THE ETHICS OF PHASE IV CLINICAL TRIALS

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Overview

This course aims to help neurologists in community practice better understand key ethical issues related to their participation as clinical researchers in Phase IV trials. This is becoming an especially important topic given the increasing emphasis on doing clinical research in private practice by influential organizations such as the American Academy of Neurology (AAN) and the National Institutes of Health (NIH).

Objectives

On completing this course, learners will have improved knowledge of the ethics of (1) subject recruitment and procedures for informed consent, and (2) subject privacy and confidentiality. Also, they will better recognize and resolve (3) the distinction between human research subjects and patients, and (4) the potential for clinical research bias in funded studies.

Why Participate in Clinical Research?

Clinical research is key to developing evidence-based patient treatments, as underscored in the AAN's NINDS Clinical Research Collaboration Colloquium occurring at the same date and time as this course. The AAN and NINDS collaborated to develop the CRC to directly engage practitioners and allow them to conduct NINDS sponsored office and community based clinical research activities, ranging from patient examinations and blood tests to more complex observations in drug and device trials. Greater numbers of practitioners trained in clinical research should increase the chance of recruiting subjects to clinical trials and allow better results with greater statistical power.

What are clinical research trials? NIH-Definitions

The NIH defines clinical research as research conducted with human subjects or on materials of human origin (e.g., tissue specimens) in which investigators interact directly with human subjects (1). This research may examine new diagnostic techniques of therapies, disease mechanisms, epidemiologic, behavioral, outcome and health services research, and includes clinical trials.

The NIH defines clinical trials as prospective studies in human subjects designed to assess the safety, efficacy, and value of one or more interventions against a control (1). These new drugs, devices, treatments, preventive measures, or techniques are selected according to a priori criteria of eligibility and assessed for specific effects or outcomes. There are four clinical trial phases:

> Phase I trials "evaluate the safety of diagnostic, therapeutic, or prophylactic drugs, devices, procedures, or techniques in healthy volunteer subjects or in patients." They involve few participants and aim to "determine pharmacologic and pharmacokinetic properties, structure/activity relationships, safe dosage range, toxicity, metabolism, absorption, elimination, or preferred route of administration.
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> Phase II trials also involve relatively few subjects (perhaps a few hundred) and aim to determine the safety, efficacy, or optimum dosage schedule of one or more diagnostic, therapeutic, or prophylactic drugs, devices, or techniques.
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> Phase III trials involve larger groups of participants (hundreds to thousands) aim to determine if there are clinically significant responses if Phase II trials suggest effectiveness.
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> Phase IV trials are intended to obtain additional data about the safety and efficacy of diagnostic, therapeutic, or prophylactic drugs, devices, or techniques that have been approved for general use.

Phase IV Trial Special Issues

Clinical trial phase IV studies have the same ethical requirements as Phase I-III trials with respect to informed consent, confidentiality, and safety protections. However, because these phase IV trials are conducted in a clinical setting and use approved products, there may be blurring of the distinction between clinical treatment and research. Also, because phase IV trials use products that are already approved for sale, they may be at risk for becoming a product marketing effort as opposed to a clinical research effort. Investigators becoming involved in Phase IV trials may have less experience with the rigors of clinical research than investigators in earlier phases of research who make more of a career of research. Even experienced researchers at distinguished institutions have been cited for committing ethical errors in clinical research trials. Because of these concerns, the subject/patient and clinical researcher must be highly vigilant in the course of phase IV trials, as must all researchers in all types phases of clinical research (8).

Conflicts of Interest and Researcher Bias: Patients and participants in clinical trials must be carefully protected from the interests and bias of the clinician/researcher. This investigator may feel pressured to meet quotas to satisfy government sponsors (such as the NIH) and industry sponsors (such as pharmaceutical companies). In these matters the clinical researcher must steer clear of conflicts of interest, by learning to avoid situations in which the primary interests of patient welfare or research integrity are disadvantaged by secondary interests such as the researcher's financial or professional gain (2).

Financial conflicts of interest include potential financial gain for the investigator, and perhaps the need to compete successfully for research funds. Due to the common practice of paying investigators per subject enrolled in the research, there is the potential for financial interests to be in conflict with human research subjects' interests. But there are also other potentially important competing interests, such as the desire for professional recognition (3). The desire for fame and fortune is a common human condition that must not compromise research integrity, as apparently occurred in the case of Dr. Woo-Suk Hwang, the stem-cell researcher and Korean national hero whose reputation was destroyed after worldwide media outlets broadcast evidence of data fabrication in his basic science research.

Pressures on Clinical Researchers: Under-recruitment of human research subjects is the bane of clinical research studies. In "Recruiting Human Subjects Pressures in Industry-Sponsored Clinical Research", The Department of Health and Human Services, Office of the Inspector General (OIG) studied how clinical researchers may be influenced in the conduct of clinical trials (4). This OIG study concluded that greater efforts were needed to ensure that recruitment of potential clinical research subjects was not coercive or misleading.

