Chapter 21
Multicenter Trials

A multicenter trial is a collaborative effort that involves more than one independent center in enrolling and following study participants. Multicenter randomized clinical trials have a long and rich history, with Hill [1] and Greenberg [2] providing general discussions of methods in the middle of the twentieth century.

In the last four decades, there has been a dramatic increase in the number of multicenter and multinational trials. Multicenter studies are more difficult and more expensive to perform than single-center studies, and they may bring less individual professional reward due to the need to share credit among many investigators. However, multicenter trials are necessary primarily because single sites cannot enroll enough participants to assess clinically important outcomes [3]. Over 40 years ago, Levin and colleagues provided many examples of "the importance and the need for well-designed cooperative efforts to achieve clinical investigations of the highest quality" [4].

The reasons for conducting multicenter trials apply even more today, with much of medicine being global in scope. It is common for large late-phase trials sponsored by industry to include a wide geographical representation. Several hundred sites might be involved, each site entering anywhere from several to a few dozen participants. While such dispersion of sites presents logistical challenges for training of personnel and data quality control, the benefits of rapid participant recruitment have generally outweighed these challenges. Another potential advantage of multicenter trials is that investigators at multiple sites, with standardized protocols, may be less prone to bias that could affect trial conduct and event ascertainment, especially in open-label trials. Participants enrolled at a single center, all under the oversight of an investigator who is academically invested in the hypothesis, may be subject to a greater likelihood of bias.

Much of the ground work for the development, organization, and conduct of a multicenter trial was laid many years ago in trials like the Coronary Drug Project

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[5] and the International Studies of Infarct Survival (ISIS) [6, 7]. This chapter will discuss the reasons why such studies are conducted and briefly review some key steps in their planning, design and conduct.

Fundamental Point

Multicenter trials are needed to enroll adequate numbers of participants in care settings that are likely to reflect diverse practice. Investigators responsible for organizing and conducting a multicenter study should have a full understanding of the complexity of the undertaking and the need for systems to assure that a common protocol is followed at each site.

Reasons for Multicenter Trials

1. The main rationale for multicenter trials is to recruit the adequate numbers of participants within a reasonable time. Many clinical trials have been—and still are—performed without a good estimate of the number of participants likely to be required to adequately test the main hypothesis. Yet, if the primary response variable is an event that occurs relatively infrequently, or small group differences are to be detected, sample size requirements will be large (Chap. 8).

   Studies requiring hundreds of participants usually cannot be done at one center, although there are some exceptions like the Deutsches Herzzentrum, in Munich, Germany, that has enrolled over 50,000 participants in a series of single site trials [8]. This site has also successfully participated in multicenter trials [9].

   Some multicenter trials have been very large. The Global Utilization of Streptokinase and Tissue Plasminogen Activator for Occluded Coronary Arteries (GUSTO) trial enrolled 41,021 patients with acute myocardial infarction at 1081 hospitals in 15 countries, with enrollment ranging from 1 to over 200 patients per center [10]. This trial had four treatment groups, and treatment with accelerated t-PA (versus the streptokinase arms) resulted in a 14% relative risk reduction (and 1% absolute reduction) in 30-day mortality, a result that changed practice. The large sample size was required to be convincingly significant ($p = 0.001$). The Women's Health Initiative (WHI) [11] was an ambitious 15-year project mandated by Congress in 1991 and sponsored by the National Institutes of Health (NIH). WHI included 161,000 postmenopausal women enrolled in 40 centers across the United States. A set of clinical trials, using a partial factorial design, included 68,132 women participants, addressed dietary modification, calcium and vitamin D supplementation, or hormone replacement therapy. The WHI provided important results that changed practice. And the program was a good investment, as shown by the fact that the $260 million cost of the WHI postmenopausal therapy trial was estimated to have a total net economic return of $37.1 billion [12, 13]. This was mainly the result of a change in practice such that women were no longer being exposed to the harmful effects of hormone

replacement therapy. The Heart Protection Study 2–Treatment of HDL to Reduce the Incidence of Vascular Events (HPS2-THRIVE) investigators took a different approach to site selection [14]. They selected 245 high-performing centers who demonstrated they had adequate patient volume to enroll large numbers of participants. These investigators randomized 25,673 patients (of the 42,424 entering the run-in phase) with prior vascular disease over 3 years at sites in the United Kingdom (89 sites), Scandinavia (84 sites), and China (72 sites) to niacin plus laropiprant versus placebo. While these trials enroll very large numbers of participants to be able to detect modest treatment effects (15% relative risk reductions), they illustrate the importance of having many sites, and selected sites, involved. The National Cancer Institute Cooperative Group (now the National Clinical Trials Network) [15] and HIV/AIDS Clinical Trials Networks [16] provide other examples of the rich history of multicenter trials.

