally the researcher has to outline any financial gain for him/herself or the department to the potential trial participant.

Ethics Committees

Ethics committees (or institutional review boards in the USA) are tasked with reviewing applications for research projects on human subjects, and can look at a wide range of aspects, from the science of the project, to its ethical viability, to practical aspects such as whether the institution and researchers have the facilities and

expertise to undertake the treatment proposed. A detailed description of the work of these committees can be found on the Central Office for Research Ethics Committees website (www.corec.org.uk).

Conclusions

The RCT is the most useful tool of the clinical researcher, providing the most secure method for evaluating medical treatments. In the 60 years since it has been in use in medicine it has evolved into a scientific discipline in its own right, with complex multidisciplinary methodology and biostatistical tenets, and with accompanying ethical predicaments both for the clinical researcher and for a patient offered participation in an RCT. These issues include trial monitoring, randomization, the use of placebos, and informed consent. These issues need careful consideration in the design and conduct of any RCT, and must meet both international guidelines and the scrutiny of a local institutional ethics committee.

See Also

Clinical Trials: Legal Aspects and Consent

Further Reading

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Legal Aspects and Consent

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Introduction

Legal and ethical concerns overlap closely in the area of clinical trials. Both legal and ethical experts focus on informed consent as the touchstone for the validity of human experimentation in the form of clinical trials. Additional concerns addressed by the law relate to the confidentiality of subjects' information, the type of controls used in clinical trials, and the potential for conflicts of interest that exist in clinical trials. In addition to the availability of possible litigation-based remedies, the law has established independent review bodies to protect research subjects in these areas.

Informed Consent

The doctrine of informed consent applies to both medical treatment and medical research. The United Nations' International Covenant on Civil and Political Rights provides that "no one shall be subjected without his free consent to medical or scientific experimentation." Just as treating physicians must obtain the voluntary, informed consent of their patients who have capacity to consent (or of the legally authorized representatives of their patients without capacity to consent), researchers similarly must obtain voluntary, informed consent from subjects or their legal authorized representatives to experiment on those human subjects.

In the clinical trials context, informed consent has been explicitly addressed in the USA as a matter of federal regulation. Other US laws and various sources of international law and policy similarly address informed consent, in accordance, for the most part, with US regulatory informed consent requirements. Universally, informed consent is seen as the

optimal result of a process of communication between researchers and subjects to ensure that subjects with legal capacity to make decisions understand the nature of the research and its risks and benefits, and voluntarily agree to participate in the research. Formally, an informed consent document, signed by both researcher and subject, must specify the information provided during that process, to memorialize both that the communication occurred and that the subject voluntarily agreed to participate.

The required contents of such informed consent documents may be clearly delineated by law, as they are under US regulations and as suggested by international medical and medical ethical organizations such as the Council for International Organizations of Medical Sciences (CIOMS). Under the US regulations, for example, all clinical trial informed consent documents must include: (1) a statement that the activity in which the subject is participating constitutes research; (2) further details about that research, its purposes, and its procedures; (3) a description of foreseeable risks and benefits to subjects; (4) discussion of treatments or procedures from which the subject (if ill) might benefit rather than participating in the trial; (5) information about the manner in which and the extent to which the researcher will maintain confidentiality of subject records; (6) for certain research, information about whether and to what extent compensation or treatment will be available if the subject is injured during the research; (7) identification of a contact person in case of questions or concerns; and (8) assurance that the subject is agreeing voluntarily and the researcher is not engaging in certain activity that would tend to coerce the subject. The informed consent document may also include additional information.

While required, and while constituting strong evidence, the informed consent document is not definitive evidence of whether the human subject gave informed consent to participation in a clinical trial. Rather, the document should serve as a memorialization of the conversation that is at the heart of the informed consent process. Various members of the team of researchers on any clinical trial, not simply the researcher whose name appears on the informed consent document, may be involved in the conversations during which subjects are told about the clinical trial and are given an opportunity to ask questions about it.

Special Populations

Certain categories of research subject have been deemed worthy of special protection in clinical trials, both generally and particularly with regard to the clinical trials' informed consent process. Children, pregnant women, fetuses, neonates, the mentally ill or compromised, and prisoners are often singled out as deserving of special consideration. More broadly, any potential subject considered to be "vulnerable" might require special care to ensure that the consent provided by that "vulnerable" subject or his/her legally authorized representative is truly informed and voluntary. CIOMS defines "vulnerable persons" as "those who are relatively (or absolutely) incapable of protecting their own interests," meaning people who "have insufficient power, intelligence, education, resources, strength, or other needed attributes to protect their own interests." Among the vulnerable, then, can be the elderly, the economically or socially disadvantaged, subordinate members of hierarchical groups such as medical or nursing students, and the seriously ill.

