Chapter 2
Ethical Issues

People have debated the ethics of clinical trials for as long as trials have been conducted. The arguments have changed over the years and perhaps become more sophisticated, but many of them involve issues such as the physician's obligations to the individual patient versus societal good; clinical equipoise; study design considerations such as randomization and the choice of control group, including use of placebo; informed consent; conduct of trials in underdeveloped areas and world regions; conflicts of interest; participant confidentiality and sharing of data and specimens; lack of publication; and publication bias.

A well-designed trial should answer important public health questions without impairing the welfare of participants. There may, at times, be conflicts between a physician's perception of what is good for his or her patient and the design and conduct of the trial. In such instances, the needs of the participant must predominate.

Ethical issues apply in all stages of a clinical trial. In this chapter, we summarize some of the major factors involving ethics in design, conduct, and reporting of clinical trials. As will be noted, several of the issues are unsettled and have no easy solution. We expect, however, that investigators will at least consider these issues in the planning stages of trials, so that high ethical standards can be applied to all trials.

Emanuel et al. [1] listed seven criteria that they considered essential to the ethical conduct of clinical research. These criteria are value, scientific validity, fair selection of participants, favorable benefit/risk balance, independent review, informed consent, and respect for enrolled participants (Table 2.1). Independent review is generally conducted by ethics review committees specifically constituted for oversight of research with human subjects. In the United States, such committees are termed institutional review boards (IRBs). Other names used outside the United States are research ethics committees, ethics committees, or ethics review committees. Although the role of ethics review committees is discussed later in this

L.M. Friedman et al., *Fundamentals of Clinical Trials*,
DOI 10.1007/978-3-319-18539-2_2

Table 2.1 Requirements for an ethical clinical trial

Requirement	Explanation
Value	Evaluate an intervention that has the potential to be of social or scientific value
Scientific validity	Use methods that will produce reliable results
Fair selection of participants	Participant selection that avoids placing the vulnerable at undue risk and avoids preferential access of attractive interventions to the privileged
Favorable benefit/risk balance	Minimize risks and maximize potential benefits, with an estimate that benefits will likely outweigh risks
Independent review	Review of design by individuals not directly affiliated with the research (for example, ethics review committees)
Informed consent	Provide information about purpose of research, procedures, and potential risks and benefits to enable participants to make voluntary decisions in a way that respects participant autonomy
Respect for enrolled participants	Protect the rights and wellbeing of participants

Adapted from Emanuel et al. [1]

chapter under Informed Consent, it must be emphasized that independent review by these committees and others, such as data monitoring boards, applies to several aspects of a trial.

We encourage the reader to seek out any of the many books and journals devoted to ethical aspects of clinical research. Those go into the issues, including ones we do not address, in considerable depth. A particularly relevant book is *The Oxford Textbook of Clinical Research Ethics*, many chapters of which relate directly to clinical trials [2]. The reader is also referred to several key documents:

1. Nuremberg Code. This was the first major international statement on the ethics of medical research, published in 1947 in response to unethical human experimentation on concentration camp prisoners in the Second World War [3]. This code outlined ethical standards for medical research with an emphasis on the requirement for voluntary consent to participation.
2. Declaration of Helsinki. Issued by the World Medical Association in 1964, and periodically amended, the Declaration of Helsinki is a comprehensive statement of the ethics of human subject research [4].
3. Belmont Report. Created by a United States federal commission in 1979, this report outlines ethical principles for clinical research [5]. The report is structured around three basic principles: respect for persons, beneficence, and justice.
4. International Ethical Guidelines for Biomedical Research Involving Human Subjects, prepared by the Council for International Organizations of Medical Sciences in collaboration with the World Health Organization, first in 1982 and amended several times, including in 2002 [6]. This document includes 21 guidelines that address ethical responsibilities in human subject research, many of which apply to clinical trials.

Fundamental Point

Investigators and sponsors of clinical trials have ethical obligations to trial participants and to science and medicine.

Planning and Design

Ethics Training

All clinical trial investigators should have training in research ethics. Understanding ethical principles, and the related regulatory requirements (see Chap. 22), is essential for responsible conduct of clinical trials. An important part of training in ethics is a review of the history of abuses in clinical research that prompted many of the guidelines and regulations that followed. These include an experiment in Tuskegee, Alabama, when treatment was withheld from around 400 African-American men with syphilis to study the course of the disease as well as the abhorrent experiments of concentration camp prisoners in the Second World War. There are a number of resources for research ethics training, including several National Institutes of Health (NIH) websites [7–9].

Does the Question Require a Clinical Trial?

An early decision relates to whether a clinical trial is even necessary. Not all questions need to be answered, and not all of those that should be answered require clinical trials. Sometimes, other kinds of clinical studies may be able to address the question at least as well as, or even better than, a clinical trial. Even if the answer may not be quite as good, the added benefits from the trial may not be worth the added risk.

Because clinical trials involve administering something (a drug, device, biologic, or procedure) to someone, or attempting to change someone's behavior, there may be adverse as well as positive results. Although some of the potential adverse consequences may be known before the trial is started, and therefore prevented or minimized, others may arise unexpectedly during the trial or be more serious than anticipated. The question being addressed by the clinical trial, therefore, must be important enough to justify the possible adverse events. The question must have relevant clinical, public health, and/or other scientific value. A trivial question should not expose study participants to risk of harm, either physical or emotional. Harm can be either a direct result of the intervention or indirect, like from withholding something beneficial. The study investigator, sponsor or funder, and

institutions where the study will be performed must all ensure that the question is sufficiently important and the trial is appropriately conducted to justify those risks.

Though the question may be important, the clinical trial may be infeasible or unethical. An obvious example is cigarette smoking—providing non-smokers with cigarettes to prove that smoking is harmful is clearly unethical. Observational studies have given us sufficient evidence to answer that question, since the relative risk is so great. The Cardiac Arrhythmia Suppression Trial (CAST) [10] was designed to determine whether suppression of ventricular arrhythmias with antiarrhythmic agents in people with heart disease would lead to a reduction in sudden cardiac death. After two of the three antiarrhythmic drugs were found to be harmful and the trial was stopped, some asked whether the study might be continued but reconfigured to demonstrate that quinidine, a long-used drug with some properties similar to the two discontinued agents, would also be harmful. The CAST investigators quickly decided that designing a trial specifically to prove harm, especially serious harm, would be unethical. Although the outcome of a trial is uncertain, the primary response variable should always be one where either benefit or noninferiority is potentially achievable.

Two kinds of trials raise ethical issues because of concerns about the balance between potential benefits to society (and perhaps to participants) and the risks of harm and discomfort to participants. In both, the likelihood of immediate benefit to the study participants exists but is remote. One involves "marketing" (also termed "seeding") trials. Such clinical trials are conducted to show that a new drug or new version of an old drug is at least as good as (i.e., noninferior to) a drug already proven to be beneficial. Other than enhancing the financial status of the industry sponsor, there may be little benefit from the new drug. Yet trial participants are being put at risk from a drug with unknown adverse effects, some of which might be serious. If the new drug has some potential improvement over the existing one, the trial might be justified. Perhaps the new drug is easier to take (e.g., once a day rather than twice a day administration, or taking a pill rather than an injection), is better tolerated, or causes fewer adverse events. One could also argue that having more than one drug with similar benefits is good for the economy, fostering lower medical care costs. But in the end, those conducting such trials should show how the question is important and how there will be meaningful benefits for patients.