2. A multicenter study may enable a more generalizable sample of the study population. Although no trial is completely representative, geography, race, socioeconomic status, and lifestyle of participants may be more similar to the general population if participants are enrolled by many centers. These factors may be important in the ability to generalize the findings of the trial. Concern has been raised that site selection for practical purposes like improving enrollment could negatively impact on generalizability of results [17].

   In the GUSTO trial, 23,000 participants were enrolled in the United States, and most of these were enrolled over a 1-year period [10]. During that year of 1992, it has been estimated that nearly 10% of all patients in the country with acute myocardial infarction treated with fibrinolytic therapy were enrolled in the trial. The participants in this "pragmatic" trial with few exclusion criteria were well represented by high-risk groups such as the elderly (12% were at least 75 years of age, and the oldest was 110 years old) [18].

   Another example of the need to anticipate how participant make-up may affect generalizability is in racial distribution. For instance, it is known that hypertension and its treatment response may vary according to race. A study of participants with hypertension from either a totally black or totally white community is likely to yield findings that may not necessarily be applicable to a more diverse population. Anticipating this, there was a special effort to enroll black participants in the Antihypertensive and Lipid Lowering Treatment to Prevent Heart Attack Trial (ALLHAT). Ultimately, 35% of participants in ALLHAT were black, [19] which allowed for exploration of racial heterogeneity of intervention effects.

3. A multicenter study enables investigators with similar interests and skills to work together on a common problem. Science and medicine, like many other disciplines, are competitive. Nevertheless, most major research accomplishments in clinical medicine now require a collaborative team approach. A multicenter trial also gives capable, clinically-oriented persons, who might otherwise not become involved in research activities, an opportunity to contribute to science. In the early years, multicenter clinical trials typically involved only major academic centers. Now, many clinical practices based in the community successfully participate in trials, and in many trials, organized community hospitals or clinics are the best enrollers.

Conduct of Multicenter Trials

One of the earlier multicenter clinical trials was the Coronary Drug Project [5]. This study provided an initial model for many of the techniques currently employed. As in all active disciplines, concepts are frequently changing and some techniques have been refined in subsequent trials. The following series of steps, a distillation of experience from a number of studies, is one reasonable way to approach the planning and conduct of a multicenter trial.

First, a planning committee should be established to be responsible for organizing and overseeing the various phases of the study (planning, participant recruitment, participant follow-up, phase out, data analysis, paper writing) and its various centers and committees. This group often consists of representatives from the sponsoring organization (e.g., government agencies, private research organizations, educational institutions, private industry), with input from appropriate consultants. Use of consultants who are expert in the field of study, in biostatistics, and in the management of multicenter clinical trials is encouraged. The planning committee needs to have authority in order to operate effectively and for the study to function efficiently.

Second, to determine the feasibility of a study, the planning committee should make a thorough search of the literature and review of other information. Sample size requirements should be calculated. Reasonable estimates must be made regarding control group event rate, anticipated effect of intervention, and participant adherence to therapy. The planning committee also has to evaluate key issues such as participant availability, availability of competent cooperating investigators, timeliness of the study, possible competing trials, regulatory requirements, and total cost. After such an assessment, is the trial worth pursuing? Are there sufficient preliminary indications that the intervention under investigation indeed might work? On the other hand, is there so much suggestive (though inconclusive) evidence in favor of the new intervention that it might be difficult ethically to allocate participants to a control group? Might such suggestive evidence seriously impede participant recruitment? Since planning for the study may take a year or more, feasibility needs to be constantly re-evaluated, even up to the time of the actual start of participant recruitment. New or impending evidence may at any time cause cancellation, postponement, or redesign of the trial. In some instances, a pilot, or feasibility study is useful in answering specific questions important for the design and conduct of a full-scale trial.

Third, multicenter studies require not only clinical centers to recruit participants, but also one or two coordinating centers to help design and manage the trial and to collect and analyze data from all other centers. There may be regional sites, academic centers that serve as academic research organizations, or contract research organizations that conduct site visits and receive data from the clinical centers. Additional centers are often needed to perform specialized activities such as key laboratory tests, imaging, and distributing study drugs. While the specialized centers may perform multiple services, it may not be advisable to permit a clinical

center to perform these services. If a specialized center and a clinical center are in the same institution, it may be important for each to have a separate staff in order to protect against unblinding and, therefore, bias. Even if unblinding or bias is avoided, there might be criticism that such a bias might have occurred and thus raise unnecessary questions about the entire clinical trial.