Persons who are ill and are contemplating participation in a clinical trial merit special consideration in the informed consent process for two reasons. First, a seriously ill person, especially one with a terminal diagnosis, is often less likely than a healthy person to listen to and comprehend information at the level that might be required to ensure informed consent to participate in a clinical trial. Such a person may also not be acting voluntarily in agreeing to participate in a clinical trial, even if there is no apparent source of coercion. This is because persons in such a position are often compliant and needy; they rely on others to be decision-makers rather than making decisions for themselves.

Second, any ill person considering participation in a clinical trial is vulnerable to the so-called "therapeutic misconception." Persons who are ill who consider participating in clinical trials to test the efficacy of proposed treatments for their illnesses usually enter into such trials seeking cures. Although a clinical trial is, by definition, experimental, and although they may be randomly assigned to control groups in which they will not receive the new treatment (and may not receive any treatment), such persons suffer from the misconception that they are being treated through the trial. Clinical trials are not the same as treatment, yet persons who are ill who sign on to be subjects in them often treat them as if they are. To the extent a subject agrees to participate in a clinical trial while operating under this "therapeutic misconception," then that subject's consent may not be informed and voluntary.

The Mentally Incapacitated

Those who are mentally incapable of giving informed consent to participation in clinical trials represent a

distinct special population worthy of mention. While researchers must obtain informed consent directly from subjects who are mentally capable of giving such consent, some researchers may desire to engage in research on subjects who do not have the ability to hear or to understand information about the clinical trials proposed. In such situations, to the extent it is appropriate to proceed at all, researchers must obtain informed consent to participation in those clinical trials by competent persons who are authorized under the law to speak for the incapacitated subjects.

The question of whether it is appropriate to proceed at all requires consideration of the level of risk to which this category of research subject may be subjected. US regulations and CIOMS guidelines, for example, emphasize that research on such subjects must involve no more than slight or minor increases above the amount of risk involved in routine examination. In some instances, as under US regulations, the amount of risk that might be tolerated may vary with the amount of benefit the research may offer either to the subjects or to the population to which the subjects belong.

Additionally, whether it is appropriate to proceed at all may depend on the type of research the researcher intends to perform and whether that research is appropriately performed on the type of mentally incapacitated subject the researcher wishes to utilize in his/her experimentation. Some subjects' inability to understand information may stem from their age; children, for example, are generally presumed by the law to be incapable of appreciating information regarding clinical trials sufficiently to consent to their own participation in them. Yet it may be important to conduct certain research on children because, again for example, children are likely to react differently from adults to certain medications; children may require different procedures than do adults; and some diseases or conditions only appear in children or are best studied when those suffering them are still children rather than adults. In such situations, it would likely be appropriate to proceed with research on children, after complying with particularized safeguards that might apply (for example, under US regulations) when obtaining the informed consent of competent persons who are authorized by the law to speak for the child-subjects. With children above 4 or 5 years of age, some form of child assent to the research is appropriate, in addition to consent from a person legally capable of giving it.

It might be less appropriate to proceed with research on subjects in certain other categories of mental capacity. The mentally ill or retarded, for example, arguably should not be used as research subjects unless the research in question relates in some way to their mental state. Research that could be conducted on the mentally capable should not be conducted on those who are mentally incapacitated. Examples of research on the mentally ill or retarded that could be appropriate, however, could include research into the neurological processes of a person with a certain level of mental retardation, or a study of the types of brain wave activity observable in a schizophrenic patient. In such situations, the research necessarily would require the participation of subjects falling into such categories of mental incapacity. Again, with special safeguards in place, then, it could be appropriate for such research to continue with the informed consent of competent persons who are authorized by law to speak for the subjects.

Yet another category of mentally incapacitated research subjects could include those who once possessed decision-making capacity but who currently are not conscious. Some researchers may desire to engage in clinical trials involving subjects in persistent vegetative states or comas. Once again, this research should not proceed if the research could be performed on subjects with mental capacity. If, however, the proposed research investigated issues related distinctly to the person in a persistent vegetative state or coma, then it might be possible for the research to proceed, as long as the researcher took special care to design the study appropriately to minimize risk and to inform and obtain consent from a competent person authorized by law to speak for the subject.