A second kind of trial, the ethics of which have been debated, is the early phase study. If these studies are performed in healthy volunteers, there is a nontrivial chance that they will be harmed, but have little opportunity to benefit, other than from whatever payment they receive as a result of their participation and from the possible contribution they provide to advancing treatment. Some people regularly enroll in such studies for the payment [11]. It has been argued that with proper attention to study design and safety monitoring, appropriate evaluation by ethics review committees, and true informed consent, these studies are ethical [12]. As always, risk must be kept to a minimum and the payment must not be so great as to encourage participants to do something that would place them at serious risk. The pros and cons of various payment models for research participants are discussed by Dickert and Grady [13]. As with other clinical research, early phase

studies are only ethical if investigators and sponsors do whatever is necessary to minimize risk. Unfortunately, instances when investigators may not have taken proper care have occurred and received widespread attention [14–16].

Some early phase studies are conducted with participants who have a disease or condition. Patients with cancer that have not responded to other therapies may volunteer for such trials, hoping that the experimental intervention will prove beneficial. Given the small size of these studies and the unfortunate fact that most interventions early in their development do not prove beneficial, there may be only a small chance of benefit. But even if there is only a slight possibility of improvement, as long as there is adequate informed consent and the expectation of benefit to society from the knowledge to be gained, most would agree that these trials can be conducted in an ethical manner [17, 18]. However, the strategy of commonly subjecting participants to experimental therapies without the ability to compare safety and harm to a control group in an unbiased way raises its own ethical issues.

On the other hand, most treatments used in medicine, including those recommended in clinical practice guidelines [19], do not have the clinical trial evidence to be certain that the benefit outweighs the risk. This suggests that we have a responsibility, when possible, to promote high-quality clinical trials to provide the evidence to guide clinical decision-making. It is ironic that consent is essential for a patient to be in a clinical trial comparing two commonly used treatments, and yet assignment to those treatments in clinical practice is routine and accepted without consent and without gaining knowledge about whether there is benefit or harm. If one accepts that randomized trials are the most reliable way to define modest treatment effects, then increasing the number and efficiency of trials should be a priority for the broader health care system, a goal of the Patient-Centered Outcome Research Institute (PCORI) [20].

Controversies in the approach to informed consent in trials that compare treatments commonly used in practice were highlighted by the Surfactant, Positive Pressure, and Oxygenation Randomized Trial (SUPPORT) [21]. This trial randomly assigned premature babies to supplemental oxygen to keep the arterial oxygen saturation at the lower end versus the higher end of standard recommendations. The six-page, single-spaced consent form included standard elements of informed consent, including a statement that lower levels of oxygen might reduce retinopathy, a known complication of higher oxygen levels. The trial showed less retinopathy with lower oxygen target, but unexpectedly higher mortality, and the results have changed practice. Meanwhile, the Office for Human Research Protections (OHRP) of the U.S. Department of Health and Human Services investigated the consent process in the trial and determined that institutional review boards failed to have the consent state that mortality might be increased in one of the treatment strategies [22]. This decision has caused concern among academic institutions about the risk of conducting trials as well as undermining attempts to streamline the consent process in pragmatic trials that are comparing standard therapies [23]. In fact, it has been argued that the participant risks involved with random assignment to commonly used standard treatments are not different than standard practice and that this should be acknowledged in the regulations [24].

It appears that most people are willing to volunteer for clinical trials, but most people are not approached to participate in trials [25]. Some have suggested that there should be a greater sense of social responsibility to participate in clinical research since current treatments are available only due to previous patients participating, and future advances will likewise depend on this participation [26]. This places the burden on clinical researchers to be responsible in designing trials that will provide reliable guidance for future care. In fact, most trials are too small to provide reliable information and many results of trials are never published [27]. Even if our current complex approach to conducting trials were simplified, the costs are still a major barrier. Moreover, relatively little funding is allocated to answering the questions that would have the greatest impact on improving public health.

Randomization

In the typical "superiority trial" described in Chap. 5, randomization is usually done on top of standard or usual therapy, which all participants should receive. The special issues related to noninferiority trials are discussed in Chap. 5. Randomization can be a problem for physicians and other clinicians who feel pressure to be able to choose the treatment that has the greatest likelihood of benefit. The investigator, however, must acknowledge uncertainty when it exists. Therefore, an objection to random assignment should only apply if the investigator believes that there is reasonable certainty that a superior therapy exists. If that is the case, he or she should not participate in a trial that randomizes participants to a therapy other than the believed superior therapy. On the other hand, if he or she truly cannot say that one treatment is better than another, there should be no ethical problem with randomization. Such judgments regarding efficacy may vary among investigators, such that there is uncertainty for some but not others. Because it is unreasonable to expect that an individual investigator should have no preference, not only at the start of a trial but during its conduct, the concept of "clinical equipoise" among the expert clinical community has been proposed [28]. Some have maintained that until an intervention has been proven beneficial, randomization is the most ethical approach and one that will provide the correct answer soonest [29–32]. It may be that "equipoise" will change over the course of a trial, as was the case in the Second International Study of Infarct Survival (ISIS-2) trial testing streptokinase for myocardial infarction. During the period of recruitment, the data monitoring committee found that there was "proof beyond reasonable doubt" that streptokinase reduced mortality for patients 0–4 h after onset of pain, and this information was shared with investigators [33]. They were told that "patients can be randomized if the responsible physician remains, in the light of this and other evidence, uncertain as to whether streptokinase is indicated" [33]. However, is it ethically justifiable for a data monitoring committee to allow participants to be randomly assigned to an arm (in this case, placebo) for which there is "proof" of higher mortality? Many would

argue that the committee should have recommended a change in the protocol with no further enrollment in this subset.

There are other situations in which consent is not possible in the traditional sense, including certain situations in which the patient is unable to provide consent (for example in the setting of cardiac arrest) and when the unit of randomization is not the patient (cluster randomized studies). An example of such a cluster randomized study is the Randomized Evaluation of Decolonization versus Universal Clearance to Eliminate MRSA (REDUCE MRSA) trial [34]. Forty-three hospitals were randomly assigned to 1 of 3 strategies of MRSA screening and patient isolation, targeted decolonization, or universal decolonization (of all patients without screening), to reduce rates of MRSA infection. Most hospitals used a central IRB. Since all regimens were standard of care and participation in the trial was anticipated to have a favorable benefit-risk balance, the requirement for patient consent was waived. Patients were given information sheets explaining the trial.

Control Group

Choice of the control group is a major design issue in clinical trials. If there is a known best therapy, one would generally expect the new intervention to be compared with that therapy, or added to it. But the optimal therapy may not be widely used for various reasons. These could include cost, unavailability of the therapy or lack of sufficient clinicians competent to administer it, lack of acceptance by the practicing clinical community, socioeconomic and cultural differences, or other factors. Depending on these circumstances, some trials may not use the best known therapy or standard of care as the control. They may rely on what the practicing communities typically do, or usual therapy [35]. Investigators and ethics review committees need to judge whether the usual therapy deprives participants of a proven better treatment that they would otherwise receive. If so, serious ethical concerns arise. A major area of disagreement has been the degree of responsibility of investigators to ensure that all participants receive the best proven therapy as a control or background care, even if usual care in the community in which the trial is being conducted is not up to that standard [36]. The appropriate control and background therapy depends, in part, on the purpose of the trial. (See also the section below, “Trials in Low- and Middle-Income Countries.”)

Considerable confusion has arisen when people talk about placebo-controlled trials, as they may refer to different kinds of designs. Often, a new intervention is added to usual care or standard care and compared against that care plus placebo. Sometimes, a new intervention is seen as a possible replacement for an existing therapy, yet for various reasons, it is not thought appropriate to compare the new intervention against the existing therapy. The commonly used therapy, for example, may not have been proven to be beneficial, or it may be poorly tolerated. Therefore, a placebo comparator is used instead of the existing therapy. Often, a blinded placebo control provides the most complete information about the risks and benefits

of a new therapy as an inert placebo is the best approximation of a neutral control. The SYMPLICITY HTN-3 (Renal Denervation in Patients With Uncontrolled Hypertension-3) trial of renal denervation for control of severe refractory hypertension is a good example of the importance of a placebo (in this case a sham procedure) [37]. Earlier randomized trials of renal denervation compared with no renal denervation, on top of optimal medical therapy, showed a major (22–32 mmHg) reduction in systolic blood pressure with renal denervation that led to widespread enthusiasm and adoption of this treatment in Europe, where the device to perform the procedure was approved based on those results. However, the sham-controlled trial found similar 12–14 mmHg reductions in systolic blood pressure with renal denervation and with the sham procedure.

