

Perspectives on Large-Scale Cardiovascular Clinical Trials for the New Millennium

Eric J. Topol, MD; Robert M. Califf, MD; Frans Van de Werf, MD; Maarten Simoons, MD; John Hampton, MD; Kerry L. Lee, PhD; Harvey White, DSc; John Simes, MD; Paul W. Armstrong MD; for the Virtual Coordinating Center for Global Collaborative Cardiovascular Research (VIGOUR) Group

Concurrent with the considerable advances in medical approaches for the treatment of patients with heart disease, there has also been steady refinement in the design and conduct of randomized clinical trials to assess new therapies. In part, this progress represents an outgrowth of the thrombolytic era, with more than 200 000 patients randomized in large-scale trials over the past decade, making thrombolysis the most intensively studied medical intervention to date.¹⁻⁶ Similarly, new therapies for heart failure,⁷⁻¹¹ prevention of restenosis,¹²⁻¹⁵ reduction in risk of sudden cardiac death,¹⁶⁻¹⁸ the use of ACE inhibitors,¹⁹⁻²⁴ and lipid-lowering therapy for coronary atherosclerosis²⁵⁻²⁷ have been extensively evaluated, and medical devices and coronary revascularization procedures²⁸⁻³⁵ have also been assessed via prospective controlled trials. The cumulative experience reflects a strong commitment of the community of practitioners caring for patients with cardiovascular disease to the use of randomized clinical trials to guide practice. This adoption of randomized clinical trials is occurring simultaneously with enormous changes in the organization of medicine, in most countries toward the formation of privatized managed care organizations with a focus on reducing cost. We believe that the practicing community has a fundamental responsibility to provide the evidence that will ensure that efforts to control cost do not sacrifice the use of therapies that benefit patients and that a balance of providers, regulators, and industry can provide a structure for effective change in medical practice through sound evidence.

Cardiovascular clinical trials have had enormous impact on daily clinical practice. The involvement of nontraditional investigators such as primary-care and community-based physicians in small to medium-size hospitals has

raised the level of awareness of clinical research methodology. Secondary gains associated with such penetration include the discovery of undertreatment, learning about the process of care delivery, and enhancing the quality of care through the reduction of variance among practitioners who adhere to a common protocol.³⁶ Indeed, the number, size, and quality of these trials have greatly increased in the past few years. Beyond current pharmacological interventions, validation of future strategies such as the new biology of gene therapy, and novel administration techniques such as intravascular local delivery, new approaches for disease prevention will rely on controlled trials in the years ahead. The properly designed and conducted randomized trial represents the final common pathway for assessing clinical efficacy. The environmental arena in which these trials must now be conducted has become increasingly complex. Most cardiovascular conditions have some form of effective therapy; as a result, a new experimental therapy will yield a more modest margin of benefit than would be seen in a comparison with a no-treatment control. This often leads to the need for a large trial of many thousands of patients, usually of international scope and high cost, and usually with an industrial sponsor involved. The need for public and peer accountability, recognition of potential conflicts of interest, and development of the complex relationships necessary to succeed pose enormous challenges.

Just as we have learned about the target therapy in many recent trials, we have greatly expanded our understanding of the critical considerations in the design, conduct, and dissemination of large-scale cardiovascular trials. In the present article, we review the literature and some insights for each of these fundamental aspects (design, conduct, and dissemination) of large clinical trials. We have used the trials that we have collaborated on in many examples, owing to our familiarity with the issues. By no means do we intend to convey that the trials we performed are exemplary; rather, they have provided experience to provoke thought about how to improve future clinical investigation.

Design Issues

The design of the clinical trial can be likened to the "architectural blueprints" of a great structure. The design phase can be intellectually satisfying, and the more forethought there is on all aspects of the trial, the better the

From Cleveland (Ohio) Clinic Foundation (E.J.T.); Duke University Medical Center, Durham, NC (R.M.C., K.L.L.); Catholic University, Leuven, Belgium (F.V.); Erasmus University, Rotterdam, Netherlands (M.S.); University of Nottingham, UK (J.H.); NHRMC Clinical Trials Centre, University of Sydney (Australia) (J.S.); Green Lane Hospital, Auckland, New Zealand (H.W.); and the University of Alberta, Edmonton (Canada) (P.W.A.).

