Chapter 6
Clinical Trials

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Learning Objectives
After completing this chapter, you will be able to:

- Understand the key elements of a clinical trial
- Be familiar with the ethical concerns in human subject research.
- Understand the role of the sponsor of clinical trials
- Know the concept of equipoise in determining when planning a clinical trial

1 Introduction

Historically, health interventions were often based upon commonly accepted practices that seemed intuitively to make sense and perhaps had some biological plausibility. However, evidence that they improved health was often limited or nonexistent. The examples of such practices are myriad. The use for many centuries of bleeding to "treat" a variety of ailments, or in my own lifetime, the routine administration of tonsillectomies and adenoidectomies to all children, are only two examples of common medical practices that have been in due course shown not to confer benefit, while posing risks to patients. Combined with the pecuniary interest that medical practitioners have traditionally had in providing interventions, it is not surprising that the playwright and essayist Bernard Shaw famously (and acerbically) wrote more than a hundred years ago in *The Doctor's Dilemma* [1] that

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A. K. Mitra (ed.), *Statistical Approaches for Epidemiology*,
https://doi.org/10.1007/978-3-031-41784-9_6

> " …the rank and file of doctors are no more scientific than their tailors…" and
>
> "That any sane nation, having observed that you could provide for the supply of bread by giving bakers a pecuniary interest in baking for you, should go on to give a surgeon a pecuniary interest in cutting off your leg, is enough to make one despair of political humanity."

Medicine has come a long way in the past hundred years, and the emphasis on evidence-based medicine and the increasing use of artificial intelligence in clinical decision-making will only increase the need for reliable evidence to use when choosing health interventions. Clinical trials are the gold standard for providing such evidence and are the focus of this chapter.

International and national regulatory agencies responsible for licensing pharmaceuticals established the International Conference (now Council) for Harmonization (ICH) with a specific mandate to establish common standards for clinical research [2]. The ICH developed Good Clinical Practice Guidelines "to provide an international ethical and scientific quality standard for designing, conducting, recording and reporting trials that involve the participation of human subjects." Importantly, "Compliance with this standard provides public assurance that the rights, safety, and well-being of trial subjects are protected, consistent with the principles that have their origin in the Declaration of Helsinki" [3]. Although ICH was established initially by the European Union and the United States, its guidelines have been widely adopted with minor variations in details and emphasis [4].

The literature on clinical trial design, conduct, analysis, and reporting is voluminous. This chapter will highlight crucial aspects of clinical trials relevant to clinicians and nonclinicians, including those who use clinical trials in their epidemiologic work.

2 What Constitutes a Clinical Trial?

For the first time, the 1962 Drug Efficacy Amendment to the United States Federal Food, Drug, and Cosmetic Act required that drug manufacturers demonstrate both the safety and efficacy of the drugs. They wanted to market and began to set standards for clinical trials used in support of new drug applications to the United States Federal Drug Administration (FDA) [5]. This act was also the origin of the clinical studies' phase 1–4 categorization (Table 6.1).

As part of that effort, the NIH (a major funder of clinical trial research) and FDA, for regulatory purposes, adopted a common definition of what constitutes a clinical trial. The current definition is as follows:

"A research study in which one or more human subjects are prospectively assigned to one or more interventions (which may include placebo or other control) to evaluate the effects of those interventions on health-related biomedical or behavioral outcomes." [6]

Box 1
Of note, a clinical study, as opposed to a limiting definition of a clinical trial, does not require a comparison group. Some of the most fundamental therapies – insulin in type 1 diabetes or penicillin for treating wound infections or pneumococcal pneumonia – were never subject to controlled trials [7, 8]. The initial prospective and carefully observed studies of insulin and penicillin were compared to historical experience, and their dramatic effects were obvious.

Table 6.1 Phases of a clinical trial of a new drug, biological process, or device

Study phase	Purpose	Usual no. of participants
Phase 1	To evaluate the safety of the drug, biological product, or device	10–50
Phase 2	Preliminary testing of efficacy and dosing amount and more detailed safety information. Usually, no comparison intervention is evaluated and not powered to detect a clinically significant effect of the intervention	<100
Phase 3	Comparative study of the efficacy of intervention; compare with standard treatment (or placebo). Important that has sample size is large enough that the study has sufficient power to show the potential benefit of the intervention	100–1000 s
Phase 4	A long-term study of side effects and benefits after licensing of a drug, biologic product, or device	>1000

There is an argument that clinical trials have become an obsession and are conducted even when the results, according to some, should be obvious. This has been highlighted by "spoof" articles on the randomized controlled studies of parachutes versus no parachutes when jumping from a plane. This argument has been debated in clinical medicine and perhaps even more intensely in development economics [9]. Dramatic interventions in which the results are immediately apparent, such as using penicillin to treat infections, are now rare. After more than 80 years of use, penicillin is still subject to clinical trials to test its efficacy for conditions where the outcome is less certain and dramatic than when first used [10]. Thus, randomized, controlled trials (RCTs), rather than personal experience and uncontrolled observations, should now serve as the basis for clinical decision making.