Efforts to boost human research subjects recruitment include sponsors offering financial and other incentives to participants and clinical investigators, advertisements and promotions by sponsor and investigators, and clinical investigators targeting their own patients or seek subjects from physician referrals, registries, organizations.

There are several ways clinical research recruitment practices may undermine the informed consent process. For instance, ethics concerns arise when a clinician investigator, pressured to recruit participants, may misuse a position of trust and authority to unduly influence patients to participate. This can involve misrepresenting the nature, risks and potential benefits of the research. This also includes practices such as contacting patients multiple times to persuade them to enroll after they've expressed no interest or already said "No!" and coercing ineligible individuals to participate in a study (e.g., by suggesting a person will get sicker or be dismissed from a hospital or nursing home if he or she declines to participate).

Another concern is breach of confidentiality, which may occur if someone other than a patient's own doctor gains access to and searches the patient's medical records without the patient's permission, and then contacts the unsuspecting patient about participation. Similar confidentiality concerns pertain to investigators inappropriately accessing patient registries, school records, mailing lists, organization memberships and other records.

Psychology, Sponsorship and Research Bias

Many clinical investigators approach their research and potential treatments with enthusiasm and hope. They may also have a sense of product loyalty and a sense of gratitude and perhaps even fear with respect to sponsors. Forgas provides psychological explanation for understanding how affective factors change investigator biases and judgments, which includes biases and judgments toward clinical trials (5).

Bekelman, Li and Gross reviewed the scope and impact of financial conflicts of interest in biomedical research by searching data sources in Medline and other sources between 1980 and 2002 (3). Their results showed statistically significant associations between industry sponsorship and pro-industry conclusions, and between industry sponsorship and restrictions on publication and data sharing. The authors concluded that financial relationships among industry are pervasive and affect research outcomes and dissemination in critical ways. In a similar vein, Lexchin, Bero, Djulbegovic, and Clark assessed Medline articles and other sources between1966 and 2002 and found a systematic favoring of products made by the company funding the research (6). Potential explanations for these findings included research study design flaws, such as selecting an inappropriate comparison drug to the one being investigated, as well as publication bias (e.g., not publishing negative or unfavorable results).

Understanding Informed Consent

Despite every effort, some human research subjects may not understand the content of the research in which they agree to participate, even if they sign the consenting documents. By definition, without understanding, there is no informed consent. It is difficult to prove that every subject understands all the points in an informed consent document. However, it is possible to design the informed consent documents and procedures to maximize the clarity of the message delivered to the potential research participant. It is also possible to debrief the potential participant and the participant's family members to ensure that the key elements of the clinical research project described in the informed consent documents have been understood.

Regrettably, it appears that: 1) Informed consent documents have grown in length and complexity over the past several years due to the growth of legal and governmental requirements for full disclosure; 2) There is inappropriate use of technical and scientific jargon; 3) There is excessive inclusion of details describing complicated research procedures by researchers who wish to have their experimental methods fully understood; and 4) There has been an increase in exculpatory language in research funded by for-profit companies at risk for costly litigation.

Consequently, some portions of informed consent documents require relatively high level reading skills to be understood. Unfortunately, many American adults have poor literacy skills and cannot read above elementary grade levels, even if they have completed a higher academic grade. Indeed, the adults who sign informed consent documents often perform several grades below their own historical levels of academic achievement on reading comprehension tests (9). Some of these adults have been out of school for many years and have simply lost their academic skills through disuse.

Other potential research subjects are cognitively impaired as a result of acute or chronic illness. Cognitive disabilities may impair the understanding of the language of informed consent, making it difficult for them to decide whether to become a research participant. The population of adults most at-risk for such impairment is individuals over age 60, the fastest growing sector of the American population.

Elderly individuals also have the highest prevalence of neurological disorders (such as stroke and Alzheimer's disease), visual dysfunction (e.g., cataracts, glaucoma) and medical problems (such as arthritis, cancer and heart disease) producing insomnia, pain, anxiety, which also affect the ability to process new information. These individuals are subject to multiple hospitalizations and medications, and often are requested to participate in medical research. An increasing body of evidence is raising greater bioethical concerns on how well these individuals understand informed consent documents.

Solutions

Clinical research is extremely important and so are patients' and human research subjects' rights. The challenge is to ensure these protections of patients and research participants without needlessly hindering new clinical findings that may ultimately benefit society.

Protecting clinical research participants from exploitation and harm is the basis for subsequent ethical requirements and regulations by agencies of institutional and federal oversight (7). Education on the proper practices and pitfalls of clinical research studies is key to a healthy network of clinical research units.

