26. ETHICAL ISSUES IN CLINICAL TRIALS
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Clinical trials are essential to establish the effectiveness and safety of interventions. In a clinical trial, researchers intervene on participants by administering a study drug and thereby exposing them to risk. Researchers must assure that the experimental intervention does not put participants at unacceptable risk. The goal of a clinical trial, which is to obtain valid information about the effectiveness and safety of interventions, may conflict with the best interests of an individual participant. In a clinical trial, many aspects of participants' care are determined by the protocol, not by a personal physician (1). The intervention may be assigned by randomization. Study personnel and participants may be blinded to what intervention is provided. Some participants may receive a placebo rather than an active drug. Adjustments in drug dosage may be determined by the protocol, not by the individualized decisions tailored to the participant's condition. Additional therapies may be limited or prohibited. Although these provisions allow the research question to be answered more rigorously, they might not be best for individual participants. For example, a participant might benefit from concurrent medications forbidden by the protocol, or from an individualized adjustment in the dose of the study drug. In such circumstances, the participant would be better off not participating in the trial. However, participants often do not appreciate how a clinical trial differs from usual clinical care, and their decisions to participate in clinical trials may not be truly informed.

The following example illustrates how each step in the design of a clinical trial may involve ethical issues. The same design features that make clinical trials rigorous may also raise ethical concerns.

STUDY 27.1. PREVENTION OF NEPHROPATHY IN PATIENTS WITH TYPE II DIABETES. *A randomized controlled trial (RCT) studied whether or not an angiotensin II receptor clocker (ARB) prevents progression of renal disease in patients with diabetes who have microalbuminuria. The control group received a placebo. All participants received the usual care for diabetes from their primary physicians.*

At the time the study was proposed, randomized trials had already shown that angiotensin-converting enzyme (ACE) inhibitors slowed the progression of nephropathy in persons with Type I diabetes. There were some smaller studies suggesting benefits in patients with Type II diabetes as well. Many physicians in clinical practice had extrapolated from published studies and were already prescribing ACE inhibitors to patients with Type II diabetes.

In Study 26.1 (2), some physicians contended that it was unethical to randomize participants to a placebo because the benefits of ACE inhibitors were already accepted. Others argued that it would be preferable to study ACE inhibitors rather than ARBs. Still others were concerned that investigators had a conflict of interest regarding background care for diabetes. Tighter control of glucose would reduce the endpoint of diabetic complications, but it would also reduce the power of the study to detect a difference between the two arms. Thus researchers, wanting the clinical trial to succeed, might be less vigorous about controlling blood glucose levels.

RANDOMIZATION

WHY IS RANDOMIZATION USEFUL?

RCTs as in Study 26.1 are the most rigorous design for evaluating interventions because randomization is the best way to make the baseline characteristics of the intervention and control groups similar. Any differences at the onset of the study could lead to a difference in outcomes between the control and active groups.

WHAT ARE THE ETHICAL CONCERNS ABOUT RANDOMIZATION?

RCTs raise particular ethical concerns because the intervention that a participant receives is determined by chance rather than by a personal physician making an individualized judgment about what is best for her. Furthermore, there are concerns that randomization may harm participants if they receive a less effective or riskier intervention. Recent meta-analyses have shown that participants in an RCT

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generally have comparable outcomes to patients who are eligible to participate but receive conventional care (3, 4). These data are controversial, because people who volunteer for clinical trials may be healthier or more compliant than eligible patients who do not enroll.

WHEN IS RANDOMIZATION JUSTIFIED?

Researchers and ethics experts agree that it is appropriate to randomize participants in clinical trials in certain circumstances, but they cannot agree on why that is the case.

The concept of equipoise

One ethical justification for assigning treatment by randomization is that the arms of the protocol are in **equipoise**. Equipoise is a concept that seems intuitively clear but is hard to define precisely. The general idea is that there is genuine uncertainty or controversy over which arm of the trial is superior. Intuitively, the concept of "equipoise" makes sense: if there is no convincing evidence that one arm is superior, the relative benefit/risk ratios of the study arms are comparable, and participants will not be harmed if they agree to allow their care to be determined by randomization rather than by an individualized decision by their personal physician. However, philosophers debate over how to define equipoise and whether randomization is most convincingly justified by equipoise, the researcher's duty to act in best interests of individual participant, or a duty of non-exploitation (5).