3 Study Design

3.1 Superiority, Equivalence, and Noninferiority Trials

When developing the hypothesis for a study, it is important to define what is to be "proved" by the study. This is fundamental for making the study results interpretable to the community that might use or benefit from the results. It is also critical for

determining the study's sample size and for the study's results to be considered valid and generalizable and thus of use to practitioners and public health officials for making informed decisions.

The majority of investigators hypothesize that a new intervention is superior to current practice or treatment. For example, a new antihypertensive agent provides greater benefits than the current therapy. Either because it results in a greater (and clinically relevant decrease in blood pressure or is associated with fewer side effects or toxicity). Because an underlying assumption for clinical trials is the state of equipoise exists – i.e., there is uncertainty as to any possible benefit of the tested intervention in relation to the current practice (see below) – "superiority" studies are also "inferiority" studies. If equipoise truly exists, there is an equivalent probability that the test intervention is worse than current practice. For this reason, all tests of the significance of the study outcome must be two tailed. It means – if the assumption is that there is a 95% probability that the differences between interventions did not occur by chance alone – that both sides of the tail of the normal distribution have been tested to see if the results are in the top 2.5% or the bottom 2.5% of the normal distribution.

A noninferiority trial aims to show that the intervention being examined in the clinical trial does not perform less well than the comparator, standard intervention. As such, the test of the significance of differences between groups is usually one sided, t hus effectively reducing the sample size needed by half.

An equivalence trial aims to show no important difference between the investigational and comparator interventions. In most studies, the comparison intervention will be the current standard, practice, or placebo if there is no currently identified effective intervention. The important context is that there are "no important" (or clinically significant) differences. A difference of ±1 mm Hg is unlikely to be considered clinically significant for blood pressure reduction. Thus, an equivalence study may be designed to show the effect on blood pressure of the intervention, and comparison treatments have a probability of 95% (assuming that a $p < 0.05$ is utilized) of differing by no more than ±1 mm Hg. With a large enough sample size, there is likely to be a "statistically significant" but "clinically insignificant" difference between any two interventions that are compared, as few are likely to have the same effect.

3.2 Parallel Group, Crossover, and Factorial Study Designs

Parallel group designs are the most common and the simplest study design. In a parallel group design, study subjects are assigned to different interventions.

In a *crossover study,* participants receive the study interventions sequentially. Crossover studies that examine clinical response require a washout period, in which any effect of the initial treatment is "washed out" so that the second treatment provided during the crossover study can be examined independently. In practice, this is hard to accomplish in studies that examine efficacy, as any benefits from the first

intervention are difficult to disentangle from the effect of the second treatment, such as if the comparative effects of diet and pharmacotherapy were compared for their effect on hypertension. Studying the pharmacokinetics of drugs is more amenable to a crossover study design. There are objective measures that the first drug has been "washed out" and thus would have little effect on the pharmacokinetics of the second drug being studied. In a crossover study, the advantage is that each study subject can serve as its control.

Factorial designs study a number of different interventions in varying combinations. For instance, a 2 × 2 factorial design of weight loss and intensive pharmacotherapy for moderate hypertension might include four groups who would receive a weight loss intervention alone; intensive pharmacotherapy alone; both interventions simultaneously; and standard therapy. .

4 Sample Size Determination

Methods for calculating sample size are discussed in detail in Chap. 17. It is important, however, to incorporate a number of consistent principles for determining sample size. There has to be a best estimate of the event rate under study in the population sampled. If there is no relevant literature, study investigators should survey the population to obtain a reliable estimate of the incidence or prevalence of the condition of interest. The difference between the study intervention and the control group (or standard intervention group) must be clinically relevant. With a large enough sample size, it is possible to show a difference between most interventions. The difference found, however, may not have any import for practice. This is not to imply that equivalence studies have no value – but the import of the equivalent intervention (a less costly intervention, for instance) must justify the clinical trial.

The study sample size must be large enough to determine if a true difference exists between interventions. This is referred to as the "power" of the study and is usually set at 80% or 90%. A study with a power of 80% has an 8 in 10 chance of finding a difference between study groups if a difference actually exists. Failure to find a difference when a true difference exists (falsely accepting the null hypothesis) is termed a "Type II" error. A "Type I error" falsely rejects the null hypotheses. The higher the power and the lower the *P* value, the larger the sample size.

Lastly, sample size determination must consider the number of study subjects who are not likely to reach the endpoint. Even if an intention-to-treat analysis is used, there need to be enough study subjects who reach the study endpoint for the proposed analysis to be valid. The higher the dropout or noncompliance rate, the larger the sample size. The allocation ratio (one-to-one, two-to-one, etc.) also will affect sample size.

5 Essential Elements of a Randomized Clinical Trial

Standardizing clinical trial design has allowed for consistent interpretation and use of trial results and comparison between trials. This is particularly true for drug and device trials, whose approval is based upon having standardized protocols and study design.