As reported by Croke [20], a major consideration when selecting clinical center investigators is availability of appropriate participants. Although this report is now old, the message remains relevant. The trial has to go where the participants are. Clearly, experience in clinical trials and scientific expertise are desirable features for investigators, but they are not crucial to overall success. Well-known scientists who add stature to a study are not always successful in collaborative ventures. The chief reason for this lack of success is often their inability to devote sufficient time to the trial. In a comprehensive study of factors associated with enrollment of eligible participants with documented myocardial infarction, Shea et al. [21] found positive correlations with institutions in which patients were cared for by staff other than private attending physicians and with the presence of a committed nurse-coordinator. While many factors have been associated with successful enrollment, none is more revealing than prior performance in conducting collaborative trials.

The selection of the coordinating center is of utmost importance. This is often a single entity, but sometimes the coordinating center functions are split between two or more units; a clinical coordinating center, a data coordinating center, and, often, a separate data analysis center. The responsibilities described here apply to any of the models, but clearly communication becomes more of an issue when there are multiple units.

In addition to helping design the trial, the coordinating center, or combination of centers, is responsible for implementing the randomization scheme; carrying out day-to-day trial activities; and collecting, monitoring, editing, and analyzing data. The coordinating center, or, when there are two or more units, the clinical coordinating center/data management center needs to be in constant communication with all other centers. Its staff has to have expertise in areas such as biostatistics, computer technology, epidemiology, regulatory policy, medicine, and management in order to respond expeditiously to daily problems that arise in a trial. These might range from simple questions, such as how to code a particular item on a questionnaire, to monitoring clinical site conduct. The single coordinating center, or the separate data analysis center, has responsibilities such as preparing data monitoring guidelines, conducting data analyses, and developing or modifying statistical methods. The staffs at these centers must be experienced, capable, responsive, and dedicated in order to handle their workloads in a timely fashion. A trial can succeed despite inadequate performance of one or two clinical centers, but a poorly performing coordinating center or data management center can materially affect the success of a multicenter trial. In extreme cases, a coordinating center may have to be changed midway through the trial. This causes serious delay and logistical problems. Thus, proper selection of the coordinating center is extraordinarily important.

A key element in any coordinating or analysis center is not only the presence of integrity, but the appearance of integrity. Any suspicion of conflict of interest can damage the trial. This is one of the reasons that pharmaceutical firms who support trials sometimes use outside institutions or organizations as coordinating centers. Because the personnel in the centers control the data and the analyses, they should be seen to have no overriding interest in the outcome of a trial. Meinert [22] has described the functions of the coordinating center in detail. See also Fisher et al. for a description of the operations of an independent data analysis center [23].

As noted, certain functions in a multicenter trial are best carried out by properly selected special centers. The advantages of centrally performing laboratory tests, reading x-rays, evaluating pathology specimens, or coding electrocardiograms include unbiased assessment, standardization and reduced variability, ease of quality control, and high-quality performance. The disadvantages of centralized determinations include the cost and time required for shipping, as well as the risk of losing study material. Even with electronic transfer of data, glitches may occur. It is also obvious that the centers selected to perform specialized activities need expertise in their particular fields. Equally important is the capacity to handle the large workloads of a multicenter trial with research-level quality. Despite careful selection of these centers, backlogs of work are a frequent source of frustration during the course of a trial.

Fourth, it is preferable for the planning committee to provide prospective investigators with a fairly detailed outline of the key elements of the study design as early as possible. This results in more efficient initiation of the trial and allows each investigator to better plan staffing and cost requirements. Rather than presenting a final protocol to the investigators, we recommended that all or selected representatives be given time to discuss and, if necessary, modify the trial design. This process allows them to contribute their own ideas, to have an opportunity to participate in the design of the trial, strengthening their commitment to it, and to become familiar with all aspects of the study. It may also improve the design. The investigators need a protocol that is acceptable to them and their colleagues at their local institution. This "buy-in" will improve participant recruitment, data collection, and final acceptance of the trial results. Depending on the complexity of the trial, several planning sessions prior to the start of participant recruitment may be needed for this process.

If there are many investigators and a number of difficult protocol decisions, it is useful to have specific groups or subsets of investigators address these issues during the planning stage. Working groups can focus on individual problems and prepare reports for the total body of investigators. Of course, if the initial outline has been well thought out and developed, few major design modifications will be necessary. Any design change needs to be carefully examined to ensure that the basic objectives and feasibility of the study are not threatened. This caveat applies particularly to modifications of participant eligibility criteria. Investigators are understandably concerned about their ability to enroll a sufficient number of participants. In an effort to make recruitment easier, they may favor less stringent eligibility criteria. Any such decisions need to be examined to ensure that they do not have an adverse

impact on the objectives of the trial and on sample size requirements. The benefit of easier recruitment may be outweighed by the need for a larger sample size. Planning meetings also serve to make all investigators aware of the wide diversity of opinions. Inevitably, compromises consistent with good science must be reached on difficult issues, and some investigators may not be completely satisfied with all aspects of a trial. However, all are usually able to support the final design. All investigators in a cooperative trial must agree to follow the common study protocol.