Equipoise is sometimes taken literally to mean an exact balance between the two arms, but this is almost never the case. Sponsors and investigators would be unlikely to propose a trial for a new drug if they did not have some evidence that it was superior to current therapy. Also as data accumulates in a clinical trial, trends emerge and the arms of the trial will no longer be in balance. In addition, results from other trials may be pertinent. It is illogical to say that equipoise must be exactly 50-50 or that a researcher may never compromise a patient's personal best interests to any degree; from this perspective, a randomized clinical trial could never be completed. If randomization may be acceptable despite some evidence favoring one arm, the crucial questions are how much imbalance between the arms is unacceptable and who decides what is acceptable. Metaphorically, the balance arm need not be exactly level, but the weight of evidence may not tip completely to one side. The concept of equipoise should be interpreted broadly in order to include interventions that may not be quite as effective as standard care, but might be less complicated, less expensive, or have fewer side effects. Our intuition is that researchers in a clinical trial may compromise a participant's interests only for very good reasons and only to a limited extent. In Study 26.1, there was some evidence to support the effectiveness of ARB, but it was not definitive.

Levels of equipoise

In practical terms, equipoise or uncertainty should exist on three different levels.

The community of scientific experts. One requirement for equipoise is that existing evidence on the research question is inconclusive. That is, experts who have critically reviewed the evidence disagree. Judgments about the superiority of one treatment or another should follow the convention that requires statistical significance at the level of $p < .05$. This determination of equipoise is made by peer reviewers, IRBs, and study sponsors when they approve an RCT.

The individual physician, acting as an investigator or a referring MD. This option often is criticized because these individual physicians might base their judgments on intuition, custom, or ignorance rather than evidence-based deliberation. However, it would be ethically troubling to ask physicians to ignore their personal clinical judgment when making recommendations to potential research participants or when carrying out a research study. In clinical practice, physicians are expected to extrapolate published evidence when making decisions for individual patients. Moreover, many patients rely on their physician's recommendations about entering a clinical trial. Physicians who believe that one arm of the trial is superior cannot refer patients to it without violating their ethical obligation to act in the best interests of their patients. Nor can such physicians in good faith serve as an investigator in the trial without violating their obligation as researchers to assure that the risks of the research are minimized and acceptable in light of the benefits.

Individual research participants. Even if experts and individual physicians believe that equipoise holds, an individual patient may decline to be randomized because he strongly prefers one of the arms. In Study 26.1, patients who would benefit from ARB or ACE inhibitors because they have congestive heart failure should not accept randomization. As another example, if a trial compares surgical and medical approaches to a disease, some persons may find the short-term risk or the long-term complications from surgery to be unacceptable, while others may not be willing to take medication daily.

If few patients are willing to be randomized to receive either treatment, as a practical matter, the

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trial cannot be carried out. Hence even if the scientific peer reviewers and the IRB judge that a randomization is appropriate, the trial will fail if referring physicians or potential participants do not agree that equipoise exists.

CHOICE OF INTERVENTIONS

The choice of interventions in a clinical trial may raise ethical as well as scientific concerns.

ACTIVE INTERVENTIONS

In Study 26.1, the choice of the active intervention was controversial. Some experts contended that ACE inhibitors should have been studied rather than ARBs. Because several ACE inhibitors were available in generic format or were going off patent, the cost of long-term therapy would be much less for ACEs than for on-patent ARBs. Thus an RCT showing that ACE inhibitors are effective would provide greater benefit to society than an RCT of ARBs. However, drug manufacturers who sponsor trials like Study 26.1 have much more incentive to study ARBs, because sales of patented drugs generate greater profits.

CONTROL INTERVENTIONS

The choice of interventions for the control group may raise ethical concerns. In some clinical trials, the choice of interventions has been criticized as biased because the control intervention was known to be ineffective for the condition studied, or was administered at suboptimal doses in the clinical trial (6). Such use of control interventions is unethical both because it puts participants at unacceptable risk and because it leads to overestimates of the benefits of investigational agent. Rigorous scientific peer review of protocols is the best safeguard against such design bias.

USE OF PLACEBO CONTROLS

Placebos are substances that are inactive for the condition being studied. Their use strengthens the rigor of a clinical trial, but also raises ethical concerns. Administering a placebo rather than no intervention at all in the control group controls for the possibility that outcomes are due to the participant's belief that the intervention will work, rather than a biological effect. However, if effective treatment is available, participants might be harmed if they receive a placebo rather than the active treatment. Placebos are ethically acceptable under several circumstances (Table 26.1).

Table 26.1. Acceptable use of placebo controls

No effective treatment exists for the condition
Participants have failed to respond to established treatment
Participants have refused established treatment
No serious or irreversible risks will occur
Alternative study designs will not produce valid conclusions

No effective treatment exists for the condition under study. Placebos are appropriate if there is no effective treatment, provided that participants understand that they might receive an inert pill and consent to this possibility. However, if an effective treatment exists for the condition being studied and is feasible to administer, intentionally withholding effective therapies would violate the ethical principle of "do no harm." A more ethically acceptable design is an "add on" design: all participants receive the current standard of care plus either the investigational agent or a placebo.