Even if a proven therapy exists, whether short-term discontinuation of that therapy for the purpose of conducting a placebo-controlled trial is harmful depends on the condition being studied. Exposing participants to serious harm by withholding beneficial treatment is unethical even in the short term. For conditions causing only mild to moderate discomfort, it may be acceptable. For example, investigators evaluating new analgesic agents might choose to use a placebo control, as long as any pain or discomfort is treated promptly. As always, there will be borderline cases that require discussion and review by ethics review committees [38].

Freedman et al. [39, 40] acknowledged that many factors are considered in deciding whether to use a placebo control. They argued that if an accepted treatment exists, much of the time a placebo control is unethical and, indeed, unnecessary. Rothman and Michels [41, 42] also maintained that in many cases a placebo, in lieu of the proven therapy, has been used inappropriately because a proven therapy existed. This debate occurred with the Enhanced Suppression of the Platelet IIb/IIIa Receptor with Integrilin (ESPRIT) trial [43–45]. The decision to use a placebo control, rather than another proven IIb/IIIa receptor inhibitor, was only allowed after it was shown that many cardiologists were not persuaded by the prior evidence, and even then only with declaration by the investigators that they were uncertain as to the benefits of IIb/IIIa inhibitors. We think that this is a valid argument as the participating investigators were informed about the current evidence and made the decision to conduct another placebo-controlled trial because they questioned the applicability of that evidence. History has supported their decision, since IIb/IIIa inhibitors are no longer strongly recommended in guidelines nor used as a standard in practice. Ethics review committees must have full knowledge and informed consent must contain the relevant information.

Before an investigator uses a placebo control, which will often be the best design, he or she should assess whether it will provide the basis for a better assessment of the active therapy and should determine that its use will not cause serious harm (due to withholding a proven effective alternative). Importantly, all participants must be told that there is a specified probability (e.g., 50%) of their receiving placebo. The World Medical Association Declaration of Helsinki (as amended in 2013) [4], the Council for International Organizations of Medical Sciences (CIOMS) [6], regulatory bodies [46], and others have guidelines for use of placebo. Miller summarizes the issues that should be considered by

investigators [47]. If life-saving treatment is available, patients should not be assigned to placebo versus an active treatment. For example, once streptokinase was shown to save lives of patients with myocardial infarction, it would no longer be ethical to compare a new fibrinolytic agent, like alteplase, with placebo. Likewise, if assignment to placebo (versus available active therapy) would likely result in any significant pain or harm, then a placebo would be unethical. A placebo control is particularly important when studying conditions with a variable course and/or frequent spontaneous remissions, when existing therapies are inconsistently effective or have serious side effects, or when frequency of the condition is so low that an equivalence trial would be impractical [47].

Protection from Conflicts of Interest

A widely expressed concern in clinical research is the potential for conflicts of interest on the part of the investigators. In the context of ethical issues, conflicts of interest can lead to bias in design, conduct, data analysis, interpretation, and reporting of findings. Conflicts of interest are generally considered in the financial context, but intellectual or other conflicts also exist [48]. Ideally, no investigator should have any interests other than the well-being of the study participants and the generation of new knowledge that will improve clinical care and public health. That is unrealistic, however, given that investigators must receive research funding to conduct research, and this funding may come from government, industry, research foundations, private investors, or others who have considerable interest in the outcome of the study. Many investigators have also spent a career attempting to advance the science, and could be disappointed if or fail to accept that their theory is incorrect. Therefore, most clinical trials find it more realistic to manage conflicts of interest rather than to avoid them completely.

The practice of disclosing financial relationships to participants and others has been reviewed and recommendations have been proposed [49]. Among these recommendations, it was noted that because many participants may not fully appreciate the impact that financial relationships might have on research design, conduct, and analysis, in addition to disclosure, IRBs and others should "play a significant role in determining the acceptability of these relationships" [49]. We think that disclosure and IRB or other oversight may be sufficient for early phase studies. It may not be sufficient, however, for late phase trials—those that are designed to have major implications for clinical practice. Most late phase clinical trials are sponsored by industry, and although the investigators enrolling and following participants may not stand to gain financially from the results of the trial, the sponsors clearly do. Therefore, analysis should be conducted, or at least validated, by groups independent of the industry sponsor. Ideally, this should also occur in trials sponsored by others. Any investigators who have significant economic interests in the outcome either should not participate or should not have opportunities to affect and publish the trial results. This may mean that the lead

investigator in multi-investigator studies or the investigator in single-investigator studies should have no major financial conflicts if the study is one likely to change practice and increase sales. Financial conflicts may also contribute to the problem of "negative" trials being less likely to be published or having their publication delayed (see Chap. 20). Trials with positive results are published more often (see Chap. 20). Other key investigators with major conflicts should also be barred from such trials. If the investigators have limited roles or only small financial investments, it may be acceptable for them to participate. We recognize that the situation is more complicated when those designing and overseeing, and perhaps co-authoring publications, are employees of the company sponsoring the trial. Nevertheless, complete openness and data analysis by an independent group remain important. The use of external independent oversight bodies and clear lines of authority may mitigate conflicts of interest. In the end, however, clinical trial results must be believed and accepted by the clinical communities. To the extent that conflicts of interest (real or perceived) lessen that acceptance, the study is impaired. Therefore, all appropriate ways of minimizing and managing conflicts should be used.

Informed Consent

Proper informed consent is essential to ethical trial conduct. Partly as a result of terrible things done in the name of clinical research, various bodies developed guidelines such as the Nuremberg Code [3], Declaration of Helsinki [4], Belmont Report [5], and International Ethical Guidelines for Biomedical Research Involving Human Subjects [6]. These guidelines lay out standards for informed consent that are commonly followed internationally. In parallel to the Belmont Report, the United States Congress passed laws that require adherence to informed consent regulations by those receiving government support—the so-called Common Rule, or Title 45 of the Code of Federal Regulations, part 46 (45 CFR 46) [50]—and those evaluating agents under the auspices of the U.S. Food and Drug Administration [51]. These regulations require that clinical research studies be reviewed by IRBs, and establish the membership and other procedures that IRBs must follow.

One of the primary roles of the IRB is to ensure that there is true, voluntary informed consent. The Common Rule and 21 CFR 50 [52] require consent forms to contain basic elements. Table 2.2 lists these as well as other elements that may be added as appropriate. Simply adhering to legal requirements does not ensure adequate informed consent [53–55]. Informed consent is a process that can take considerable time and effort; it is not simply a matter of getting a form signed. In many, perhaps most, clinical trial settings, true informed consent can be obtained. Potential participants have the capacity to understand what is being requested of them, they have adequate time to consider the implications of joining a trial, ask questions, and take information home to review and discuss with their families and personal physicians, and they are familiar with the concepts of research and