Although a good protocol will provide guidance for all major issues that are anticipated, investigators will always have questions as they begin a trial that need to be addressed in a systematic way. This information should be shared with all investigators, in newsletters, in a question and answer format that could exist on a website, or (when necessary) with protocol amendments. This is part of a broader theme in multicenter trials: the importance of effective communication. It is the responsibility of coordinating centers to keep in frequent contact (by telephone, e-mail, texting, visits) with all the enrolling centers. An informative and interactive website can be helpful. The study leaders also need to maintain contact with the various centers and committees, closely monitoring the conduct of the trial.

Fifth, an organizational structure for the trial should be established with clear areas of responsibility and lines of authority and communication. Many have been developed [24–26]; the one outlined below has stood the test of time.

Steering Committee—This committee provides scientific direction for the study at the operational level. Its membership may be made up of some or all of those who were on the planning committee (including sponsor representation), plus a subset of investigators participating in the trial. In international trials, it has become conventional to have at least one "national coordinator" investigator from each major country to represent those investigators and to address country-specific issues. Depending on the length of the study, some investigators may be chosen or elected for part of the trial. Subcommittees are often established to consider on a study-wide level specific issues such as adherence, quality control, classification of response variables, and publication policies and review and then report to the Steering Committee.

It may also be important to authorize a small subgroup to make executive decisions between Steering Committee meetings. These committees are sometimes referred to as executive committees or as operations committees. Most "housekeeping" tasks and day-to-day decisions can be more easily accomplished in this manner. A large committee, for example, is unable to monitor a trial on a daily basis, write memoranda, or prepare agendas. Since committee meetings can rarely be called at short notice, issues requiring rapid decisions must be addressed by an executive group. It is important, however, that major questions be discussed with the investigators.

Subcommittees—Often, subcommittees of the Steering Committee are established. For example, there is often the need for a system for central evaluation of events, and this could be done by an Events Classification Subcommittee. Adjudication of events, with the participants' identities and intervention groups blinded, helps to assure unbiased classification of reported events and to ensure consistent application of criteria for particular events. Other subcommittees might look for ways to

improve participant accrual or adherence. In some trials, the subcommittee structure has become too complex and can lead to inefficiencies. Trials with few centers function best with a simple structure. If committees, subcommittees, and task forces multiply, the process of handling routine problems becomes difficult. Studies that involve multiple disciplines especially need a carefully thought out organizational structure. Investigators from different fields tend to look at issues from various perspectives. Although this variety can be beneficial, under some circumstances it can obstruct the orderly conduct of a trial. Investigators may seek to increase their own areas of responsibility and, in the process, change the scope of the study. What starts out as a moderately complex trial can end up being an almost unmanageable undertaking.

Data Monitoring Committee—This scientific body, which goes by various names (see Chap. 16), should be independent of the investigators and any sponsor of the trial. Its primary role, to the extent possible, is to ensure participant safety and study integrity. To accomplish this, it is charged with reviewing and approving the protocol; periodically monitoring baseline, harmful effects, and response variable data; and evaluating center performance [27]. In light of concerns about clinical trial integrity, [28–30] the independence of this group is especially important. It usually reports to either the study sponsor or the chairperson of the planning or steering committee. The coordinating or data analysis center should present tabulated and graphic data and appropriate analyses to the data monitoring committee for review. The committee has the responsibility to recommend early termination in case of unanticipated harm, greater-than-expected benefit, or high likelihood of indifferent results (see Chap. 16). Members of this committee should be knowledgeable in the field under study, in clinical trials methodology, and in biostatistics. An ethicist and/or a participant advocate may also be part of this group. The responsibilities of the monitoring committee to the participants, as well as to the integrity of the study, should be clearly established and communicated to the participants. These responsibilities for participant safety are particularly important in double-blind studies, since the individual investigators are unaware of the group assignments and which group is associated with various adverse events.

Unfortunately, the organizational structure of many trials conducted by industry excludes meaningful involvement of independent experts in trial design, conduct, and analysis. There is a need for academic trialists, including those at agencies such as the National Institutes of Health, to work with the public and health care providers to advance the conduct, quality, and relevance of clinical trials that address health care priorities [31].