Participants have failed to respond to established treatment. A placebo would not harm persons who fail to respond to the standard treatment or cannot tolerate it, because they would not benefit from the treatment they have foregone.

No serious or irreversible risks to participants. In mild, self-limited conditions, such as allergic rhinitis, insomnia, mild hypertension, and pain from a dental extraction, participants would not suffer significant harm if they received a placebo. Indeed, many patients with these conditions decide not take medications. Potential participants need to be informed that effective interventions are available outside the research study.

Informed refusal of standard therapy. Participants may be entered into a placebo-controlled trial if

STUDY 27.2. PLACEBO-CONTROLLED TRIAL OF ACELLULAR PERTUSSIS VACCINE. *In Italy in 1992, a pertussis vaccine was not required for children, and the national vaccination rate was about 40%. A major reason for this low rate of vaccination was the perception that the whole-cell pertussis vaccine had an unacceptable rate of complications. A randomized clinical trial in Italy compared two acellular vaccines with the whole cell vaccine currently used in the U.S. and with placebo. The two acellular vaccines were found to be immunogenic, effective, and safe, while the effectiveness of the whole-cell vaccine was unexpectedly low. Adverse events were much more frequent with the whole-cell vaccine*

they have made an informed refusal of standard and effective therapy (7). The criteria for judging that they are informed should be strict. For example, participants should be administered a questionnaire to ascertain that they understand the availability of effective treatment and the risks that might occur if they forego it. The more serious the condition and the potential harm from omitting standard therapy, the stricter the criteria should be. Also, such participants should be offered the opportunity to change their minds, withdraw from the clinical trial at any time, and receive standard treatment.

In Study 26.2, relatively few children in Italy received pertussis vaccine, because of parental concerns about side effects. Parents who strongly preferred their children to receive an active vaccine could choose to receive the licensed whole-cell vaccine outside the trial. Thus, the trial was carried out in children whose parents were willing to forego an active vaccine.

More controversially, placebos may be acceptable under the following circumstances:

Alternative study designs will not produce valid conclusions. In some situations, if placebo controls are not used, the research question cannot be answered in a rigorous manner. One such situation is that the difference in outcomes between standard treatment and placebo for the condition varies greatly from one clinical trial to another.

In major depression, about one-third of well designed and well conducted clinical trials fail to distinguish a drug that is known to be effective from a placebo (8). The percentage of people responding to antidepressants varies greatly from trial to trial. This is due to a number of reasons, including great variability in response from person to person, spontaneous remissions, refractory cases, and modest efficacy.

STUDY 27.3. VARIABLE OUTCOMES IN CLINICAL TRIALS FOR DEPRESSION. A placebo-controlled RCT is proposed for a new antidepressant. Participants will be persons with major depression. They will be informed that standard therapies for depression are available outside of the trial.

In Study 26.3, if a new intervention is compared only to standard therapy (an active control design), the study results will be difficult to interpret if no significant difference is found between the two arms. Without a placebo comparison arm, the FDA has determined that it would be impossible to determine whether both drugs are effective in this trial or if both are no better than placebo. Hence without placebo controls, the study might not yield valid knowledge, and therefore any risk to participants would be unethical.

However, strict measures need to be taken to assure that risks to participants are acceptable and minimized in such placebo-controlled trials (9). Serious or life-threatening outcomes might occur if an exacerbation of depression is not treated promptly. In Study 26.3, participants need to be monitored closely for the development of suicidality. Because severely depressed persons may not take the initiative to seek care, it would be prudent to enroll only persons who have someone who can help monitor their condition and help them seek medical care if needed. The participant (as well as a relative, partner, or close friend) should be educated on the importance of reporting symptoms of worsening depression or suicidality immediately to the investigators. Investigators need to be available at all times to respond to such serious adverse events. Appropriate plans must be made to remove suicidal patients promptly from the study and provide individualized treatment, which might include off-study medications and voluntary or involuntary hospitalization. When participants are removed from the trial because they are suicidal, they should be counted as a treatment failure.

Placebo-controlled trials are also appropriate, even though effective treatment are available, in conditions that have a waxing-waning course or spontaneous remissions or whose therapies are only partially effective and have serious adverse effects (9).

It may not be acceptable to carry out a placebo-controlled trial in resource-poor countries that would be considered unethical in the U.S. For instance, such trials are not appropriate simply because people in the host country cannot afford therapies used in the U.S. As discussed in Chapter 23, such trials need to address a health care priority in the country and alternative study designs that did not use a placebo would not produce valid conclusions.