In all these situations, a variety of persons could be legally empowered to consent to research on behalf of mentally incapacitated subjects, as long as the research at issue was of the type that required participation of mentally incapacitated subjects rather than mentally capable subjects. An incapacitated research subject who once had decision-making capacity may have designated, through a legal instrument such as a durable power of attorney, a person to make decisions on his/her behalf in such situations; such a designation would accord the designee presumptive ability to consent on the subject's behalf. If the incapacitated research subject previously had not designated such a decision-maker – either through inactivity or through legal inability to do so, as with children or those who have always lacked mental capacity – the law generally will provide a list of persons (proxy decision-makers) who can, in the absence of contrary designation, make decisions on behalf of incapacitated persons.

The courts offer resources that should be accessed if there exist any questions. Questions could range

from whether proposed research involving the incapacitated should proceed at all, whether a designee or proxy decision-maker can consent to research rather than or in addition to medical treatment, or whether a particular designee or proxy decision-maker is an appropriate person to consent on a particular subject's behalf. Guardianship proceedings may be instituted to ensure that the person consenting to a research subject's participation is acting in the subject's best interests, or the court may be asked otherwise to decide whether the subject him/herself – assuming he/she was once mentally capable of consenting to participation in clinical trials research – would have consented to the research in question.

Use of Placebos

Another concern arises from the potential for subject misunderstanding when placebos are used as controls in clinical trials. Placebos are inert or ineffective substances or procedures. Examples include sugar pills and sham surgery. In a clinical trial, placebos may be administered to or used with a control group because the researchers conducting the trial wish to test how well subjects receiving a new drug or treatment do in comparison with subjects receiving no drug or treatment. To ensure blindness or double-blindness, all subjects in such a trial must receive something that looks like a drug or treatment. Otherwise, the subjects or the researchers (or both) would know exactly which subjects were receiving the drug or treatment being tested (those getting something) and who were not (those getting nothing).

Some argue that clinical trials should never incorporate placebos if a standard drug or treatment exists for the condition in question. In such cases, the argument goes, the new drug or treatment should only be tested against the current standard drug or treatment. Others respond that even if a current drug or treatment exists, it is valuable to know how effective the new one is as compared with both the current standard and the result occurring when people take or do nothing to treat the condition in question. The law does not prohibit use of placebos in clinical trials, but it does require (1) that use of placebos be appropriate under a risk/benefit analysis of the design of each clinical trial and (2) that those subjects participating in placebo-controlled clinical trials truly give informed consent to such participation.

In some cases of placebo use, true informed consent may not be possible. Misunderstandings can easily arise, and can rise to the level of legal problems, when a subject participates in a clinical trial involving the administration of placebos to a control group without understanding that to be the case. Such misunderstandings are particularly probable in two settings. First, they may be particularly probable when the subject is ill and is participating in a clinical trial testing a drug or treatment for his/her illness. Second, they may be particularly probable when physicians from the developed world are conducting clinical trials in developing countries. In either case, the vulnerable nature of the population being studied in the trial suggests a need to be particularly careful in the informed consent process. The subject who is ill may be likely not to focus on the information provided about placebos because of his/her desire to participate in the trial as a chance for a cure. The subject from a developing country may be likely not to understand information provided about placebos because of communication difficulties, cultural differences, or other variables.

Other Legal Concerns

In addition to informed consent, two additional subjects raise particularly important potential legal issues, although they do not constitute an exhaustive list of legal concerns that could arise in the course of a clinical trial. These additional issues are confidentiality and conflicts of interest.

Confidentiality

Medical information always receives a special level of protection under the law. The confidentiality of medical records must be maintained except in particularly delineated situations, and so it is with information about a subject in a clinical trial. While information about the subjects' reactions to and success or lack of success with the treatment or drug being studied is important to the clinical trial, the identities of subjects are never to be reported and in most cases are not to be revealed to anyone except researchers. Similarly, other information about the subject learned during the course of the trial may not be revealed except in certain narrow circumstances. One example might be information learned during the taking of the subject's medical history.

Exceptions do exist. In some cases, the law requires disclosure despite the general rule of confidentiality. For example, if something learned during a medical exam in the course of a clinical trial indicates currently ongoing elder, child, or spousal abuse, most jurisdictions will require that the information be reported to the appropriate authorities. Similarly, if something learned indicates that a crime has been committed, the law may require reporting to the appropriate authorities. So too must researchers report medical

information tending to suggest the existence of a public health problem, such as a sexually transmitted disease or a communicable disease considered a threat to public health.