Table 2.2 Informed consent checklist—basic and additional elements

Basic elements
A statement that the study involves research
An explanation of the purposes of the research
The expected duration of the subject's participation
A description of the procedures to be followed
Identification of any procedures that are experimental
A description of any reasonably foreseeable risks or discomforts to the subject
A description of any benefits to the subject or to others that may reasonably be expected from the research
A disclosure of appropriate alternative procedures or courses of treatment, if any, that might be advantageous to the subject
A statement describing the extent, if any, to which confidentiality of records identifying the subject will be maintained
For research involving more than minimal risk, an explanation as to whether any compensation and any medical treatments are available if injury occurs and, if so, what they consist of, or where further information may be obtained
An explanation of whom to contact for answers to pertinent questions about the research and research subjects' rights, and whom to contact in the event of a research-related injury to the subject
A statement that participation is voluntary, refusal to participate will involve no penalty or loss of benefits to which the subject is otherwise entitled, and the subject may discontinue participation at any time without penalty or loss of benefits to which the subject is otherwise entitled
Additional elements, as appropriate
A statement that the particular treatment or procedure may involve risks to the subject (or to the embryo or fetus, if the subject is or may become pregnant), which are currently unforeseeable
Anticipated circumstances under which the subject's participation may be terminated by the investigator without regard to the subject's consent
Any additional costs to the subject that may result from participation in the research
The consequences of a subject's decision to withdraw from the research and procedures for orderly termination of participation by the subject
A statement that significant new findings developed during the course of the research, which may relate to the subject's willingness to continue participation, will be provided to the subject
The approximate number of subjects involved in the study

From the Code of Federal Regulations [50]

voluntary consent. As discussed in the "Privacy and Confidentiality" section below, investigators may share data and biospecimens with other researchers, while following federal guidelines. If such sharing is planned or required by the sponsor, the informed consent material must make it clear that sharing will occur and that the data may be used for purposes other than those of the trial for which the person is volunteering.

Sometimes people may not understand that a clinical trial is a research endeavor. They may believe that they are receiving therapy for their condition. This may happen in early phase trials of new drugs that are being developed for serious, untreatable diseases, or in any clinical trial testing a promising intervention for a

serious or chronic condition. Patients may view the trial as the last or best possibility for cure. Sometimes clinicians are also researchers and may seek to enroll their own patients into clinical trials. These situations can lead to what has been termed "therapeutic misconception" [56]. The distinction between research, an experiment in essence, and clinical care may blur. Extra effort must be made to provide patients with the information needed to judge the merits of volunteering for research, separate from their clinical care.

The situations where participant enrollment must be done immediately, in comatose patients, or in highly stressful circumstances and where the prospective participants are minors or not fully competent to understand the study are more complicated and may not have optimal solutions. In the United States, FDA [57] and Department of Health and Human Services [58] guidelines allow for research in emergency situations, when informed consent is not possible. Under these regulations, IRBs may approve the study without informed consent as long as a series of special conditions has been met, including that there has been community consultation and a safety committee is formed to monitor accumulating data. Similar research is also allowed in Canada [59] and under the European Medicines Agency (EMA) Guidelines for Good Clinical Practice [60]. A trial of fibrinolytic therapy versus placebo in the context of resuscitation for cardiac arrest was successfully conducted under the EMA guidelines [61] and a trial of therapeutic hypothermia for patients with out-of-hospital cardiac arrest was conducted under Department of Health and Human Services guidelines [62]. In these trials, local ethics committees agreed that the trial could be done without informed consent prior to enrollment. Instead, consent was later given by surviving participants or their family members or others.

Some have questioned research in emergency settings because of the lack of prior informed consent, and several such clinical trials have been quite controversial. An example is a trial of a product intended to be used as a blood substitute in trauma patients [63]. Because patients were unconscious at the time of administration of the blood substitute, consent could not be obtained. Therefore, community consultation was obtained before local IRBs approved the study. However, there were allegations that safety problems noted in earlier trials of the agent were not published or otherwise disclosed to those bodies. We do not take a position on the merits of this particular trial, and we support the concept of being able to conduct important research in settings where full informed consent before enrollment is not possible. The sponsors and investigators, though, must be completely open about all data relevant to the conduct of such studies and must follow all local regulations [64]. Failure to do so harms not only the unwitting participants, but the entire field of research in emergency settings.

For pragmatic, simple trials that are comparing treatments that are each standard of care, a streamlined approach to consent has been proposed [65]. Just as a "learning health care system" integrates clinical research with care, a simple consent process could be integrated into patient care with an explanation of the research, of the fact that either treatment is approved and standard, and that it is uncertain which is better.

Research on prisoners is restricted [66] due to a history of violation of ethical principals in the population and since informed consent free of the appearance of possible coercion is difficult to establish.

Also contentious is the practice of obtaining consent from participant surrogates when the study participant is unable to provide fully informed consent. This typically happens with research in minors, when parents or other guardians make the decision. Special review is required for pediatric research; requirements vary depending on the expected risks from the study [50]. Other situations, such as research in emotionally or mentally impaired individuals, also have generated discussion and guidelines regarding use of surrogate consent [67, 68]. Less clear is the use of surrogate consent for potential study participants who are temporarily unable to understand the nature of the study and give consent. This issue arose in research in people with acute respiratory distress syndrome [69]. Suggestions for accommodating research in such situations include risk assessment, determination of patient capacity, and reconsent [70]. As in all such situations, judgment on the part of investigators, sponsors, IRBs, and others will be required and second-guessing will inevitably occur.

The right to withdraw consent to continue in a trial, including withdrawing consent to continue to receive study interventions and undergo study procedures, is another important ethics principle. Less clear is to what extent participants have the right or option to refuse to have any type of follow-up, since determining major outcomes as well as serious adverse outcomes, including death, is essential in many trials to interpret the results and entails minimal risk to participants. If the initial consent declares that participants may withdraw from intervention and all study procedures but that vital status will be obtained at the end of the study regardless, this may be an appropriate compromise. This can protect the contributions of others who have placed themselves at some risk with the understanding that their participation may help future patients, while minimizing risk and discomfort to those who wish to withdraw.

Conduct

Trials in Low- and Middle-Income Countries

Many large multicenter clinical outcome trials are international, and they are becoming more so [71] (see Chap. 21). Most diseases are global. The ability to enroll and follow participants in more than one country assists in enrollment and may help in generating results that are generalizable to different populations and settings. However, trials that are conducted in low- and middle-income countries can raise ethical issues. Are they conducted in those regions because the disease of interest is prevalent there, and the results relevant to the region? Or are the countries or regions selected primarily for convenience, low cost, or fewer administrative and

regulatory burdens? The control group may be receiving less than optimal care, and thus may have a higher event rate, permitting a smaller, shorter, and less expensive trial. If the trial is conducted for those reasons, it may be unethical. Some have said that the investigators are obligated to ensure that all participants receive optimal care without regard to usual practice in the country where the trial is being conducted. Others have maintained that it is sufficient if the participants receive care at least as good as what they would receive had they not been in the trial, or care that is better than standard care for their setting. This was the argument of the investigators in a tamoxifen trial of adjuvant oophorectomy and tamoxifen in the treatment of breast cancer in Vietnamese and Chinese women. State-of-the-art treatment by United States standards (including radiation) was not available and not likely to be available. What was being tested was whether a simple and affordable treatment like tamoxifen would be better than what was available [72].

Extrapolation of study results from less developed regions to highly developed countries with very different health care systems and standards of care, and vice versa, has also been questioned. While it is clear that risk and event rates tend to be higher in low-income countries [73], some studies have suggested that the treatment effects may indeed be different [74, 75].

After the trial ends, what is the obligation of the investigators to provide an intervention shown to be beneficial, both to the study participants and to the broader population in a low-income country? This and other similar issues have no easy answers. We believe, however, that trials should only be conducted in places and with participants likely to benefit from the results and with informed consent procedures that clearly describe what will be done at the end of the trial. The results from the trial must be able to be applied to clinical practice in the population from which the participants came [76].

Recruitment

Recruitment of trial participants is often one of the more challenging aspects of conducting a clinical trial (see Chap. 10). Unless an adequate number of participants are enrolled to generate the number of outcomes needed, the trial will not be able to answer the questions about benefit and harm. Therefore, there is great pressure to recruit an adequate number of participants and to do so as quickly as possible. The use of some financial incentives, such as "finder's fees" (i.e. payment to physicians for referring participants to a clinical trial investigator), is inappropriate in that it might lead to undue pressure on a prospective participant [77]. This differs from the common and accepted practice of paying investigators a certain amount for the cost and effort of recruiting each enrolled participant. Even this practice becomes questionable if the amount of payment is so great as to induce the investigator to enroll inappropriate participants [13].