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BLINDING

Blinding of investigators and participants, which helps prevent bias, can raise ethical problems. Blinding eliminates bias in the ascertainment of endpoints. It also minimizes the clinical impact of a participant's belief that she is receiving an effective intervention (so-called placebo effects). However, blinding could be detrimental if the patient suffers a serious adverse event that might be related to the study intervention. Thus, there must be a procedure to override blinding when necessary to provide needed medical care to a participant. Blinding often is imperfect because participants can determine what intervention they are receiving because of adverse effects.

STUDY 27.1 CONTINUED. If a participant in Study 1 develops life-threatening hyperkalemia, the blind should be broken. If the participant was on ARB, it would be reasonable to monitor the potassium level carefully after stopping the study medication to ensure that the potassium returns to normal. If the participant was on placebo, a workup for other causes of hyperkalemia would be indicated.

BACKGROUND CARE

Background care or concurrent care is the care participants receive for the condition being studied in addition to the study or control intervention. Protocols commonly specify what background care will be permitted; this standardization enhances the internal validity of the study. Ethical concerns arise if the quality of background care is substandard. In Study 26.1, background care for diabetes includes counselling on diet and exercise and home glucose monitoring. These interventions are known to improve glucose control and thereby reduce the progression of nephropathy. However, they also reduce the power of the study to detect a difference between the two arms. Thus study staff might unconsciously underemphasize lifestyle changes and self-management. Further dilemmas arise if a study adopts "usual care" for background care, but the quality of care available to participants is known to be substandard. Even though the researchers are not personally providing a substandard level of care, they have some responsibility for the care participants receive for the condition they are studying. If investigators allow substandard care to continue without comment, participants may infer that the experts approve it. Researchers can address concerns about background care by providing treating physicians with results of clinical tests carried out as part of the research project and offering referring physicians suggestions. For example, in Study 26.1, investigators should provide results of hemoglobin A1c and cholesterol tests and suggest prescribing statins or increasing the dose to meet target goals for cholesterol management. Alternatively, to avoid a conflict of interest, the investigators might arrange for independent diabetes experts to monitor these tests and make recommendations. For persistently suboptimal glucose control, the study might offer treating physicians the opportunity to refer participants to free counseling for diet and exercise that is provided by clinicians independent of the study and blinded to the intervention the participant receives. In addition, investigators should also provide care for conditions that might affect the endpoint of the trial; for example, untreated hypertension needs could cause progression of renal insufficiency.

A related issue is ancillary care, care for other conditions that are not the object of study. In countries with a well-functioning health care system, participants can be referred to their usual source of medical care. Chapter 23 discusses the issue of ancillary care in resource-poor settings, where access to basic health care is compromised.

STANDARDIZATION OF INTERVENTIONS

Protocols commonly specify the doses of medications and the circumstances in which the doses may be changed. Such standardization increases the internal validity of the study. However, it can be problematic if participants do not appreciate that decisions about their medications are determined by the protocol, and not by individualized decisions about what is in their best interests. The ethical tension between scientific rigor and acting in the best interests of individual participants can be alleviated if the study is designed as a "large simple trial," in which participants are allowed to receive a broad spectrum of background care in addition to the study intervention (5). Furthermore, participants may be recruited from diverse populations and practice settings (10). Such pragmatic trials also have the advantage of greater external validity because they are directly applicable to decision-making in clinical practice.

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CHOICE OF ENDPOINTS

Clinical endpoints such as death, myocardial infarction, functional status or disease-related quality of life are meaningful to patients. Rigorous evidence that an intervention improves such clinical endpoints provides a strong basis for a change in medical practice. However, demonstrating an impact on clinical endpoints may require a large number of participants or a prolonged trial.

To make trials smaller and shorter, **intermediate markers**, such as laboratory measurements or physical signs, may be considered instead of a clinical endpoint. Intermediate markers are commonly used in Phase I studies, which are too small and short to see changes in clinical endpoints. For example, in a Phase I cancer trial, improvement in tumor markers such as Prostate Specific Antigen (PSA) or stabilization or reduction in tumor size may justify moving to a Phase II study.

Intermediate markers, however, should be used with great caution. In a number of clinical trials, an intervention had a beneficial effect on intermediate markers but a detrimental effect or no effect on clinical endpoints. Examples of such discrepancies include (11, 12):

- Flecainide, encainide, and moricizine suppress ventricular arrhythmias after a heart attack but increase mortality.
- Milrinone and flosequinan improve cardiac output and exercise tolerance but increase mortality in CHF.
- Chemotherapy with 5-fluorouracil (5FU) improves complete and partial response rate of patients with advanced colon cancer but has no impact on overall survival.
- Fluoride increases bone mass but also increases vertebral fractures in patients with osteoporosis.
- Topical antibiotics reduce the incidence of nasal cultures of *Staph aureus* in surgical patients but do not reduce infection at surgical sites.