Correspondence to Eric J. Topol, MD, Department of Cardiology, Desk F25, Cleveland Clinic Foundation, 9500 Euclid Ave, Cleveland, OH 44195. E-mail topole@cesmtp.ccf.org.

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blueprints will be. At first glance, it might be perceived that the key parameters involved in a clinical trial are a description of the patient inclusion and exclusion criteria and the dosage and timing of the therapeutic agent to be studied. Such a superficial appraisal belies the numerous levels of planning, the foundation for a successful project, and how the attention to detail results in its ultimate consummation. It is critical to achieve as much symmetry as possible between the control and experimental limbs of the project. Just as blueprints provide views of the design with respect to multiple elevations and perspectives, the design of a trial as reflected in the protocol, the case report form, the organization of the committees, and the contract with sponsors are each key elements.

Primary and Secondary Hypotheses

The first step in design is to frame the main hypothesis. The entire project is centered about a single question, and the statistical power built into the trial will generally suffice only for the primary hypothesis that involves the whole study population. The more clear-cut the main question of the study is, the more definitive will be the results and interpretation. However, the value of important secondary hypotheses and ancillary studies should not be underestimated. Features and advantages of substudies in large-scale randomized trials are presented in Table 1. The mechanism of the primary hypothesis should be explored, if at all possible. Such was the case in the GUSTO-I trial,^{1,37} in which an angiographic ancillary project, performed in 6% of the overall study population, provided extensive data concerning the mechanistic advantage of early and complete infarct vessel patency, which formed the underpinning and explanation for the main trial mortality results. Another example of a substudy to help understand mechanisms is the use of a smaller angiographic sampling in a large-scale trial testing an agent to limit restenosis after percutaneous coronary intervention.³⁸ While avoiding the large expense incurred by requiring systematic follow-up angiography on the entire population, one can assay the true clinical outcomes in the overall popu-

lation and, at the same time, gain insight about the effects on coronary anatomy in a subgroup of patients who undergo repeat angiography.

Many other secondary hypotheses can be pursued. In the present era of severe cost constraints and consciousness about patient preferences, an understanding of the effects of therapy versus economic and quality-of-life outcome data is essential. Prospective design of a system to collect all of the relevant use of resources³⁹ is necessary, and baseline and serial measurements of functional status and the patient's assessment of his or her quality of life must be addressed. As new therapies are explored in the years ahead, the benefits of reducing cost or improving the quality of life, even without any measurable improvement in clinical outcomes, will be more heavily prioritized. Particularly in evaluating new therapies for heart failure, a critical tradeoff between effects on longevity and quality of life requires careful consideration.

The major structure of a large trial enables the clinical community to answer multiple important questions at a fraction of the cost of mounting an individual study of each question. The context of a well-characterized, large, prospectively defined population provides an ideal opportunity to determine whether a new test has merit as a surrogate for clinical outcomes or for elucidating the mechanism of the effects of a new therapy. Ancillary projects also offer opportunities to decentralize leadership and delegate opportunities for project development among the many talented investigators whose different interests and strengths contribute to the central organization. Because large-scale trials tend to underrecognize the many physicians and nurse investigators who are pivotal to the success of the overall project, ancillary studies are also an attractive vehicle to generate enthusiasm and a sense of empowerment at a more local level.

Case Report Form

Also at the outset of the project, the development of a streamlined data collection form and system is essential. This practice has evolved substantially in the past decade.