Sixth, despite special problems, multicenter trials should try to maintain standards of quality that do not differ from those in carefully conducted single-center trials (see Chap. 11). Strong emphasis should be placed on training and standardization so that the protocol is carried out in the intended fashion across centers and regions. It is obviously extremely important that staff at all centers understand the protocol definitions, and how to complete forms and perform tests. Differences in performance among centers, as well as between individuals in a single center, are

unavoidable. They can, however, be minimized by proper training, certification procedures, retesting, and when necessary, retraining of staff. An attractive, functional, interactive website with updated training materials and other resources is an important tool in large trials. The National Heart, Lung, and Blood Institute (NHLBI)-sponsored International Study of Comparative Health Effectiveness with Medical and Invasive Approaches (ISCHEMIA) trial website provides such an example [32]. These efforts need to be implemented before a trial gets underway (See Chap. 11 for a discussion of quality control). In trials that require specific training and expertise, a clinical center should not be allowed to begin enrolling participants until it has demonstrated the capability of performing necessary procedures. Investigator meetings are generally important to the successful conduct of the trial because they provide opportunities to discuss common problems and review proper ways to collect data and complete study forms.

Seventh, there needs to be close monitoring of the performance of all centers. Participant recruitment, quality of data collection and processing, quality of laboratory procedures, adherence of participants to protocol, and loss to follow-up should be evaluated on an ongoing basis. Regulatory requirements for investigators are outlined in Chap. 22. Table 21.1 lists some of the major responsibilities of the principal investigator at enrolling centers.

Electronic tracking tools allow this to be done in an efficient and systematic way, as long as standardized reports effectively capture and display the information. It is important to track overall performance as well as performance by center.

Many industry-sponsored multicenter trials that employ contract research organizations conduct extensive auditing and quality assurance. This is quite costly and how much benefit it provides has been questioned [33]. See Chap. 11 for further discussion of this topic.

In most clinical trials, recruitment of participants is difficult. In a cooperative clinical trial, however, there is an opportunity for some clinical centers to compensate for the inadequate performance of other centers by exceeding their predetermined recruitment goals. The clinical centers should understand that, while friendly competition keeps everybody working, the real goal is overall success, and what some centers cannot do, another perhaps can. Therefore, it is important to encourage the good centers to recruit as many participants as possible. There may be a limit, however, if one center, region, or country (in the case of international trials) starts to dominate enrollment. At some point, recruitment might need to be capped if the study is to be seen as truly multicenter.

Eighth, publication, presentation, and authorship policies should be agreed upon in advance. Authorship becomes a critical issue when there are multiple investigators, many of whose academic careers depend on publications. There is no completely satisfactory way to recognize the contribution of each investigator. A common compromise is to put the study name immediately under the paper title and to acknowledge the writers of the paper, either in a footnote or under the title, next to the study name. All key investigators are then listed at the end of the paper. The policy may also vary according to the type of paper (main or subsidiary). The group authorship of manuscripts from multicenter trials was challenged by some medical

Table 21.1 Principal investigator's major responsibilities at research sites

1. Be familiar with ethical principles (see Chap. 2), including as outlined in the Belmont Report: respect for persons, beneficence, justice
2. Be familiar with US federal regulations as defined in the Code of Federal Regulations (CFR) (see Chap. 22)
   (a) Health and Human Services, for federally funded research
      i. 45 CFR 46 (Health and Human Services, Protection of Human Research Subjects)
         1. Subpart B (pregnant women)
         2. Subpart C (prisoners)
         3. Subpart D (children)
   (b) FDA, for FDA regulated products
      i. 21 CFR 50 (informed consent)
      ii. 21 CFR 54 (financial disclosure)
      iii. 21 CFR 56 (IRB)
   (c) Health and Human Services, for privacy including for all human subjects research
      i. 45 CFR 46, 160, 164 (HIPAA)
3. Understand the requirements of the responsible Institutional Review Board (IRB) and the need to follow them
4. Be responsible for oversight of the trial and delegation of research responsibilities, with appropriate training and experience of staff
5. Recruit participants in a fair and equitable way (see Chap. 10)
6. Develop process of informed consent (see Chap. 2), with IRB approval of that process, with consent obtained by the PI or a delegated research staff member who is identified as "key personnel" in the IRB approval; and maintain documentation of informed consent (generally for at least 3 years)
7. Do not enroll patients without prior IRB approval, and not make changes to the protocol without prior IRB approval
8. Comply with reporting requirements of adverse events, protocol deviations, unanticipated problems involving risks to participants or others, or irregularities (like loss of consent documentation) (see Chap. 12)
9. Be available, or have a designated research staff member available, to participants to answer questions
10. Notify the IRB and seek approval for change to a new principal investigator

(The focus is on the essential need to protect the rights and welfare of research participants (adapted from Duke University and from United States Health and Human Services clinical research training materials))

journals and defended by others [34–36]. It remains common, but typically with an identified writing committee to take responsibility (see Chap. 20).