Intermediate markers were misleading surrogates for clinical outcomes in these studies. Inferring that the study intervention is effective solely on the basis of intermediate markers would have led to serious errors. Had clinical practice changed on the basis of these findings, many patients would have been seriously harmed. Thus in Phase III studies, intermediate markers, no matter how plausible, should be used as surrogates for clinical outcomes only if they have been formally validated as predicting clinical outcomes.

In summary, the choice of interventions, subjects, and endpoints can only be addressed in the context of the specific clinical trial. Integrated scientific and ethical review helps assure that these issues are addressed appropriately. First, the study should receive rigorous scientific peer review by experts independent of the study. These experts can determine whether or not the existing evidence already indicates that one arm of the study is superior to the other(s), whether or not the end-points are meaningful, what the medical risks are, and which participants might be at increased risk of adverse events. Second, an IRB reviewing a clinical trial should have access to the scientific reviewers' recommendations on these issues and take them into account during its deliberations. The IRB should include members or consultants with scientific and clinical expertise pertinent to the study.

SELECTION OF SUBJECTS

The inclusion and exclusion criteria for a clinical trial may raise ethical concerns. Investigators need to decide, for example, whether to study the early or late stages of a disease or condition. Enrolling persons in the late stages of the disease, whose prognosis is limited, might limit the potential loss of quality-adjusted life years if serious adverse events occur. However, depending on the disease and the condition, an intervention may fail to benefit patients with advanced disease but still benefit persons in the early stages of the disease.

Researchers should exclude persons who are **at greatly increased risk** for harm from the investigational or control intervention in the study. For example, persons should be excluded if they already have significant impairment in an organ system where the investigational agent causes adverse events to occur.

Persons should also be excluded if they **need to take the investigational agent** and will be harmed if they do not receive it.

In Study 27.1, enrolling patients with impaired glomerular filtration would increase the number of clinical endpoints and shorten the length of the study. However, persons who already have significant renal failure might not respond to an intervention that would be effective in persons with early stage nephropathy. Hyperkalemia is one adverse effect of ARBs. Thus the study might exclude persons who have a history of hyperkalemia or who need to take other medicines that can cause hyperkalemia. Finally, participants with congestive heart failure in addition to diabetes could be significantly harmed if they received a placebo rather than ARB and therefore should be excluded from the trial.

INFORMED CONSENT

Although investigators and IRBs pay great attention to consent forms, many participants – the majority in some studies – have fundamental misunderstandings about the purpose and nature of clinical trials (13-17). Participants often do not understand how clinical trials differ from standard treatment – this is often called "therapeutic misconception" (18). Furthermore, they commonly do not understand that they may be in a control group rather than the intervention group and that being in a clinical trial may restrict their therapeutic options (18). Thus, investigators should try to improve comprehension of participants, for example by spending more time talking with them.

For certain clinical trials, consent might be particularly problematic (19):

- Phase 1 clinical trials whose aim is to determine the maximum tolerated dose of a new investigational agent
- Placebo-controlled trials in which treatment of proven efficacy is withheld
- Trials in which invasive procedures such as biopsies are performed solely for research purposes
- Trials of interventions for which participants have high hopes of success, such as stem cell transplantation (20). Chapter 28 discusses ethical issues in stem cell clinical trials in more detail.

In these circumstances, the balance of benefit to risk might not be as favorable as in standard care.

Although many researchers and IRBs focus on disclosure of information, it may be more important ethically for researchers to ask eligible participants questions to check whether or not they comprehend key information about the trial. Chapter 6 recommends that clinical trial participants need to appreciate:

- How research is different from clinical care
- That the effectiveness of the research intervention is unknown
- That the research intervention has risk
- That the interventions are determined by chance and not by what a physician believes is best for the individual participant

If a participant does not understand these issues, the investigators need to spend more time talking with him or her, until their misunderstandings are corrected.

Trials where many participants have low literacy or poor access to health care present particular challenges. Chapter 6 discusses how to overcome such barriers to consent.

Consent must be voluntary as well as informed. If an investigator in a clinical trial enrolls her own patients as participants, they are ethical concerns because patients may be reluctant to say no to a physician on whom they depend for ongoing care.

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DATA MONITORING

As data are collected in a clinical trial, they should be monitored to address the questions in Table 26.2. Data monitoring and interim data analyses are needed to determine whether it is ethical to continue the trial as planned.

Table 26.2. Questions for data monitoring and interim data analysis

Are the risks and benefits substantially different than expected?
Has one arm been proven to have more benefit?
Has one arm been proven to have more harm?
Will the trial be unable to give a valid answer to the research question?

If the answer to any question is yes, several additional questions need to be posed:
Should the trial be continued?
Should the protocol be modified?
Should the informed consent process be modified?