TABLE 1. Features and Advantages of Substudies in Large-Scale Randomized Trials

Substudy Design	Example	Advantages
Linking baseline risk factor information to clinical outcomes	Multivariable regression model of mortality	An economical way of collecting important information on prognostic value of patient characteristics and patterns of care within the clinical trial
Determining any heterogeneity of treatment effects across different subgroups	Sex or age differences	This information can be collected only within a randomized trial
Randomizing a subgroup to a second question	TPA vs angioplasty in GUSTO II	Same strengths and weaknesses as factorial design
Identifying possible mechanisms of action of therapy	Measuring intermediate outcome measures, angiographic studies, coagulation studies	Although this study could be conducted separately, it provides some economics and is being conducted in a setting closer to routine clinical practice (emulated by the large-scale trial structure)
Linking mechanisms of treatment/surrogate outcomes to main clinical outcomes	Improved coronary perfusion in GUSTO I	This can help determine to what extent the observed treatment effect is consistent with a possible treatment mechanism
Collecting information on secondary outcomes	Quality-of-life and cost-effectiveness assessments	Efficiency; more valid assessment for cost-effectiveness than a separate study; intercountry practice variations around a single well-defined disease entity

GUSTO I indicates Global Utilization of Streptokinase and Tissue Plasminogen Activator for Occluded Coronary Arteries; GUSTO II, Global Use of Strategies to Open Occluded Coronary Arteries.

Trials conducted through the 1980s in the United States had case report forms typically numbering more than 100 pages, and the vast majority of the data collected were never used. Optimally, the investigators will be able to focus early on the main and predefined ancillary hypotheses and on precisely what data are needed to resolve these questions. The cost of a trial is also heavily influenced by the length and breadth of the case report form process. This problem is partly addressed through substudies in which more detailed information can be collected on a representative sample for a supplementary question not needing the participation of all investigators or patients. With the delineation of the specific goals of the analyses, the case report form can be kept as simple as possible. The shorter the forms, the more likely it is that they will be completed accurately and in a timely fashion. The major point is that the data collected should be complete for the goals of the project, but the form should be succinct and straightforward. Finally, the case report form should be pretested at sites with experienced research coordinators.

Placebo and Active Drug Control Therapy

Ideally, all trials that are testing a drug intervention would have a placebo control arm with a double-blind administration. This design feature promotes rigor and objectivity in many features of the trial, including evaluation of the principal end points, compliance with study medication, uniformity of postintervention care, and attribution of adverse effects. In comparing one drug with another active drug, a "double-dummy, double-blind" technique is highly desirable whereby either one of the active drugs or the placebo counterpart is administered.

Although the use of a placebo control is usually preferred, a number of factors can modulate this decision. First, a physically identical-appearing placebo needs to be available that is functionally inert or has effects that are well characterized and has no toxicity. Second, the disparity between benefits of the active drug and placebo (eg, the impact of β -blockers on heart rate) may be apparent to the investigator team and compromise the blinding.

A placebo control per se may also affect the results of the trial. For example, if the time to administration of a drug is pivotal, as is the case with thrombolytic intervention for acute myocardial infarction, and the nature of a double-dummy placebo administration interferes with timeliness of therapy, then the true effect of the experimental therapy may be compromised. Furthermore, a placebo infusion can be a source of logistical difficulty or morbidity. Hence, in the GUSTO-I trial, which tested combination thrombolytic therapy with intravenous heparin, a placebo infusion would have necessitated an extra intravenous line for more than 30 000 patients who were not assigned to this strategy.⁴⁰ Although an extra intravenous line may appear to be routine, it would involve additional time required to gain access, greater cost, and in the setting of such therapy, an increased propensity for bleeding at the site. In trials with all-cause mortality as the principal end point, the value and importance of blinding and placebo control are less critical. In such circumstances, it is highly unlikely that mortality would be affected by knowledge of the actual treatment. Variation in postrandomization ancillary care has been raised as a potential confounding factor that could alter the observed treatment effect, but this has not been demonstrated.⁴⁰ Furthermore, the open de-

signs of GISSI-1 and GISSI-2/International^{2,4,5} were independently validated by the placebo-controlled trials of ISIS-2 and ISIS-3, respectively.^{3,6} In summary, although attempts to incorporate a placebo and blinded design are desirable, in some instances an open design may be deemed acceptable. Pharmacological trials without placebo and the use of double blind are still valid if the outcome assessment is objective and unbiased. Whereas device trials cannot usually be blinded (eg, stenting versus balloon angioplasty), their scientific rigor can be enhanced by randomization, independent adjudication of clinical events, and unambiguous end points.