5.1 Standardized Study Protocol and Registration of a Study

There are a number of sets of guidelines for the design of RCTs issued by various regulatory authorities and international organizations [11]. All RCTs should use a standardized protocol that is submitted to a study trial registry in advance of the initiation of the study. The largest primary international registry – www.clinicaltrials.gov – is maintained by the United States National Library of Medicine and, at the time of writing, has more than 400,000 clinical studies from 221 counties registered with it [12]. There are other important national and regional registries, including for the European Union [13] and for Africa [14]. There is also the WHO-maintained site that collates data from a number of different registries [15]. Many countries require that clinical studies be registered with their national directory.

Study registries serve a number of important purposes. They help ensure that in the analysis of study outcomes, researchers adhere to a priori hypotheses rather than conducting post hoc analyses that are subject to researcher bias. They also allow national governments to know what research is being conducted within their borders. This is an especially important consideration in lower income countries, where much of the research is funded by external sources, and the suspicion is that local residents are being exploited for the benefit of others. Registries allow investigators contemplating a study to know what clinical studies are underway or completed but are yet to be published. Thus, avoiding duplication of effort.

5.2 Hypothesis and Outcome Measures

It is essential to have a well-defined a priori hypothesis and outcome measures for testing in the clinical trial. For instance, if the hypothesis is that the intervention being tested (a drug, weight loss, exercise) will reduce blood pressure, the outcome measure has to be specific. The hypothesis needs to state the amount that either the diastolic or systolic blood pressure will fall; after how long an intervention this will be measured; how sustained the fall in blood pressure will be; and how many blood pressure measurements will be used to determine the endpoint of a decrease in blood pressure. This specificity is crucial for assuring that investigator bias does not

affect the reporting of the study results. The investigation chooses an endpoint after study completion that is most conducive to showing the intervention in the best possible light.

5.3 Equipoise Between the Intervention and Comparison Group

Clinical equipoise exists when there is no definitive evidence to support the superiority of the intervention in a clinical trial over the comparator group. Based on existing information, the null hypothesis exists (i.e., the interventions compared are equivalent in their efficacy and safety), and the study intends to disprove the null hypothesis. The existence of equipoise is an essential element for the ethical conduct of clinical trials. If there is clear evidence that one of the intervention arms was superior, it is unethical to conduct the clinical trial, as one group would knowingly be receiving inferior therapy.

Determining if equipoise exists is not straightforward. One consideration is how much emphasis to place on previous studies, especially if there is only a single previous study of the intervention under consideration. There is ample evidence of considerable variance between studies. Thus, the results of a previous study may not be determinative.

The impetus for most studies is the assumption that the intervention being evaluated will be superior to the comparator standard therapy. The study results will reject the null hypothesis. In addition, it is unlikely that there is "personal equipoise" among the investigators conducting the study. As they are often involved in inventing or designing the intervention to be tested and thus are motivated by the belief that it is superior to currently used therapies. Belief does not equal evidence, however, and thus the need for clinical trials if there is insufficient evidence, after a thorough review of the published literature and accessible unpublished literature, that the proposed therapy is indeed superior in efficacy to current therapy.

A related problem is the conduct of studies in poor, resource-constrained communities where the standard of care differs from that in rich countries. It is ethical to compare a new intervention to the current standard of care in the community where the study is being conducted [16]. Should the comparison be to the higher standard available in more affluent communities? Even though it is unlikely that standard will ever be available in the community where the study is being conducted. There are increasing arguments that communities where the study will be conducted, should have a role in what studies are conducted, and how they are conducted [17].

5.4 Blinding (Masking) of Study Interventions

Blinding (or masking) refers to keeping persons unaware of which study interventions are provided to study subjects. A single-blinded study refers to assuring that the study subject herself of himself being unaware of which of the study intervention they are receiving. A double-blinded study refers to the study subject and study personnel being unaware of the intervention provided.

Analysis of study outcomes should be conducted blinded to the intervention provided to the groups compared in the analysis. This requires someone not involved with study implementation, analysis of results, unblind the study, and group participants by the intervention they received.

Blinding is important to reduce bias – intended or subconscious – in determining study outcome. Investigators for the most part are advocates of the experimental intervention that they are studying. They often have developed, studied, or promoted one of the interventions under study. Most, but not all, studies have shown a larger treatment effect in nonblinded than in blinded studies [18, 19].

Effective blinding, especially double blinding, is easier conceptually than in practice. Blinding is presumably easiest in drug intervention trials. It is hard, for instance, to blind surgical versus nonsurgical interventions or different behavioral interventions. Even in drug trials, drugs being compared may differ in taste, smell, consistency, and side effects. This may, in part, be overcome by using a double-dummy technique. Each treatment group is given one active agent and one inactive agent to resemble the other agent used in the study. Even this will not overcome the potential for side effects – such as diarrhea – that are more common with one agent – to bias investigators involved in the study.

Lack of blinding is not an absolute impediment to the validity of study results. To the degree possible, outcomes should be clearly defined with a reliably measurable outcome. In a study that compared weight-loss intervention and drug therapy to reduce blood pressure, even though the intervention cannot be blinded from either the study participant or investigative staff. The outcome measure – change in blood pressure – can be reliably measured and is subject to limited observer bias especially if there is adherence to methods for performing blood pressure measurements detailed in a study operations manual.