DATA MONITORING PROCEDURES

To address these questions, the protocol should contain a data monitoring plan that addresses the following procedural questions:

When will data be monitored?

The protocol should specify when data will be monitored. In Phase I studies, data are typically analyzed after a few participants have completed the protocol. In a classic dose-escalation protocol, three participants receive each dose, and data from each cohort is examined before proceeding to the next dosage level. In some circumstances, such as first-in-human studies of highly innovative interventions, data from each participant should be evaluated before the next participant is enrolled.

In Phase III studies, often three interim analyses are planned, for example when 25%, 50%, and 75% of the planned participants are enrolled, or when these percentages of endpoints are observed. However, data monitoring schedules should be individualized for each trial.

Who will monitor data from the trial?

The most rigorous way to carry out interim analyses of the data as it accrues is through a data and safety monitoring board (DSMB) that is independent of the investigators and the sponsor (21). The DSMB can be unblinded while the investigators remain blinded, so that the study can proceed without bias.

The DSMB also examines unblinded data on safety and efficacy, looking at differences between the active and control arms. These unblinded data are kept confidential from the investigators and sponsor, so that no bias is introduced into the trial.

The protocol should specify what data will be examined at each data monitoring session and what findings will lead to changes in the protocol. The DSMB receives data from the statistical center at each planned interim analysis. The DSMB examines data on patient accrual, retention, protocol violations, and missing data. These data, as well as aggregate data on adverse events, are often shared with the study leadership and sponsor in an open session. The DSMB also examines adverse events and outcomes data by treatment arm in a closed session that the investigators and sponsor do not attend; the DSMB may unblind the arms during the closed session if needed.

Investigators can obtain more information about DSMBs at a number of websites. NIH has guidance on DSMBs on its website at http://grants.nih.gov/grants/guide/notice-files/not98-084.html. The National Cancer Institute (NCI) has detailed guidance regarding DSMBs, including examples of plans for DSMBs, at the website http://www.cancer.gov/clinicaltrials/conducting/dsm-guidelines/page1. In addition, research institutions often have model DSMB policies on their IRB website.

Because DSMBs are costly, they are used primarily in Phase II/III trials. The NIH requires their use in the Phase III trials that it funds. However, for other studies, alternative options for data monitoring may be appropriate (22). In Phase I studies, the principal investigator, a colleague of the PI, or the study sponsor may monitor the data for unexpected harm. However, these alternative arrangements may raise concerns about conflicts of interest.

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ARE THE RISKS AND BENEFITS SUBSTANTIALLY DIFFERENT THAN EXPECTED?

Serious unexpected adverse events (AEs) related to the study agents may alter the risk/benefit ratio to the point that it is unacceptable or the risks are no longer minimized. Unexpected AEs are those that are not mentioned in the protocol or are more frequent or serious than anticipated. The DSMB also reviews whether the serious unexpected adverse events are related to the study or control agents. The DSMB may recommend additional or more frequent measurements to ascertain the incidence, severity, or mechanism of the AEs.

If so, the balance of risks and benefits in the trial needs to be reassessed to determine if the risks are still acceptable and minimized.

In some cases, the DSMB might recommend or require protocol modifications such as reducing the dose of the investigative agent or excluding participants who are at greatly increased risk for adverse events.

HAS ONE ARM BEEN PROVEN TO HAVE MORE BENEFIT?

Interim data analyses raise complex ethical and statistical issues, as the following study illustrates (23-25).

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STUDY 27.4. STOPPING A TRIAL EARLY FOR BENEFIT. *In the ASCOT trial, participants with hypertension and other cardiac risk factors were randomized to receive an atenolol-based regimen (a thiazide diuretic could be added after a maximal dose of atenolol) or an amlodipine-based regimen (an ACE inhibitor could be added after a maximal dose of amlodipine). The trial enrolled over 19,000 patients. After an average of 4.6 years of follow-up, the DSMB found on interim analysis a non-significant trend in the primary endpoint, heart attack plus cardiac death, in favor of amlodipine regimens. Moreover, there was a highly significant trend in one of the seven secondary endpoints, stroke, favoring the amlodipine arm ($p < 0.00004$). Even taking into account that there were seven secondary endpoints, this p-value exceeded the stopping rule at the first analysis. The DSMB recommended stopping the trial on the basis of this secondary endpoint. However, after discussions with the leadership and other experts, it was agreed to continue the trial. Because beta-blockers were widely prescribed for hypertension, it was judged that more compelling evidence was needed to change clinical practice. Furthermore, an independent endpoint committee was still adjudicating some endpoints.*

At a second interim analysis after 5.5 years of follow-up, there continued to be a non-significant trend in favor of amlodipine for the primary cardiovascular endpoint and a significant trend for stroke. In addition, there was a trend favoring amlodipine in total mortality (13.9 / 1000 participant years vs. 15.5, $p = 0.0247$, which did not meet the statistical stopping rule) and in new-onset diabetes ($p < 0.001$, which met the stopping rule). The DSMB again recommended stopping the trial, and the trial was halted.