Study participants may (and at times should) be paid for their involvement in clinical trials. Typically, payment is meant to compensate them for the time, effort,

and expense of attending clinic visits. Studies that enroll healthy volunteers (usually phase I studies) will often provide payment beyond reimbursement for expenses. The amount generally depends on the time required and the amount of pain and risks involved in any procedures. As with paying investigators, when the amount is such that people, whether they are healthy volunteers or patients, might make unwise or dangerous decisions, it becomes excessive. Participants should not be paid more for taking on more risk. Ethics review committees often have guidelines as to appropriate payment amounts for various kinds of studies and procedures and must ensure that the amount provided does not create an undue influence.

As discussed in Chap. 9, many potentially eligible trial participants may be on medication. This treatment may be for the condition that will be studied or some other reason. In order to assess the participant's condition at baseline, the investigator may be tempted to withdraw medication, at least temporarily. For example, one might be interested in enrolling people at high risk of cardiovascular disease, and thus try to accrue those with hypertension. But an accurate baseline blood pressure might not be obtainable in those already on treatment. It might not even be clear that the participant already on antihypertensive drugs would have met the eligibility criteria if not on medication. Should one withdraw the drug or simply accept that those on treatment probably truly had hypertension, especially if while on treatment they still have high normal blood pressures? Usually, the latter is the better course of action.

Safety and Efficacy Monitoring

Occasionally, during a trial, important information relevant to informed consent derives either from other studies or from the trial being conducted. In such cases, the investigator is obligated to update the consent form and notify current participants in an appropriate manner. A trial of antioxidants in Finnish male smokers (the Alpha-Tocopherol Beta Carotene Cancer Prevention Study) indicated that beta carotene and vitamin E may have been harmful with respect to cancer or cardiovascular diseases, which was contrary to earlier observational studies [78]. Because of those findings, investigators of the ongoing Carotene and Retinol Efficacy Trial (CARET) informed the participants of the results and the possible risks [79]. CARET was subsequently stopped earlier than planned because of adverse events similar to those seen in the Finnish trial. The investigator of a third trial of antioxidants, the Age-Related Eye Disease Study (AREDS), then notified participants (with a focus on the smokers) of the findings from both the Finnish study and CARET [80, 81].

Five trials of warfarin in patients with atrial fibrillation were being conducted at approximately the same time [82] in the late 1980s. After the first three ended, showing clear benefit from warfarin in the reduction of strokes, the remaining two found it difficult ethically to continue. Interim results from the Heart and Estrogen/progestin Replacement Study (HERS) [83] and a Women's Health Initiative (WHI)

[84] evaluation of estrogen suggested that thromboembolic adverse events that had not been clearly presented in the informed consent were occurring. In both studies, the data and safety monitoring boards debated whether the studies should stop or continue with additional actions taken. The trials continued, but participants in those trials and medical communities were notified of these interim findings of embolic risk [85, 86]. Not only is such a practice an ethical stance, but a well-informed participant is usually a better trial participant. How much data should be provided to study participants and when, and the role of independent safety monitoring groups in this decision, are still areas of debate [87].

The issue of how to handle accumulating data from an ongoing trial is a difficult one, and is further discussed in Chap. 16. With advance understanding by both participants and investigators that they will not be told interim results unless they show conclusive benefit or harm, and that there is a responsible safety monitoring group, ethical concerns should be lessened if not totally alleviated.

Early Termination for Other Than Scientific or Safety Reasons

Clinical trials are only ethical if there are adequate resources to conduct them and see them to completion. Trials may (and should) be stopped early if there are safety concerns or if there are scientific reasons to do so (see Chap. 16). It is inappropriate, however, to stop a trial early because the sponsor changes its mind about research agendas or marketing priorities, or failed to adequately plan for sufficient resources. In such cases, participants who enrolled did so with the understanding that they would be helping to advance medical knowledge. In the process, they put themselves at possibly considerable risk based, in part, on that understanding. To fail to complete the study is a serious breach of ethics. An example of when this happened is the Controlled Onset Verapamil Investigation of Cardiovascular End Points (CONVINCE) trial [88]. Partway through follow-up, the sponsor ended the study for reasons other than scientific or safety concerns. As noted in an editorial by Psaty and Rennie [89], "the responsible conduct of medical research involves a social duty and a moral responsibility that transcends quarterly business plans. . .."

In another situation, an investigator with inadequate funds to complete his trial solicited money from participants in the trial so that he could continue purchasing the experimental drug [90]. Because the trial was being conducted in patients with a fatal condition, amyotrophic lateral sclerosis, the study participants viewed the trial as a last hope and were therefore under considerable pressure to donate. We view such actions as completely unethical. Plans for conducting the trial, including obtaining experimental agents, must be in place before the trial begins.

With all trials, investigators need to plan in advance how they will handle end-of-study issues such as whether participants will have continued access to the intervention and transition to appropriate medical care.

Privacy and Confidentiality

The issues of privacy and confidentiality have received considerable attention. The widespread uses of electronic media have made many people concerned about the privacy of their medical records, including research records. Electronic medical records have simplified the tasks of finding potentially eligible participants for trials, conducting international multicenter studies, following up on participants during and after the studies, and sharing data with other researchers. They have also led to laws restricting what kinds of medical records can be shared and with whom, in the absence of clear permission from the patients. In the United States, the Health Insurance Portability and Accountability Act (HIPAA) primarily addresses privacy issues in clinical practice [91]. However, there are clinical research provisions that affect how investigators identify, contact, and obtain informed consent from prospective participants, and how study data are maintained and provided to others [91] (see also Chap. 10). These laws, in turn, have generated articles pointing out the increased difficulty in conducting clinical research. Policies encouraging or mandating sharing of data and biospecimens from research studies [92–94] may conflict with the objectives of maintaining confidentiality. If data are shared with other researchers for unspecified purposes, might participants who volunteered for a trial object to their data being used for goals of which they might not approve? If the original informed consent does not allow for use of the biospecimens by others or for purposes different from the stated ones, either the biospecimens cannot be shared or new informed consents must be obtained. The increasing availability and use of genetic material adds to this conflict. Fear of employment or health insurance discrimination based on genetic information may make some people unwilling to participate in trials if complete confidentiality cannot be ensured. It is probably not possible to share data and specimens that are useful to the recipient investigator while also completely removing all participant identifiers. Some compromises are inevitable. At the current time, there are no clear solutions to these issues, but trial participants must have a right to make informed choices. Clinical trial investigators need to be aware of the concerns, and to the extent possible, plan to address them before the study starts.

Data Falsification

There has been concern about falsification of data and entry of ineligible, or even phantom, participants in clinical trials (see Chap. 10). A case of possible falsification that gained considerable attention was a trial of bone morphogenetic protein-2 in the management of fractures due to combat injuries [95]. An editorial in the journal that published the article, which had purported to show benefit from treatment, said that “much of the paper was essentially false” and announced the article’s withdrawal [96]. A trial of lumpectomy and radiation therapy for breast

cancer was severely harmed because of falsified data on a small number of participants at one of many enrolling sites. The overall results were unchanged when the participants with the falsified data were not included [97, 98]. Nevertheless, the harm done to the study and to clinical trials in general was considerable. We condemn all data fabrication. It is important to emphasize that confidence in the integrity of the trial and its results is essential to every trial. If, through intentional or inadvertent actions, that confidence is impaired, not only have the participants and potentially others in the community been harmed, the trial loses its rationale and ability to influence science and medical practice. Chapter 11 reviews issues of ensuring data quality.