5.5 Randomization and Concealment of Allocation

Random, concealed allocation to intervention groups is, by definition, an essential component of an RCT and helps in minimizing any selection bias in the intervention groups under study.

Randomization refers to assignment of study subjects by chance to one of the groups in the clinical trial. This is done by using either a random number table or now more commonly a computer-generated random number list to assign sequential

study subjects to an intervention. The random number list links to treatment intervention in a consistent way. For instance, all even numbers on the random number list can be assigned to treatment A and odd numbers to treatment B. If there are three interventions, an option would be for treatment or intervention A to be assigned to all sequential numbers 1–33 on the random number list; intervention B to numbers 34–66, and intervention C to numbers 67–99 [20].

Interventions are allocated sequentially to patients enrolled in the study. Persons not involved in study enrollment or implementation must link random numbers and treatment groups. The sequence of study group assignments is concealed from persons enrolling patients in or carrying out the study. Absent such concealment from persons responsible for study enrollment, there is considerable potential for biasing the study results. Take the example of a study of an anti-hypertensive agent. Suppose the persons responsible for enrolling study subjects knew that the next allocated intervention was the drug they hoped to prove efficacious. In that case, they might discourage an otherwise eligible patient with potentially confounding conditions lessening therapeutic efficacy (obesity and history of smoking) from enrolling in the study. They would then wait to enroll a patient they thought was more likely to respond to their preferred intervention.

Concealment is done even when the study intervention cannot be masked by those conducting the study or providing care for the study subject. For instance, if the comparison was between drug therapy alone and exercise and weight loss programs to reduce hypertension, it is impossible to mask the intervention from those implementing the study and caring for study subjects. Even so, treatment allocation can and should be concealed.

5.6 Methods of Randomization

There are a number of ways in which randomization can be done. The simplest is *sequential randomization*. In this approach, there is a single sequential, random list for all subjects enrolled in the study. This works fine for large studies, where any chance of imbalances is likely minimal. In smaller studies, the chances of imbalance in assignment are greater (think of flipping a coin 20 times or 2000 times).

Using a *block randomization* method can minimize the risk of imbalance in study assignment. In a block randomization method, a block of defined numbers is identified in which there is an equal balance of study assignments. For instance, if a block size of six is chosen, and there are two study arms, three study subjects would be assigned to each treatment arm. This assures that even in small studies, there cannot be marked differences in subjects assigned to different treatment arms. A block randomization method also minimizes any temporal effects that might affect assessment of interventions.

A problem with block randomization is the potential to predict allocation, especially if it is not possible to blind interventions. Assuming a set block size of six, it can quickly become apparent to study personnel that there will be equal assignment

to the two study arms within each sequential six-study subject assignment. It would then become apparent that the next allocation would be to the latter group after a sequence in which three subjects have been assigned to drug therapy and two to weight loss and exercise.

A *permuted block randomization* method helps avoid this problem. In this method, the size of blocks varies. This diminishes but does not eliminate, study personnel from anticipating the next study allocation in an unblinded study with block randomization. As the size of blocks is likely to be limited, a good "card counter" could of course figure out the sequence of blocks. In practice, this is unlikely to happen.

There are additional permutations of block randomization. For multicenter studies, there can be separate randomization for each site. When there are especially important confounders that investigators want to control for, *stratified randomization* is used.

5.6.1 Community or Cluster Randomization

Randomization by groups or clusters is used when the intervention is at group rather than individual level. To refer back to a blood pressure example. Suppose investigators aim to show the benefit of reducing blood pressure through a clinic-based public education effort, with outreach by community health workers. In that case, the level of randomization is likely to be the clinic, or a health district, rather than individuals. If the randomization was by community health workers rather than a clinic, there would likely be "contamination" because of the adjacency between persons. Some persons might not have a community health worker assigned to implement the public education effort, but their neighbors might have. Additionally, another community health worker at the same clinic assigned to implement the public health outreach effort might influence the community health worker not trained in the outreach program. To prevent such contamination, clinics, or even health districts, might be the unit of randomization. There are specific challenges when randomizing clusters [21] especially because the possibility of confounding and bias is likely to be much greater when the unit of randomization is a cluster. It is important to have knowledge of the communities or units to be included in the clusters and ensure that they are similar in terms of characteristics that might potentially confound the outcome. It is also important that the clusters are geographically distant enough to avoid a spillover effect.

5.6.2 Defining the Population Enrolled in the Study

If a study's results are widely applicable to others with the same condition, it is important to define the population enrolled in the trial. This includes the general population from whom study subjects were selected (hospital-based or clinic population, all consecutive eligible patients, or a convenience sample when study staff is

available to enroll patients). Inclusion and exclusion criteria need to be clearly defined. To continue the example of the study of an antihypertensive agent, the investigators need to specify the severity of the hypertension of enrolled patients; were morbidly obese persons or smokers excluded; the duration of preexisting hypertension; previous drug therapy; the gender of participants; their ethnicity; and their socioeconomic status. Clearly defining the population studied allows others to understand the potential utility and generalizability of the study findings.