Dosage of a Drug

Of all the issues to address in the design of a large-scale pharmacological trial, dosage of the study drug is perhaps the most fundamental.⁴¹⁻⁴³ For a new drug in phase II development, available data are frequently insufficient to allow confident dosage selection. Typically, relatively small numbers of patients are evaluated in phase II studies with multiple dosing regimens, such that clinical end-point effects are difficult to interpret and differences may well have occurred by chance. In addition, when there is a safety concern but the adverse event is infrequent, such as 0.5% intracerebral hemorrhage with thrombolytic therapy, safety cannot be ensured from phase II investigation. Accordingly, we advocate a blend of phases II and III using the "pick the winner" approach (Fig 1). This method is to be differentiated from the "play the winner" term that has been applied to a specific adaptive randomization scheme. This concept is intended to describe a trial in which the initial part is dedicated to testing different dosages of the experimental agent in larger numbers of patients. For example, in the PARAGON trial (Platelet Iib/IIIa Antagonist for the Reduction of Acute coronary syndrome events in a Global Organization Network), a phase A was built in to study two different doses of the platelet antagonist lamifiban, with or without concurrent intravenous heparin. At the end of phase A, plans were made for an independent Data and Safety Monitoring Committee to review the data to advise the Steering Committee which strategy of the four experimental arms to test in the full, continued project. Such a "pick the winner" approach is attractive because it harnesses the network of the large-scale trial to quickly enroll patients and ascertain with more precision vital data about both safety and efficacy. If the data are independently reviewed and the decision regarding the