From an ethical perspective, if interim data already prove that one arm is significantly more beneficial, continuing the study as planned would be ethically problematic because it would delay providing the more effective intervention to participants in the other arm and to patients outside the trial. From a statistical viewpoint, however, trends seen on early interim analysis may be misleading because they may be reversed as more endpoints accrue. There is considerable fluctuation in interim trial results over time due to random variation (26). Furthermore, multiple analyses of data increase the likelihood of finding a difference between the two arms by chance when in reality no difference exists (a Type I error).

Statistical stopping rules address these issues by requiring a more stringent level of statistical significance (alpha) at each interim analysis than at the end of the trial. Generally the alpha level at the first interim analysis is very small, and the alpha level at the final analysis is close to the two-sided alpha level of 0.05 for the completed study. The choice of stopping rules should be specified in the protocol. Unfortunately, DSMBs often do not apply proper statistical stopping rules and may base stopping decisions on an inadequate number of endpoints (27). As a result, clinically improbable effect sizes are sometimes reported when clinical trials are stopped early (28). This may lead to bais in systematic reviews (27). Some critics assert that stopping trials early for benefit leads to systematic overestimation of the magnitude of benefit (27). It is to be expected on statistical grounds, however, that point estimates of effectiveness are higher in trials that are stopped at interim monitoring for efficacy than in similar trials that are completed as planned (29). Another important consideration is that stopping trials at interim analysis precludes gathering information on important long-term endpoints, such as long-term survival or recurrence of disease (26).

There often is an ethical tension between the short-term well-being of participants in the trial and the discovery of important new knowledge (30). Stopping an inferior intervention may protect trial participants from short-term harm. However, both future patients and trial participants have an interest in having the trial answer important research questions, for example regarding long-term outcomes or continuing the trial to see if trends on secondary endpoints become statistically significant. In some cases, stopping a study at interim analysis makes it very unlikely that additional important questions will ever be answered. Moreover, in some circumstances, stopping a trial prematurely may decrease its impact on clinical practice, because practicing physicians may not find conclusions based on interim analyses persuasive. For example, this may occur if a trial finds that a widely used treatment is less effective or less safe than the experimental intervention. As a result, future patients may be harmed by continuing to receive the inferior intervention. This dilemma can only be resolved in the context of a specific trial and clinical condition, taking into account all the data available at the time of the interim analysis.

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HAS ONE ARM BEEN PROVEN TO HAVE MORE HARM?

If the interim data proves that one arm causes significantly more harm than the other, continuing the trial would subject participants in that arm to excessive harms.

STUDY 5. STOPPING A TRIAL EARLY FOR HARM. *In the Cardiac Arrhythmia Suppression Trial (CAST), the antiarrhythmic drugs flecainide, encainide, and moricizine were compared to placebo in heart attack survivors with ventricular premature beats. When this study was carried out, antiarrhythmic drugs were widely used in clinical practice in patients with myocardial infarction, because they were known to suppress ventricular arrhythmias. Only participants whose ventricular arrhythmias were suppressed by one of the study drugs were randomized into the trial. At interim analysis after ten months of follow-up, flecainide and encainide had a higher mortality than the placebo group (7.7% vs. 3.0%) and higher cardiac mortality (4.5% vs. 1.2%). The DSMB recommended stopping the trial.*

Interim data suggesting that the experimental intervention is harmful has been called "the agonizing negative trend (31)." Decisions to stop a trial because of harm may be difficult because the DSMB can make two types of errors. One error is stopping a trial too soon. If the evidence of harm is weak, the rejected intervention might be shown to be beneficial if the trial had continued. Furthermore, stopping a trial too soon may fail to provide sufficient evidence to persuade physicians to abandon a harmful drug that is being used in clinical practice (32). The opposite error is continuing a harmful trial longer than necessary and causing more participants to be harmed by a risky intervention.

In Study 5, the DSMB allowed the trial to continue after it was already extremely unlikely that these drugs would be shown to improve mortality. Because antiarrhythmic drugs were widely used in clinical practice, the DSMB believed that it was important to show that these drugs increased mortality, rather than simply having no benefit. Study 5 produced the counterintuitive finding that these drugs increased mortality even though they had a beneficial effect on the surrogate endpoint. These results had a dramatic impact on clinical practice.