6 Trial Organization and Management

Clinical trials require a clearly defined organizational structure, with each element of the organization having a defined set of responsibilities. The days when a fearless medical investigator had an inspired insight and went and tested that insight on patients without reference to any bureaucratic structures belongs to the era of black-and-white films and nineteenth century novels.

6.1 Study Sponsor

All clinical trials should have a defined sponsor. The sponsor is the "individual, company, institution, or organization that takes responsibility for initiating, managing, and/or financing a clinical study or trial" [22]. For commercially initiated and funded clinical trials, the company funding the trial is the sponsor. When noncommercial organizations – such as the United States National Institutes of Health – initiate and fund a clinical trial, they may serve as the sponsor. This is especially so for multicenter trials. For investigator-initiated noncommercial research, the investigator's employer – most commonly a university or hospital – is usually the sponsor. The funding source is not always the study sponsor. Such as when a commercial entity funds university-based research initiated by university research staff. The sponsor has ultimate responsibility (and liability) for a clinical trial, ensuring that a trial is of sound quality – both scientifically and ethically.

Depending on the size and complexity of the study, clinical trials may be three levels of oversight and responsibility.

6.2 Trial Management Group

The first level of responsibility for conducting the study always lies with the investigative team members, who have day-to-day responsibility for conducting the study according to protocol and expeditiously. For large and complex studies, and especially for multicenter studies, a committee of investigators – variously termed the

"Trial Management Group" – is commonly established [23]. Such a committee consists of persons actively designing and conducting the study. There should be clearly defined standard operating procedures (SOPS) for the study, so that actions by all staff carrying out the study are consistent, and observations are recorded in a consistent manner.

6.3 Data Monitoring and Safety Boards (DMSB, or Data Monitoring Committee)

These are composed of persons independent of the study – i.e., not employed by the sponsor of the organization under whose aegis the study is being conducted and have no potential financial conflicts of interest posed by the interventions under study. The DMSB is responsible for reviewing interim or cumulative data for study-related adverse events; for evidence of efficacy before full enrollment in the study is completed; for quality of study data; timeliness of study enrollment and predicated completion; and protocol violations. Interim analysis to examine the efficacy of the intervention before planned study completion (or inferiority of the intervention) is done at pre-agreed intervals incorporated in the study protocol. The statistical analysis must account for the effect that multiple looks at study results will have the significance level required to assure that the results are unlikely to reflect chance alone (i.e., the more frequent examination of the results, the more likely that the null hypothesis will be rejected by chance alone).

6.4 Trial Steering Committee

The sponsor may delegate their senior-level oversight responsibility to a Trial Steering Committee. This committee includes both persons involved with study implementation and independent members, with one of the latter serving as the chair of the committee. Laypersons or representatives of the sponsor may serve on the committee. The committee regularly reviews the study's progress to its objectives; receives reports and recommendations from the Data Monitoring and Steering Committee; and reviews information from external sources that may affect the study (such as other contemporaneous studies that definitively show toxicity or efficacy of the intervention under study). The Trial Steering Committee in consultation with the investigators and the sponsor makes decisions on the premature termination of the study (or prolongation beyond the expected completion date).

Not all studies, especially less well-funded smaller studies, will have this complexity of formal organizational structure and oversight. They should nonetheless adhere to all of the same principles for good clinical practice and assurance of ethical conduct. This is often done by preexisting structures in institutions, such as

ethical review committees (Institutional Review Boards) and preexisting scientific review committees.

Contract-research organizations, which commonly carry out studies on behalf of commercial sponsors, often establish a DMSB and Trial Management Committee or their equivalent [24]. When this is the case, conflicts may arise in larger studies involving other institutions, especially academic institutions, where the relationships and authority have not been clearly defined [25].

7 Data Analysis and Reporting

Data analysis and reporting of clinical trials should derive from a clearly defined hypothesis and trial objectives stated in the study proposal and protocol. A detailed analysis plan should be included in the proposal and adhered to upon study completion. The analysis should be conducted blindly – before it is known which intervention was provided to the groups under study.

In practice, this means that at the end of the study, a person not associated with the team implementing the study, or involved in the analysis, should identify the intervention assigned to each study subject. The persons conducting the analysis then do so without knowledge of the intervention received by each group.

Outcome measures should be clearly defined in the study protocol. As much as possible, the outcome measures should be objective, quantifiable, and not subject to interpretation by the study investigators. When an outcome measure is not easily quantifiable – or subject to a degree of interpretation – someone other than the study investigator should interpret any results pertinent to the study outcome.

There are several options as to which study subjects should be included in the analysis results. The commonly recommended *intention-to-treat analysis* includes all study subjects assigned to treatment intervention. No matter if they withdrew from the study before receiving any treatment, were noncompliant with the intended intervention, or left the study before the assessment of study endpoints.

The intention-to-treat analysis is conservative and likely to underestimate the effect of the intervention. This may especially be so when there are a large number of study subjects who never received the intervention or dropped out of the study before a final endpoint is reached. Especially for studies with a binary outcome where patients who left before the outcome is assessed are considered “treatment failures” for analysis.