Involvement of representatives of the sponsor as authors of the main manuscripts from a major trial can be contentious, especially if it is a commercial firm that stands to benefit from a favorable presentation of the trial results. Most sponsors accept a hands-off policy and leave it to the investigators to write the scientific papers, although including sponsor members of the research team who provided important intellectual contributions can be appropriate. Typically, an industry sponsor is given 1 month to preview the main results manuscript, to allow time to

deal with patent or regulatory issues. This review should not unnecessarily delay the publication of the main trial results. Regrettably, there are examples of interference that are in conflict with academic freedom. These policies should be clearly defined in the contract between the sponsor and the investigators.

In one four-center trial, the investigators at one of the centers reported their own findings before the total group had an opportunity to do so [37, 38]. Such an action is not compatible with a collaborative effort. It undermines the goal of a multicenter trial of having enough participants to answer a question and, perhaps more importantly, the trust among investigators. Academic institutions have taken a strong stand against this principle of collaboration and in defense of academic freedom for each investigator. However, we believe that those unwilling to abide by the rule for common authorship should not participate in collaborative studies.

Creating a publication charter in advance and having all parties agree to abide by it provides important protection against misunderstandings. However, fair recognition of junior staff will always be difficult [39]. Study leadership often gets credit and recognition for work done largely by people whose contributions may remain unknown to the scientific community. One way to alleviate this problem is to appoint as many capable junior staff as possible to subcommittees. Such staff should also be encouraged to develop studies ancillary to the main trial. This approach will enable them to claim authorship for their own work while using the basic structure of the trial to get access to participants and supporting data. Such ancillary studies may be performed on only a subgroup of participants and may not necessarily be related to the trial as a whole. Care must be taken to ensure that they do not interfere with the main effort, either through unblinding, by harming the participants, or by causing the participants to leave the trial. Sackett and Naylor discuss the issues for and against allowing publication of ancillary studies before the main trial is completed [40].

Globalization of Trials

As noted earlier, many multicenter clinical trials are international; there are several reasons for this. One, it provides greater numbers of potential participants, allowing for quicker accrual. Two, the broader populations may allow for wider generalization of results. It is not simply people from one country with one medical care system who are enrolled; the data from the trial apply to many sorts of people with very different medical systems. Three, it may be easier and less expensive to screen people in some regions. Even in NIH-sponsored trials, an increasing proportion of participants are being enrolled internationally, largely due to inability to enroll enough patients at centers in the United States [41] (see Fig. 21.1).

There are, however, limitations and concerns with globalization of trials. As discussed in Chap. 2, the ethics of enrolling participants from underdeveloped countries or areas can be problematic [42]. It is unethical to enter people into a trial simply to save money, or because the regulatory oversight is less rigorous,

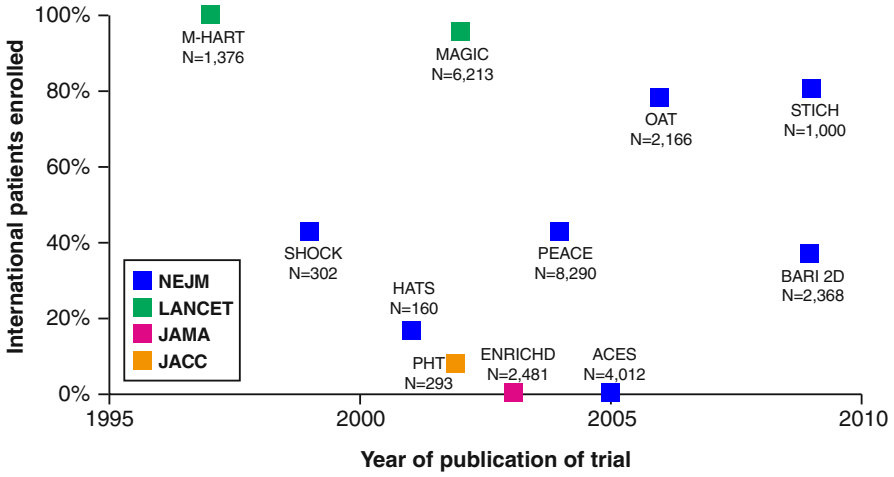

Fig. 21.1 International enrollment in NIH-sponsored randomized trials of coronary disease [41]

when there is little likelihood that the population will benefit from or have access to the trial intervention. Logistics of implementing international trials may be daunting. In addition to multi-language communication, there is the issue of translating forms and questionnaires. Not all forms, particularly those that have been validated in certain groups, may be usable in very different communities and cultures. Transporting drugs and other materials across borders may not be simple. In addition, each country has its own regulatory structure that must be negotiated.