Reporting

Publication Bias, Suppression, and Delays

All investigators have the obligation to report trial results fully and in a timely fashion. As discussed in Chap. 20, it is well known that publication bias exists. Positive or exciting findings are more likely to be published than null results. In one survey of 74 trials of antidepressant agents, 38 were considered to have results favorable to the intervention. All but one of these were published. Of the 36 studies considered not to have favorable results, 22 were not published. Eleven others were published in ways that obscured the lack of favorable results [99]. Heres and colleagues examined trials of head-to-head comparisons of second-generation antipsychotic agents [100]. Ninety percent of the trials sponsored by industry were reported in favor of the sponsor's drug. Interestingly, this occurred even with trials that compared the same drugs, but the outcome changed when the sponsor was a different company. Clearly bias and conflicts of interest can have important effects on publication and interpretation of results.

It is more probable that large, late phase trials will be published regardless of the results than will small, early stage trials. There are exceptions, however. As discussed in Chap. 5, the results of the second Prospective Randomized Amlodipine Survival Evaluation 2 (PRAISE-2) trial [101], although presented in 2000, were only published 13 years after the trial was completed [102]. The problem of delayed or absent publication is undoubtedly true of other trials with disappointing outcomes.

An important advance in ensuring publication is that many journals [103], sponsors such as the NIH [104], and the FDA [105] require that trials be registered at initiation in one of several accepted registration sites. Although it is not a complete solution to the problem of failure to make public the results of all trials, registration allows for easier tracking of trials that are initiated but perhaps never completed or never published. An analysis of trials registered on ClinicalTrials.gov [106] showed from a sample cohort that only 78 of 150 (52%) had associated publications within 2 years after results posting.

We take the position that the results of all clinical trials should be published in a timely way regardless of the findings. It is important that the totality of the information, pro and con, be available so that those designing other studies and clinicians can make informed decisions. If the study results are not published, it is also unfair to the participants who volunteered for a trial with the understanding that they would be helping medical research. So-called "gag clauses" in industry-sponsored trials [107] are both antithetical to academic freedom and contrary to ethical practice.

Conflicts of Interest and Publication

All researchers have biases of some sort. It is understandable that an investigator's perspective will enter into a publication, even though best efforts are made to be objective in reporting and interpreting study results. For this reason, many journals, and most high-profile ones, require that authors disclose their potential conflicts of interest [108]. In addition, many multi-investigator studies have publication policies that exclude from authorship those with major conflicts of interest.

More extreme is "ghost authorship," where the papers are written by employees of the sponsors, who are not listed as authors, and the academic-based investigators, who may have had little or no role in drafting the manuscript, are given authorship credit. We deplore this practice. We also deplore the practice of listing as authors anyone who did not truly contribute to the research. In response to concerns about "ghost authorship," many journals now ask for the contribution of each listed author when the manuscript is submitted for publication (see Chap. 19 for further discussion of these issues).

References

1. Emanuel EJ, Wendler D, Grady C. What makes clinical research ethical? *JAMA* 2000;283:2701-11.
2. Emanuel EJ, Grady C, Crouch RA, et al (eds.). *The Oxford Textbook of Clinical Research Ethics*. Oxford: Oxford University Press, 2008.
3. U.S. Department of Health & Human Services website. The Nuremberg Code. Available at: http://www.hhs.gov/ohrp/archive/nurcode.html. Accessed January 14, 2015.
4. World Medical Association website. WMA Declaration of Helsinki – Ethical Principles for Medical Research Involving Human Subjects. Available at: http://www.wma.net/en/30publications/10policies/b3/index.html. Accessed January 14, 2015.
5. U.S. Department of Health & Human Services website. The Belmont Report: Ethical Principles and Guidelines for the Protection of Human Subjects of Research. The National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research. April 18, 1979. Available at: http://www.hhs.gov/ohrp/humansubjects/guidance/belmont.html. Accessed January 14, 2015.

6. Council for International Organizations of Medical Sciences, World Health Organization. International Ethical Guidelines for Biomedical Research Involving Human Subjects. Available at: http://www.cioms.ch/publications/layout_guide2002.pdf. Accessed January 14, 2015.
7. National Institutes of Health Clinical Center, U.S. Department of Health & Human Services. Ethics in Clinical Research. Available at: http://clinicalcenter.nih.gov/recruit/ethics.html. Accessed January 14, 2015.
8. National Institutes of Health Clinical Center, U.S. Department of Health & Human Services. Clinical Research Training On-Line. Available at: http://cc.nih.gov/training/training/crt.html. Accessed January 14, 2015.
9. National Institutes of Health Clinical Center, U.S. Department of Health & Human Services. Ethical and Regulatory Aspects of Clinical Research. Available at: http://www.bioethics.nih.gov/courses/index.shtml. Accessed January 14, 2015.
10. Preliminary report: effect of encainide and flecainide on mortality in a randomized trial of arrhythmia suppression after myocardial infarction. The Cardiac Arrhythmia Suppression Trial (CAST) Investigators. *N Engl J Med* 1989;321:406-412.
11. Elliott C. Guinea-pigging: healthy human subjects for drug safety trials are in demand. But is it a living? *New Yorker* 2008;7:36-41.
12. Jonsen AR, Miller FG. Research with healthy volunteers. In: Emanuel EJ, Grady C, Crouch RA, et al (eds.). *The Oxford Textbook of Clinical Research Ethics*. Oxford: Oxford University Press, 2008:481-487.
13. Dickert N, Grady C. Incentives for research participants. In: Emanuel EJ, Grady C, Crouch RA, et al (eds.). *The Oxford Textbook of Clinical Research Ethics*. Oxford: Oxford University Press, 2008:386-396.
14. Savulescu J, Spriggs M. The hexamethonium asthma study and the death of a normal volunteer in research. *J Med Ethics* 2002;28:3-4.
15. Suntharalingam G, Perry MR, Ward S, et al. Cytokine storm in a phase 1 trial of the anti-CD28 monoclonal antibody TGN1412. *N Engl J Med* 2006;355:1018-1028.
16. St Clair EW. The calm after the cytokine storm: lessons from the TGN1412 trial. *J Clin Invest* 2008;118:1344-1347 (correction *J Clin Invest* 2008;118:2365).
17. Agrawal M, Emanuel EJ. Ethics of phase 1 oncology studies: reexamining the arguments and data. *JAMA* 2003;290:1075-1082.
18. Joffe S, Miller FG. Bench to bedside: mapping the moral terrain of clinical research. *Hastings Cent Rep* 2008;38:30-42.
19. Tricoci P, Allen JM, Kramer JM, et al. Scientific evidence underlying the ACC/AHA clinical practice guidelines. *JAMA* 2009;301:831-841.
20. Patient-Centered Outcomes Research Institute website. Available at: http://www.pcori.org/. Accessed January 14, 2015.
21. SUPPORT Study Group of the Eunice Kennedy Shriver NICHD Neonatal Research Network, Carlo WA, Finer NN, et al. Target ranges of oxygen saturation in extremely preterm infants. *N Engl J Med* 2010;362:1959-1969.
22. Human Research Protections under Federalwide Assurance (FWA) 5960. http://www.hhs.gov/ohrp/detrm_letrs/YR13/mar13a.pdf. Accessed January 14, 2015.
23. Lantos JD. The weird divergence of ethics and regulation with regard to informed consent. *Am J Bioeth* 2013;13:31-33.
24. Lantos JD, Spertus JA. The concept of risk in comparative-effectiveness research. *N Engl J Med* 2014;371:2129-2130.
25. Research America: An Alliance for Discoveries in Health. Research Enterprise Survey, February 2010 (slide presentation). Available at: http://www.researchamerica.org/uploads/ResearchEnterprisePoll.pdf. Accessed January 14, 2015.
26. Schaefer GO, Emanuel EJ, Wertheimer A. The obligation to participate in biomedical research. *JAMA* 2009;302:67-72.