A *per-protocol* analysis includes only those subjects who adhered fully to the proposed intervention. This most clearly resembles an effectiveness trial, which measures the beneficial effects of the intervention in real-world settings. In the context of a clinical trial, especially one in which the intervention cannot be blinded, per-protocol analysis lends itself to study bias by excluding investigators of study subjects they think are less likely to respond to the intervention. In a meta-analysis, per-protocol analyses showed a modestly greater treatment effect than intention-to-treat analyses [26].

A *modified intention-to-treat* analysis can be used, for instance, excluding study subjects who were never exposed to the intervention [27]. Sensitivity analyses can be conducted to assess the effect of missing data, including uncertain study outcomes, minor-protocol violations, or treatment effects within subgroup of patients [28]. Sensitivity analyses give an idea of the robustness of study findings, but should be clearly identified as a post hoc analysis. Another method is the *complier average causal effect (CACE*) analytic method, which has especially been used in adaptive intervention designs, where the study subject assigned to the intervention arm can decide what if any, intervention they accept [29]. CACE attempts to identify individuals in the control group who would have complied with the treatment given the opportunity to do so and uses this subset to compare to those in the intervention group accepting the intervention.

A standardized flowchart, such as the one developed by CONSORT ("Consolidated Standards of Reporting Trials") shown below, should be used to report subject study participation (Fig. 6.1).

Because of the equipoise assumption underpinning most clinical trials – that there is true uncertainty about the superiority or inferiority of any of the study interventions – the most common underlying basis for analysis is the null hypothesis. The null hypothesis assumes that there is no true difference between the interventions. Statistical inference is used to determine if the null hypothesis is true or if it is rejected (i.e., one intervention performs differently than other interventions).

A basic assumption underlying the testing of the null hypothesis is the groups under study are drawn from the same population and are thus comparable. Hence, the need for random assignment to minimize variances between the two populations.

No matter how large the sample, two samples of the same population will rarely be the same. Chance alone will result in differences in the samples – even if the populations are very similar. Thus, statistical testing is needed to determine if the differences between the sampled populations under study – those receiving different interventions – occurred by chance alone or represent a true difference.

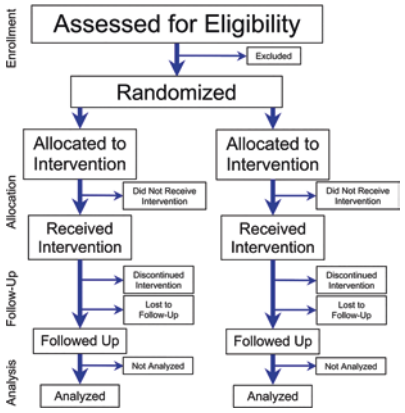

Fig. 6.1 CONSORT flow diagram of the progress through the phases of a parallel randomized trial of two groups [30]

Different tests of statistical significance are used depending on the outcome measures being compared – continuous variables, for instance (the absolute value of systolic blood pressure) or a categorical outcome (diastolic blood pressure ≥ 130 mmHg). The statistical methods used to test these differences are described in detail in Chaps. 17, 21, and 22 of this book.

Several conventions govern the statistical inferences that are reported. One is that when differences are seen between groups, to reject the null hypothesis, we require that the differences between populations had only a 5% chance (a "*p*-value" of 0.05) of occurring by chance alone. Inversely, there is a 95% probability that the differences seen between groups represent a true difference. This type of error – invalidly rejecting the null hypothesis – is termed a Type 1 error. There is, however, nothing sacrosanct about a *P* value of 0.05. Using a more restrictive threshold for statistical inference is just as valid – for instance, a *P* value of 0.01. If a statistical significance test met this threshold, there would only be a one in one-hundred chance that the differences observed between groups occurred by chance alone. Conversely, a *P* value >0.05 or 0.01 does not mean that is no possibility of benefit. It may be that larger studies are required or that subsequent studies may show an effect in similar or different populations.

A common way of expressing results in clinical trials is to show the 95% confidence intervals (CI) for the difference between the groups under study. If the 95% CIs (or 99% if one wants to be more restrictive) for the difference between groups do not include zero, then the null hypothesis is rejected, and the interventions being compared are assumed to be truly different in their effect on the population under study. 95% or 99% CIs are congruent with *P* values of 0.05 and 0.01.

Most major clinical journals have adopted standardized reporting of clinical trial results using the CONSORT guidelines [31]. These guidelines required reporting all relevant elements of a clinical trial, including the study title and abstract; introduction; methods; results; discussion; and other important information, including the source of funding and access to the study protocol. The guidelines specify the details required in each reporting section. This reporting format provides, along with the CONSORT study subject flow diagram, for consistent interpretation of study results. In addition to reporting parallel group randomized trials, CONSORT has guidelines for reporting cluster randomized trials, noninferiority and equivalence trials, nonpharmacological treatments, herbal interventions, and pragmatic trials. Using these standardized guidelines also enhances the feasibility of meta-analyses incorporating multiple studies.