Clinician participation in clinical trials requires knowledge of the requirements and pitfalls of human subject protections, patient privacy, good clinical research practices, and awareness of pressures that may affect the

ethical practice of clinical research. It also requires continued dialog at the level of Institutional Review Boards (IRBs) and federal agencies (such Health and Human Services and its subunits, the CMS and NIH) and response to constantly emerging concerns and questions as new diseases, drugs, devices arise and cultural mores change.

Yet, not everyone agrees on the answers to questions of clinical ethics. The underlying institutional, federal and international guidelines, requirements and regulations and may be unclear even to experts (7). For instance, should searching medical records for research participants be construed as a breach of confidentiality? Should sponsors be allowed to offer bonuses to investigators for successfully recruiting subjects? Should physicians be allowed to receive fees for referring their patients as potential subjects for a clinical trial? How much should a sponsor or investigator be allowed to compensate a research participant before the reward is coercive, in the sense that a reasonable person would find it hard to refuse? Should the financial arrangements between sponsors and investigators be disclosed to potential subjects?

While experts ponder these questions, there are practical issues that clinical investigators can consider to improve the quality of their clinical research trials.

Suggestions

There are many rewards for engaging in clinical research (10). If you are convinced you want to engage in clinical research for good reasons, be mindful of the rigors of human research subjects protections. Besides following Federal and Institutional guidelines, the best way to practice ethical clinical research is to know what you are getting into.

Continued education is a key to addressing the evolving ethical challenges in clinical research practice. Take courses on clinical research like the ones being offered by the Academy. For example, the American Academy of Neurology, as part of its patient safety and quality assurance initiatives, has instituted a program of health literacy training for neurologists. This effort is relevant to improving the informed consent process in clinical trials as well as to other areas of professional activity, inasmuch as health illiteracy and miscommunication have been linked with missed appointments, noncompliance with treatment, adverse medical outcomes and errors, and malpractice cases.

It is difficult to list of every item to consider during clinical research trials because research projects and participants differ widely, and the processes and regulations governing clinical research activities continue to evolve on local and national scales. However, there are a few “evergreen” issues and rules of thumb to keep in mind. For example, and in no particular order:

- Make it clear that the issue of whether the study drug is the best treatment remains a research question.
- Be ready to start a necessary non-study drug or treatment, even if it means a participant must drop out from the study.
- Be careful about charging patients for treatment of secondary problems incurred due to a study drug.
- Be sure to provide appropriate oversight and education of office personnel helping you to coordinate and conduct clinical trials.
- Verify every piece of data entered on study sheets. Don’t enter “normal” for items that you or your coordinator may have forgotten to check- such as an item of an otherwise normal physical exam.
- Be ever mindful of patient and participant privacy and keep all paper and electronic records in a secure place or database.
- Avoid releasing research data linked to participant identifiers such as social security numbers, addresses, phone numbers, and the like.
- Be careful about allowing insurers, companies or private individuals access to peoples data or pictures of their faces. Similarly, be careful about showing video information on study participants without their specific permission and be careful about what potential participant identifiers or pictures you might present at meetings and submit for publication.
- Examine the reasons for inclusion or exclusion of children, women, minority subjects or prisoners.

Besides keeping a checklist for yourself and your research staff of good clinical research practices, also encourage questions and consider providing a list of questions for patients or participants to ask. For instance:

- What is the purpose of the research?
- Has the research been approved by an institutional review board?
- What does the research involve for persons with dementia?
- Will the patient benefit from participation?
- Will the patient be given injections or tablets?
- Will the patient have to undergo blood tests or other investigations?
- Will it involve discomfort or cause distress or anxiety?
- Will there be side-effects or risks and how serious could they be?
- Is a patient insured against any harm from participating in the study?
- Will participation require extra visits to the hospital and who will pay for these trips?
- Where would a patient have to attend and how often?
- How long will the study continue?
- Might a patient end up in a comparison group that receives a placebo or no treatment?
- If the research involves treatment, can patients continue to receive the treatment after the study ends?
- Will a patient need to have further medical checks after the study ends?
- Again, who will pay?
- What will patients be told after the research study is completed?
- Will unexpected and heretofore unknown diagnoses such as cancer, heart disease, diabetes, kidney disease or stroke be disclosed?
- Who can a patient or caregiver talk to if he or she has questions or problems?

Besides encouraging participants to ask questions, be prepared to update them on any complications affecting them or other participants. Keep participants informed on new drug developments that may make them wish to change course. Be prepared to negotiate with insurance companies to foot coverage when necessary and make it clear to participants when this not an option. Monitor yourself, your research team, your operational practices, and your sponsors continually and ask:

- Am I following guidelines?
- How do I know my research coordinator is telling me the right thing?
- Is the sponsor being frank with my patients and me?
- What is the agenda or influence of any middlemen whose livelihood depends on moving drugs to new markets?
- Is there a place for product loyalty or drug company loyalty?

Continue to revise your approach as your research experience and portfolio grow and you and your clinical research staff engage in exciting new projects, meet new participants, and encounter novel research situations, challenges and regulations.

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