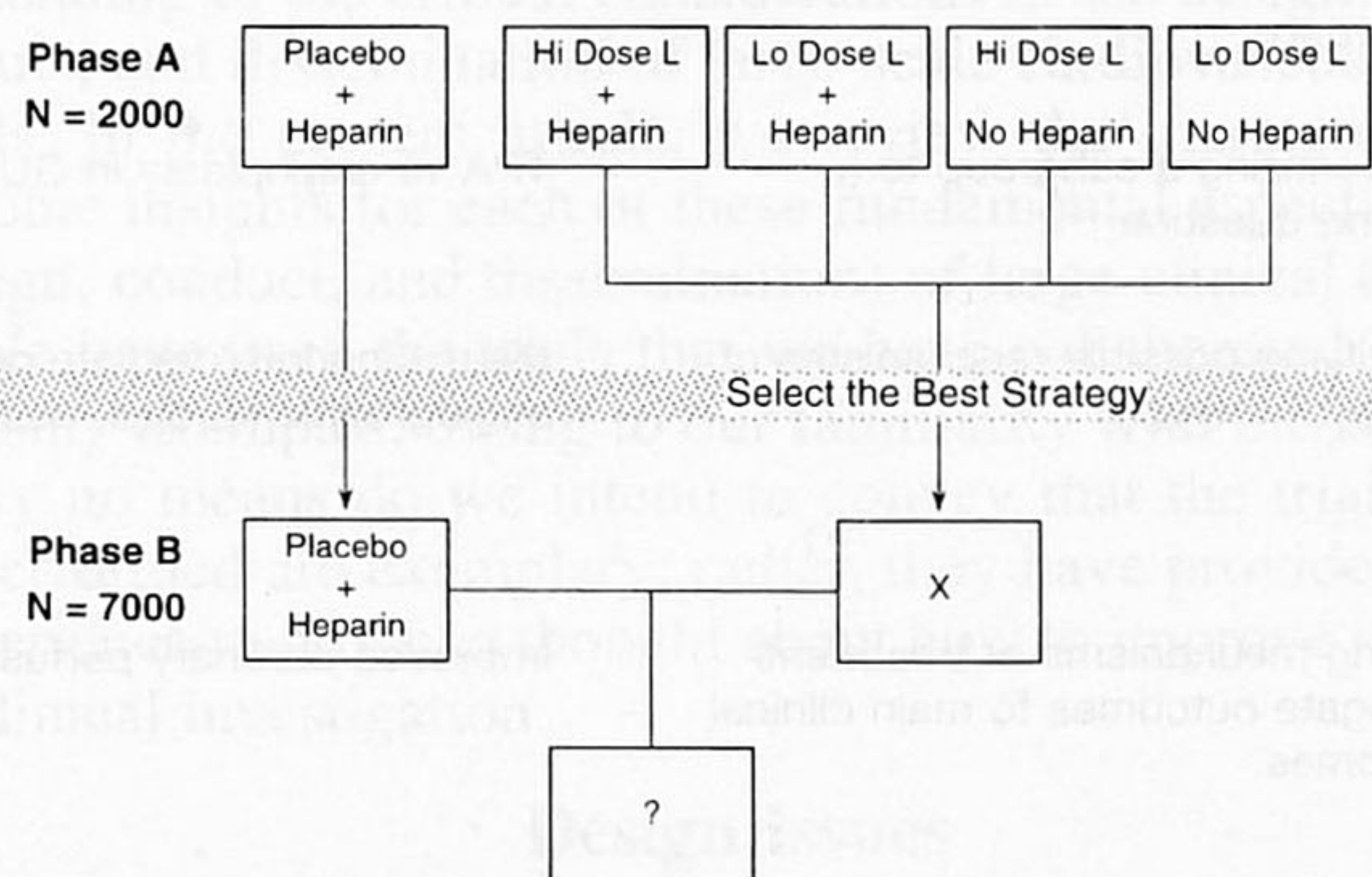


FIG 1. PARAGON Trial "pick the winner" design. In phase A of 2000 patients, one of four experimental arms will be selected to go into phase B, the continuation of the pivotal trial, without stopping enrollment in the overall project.

preferred dose is made relatively early in the trial, "minimal loss" or statistical penalty for the patients is accrued. Hence, the overall trial can include patients studied in phase A for that dose selected for testing in phase B. It is crucial that either larger phase II efforts or a dose-selection strategy (such as the aforementioned) be considered in future trials, since recent experience has underlined the hazards of selecting the dosage in a sample of inadequate size.^{41,42} It is very expensive and consumptive to have multiple (more than two doses) arms of a large-scale trial; however, comprehensive dose-response relationships about a new pharmaceutical are essential to more fully understand the safety and efficacy profile of the agent. The more data that can be accrued on multiple doses, the better the ultimate design. We believe incorporation of dose-finding studies is a logical adaptation of phase III trials to expand information on new agents and circumvent inconclusive or unnecessarily adverse criticisms of a large-scale trial.

Inclusion, Exclusion, and Universe Log

Simplifying the design and the conduct of a large trial is facilitated by limiting exclusion criteria to, ideally, fewer than four or five conditions. The objective is to create a positive mindset among investigators about the ease of enrollment rather than the difficulty. A short list of exclusion criteria is easy to recall and usually characterizes a broad-based population. Extrapolating the results to clinical practice is facilitated by maintaining an exclusion log. Although it is laborious and expensive to maintain a list of all patients screened or eligible but not entered into a large trial, their major outcomes can be acquired in 1 or 2 weeks as a sample "universe" of the overall population studied. Such an approach was used in the Bypass Angioplasty Revascularization Investigation (BARI)³² and Coronary Angioplasty Versus Excisional Atherectomy Trials (CAVEAT)²⁸ and was useful in addressing the generalizability of the results. In addition to providing a denominator for patients studied and a basis for wider extrapolation of the results, another major function of an entry log is to enhance recruitment. This may also accent the importance of recruiting a true cross section of the population with full representation of women and minorities by raising consciousness during the conduct of the study.