In other trials, there may be evidence of an increase in a serious but nonfatal adverse event that is statistically significant but relatively infrequent. Under these circumstances, a DSMB might decide to continue a trial but institute protective measures, such as scheduling more frequent interim analyses, excluding participants at high risk of developing the harm, and informing participants in of the risk (33).

WILL THE TRIAL BE UNABLE TO GIVE A VALID ANSWER TO THE RESEARCH QUESTION?

The power of a trial may become unacceptably low if there is very low enrollment or far fewer than expected outcome events. Furthermore, the validity of a trial may be compromised by frequent protocol violations or high drop out rates. If these problems occur, the DSMB may request that the investigators develop an action plan to correct the problems. For example, if enrollment falls well below projections, the investigators may add more sites, seek IRB approval to change the method of recruitment, provide additional training or support for study staff, or extend the duration of the study.

If steps to correct these problems are unsuccessful, prospect of gaining valid and generalizable knowledge. Thus it would be unethical to continue to expose participants to any risk and inconvenience.

ACTIONS AFTER INTERIM DATA ANALYSIS

In some situations, interim results and analyses may make it unethical to continue a clinical trial. In a Phase I trial, early data may already show unacceptable toxicity, for example, causing unexpected deaths that are definitely or probably associated with the investigational agent. The following examples from Phase III studies also raise the issue of terminating the trial.

Should the trial be continued?

If interim data show conclusively that one arm has more risk, that one arm is more effective, or that the trial will not provide a valid answer to the research question, it would be unethical to continue the

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study. Under these circumstances, continuing the trial would expose participants to the risks and inconvenience of participating in the clinical trial but offer the prospect of gaining little or no additional scientific knowledge. Compelling evidence of harm or benefit might be found in interim data or in the results of other clinical trials.

Should the protocol be modified?

Changes to the protocol might be required to reduce risk to participants, to enhance the power of the study, or to increase the validity of the data.

Should the informed consent process be modified?

In some situations, interim findings need to be discussed with participants because they would alter the willingness of persons to enroll in the trial or to continue to participate in it. For instance, there may be evidence of unanticipated adverse events or results from another clinical trial on the same condition that might be pertinent to a person's willingness to enroll in or continue in the trial. Providing such data to participants does not necessarily lead to a large number of participants dropping out of the trial (26).

After answering these questions, the DSMB sends a report to the study sponsor and leadership. It makes recommendations whether to continue or stop the trial and describing any changes that should be made to the consent process or protocol. The study sponsor and leadership decide whether to accept the recommendations and communicate any protocol changes to site investigators, who pass it on to their local IRB. IRBs need to approve any protocol modifications.

CONTRACT RESEARCH ORGANIZATIONS

Contract research organizations (CROs) contract with clinical trials sponsors to carry out such activities as recruiting participants, collecting data, analyzing data, and writing articles (34, 35). CROs are involved an increasing proportion of clinical trials and are now participating in the majority of clinical trials. Many are for-profit companies, although a few are associated with academic health centers. CROs offer the advantages of greater efficiency and lower cost, often because they carry out research in low-cost countries. However, because they depend on continued contracts from sponsors, critics have alleged that they distort the science and place participants at risk in order to please sponsors. Both for-profit and academic-affiliated CROs have been criticized for alleged bias, incomplete disclosure of financial COIs, cases of serious injury to participants, and inexperienced and less educated staff (34, 35).

RESPONSIBILITIES OF AUTHORS

As Chapter 13, discusses, authors of scientific publications have ethical responsibility to vouch for the integrity and completeness of their findings. Authors should have access to all data from the trial and full control over data analysis and the writing and submission of the manuscript. Two serious ethical concerns about publication of clinical trials have recently been raised. First, some articles have been written by employees of drug companies that sponsored the trial for a university-based researcher who serves as the lead author, but these ghostwriters are not named as authors or acknowledged in the paper (36, 37). As Chapter 13 show, this practice is dishonest, fails to give credit where it is deserved, and masks conflicts of interest. Second, negative findings from some clinical trials have not been published, or their publication has been markedly delayed (*see* Box 1.1 in Chapter 1). Failure to publish clinically significant negative results is unethical and might cause serious harms to patients. To prevent such misconduct, all clinical trials must be registered at the onset in an acceptable public clinical trials registry (38). New requirements are being established to require timely reporting of results in a clinical trials registry as well.

TAKE HOME POINTS

1. Each step of a RCT – randomization, the selection of interventions, the choice of endpoints, eligibility and exclusion criteria – raises ethical issues that need to be addressed in conjunction with scientific and design issues.
2. Randomization is ethically appropriate if the arms of the trial are in equipoise. .
3. Placebo controls are justified if in certain circumstances.
4. Persons who are at greatly increased risk for harm should be excluded from the trial.
5. The protocol should present a sound plan for data monitoring and interim data analyses.

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