Conflicts of Interest

Two types of conflicts of interest may exist between researcher and subject in a clinical trial. The first, which is inherent in any setting involving medical research, does not necessarily lead to a legal problem. Specifically, the interests of researchers are always at odds in some senses with the interests of the human subjects of their clinical trials. Researchers and subjects often have different goals, and subjects often expect researchers to have mindsets corresponding to the subjects' goals rather than to the researchers' actual goals. Especially if they are operating under the "therapeutic misconception" described above, subjects often expect researchers to be looking out for their (the subjects') well-being or best interests. Such expectations are enhanced when the subjects participating in a trial are both ill and patients of the physician conducting that clinical trial. Physicians seek to benefit their patients, but researchers engage in clinical trials to obtain generalizable data tending to prove or disprove a hypothesis rather than to benefit any particular subject. Researchers thus have different focuses than subjects, and their goals likely differ from the goals of the subjects. Such an inherent conflict of interest does not necessarily create a legal concern, for if it did, all clinical trials would be legally suspect. Rather, legal implications may arise from this inherent conflict of interest if, among other scenarios, a subject were found to lack sufficient knowledge or understanding of the parties' roles and goals to have given valid informed consent.

Conflicts of interest may also arise in the clinical trials context in a more explicit way. A researcher may have a monetary or prestige-based stake in a clinical trial's outcome. If significant enough, that stake may give the researcher an incentive to falsify data, to ignore data, or otherwise to manipulate data so that the trial produces the outcome that most benefits the researcher. Thus, conflicts of interest may give rise to legal issues of fraud or other research misconduct.

For example, it is often the case that a number of researchers are conducting clinical trials on the same or very similar drugs or treatments. The researcher who first reaches a scientifically supportable conclusion and publishes his/her findings has the prestige of having made the discovery in question, even if others follow closely. A researcher conducting a trial that is substantially the same as or similar to trials others are conducting thus has an incentive to ignore inconsistent data or signs of problems in an effort to publish his or her findings first. Similarly, if a researcher owns a significant amount of stock in the pharmaceutical company that manufactures a drug the researcher is testing in a clinical trial, the researcher has an incentive to manipulate data so that the drug is shown to be safe and effective. If the drug is shown to be safe and effective, it can be marketed, earning money for the pharmaceutical company and indirectly producing a monetary gain for the researcher because his/her stock in that company will rise in value due to increased earnings from the drug.

Both these situations, should they materialize and cause injury to a subject, would present legal issues of fraud or other research misconduct. The law sometimes attempts to deal proactively with the latter situation. In such instances, in which there exists tangible evidence tending to suggest in advance special cause for concern about a potential conflict of interest, the law (at least under US regulations) will require up-front disclosure by the researcher. Such disclosures must be made to bodies overseeing the clinical trials, although some argue that such disclosures should be made to the human subjects themselves.

Reviewing Committees or Boards

Independent bodies have been established to review the protocols, or descriptions, of clinical trials before such trials begin. Review by such independent entities ensures that the legal and ethical concerns described above, as well as others, have been considered by someone other than the researcher or another interested party. Such reviewing bodies are called institutional review boards, or IRBs, in the USA and names such as ethical review committees, research ethics committees, or ethics review committees in other countries. Although based at the institutions through which the clinical trials are conducted, they are required by law to have what is hoped to be sufficient diversity of membership and a sufficient number of unaffiliated members to ensure independence. They exist to protect the human subjects of clinical trials by considering, among other things, whether it appears the subjects will be given every opportunity to give informed consent, the extent to which the subjects' confidentiality will be maintained, and whether the risks and benefits of each proposed trial seem to be

reasonable, both absolutely and in comparison to each other. Not only must a clinical trial protocol be submitted to such an independent body for review and approval before a trial may be conducted, but the reviewing body will also continue to monitor the trial until the trial has concluded.

These bodies are expected to take special care in reviewing clinical trials being performed on vulnerable populations. International research raises special concerns when the researchers hail from a developed country and the subjects of their clinical trials reside in poor, developing countries. Some of the main concerns that have arisen include whether the subjects in those developing countries are truly giving voluntary, informed consent and whether the risks those subjects are being asked to take are reasonable in relation to the benefits that may accrue to them or to citizens of their country. With regard to the latter concern, some have suggested that the law should provide that clinical trials cannot take place in developing countries unless the drugs or treatments resulting from the trials will be made available in those countries after the conclusion of the trials.

See Also

Clinical Trials: Good Clinical Practice and Ethical Aspects; **Consent:** Treatment Without Consent; Confidentiality and Disclosure; **Medical Records, Access to**

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