End Points

The principal end point for a large-scale cardiovascular trial should generally be all-cause mortality. The most important trials of the past decade have had mortality as the sole end point. For example, the debate over the cholesterol hypothesis remained until the Scandinavian Simvastatin Survival Study (4S)²⁵ ultimately showed that the use of a cholesterol-lowering agent reduced all-cause mortality. Before this trial, it was debated that either mortality reduction had not been demonstrated or the reduction in cardiovascular mortality was offset by an increase in other causes of death, such as suicide or cancer. Death from any cause is an end point that does not require adjudication. It is objective, ascertainable in all patients, and should be regarded as the reference standard for the primary end point of a major clinical trial, provided that the disease under study has an adequate frequency of fatal end points.

Trials in congestive heart failure are especially well suited for a mortality end point, given the high frequency of this end point in this condition. In many cardiovascular diseases, however, mortality is infrequent during short-

term follow-up. For conditions such as unstable angina or coronary revascularization in patients without acute myocardial infarction, the death rate within 30 days or 6 months is only 3% to 5%.³⁶ This makes demonstration of a treatment survival benefit exceedingly difficult. In these clinical settings, a clinically meaningful benefit may include reduction of both death and nonfatal myocardial infarction. The widely accepted composite of death and myocardial infarction represents a logical continuum from death of a patient to myocardial tissue necrosis and serves as a robust parameter in ischemic heart disease trials. Paradoxically, the diagnosis of myocardial infarction may be surprisingly difficult. There are many patients who have only enzymatic evidence of infarction without the classic clinical stigmata of chest discomfort or ECG changes. These events of "micronecrosis," which may accompany percutaneous coronary interventions, have been shown to carry an important adverse long-term prognosis, with an excess of mortality on extended follow-up.^{44,45} When the infarction is a non-Q-wave event, the adjudication process can be quite complex, with significant variation in results obtained by the events review committee compared with the site-investigator-recorded infarct event rate.²⁸ A threshold value for abnormality of the serum creatine kinase myocardial band (CK-MB) isoenzyme, irrespective of clinical or ECG criteria, needs to be defined. A recent consensus conference suggested that after a percutaneous revascularization procedure, not only a threefold excess of CK-MB above the upper laboratory normal limit be considered a significant myocardial infarction but also that all excesses of CK-MB be tallied because even slight abnormalities were correlated with worse clinical outcomes. With attention to a rigorous prospective definition of myocardial infarction at the outset of the trial and meticulous blinded review by an adjudication committee, the potential for ensuring the authenticity of this end point can be enhanced. During a trial with myocardial infarction as an end point, there should be verification of the accuracy and reliability of the adjudication committee. In tallying the end point for such a trial, patients can be "counted" only once even though an individual may have a myocardial infarction preceding death.

The approach to clinical end points beyond death and nonfatal infarction is more complex. "Composite" end points, such as death, myocardial infarction, or need for revascularization in percutaneous revascularization^{31,46} and death, myocardial infarction, or refractory ischemia for unstable angina,⁴⁷ have been assembled. The composite may be a valuable means of enriching the quantity of supporting evidence to test a new drug or device, but the confounding features of some of these end points sometimes make them unreliable surrogates for mortality. First, each parameter in the composite may not be of equal importance. Hence, for the patient who has a balloon angioplasty, death is obviously the most serious consequence, whereas the need for a second angioplasty is less serious. Because these composites do not usually incorporate an ordinal ranking or relative weight, each component of the end point is considered equivalent. Notwithstanding the difficulty of weight assignment for end points,⁴⁸ it is still possible to rank-order the severity of the components. Statistical methods for comparing treatments that take such ranking into account are readily available. Second, the adjudication of other nonfatal end points can be very difficult. End points such as "refractory angina" are ambigu-