27. Califf RM, Zarin DA, Kramer JM, et al. Characteristics of clinical trials registered in ClinicalTrials.gov, 2007-2010. *JAMA* 2012;307:1838-1847
28. Freedman B. Equipoise and the ethics of clinical research. *N Engl J Med* 1987;317:141-145.
29. Shaw LW, Chalmers TC. Ethics in cooperative clinical trials. *Ann N Y Acad Sci* 1970;169:487-495.
30. Byar DP, Simon RM, Friedewald WT, et al. Randomized clinical trials. Perspectives on some recent ideas. *N Engl J Med* 1976;295:74-80.
31. Spodick DH. The randomized controlled clinical trial. Scientific and ethical bases. *Am J Med* 1982;73:420-425.
32. Royall RM, Bartlett RH, Cornell RG, et al. Ethics and statistics in randomized clinical trials. *Stat Sci* 1991;6:52-88.
33. Intravenous streptokinase given within 0-4 hours of onset of myocardial infarction reduced mortality in ISIS-2. *Lancet* 1987;1:502.
34. Huang SS, Septimus E, Kleinman K, et al. Targeted versus universal decolonization to prevent ICU infection. *N Engl J Med* 2013;368:2255-2265.
35. Dawson L, Zarin DA, Emanuel EJ, et al. Considering usual medical care in clinical trial design. *PLoS Med* 2009;6:e1000111.
36. Holm S, Harris J. The standard of care in multinational research. In: Emanuel EJ, Grady C, Crouch RA, et al (eds.). *The Oxford Textbook of Clinical Research Ethics*. Oxford: Oxford University Press, 2008:729-736.
37. Bhatt DL, Kandzari DE, O'Neill WW, et al.; SYMPLICITY HTN-3 Investigators. A controlled trial of renal denervation for resistant hypertension. *N Engl J Med* 2014;370:1393-1401.
38. Temple RJ, Meyer R. Continued need for placebo in many cases, even when there is effective therapy. *Arch Intern Med* 2003;163:371-373.
39. Freedman B, Weijer C, Glass KC. Placebo orthodoxy in clinical research. I: Empirical and methodological myths. *J Law Med Ethics* 1996;24:243-251.
40. Freedman B, Glass KC, Weijer C. Placebo orthodoxy in clinical research. II: Ethical, legal, and regulatory myths. *J Law Med Ethics* 1996;24:252-259.
41. Rothman KJ, Michels KB. The continuing unethical use of placebo controls. *N Engl J Med* 1994;331:394-398.
42. Michels KB, Rothman KJ. Update on unethical use of placebos in randomised trials. *Bioethics* 2003;17:188-204.
43. O'Shea JC, Hafley GE, Greenberg S, et al. Platelet glycoprotein IIb/IIIa integrin blockade with eptifibatide in coronary stent intervention: the ESPRIT trial: a randomized controlled trial. *JAMA* 2001;285:2468-2473.
44. Mann H, London AJ, Mann J. Equipoise in the enhanced suppression of the platelet IIb/IIIa receptor with integrilin trial (ESPRIT): a critical appraisal. *Clin Trials* 2005;2:233-241.
45. Tcheng J. Comment on Mann et al. *Clin Trials* 2005;2:242-243.
46. International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use: ICH Harmonised Tripartite Guideline: Choice of Control Group and Related Issues in Clinical Trials E10 (July 2000). http://www.ich.org/fileadmin/Public_Web_Site/ICH_Products/Guidelines/Efficacy/E10/Step4/E10_Guideline.pdf
47. Miller FG. The ethics of placebo-controlled trials. In: Emanuel EJ, Grady C, Crouch RA, et al (eds.). *The Oxford Textbook of Clinical Research Ethics*. Oxford: Oxford University Press, 2008:261-272.
48. Levinsky NG. Nonfinancial conflicts of interest in research. *N Engl J Med* 2002;347:759-761.
49. Weinfurt KP, Hall MA, King NM, et al. Disclosure of financial relationships to participants in clinical research. *N Engl J Med* 2009;361:916-921.
50. Code of Federal Regulations, Title 45, Part 46. Available at: http://www.hhs.gov/ohrp/humansubjects/guidance/45cfr46.html. Accessed January 14, 2015.
51. Code of Federal Regulations, Title 21. Available at: http://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfcfr/CFRSearch.cfm. Accessed January 14, 2015.

52. Code of Federal Regulations, Title 21, Part 50. Available at: http://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfcfr/CFRSearch.cfm?CFRPart=50. Accessed January 14, 2015.
53. Cassileth BR, Zupkis RV, Sutton-Smith K, et al. Informed consent -- why are its goals imperfectly realized? *N Engl J Med* 1980;302:896-900.
54. Grunder TM. On the readability of surgical consent forms. *N Engl J Med* 1980;302:900-902.
55. Howard JM, DeMets D. How informed is informed consent? The BHAT experience. *Control Clin Trials* 1981;2:287-303.
56. Henderson GE, Churchill LR, Davis AM, et al. Clinical trials and medical care: defining the therapeutic misconception. *PLoS Med* 2007;4:e324.
57. U.S. Food and Drug Administration. Exception from informed consent requirements for emergency research. Available at: http://www.fda.gov/downloads/RegulatoryInformation/Guidances/UCM249673.pdf. Accessed January 14, 2015.
58. Federal Register, volume 61, October 2, 1996. 45 CFR Part 46, pages 5131–3; Department of Health & Human Services, Waiver of Informed Consent Requirements in Certain Emergency Research. Available at: http://www.hhs.gov/ohrp/policy/hsdc97-01.html. Accessed January 14, 2015.
59. Tri-Council Policy Statement: Ethical conduct for research involving humans (amended 2005). http://www.ncehr-cnerh.org/english/code_2/. Accessed January 14, 2015.
60. European Medicines Agency ICH Topic E6 (R1) Guideline for Good Clinical Practice, January 1997 (corrected July 2002). Available at: http://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2009/09/WC500002874.pdf. Accessed January 14, 2015.
61. Bottiger BW, Arntz HR, Chamberlain DA, et al. Thrombolysis during resuscitation for out-of-hospital cardiac arrest. *N Engl J Med* 2008;359:2651-2662.
62. Kim F, Nichol G, Maynard C, et al. Effect of prehospital induction of mild hypothermia on survival and neurological status among adults with cardiac arrest: a randomized clinical trial. *JAMA* 2014;311:45-52.
63. Burton TM. Despite heart attack deaths, PolyHeme still being tested on trauma patients. *Wall Street Journal* February 22, 2006.
64. Kipnis K, King NM, Nelson RM. Trials and errors: barriers to oversight of research conducted under the emergency research consent waiver. *IRB* 2006;28:16-19.
65. Kim SY, Miller FG. Informed consent for pragmatic trials--the integrated consent model. *N Engl J Med* 2014;370:769-772.
66. U.S. Department of Health & Human Services. Frequently Asked Questions About Human Research. Available at: http://answers.hhs.gov/ohrp/categories/1568. Accessed January 14, 2015.
67. Karlawish JH. Research involving cognitively impaired adults. *N Engl J Med* 2003;348:1389-1392.
68. Rosenstein DL, Miller FG. Research involving those at risk for impaired decision-making capacity. In: Emanuel EJ, Grady C, Crouch RA, et al (eds.). *The Oxford Textbook of Clinical Research Ethics*. Oxford: Oxford University Press, 2008:437-445.
69. Steinbrook R. How best to ventilate? Trial design and patient safety in studies of the acute respiratory distress syndrome. *N Engl J Med* 2003;348:1393-1401.
70. Silverman HJ, Luce JM, Schwartz J. Protecting subjects with decisional impairment in research: the need for a multifaceted approach. *Am J Respir Crit Care Med* 2004;169:10-14.
71. Glickman SW, McHutchison JG, Peterson ED, et al. Ethical and scientific implications of the globalization of clinical research. *N Engl J Med* 2009;360:816-823.
72. Love RR, Duc NB, Allred DC, et al. Oophorectomy and tamoxifen adjuvant therapy in premenopausal Vietnamese and Chinese women with operable breast cancer. *J Clin Oncol* 2002;20:2559-2566.
73. Orlandini A, Díaz R, Wojdyla D, et al. Outcomes of patients in clinical trials with ST-segment elevation myocardial infarction among countries with different gross national incomes. *Eur Heart J* 2006;27:527-533.