Some countries may present particular challenges in regulatory approval, such as China where the process may take over a year for drug trials. In India, concerns over unethical trial practices have led to laws requiring trial sponsors to cover medical costs of trial-associated adverse outcomes and to requirements to video record the informed consent process. These regulatory and legal requirements resulted in unwillingness to include Indian sites in many trials. At least 35 NIH trials were put on hold in India in 2013, although many subsequently resumed [43, 44].

Interpretation of regionally diverse results may be questioned. Are the overall results relevant to all countries? Does the culture, social structure, or medical care system (including concomitant medications and other treatment) affect the outcome? Does each trial participant need minimal standard background care? If so, this must be specified in advance in the protocol. An example of a trial that examined effect by geography is the Platelet IIb/IIIa in Unstable angina: Receptor Suppression Using Integrilin Therapy (PURSUIT) trial [45]. Relative reductions in the primary response variable (a combination of death or myocardial infarction) varied among geographic regions. In trials of beta blockers in heart failure, there appears to have been a consistently lesser treatment effect in the United States than in other countries, for unclear reasons [46] (see Fig. 21.2).

The Treatment of Preserved Cardiac Function Heart Failure With an Aldosterone Antagonist (TOPCAT) trial included about half of patients from Russia and

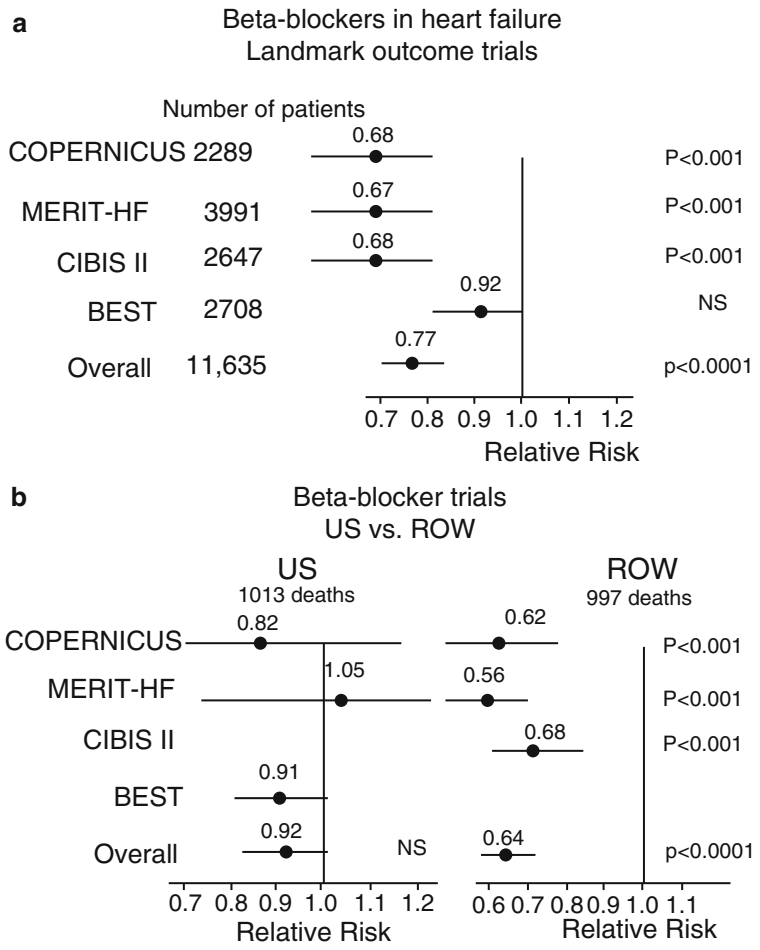

Fig. 21.2 Effects of beta blockers on all-cause mortality in major heart failure trials [46]. *Panel* (**a**) is overall, *panel* (**b**) contrasts the United States and rest of world (ROW), with p values in *panel* (**b**) for effects in ROW, and NS referring to non-significant p-value for the overall effect in the U.S.