8 Ethical Considerations and Informed Consent

There are common ethical principles underlying all human subject research, including clinical trials. These principles are detailed in a number of statements that underpin the ethical conduct of research. The first systematic and widely accepted set of principles was the Nuremberg Code, which was formulated in 1947 during the

trial of Nazi doctors who tortured and murdered prisoners and concentration camp inmates under the guise of doing medical research [32]. The Nuremberg Code emphasized the need for the voluntary consent of anyone who entered into a research study; the right of the study subject to withdraw from the study at any time; the need to minimize risk; to balance risk with the potential benefit of the experiment; and for a valid scientific premise for the research. The Nazi doctors who professed to conduct research did none of these things.

The Helsinki Declaration of the World Medical Association has further adapted and expanded upon the Nuremberg Code [33] as the ethical guidelines developed by the Council for International Organizations of Medical Sciences (CIOMS) in conjunction with the WHO [34]. The US government has also issued a set of principles and guidelines for the ethical conduct of research – the Belmont Report [35] – which highlighted three core ethical concepts – respect for persons, beneficence, and justice. This in turn guides ethical activities concerning informed consent, assessment of risks and benefits, and selection of research subjects.

Emanuel, Wendler, and Grady 2020 synthesized these guidelines and identified seven basic principles underpinning the ethical conduct of research [36]:

(i) Value – the research must enhance health or knowledge
(ii) Scientific validity
(iii) Fair subject selection
(iv) Favorable risk–benefit ratio
(v) Independent review
(vi) Informed consent
(vii) Respect for enrolled subjects

Procedures and rules governing ethical research derive from these ethical precepts. In the United States, federal regulations (Code of Federal Regulations Title 45 Part 46) codify the rules governing research with human subjects [37]. These regulations have been adopted by most United States government departments and apply to all research conducted by United States government employees, research funded by the United States government, and institutions supported by the US government. Most other countries have similar regulations for the ethical conduct of research.

One of the fundamental elements arising from the Belmont report, and the Code of Federal Regulations, is the need for independent panels (termed Institutional Review Boards in the United States, and Ethical Review Committees in many locales) to review the ethics of all proposed clinical research. This ethical review has to be conducted along with creditable research review that assures the research's value and validity. The format and structure of the ethical review committees is established in the Code of Federal Regulations. Most institutions where research is conducted will have such review boards or will have a cooperative agreement with ethical review boards at other institutions.

Table 6.2 Ethical responsibilities of a principal investigator in a clinical trial

Responsibility of Principal Investigator (PI)	Comment
Obtains approval for the study from the Institutional Review Board (IRB)	Most IRBs have a set format that is used for this application. Approval must be obtained before any subjects are enrolled in the study. The PI must be assured that the IRB meets the requirements for IRB as specified in 21 Code of Federal Regulation Part 56 [37]
Must conduct study according to the approved protocol	Changes to protocol need to be approved by IRB with notification to the sponsor
Takes responsibility for personally conducting or supervising the study	Virtually all studies – and especially large studies – involve a team of investigators and staff. The principal investigator and the sponsor are responsible for conducting the study according to all ethical guidelines
Assure all involved with the study, including all staff, are aware of ethical requirements.	This requires active educational efforts by the principal investigator, the study sponsor, and the IRB to ensure that staff has demonstrated knowledge of ethical requirements and their implementation
Assures that informed consent – written or oral – is properly obtained from study subjects	See details of informed consent requirements in Table 6.3
Report adverse events to the sponsor (and ensure that they are reported to IRB)	It is important to report anything that can be considered an adverse event. It must also ensure that the data monitoring and safety committee (if one was constituted) has information on adverse events available to it during its regular reviews
Maintain all study records and ensure they are accessible	This includes all patient documentation and original copies of the informed consent form if written informed consent is obtained on paper. If electronic forms are used, they must ensure that they are secure, remain confidential, and have robust systems to ensure that they remain accessible
Most report any potential conflict of interest to the sponsor and IRB	This particularly applies to financial conflicts and to all staff involved in the study

In the United States, principal investigators for drug studies aimed at obtaining an investigational new drug application (IND) must sign a legally binding Federal Drug Administration form – FDA 1572 – that specifies the responsibility of the investigator for the ethical conduct of the study [38]. Mandated responsibilities of the principal investigator are summarized in Table 6.2:

Consent is meaningless if it is simply a formality. Similarly, study subjects must be kept appraised of their progress and progress of the study. The major components of an informed consent form are as follows (Table 6.3).

Table 6.3 Elements of informed consent form [37, 39]

Element required for informed consent	Comment
Language	The written form should avoid scientific or medical jargon and be written in language that can be comprehended by persons with basic literacy and education
Description of study	This should include a statement that the study involves research, the purposes of the research, the proposed duration of the study and duration of the subject's participation, and identification of interventions that are experimental. This should include the proposed number of persons to be enrolled in the study. If the study protocol is changed during the study in ways that may affect the study participant, additional consent should be obtained
Risks and discomfort	The focus should be on likely risks and discomforts, especially those that are potentially serious. An exhaustive detailed description of remote and unknown risks is likely to decrease the clarity of the consent form and lessen the understanding by the potential study participant
Benefits of participation in the study	This should include both potential benefits to the study subject and benefits that might accrue to others as a result of the study
Alternative interventions or treatments	If other interventions are available, this must be explained to the study subject. This should include the pros and cons of each option
Confidentiality	The study subject should be informed of who else besides study investigators and staff might have access to their records. It should also specify if their identifying information were available to those having access
Compensation and medical treatment in event of injury	The consent form should specify if compensation or treatment in the event of an adverse outcome or injury resulting from the study is available and how to access such support. Compensation or free medical care for study subjects in the event of an adverse outcome or injury resulting from clinical trials is not mandatory in the United States [40]. Compensation requirements also vary in other countries [41]
Voluntary participation	The form has to make clear that study participation in voluntary and that the study participant can withdraw from the study at any time without jeopardizing their right to the current standard of care
Contact information	The informed consent form must contain information on who the study subject can contact with questions and how to contact them. This contact information should be valid even after the study subject completes their direct participation in the study