74. Vickers A, Goyal N, Harland R, et al. Do certain countries produce only positive results? A systematic review of controlled trials. *Control Clin Trials* 1998;19:159-166.
75. O'Shea JC, Califf RM. International differences in cardiovascular clinical trials. *Am Heart J* 2001;141:875-880.
76. London AL. Responsiveness to host community health needs. In: Emanuel EJ, Grady C, Crouch RA, et al (eds.). *The Oxford Textbook of Clinical Research Ethics.* Oxford: Oxford University Press, 2008:737-744.
77. Lind SE. Finder's fees for research subjects. *N Engl J Med* 1990;323:192-195.
78. The effect of vitamin E and beta carotene on the incidence of lung cancer and other cancers in male smokers. The Alpha-Tocopherol, Beta Carotene Cancer Prevention Study Group. *N Engl J Med* 1994;330:1029-1035.
79. Miller AB, Buring J, Williams OD. Stopping the Carotene and Retinol Efficacy Trial: The Viewpoint of the Safety and Endpoint Monitoring Committee. In: DeMets DL, Furberg CD, Friedman LM (eds.). *Data Monitoring in Clinical Trials: A Case Studies Approach.* New York: Springer, 2006: 220-227.
80. Age-Related Eye Disease Study Research Group. The Age-Related Eye Disease Study (AREDS): design implications. AREDS report no. 1. *Control Clin Trials* 1999;20:573-600.
81. Age-Related Eye Disease Study Research Group. A randomized, placebo-controlled, clinical trial of high-dose supplementation with vitamins C and E, beta carotene, and zinc for age-related macular degeneration and vision loss: AREDS report no. 8. *Arch Ophthalmol* 2001;119:1417-1436
82. Tegeler CH, Furberg CD. Lessons from warfarin trials in atrial fibrillation: missing the window of opportunity. In: DeMets DL, Furberg CD, Friedman LM (eds.). *Data Monitoring in Clinical Trials: A Case Studies Approach*. New York: Springer, 2006:312-319.
83. Hulley S, Grady D, Bush T, et al. Randomized trial of estrogen plus progestin for secondary prevention of coronary heart disease in postmenopausal women. Heart and Estrogen/progestin Replacement Study (HERS) Research Group. *JAMA* 1998;280:605-613.
84. Rossouw JE, Anderson GL, Prentice RL, et al. Risks and benefits of estrogen plus progestin in healthy postmenopausal women: principal results from the Women's Health Initiative randomized controlled trial. *JAMA* 2002;288:321-333.
85. Hulley SB, Grady D, Vittinghoff E, et al. Consideration of early stopping and other challenges in monitoring the Heart and Estrogen/Progestin Replacement Study. In: DeMets DL, Furberg CD, Friedman LM (eds.). *Data Monitoring in Clinical Trials: A Case Studies Approach*. New York: Springer, 2006:236-247.
86. Wittes J, Barrett-Connor E, Braunwald E, et al. Monitoring the randomized trials of the Women's Health Initiative: the experience of the Data and Safety Monitoring Board. *Clin Trials* 2007;4:218-234.
87. Peppercorn J, Buss WG, Fost N, et al. The dilemma of data-safety monitoring: provision of significant new data to research participants. *Lancet* 2008;371:527-529.
88. Black HR, Elliott WJ, Grandits G, et al. Principal results of the Controlled Onset Verapamil Investigation of Cardiovascular End Points (CONVINCE) trial. *JAMA* 2003;289:2073-2082.
89. Psaty BM, Rennie D. Stopping medical research to save money: a broken pact with researchers and patients. *JAMA* 2003;289: 2128-2131.
90. Marcus AD. Paying to keep your drug trial alive. *Wall Street Journal*. April 10, 2007.
91. National Institutes of Health, U.S. Department of Health & Human Services. Health Insurance Portability and Accountability Act (HIPAA). Available at: http://privacyruleandresearch.nih.gov/. Accessed January 14, 2015.
92. National Institutes of Health, U.S. Department of Health & Human Services. NIH Data Sharing Policy and Implementation Guidance (updated March 5, 2003). Available at: http://grants.nih.gov/grants/policy/data_sharing/data_sharing_guidance.htm. Accessed January 14, 2015.

93. Policy for Sharing of Data Obtained in NIH Supported or Conducted Genome-Wide Association Studies (GWAS). Available at: http://grants.nih.gov/grants/guide/notice-files/NOT-OD-07-088.html. Accessed January 14, 2015.
94. Zarin DA, Tse T. Medicine. Moving toward transparency of clinical trials. *Science* 2008;319:1340-1342.
95. Wilson D, Meier B. Doctor falsified study on injured G.I.'s, Army says. *The New York Times*. May 12, 2009.
96. Scott J. Withdrawal of a paper. *J Bone Joint Surg Br* 2009;91:285-286.
97. Fisher B, Anderson S, Redmond CK, et al. Reanalysis and results after 12 years of follow-up in a randomized clinical trial comparing total mastectomy with lumpectomy with or without irradiation in the treatment of breast cancer. *N Engl J Med* 1995;333:1456-1461.
98. Angell M, Kassirer JP. Setting the record straight in the breast cancer trials. *N Engl J Med* 1994;330:1448-1450.
99. Turner EH, Matthews AM, Linardatos E, et al. Selective publication of antidepressant trials and its influence on apparent efficacy. N *Engl J Med* 2008;358:252-260.
100. Heres S, Davis J, Maino K, et al. Why olanzapine beats risperidone, risperidone beats quetiapine, and quetiapine beats olanzapine: an exploratory analysis of head-to-head comparison studies of second-generation antipsychotics. *Am J Psychiatry* 2006;163:185-194.
101. Packer M, Carson P, Elkayam U, et al. Effect of amlodipine on the survival of patients with severe chronic heart failure due to a nonischemic cardiomyopathy: results of the PRAISE-2 study (prospective randomized amlodipine survival evaluation 2). *JACC Heart Fail* 2013;1:308-314.
102. Pfeffer MA, Skali H. PRAISE (prospective randomized amlodipine survival evaluation) and criticism. *JACC Heart Fail* 2013;1:315-317.
103. International Committee of Medical Journal Editors. Uniform requirements for manuscripts submitted to biomedical journals: writing and editing for biomedical publication (updated October 2008). Available at: http://www.icmje.org/. Accessed January 14, 2015.
104. Clinical Trials Registration in ClinicalTrials.gov (Public Law 110-85): Competing Applications and Non-Competing Progress Reports. Available at: http://grants.nih.gov/grants/guide/notice-files/NOT-OD-08-023.html. Accessed January 14, 2015.
105. Federal Register, volume 73, Number 99, May 21, 2008. Available at: http://edocket.access.gpo.gov/2008/E8-11042.htm. Accessed January 14, 2015.
106. Zarin DA, Tse T, Williams RJ, et al. The ClinicalTrials.gov results database--update and key issues. *N Engl J Med* 2011;364:852-860.
107. Steinbrook R. Gag clauses in clinical-trial agreements. *N Engl J Med* 2005;352:2160-2162.
108. Drazen JM, Van Der Weyden MB, Sahni P, et al. Uniform format for disclosure of competing interests in ICMJE journals. *N Engl J Med* 2009;361:1896-1897.