Georgia and half from the Americas. The populations in these regions differed at baseline, with more of the patients in Russia and Georgia being characterized by prior myocardial infarction and prior heart failure hospitalization [47]. There was a four-fold higher rate of the primary outcome of cardiovascular death, aborted cardiac arrest, or heart failure hospitalization in Russia and Georgia than in the Americas, and the treatment benefit observed with spironolactone in the Americas was not seen in Russia and Georgia. Spironolactone did not have the degree of effect on laboratory values (potassium and creatinine) in Georgia and Russia that it did in the Americas [48]. Related regional differences in composition and outcome

of populations with heart failure with preserved ejection fraction have been observed in other clinical trials [49]. These findings suggest that the diagnosis, management, outcomes, and response to therapy of heart failure with preserved ejection fraction may be different in different geographic regions. This regional heterogeneity will in turn impact on the results of clinical trials.

The Platelet inhibition and Patient Outcome (PLATO) trial, which studied ticagrelor versus clopidogrel after acute coronary syndromes, provides an even more striking example of heterogeneity of treatment effect according to country [50]. Overall, there was a 16% relative risk reduction in the primary composite outcome. In the United States, which included 8% of the patients, the hazard ratio was 1.27, and in other countries, 0.81, with a p value for the interaction of 0.0095 [51]. There is also evidence that it may be related to, and even explained by, the higher dose aspirin used in the United States [51].

In these examples, chance still may be the most likely explanation. However, investigators need to consider, in advance, whether combining results from geographically and culturally different sites is appropriate. In any case, if a robust and consistent treatment effect is desired to be demonstrated in the United States population, or in any specific population, enrolling a sufficiently large portion from that population is important. Vickers et al. [52] found that some countries tended to produce results more favorable to the new intervention than other countries, though publication bias was the likely reason.

Large, Simple Trials

Large, simple trials [53] are a subset of multicenter trials that typically involve a large number of participating centers, many of which are non-academic institutions representative of general practice. Education, training, and standardization may need to be more focused and streamlined compared with other trial models. For example, in streamlined trials background care may be left to the caring physician such that standard of care is the goal, although for many trials, encouraging high quality standard of care may be important for the results to be accepted as relevant. Clinician-investigators need to understand the basic concepts and intent of clinical trials and how the rules of research, which may sometimes seem arbitrary, [54] differ from the way they practice medicine (See Chap. 2). The reliance on hard endpoints such as all-cause mortality, and limited data collection, tends to reduce the need for elaborate quality control procedures.

Successful conduct of streamlined trials has become more difficult with more complex and heterogeneous regional regulatory requirements, which have caused large trials to be very expensive. The expense related to complexity and various barriers that do not result in improved quality has far reaching consequences, including resulting in an inability to conduct many trials that are necessary to guide clinical care. In response to these barriers, recommendations have been made to simplify procedures for large, simple trials [55–57].

The U.S. Food and Drug Administration (FDA), in partnership with Duke University in the Clinical Trials Transformation Initiative (CTTI), [58] has made a concerted effort to provide guidance to promote streamlining when appropriate. For example, in December 2012, a guidance was issued for simplified adverse event reporting in large, simple trials [59] and in August 2013, another guidance was issued for risk-based monitoring of trial conduct and data [60].

There are examples in which randomized clinical trials have been successfully conducted on the platform of clinical registries [61], such as the Thrombus Aspiration during ST-segment Elevation myocardial infarction (TASTE) trial that randomized over 7000 patients in less than 3 years (80% of all eligible acute myocardial infarctions in Sweden during the enrollment period) to thrombus aspiration or control for an estimated total US$300,000 marginal cost [62] (see Chap. 10, Fig. 10.4). Another pragmatic trial, INforming Fresh versus Old Red cell Management (INFORM), is planning to randomize 31,497 patients undergoing blood transfusion to freshest versus standard (older) blood for transfusion at five medical centers in Canada, Australia, and the United States as of December 2014. In this trial, consent is waived and in-hospital data are collected using the electronic health record such that the cost is a fraction of what would be typical for a trial of this size [63].

Another example of a streamlined approach to integrating clinical trials and clinical practice comes from the NIH Health Care Systems Research Collaboratory. Launched in 2006, this program supports demonstration projects in which health care organizations partnered with researchers conduct pragmatic clinical trials in everyday health care settings. One such project was The Randomized Evaluation of Decolonization versus Universal Clearance to Eliminate MRSA (REDUCE MRSA), a cluster randomized trial of 43 hospitals (including 74 intensive care units and 74,256 patients) testing whether daily antiseptic baths and a nasal antibiotic were more effective than other procedures to decolonize patients to prevent staphylococcal infections in intensive care units [64]. The Collaboratory group has outlined key steps to develop successful partnerships between health care systems and researchers to conduct pragmatic clinical trials that address important gaps in knowledge to improve patient care. These steps include building partnerships, defining the important questions, assessing feasibility, involving stakeholders in the design, and implementing workflow [65].

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