Box 2

The study personnel involved in obtaining consent should not consider the informed consent process a formality or obstacle to overcome. Though there is always pressure to meet study enrollment targets, study staff have an ethical obligation to ensure that consent is truly informed and voluntary. As with all aspects of the ethical conduct of clinical trials, the onus falls upon the principal investigator and study staff to internalize the values of ethical behavior and act accordingly. No set of rules and guidelines alone can ensure the ethical conduct of studies absent staff embodying those values [37].

Distributive justice is an additional critical element of the ethical conduct of studies but one that is less amenable to formal guidelines and regulations. Rather than primarily involving conduct involving individual study subjects, it often deals with larger social issues – the "fair allocation of society's benefits and burdens" [42]. Most of the statements on ethical principles of clinical research were in part motivated by clear violations of distributive justice. Disadvantaged members of society – the poor, prisoners, persons of color, and persons living in poor countries – bore the burden of potentially (or self-evidently) dangerous research without having access to the potential benefits of research.

The issue of distributive justice also extends to women and children, as clinical research and trials often excluded them. A larger issue of distributive justice is the allocation of research funds. Pharmaceutical companies drive much clinical research. Given the drive for profits, much of the research is aimed at lucrative segments of the pharmaceutical market – often drugs for chronic illnesses of older persons in rich countries. This has led to a proliferation of "me-too" studies aiming to identify drugs similar to already proven therapies [43]. Although there may be a benefit to some of these drugs, the larger question remains if some of these societal resources could more justly be directed to other conditions, especially those in resource-constrained countries where the potential societal benefit is much more significant.

9 Further Practice

1. Which of the following are **not** required elements of a clinical trial (choose all that apply):

   (a) Involves human subjects
   (b) Prospective enrollment
   (c) Blinding of participants
   (d) At least one comparison group
   (e) Randomization of study participants to different interventions

2. Match the phase of the clinical study to what is done in the phase of the study: Study phase: 1; Study phase: 2; Study phase: 3; Study phase: 4.
   Match phases 1 through 4 with:

   (a) Preliminary testing of efficacy and dosing amount and more detailed safety information
   (b) A long-term study of side effects and benefits after licensing a drug, biological product, or device
   (c) To evaluate the safety of a drug, biological product, or device
   (d) Comparative study of the efficacy of intervention; compare with standard treatment (or placebo)

3. Equipoise in clinical trials refers to which of the following:

   (a) The correct matching of intervention and control groups
   (b) The lack of bias in the selection of participants
   (c) The lack of bias in data analysis
   (d) Lack of evidence of the superiority of any of the trial interventions

4. Double-blinding in a clinical trial refers to the following:

   (a) The study participant does not know the identity of the drug used
   (b) The investigators do not know the identity of the drug used
   (c) Both the participant and the investigators do not know the identity of the drug used

5. Blinding of a clinical trial reduces

   (a) Bias
   (b) Confounding
   (c) Both

6. A problem with block randomization is the potential to predict treatment allocation – True or False
7. The study sponsor is the entity that is responsible for:

   (a) Carrying out the day-to-day conduct of a clinical trial
   (b) Analyzing the study results
   (c) Initiation, management, and/or financing of a clinical study or trial
   (d) Writing the report of the study

8. An intention-to-treat analysis excludes which of the following groups:

   (a) Study subjects who do not complete the study
   (b) Study subjects who never received the study intervention
   (c) Study subjects that completed the study but did not adhere to the study protocol
   (d) None of the above

9. The null hypothesis assumes:

   (a) That groups being compared can never be the same
   (b) The groups being compared will only differ because of sampling error
   (c) That there is no statistically significant difference between the groups being compared

10. Ethical responsibilities of a clinical trial principal investigator include (select all that apply):

    (a) Obtain approval for the trial from an authorized, ethical review committee
    (b) Conduct the study according to the approved protocol
    (c) Decide if a study should be stopped because of the frequency of adverse reactions to one of the study interventions

(d) Have a responsibility to reimburse study subjects if they suffer harm from the study intervention
(e) Assures that informed consent is obtained from study subjects

Answer Keys

1. (c) and (e)
2. 2 phase 1 matches to c; phase 2 matches to b; phase 3 matches to d; phase 4 matches to b
3. (a)
4. (c)
5. (a)
6. True
7. (c)
8. (d)
9. (c)
10. (a), (b) and (e)

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