TABLE 2. Surrogate Laboratory Indices and Clinical End Points

Clinical Setting	Surrogate End Point	Paradoxical or Unanticipated Finding
Arrhythmias	PVCs	Antiarrhythmics that suppressed PVCs increased mortality
Congestive heart failure	Hemodynamics of increased cardiac output, reduced pulmonary capillary wedge pressure	Inotropic agents that improved hemodynamics worsened mortality
Ischemic heart disease	Angiographic stenosis and acute coronary events	Plaque rupture occurs most often with nonsignificant stenosis; regression trials, while not demonstrating significant regression of stenosis, yielded >25% reduction of myocardial infarction events; residual stenosis after successful thrombolysis is often innocent and the vessel is stable

PVC indicates premature ventricular contraction.

Reprinted in part with permission from Topol EJ, Nissen SE. Our preoccupation with coronary luminology. *Circulation*. 1995;92:2333-2342.

ous, because the criteria of the treating physicians may vary considerably. Third, whenever a composite end point is used, the interpretation of the data requires attention to directionality and consistency for each parameter. For example, should a new therapy markedly reduce the need for repeat revascularization on the one hand yet increase frequency of death and myocardial infarction on the other, there would obviously be concern as to how to reconcile this paradox. Since the less important end points may be more frequent, thereby achieving statistical significance, "insignificant" differences in mortality rates from a small study could translate into important public health concerns if the study led to widespread application of the therapy. Therefore, consistent directionality of the effects for the various components of a composite is quite important. Fourth, a composite end point may include adverse effects of the intervention, such as "major bleeding" in the case of a new thrombolytic agent or antithrombotic, or potentially, laboratory parameters can be used as items in the composite. Both of these factors, inclusion of safety or laboratory-derived parameters, tend to further dilute the value of the composite event rate, which is the key clinical efficacy parameter for the trial. Furthermore, the directionality of the effect of an experimental intervention on efficacy and safety measures is often not consistent. Whereas increasing the number of parameters in the composite end point may augment event frequency and thereby reduce the necessary sample size and cost of the trial, the potential impact of the trial may become progressively compromised with the inclusion of an untoward number of soft end points. A new, proposed composite event rate not previously validated by a large-scale trial should be carefully reviewed with governmental regulatory authorities as well as the medical community before proceeding.

Other end points that need to be assessed in clinical trials include the safety profile, the effects on cost, and quality of life. Collection of data on safety is usually straightforward, but an adjudication process may be necessary for certain important events. For example, in GUSTO-I,¹ all neurological abnormalities were reviewed by a Stroke Committee, with the pertinent data from brain imaging and the clinical records at their disposal. Such a review process allowed categorization of the strokes with respect to hemorrhagic, nonhemorrhagic, and other types. Importantly, this mechanism also provided a scoring of neurological disability and set the potential for the composite of death or nonfatal disabling stroke in GUSTO-1.⁴⁹ This end point is a useful measure of the "net clinical benefit," denoting the balance in survival benefit versus hemorrhagic stroke risk. Avoidance of double-counting (counting a patient with a fatal stroke as having two end points, death and stroke) is especially important given the

fatality rate of >65% for hemorrhagic stroke.⁴⁹ In contemporary medicine, one cannot overemphasize the issue of cost among many competing beneficial therapies; decisions about which therapy to use will have to be based in part on the degree of expected benefit per unit cost. Collecting cost and quality-of-life data prospectively is critical to future large-scale trials. Although not necessary or suitable for all trial patients, it is quite practical for a substudy of randomly selected patients.²⁸ These cost-benefit studies should have the same rigor of prospective design and hypothesis testing as the primary clinical outcome study.^{40,50}

Surrogate End Points

Recent cardiovascular trials have provided vivid examples to demonstrate that surrogate end points can be misleading in guiding therapy. As summarized in Table 2, several surrogate end points have later been found to be frankly dissociated from the principal end point of mortality. For example, in the Cardiac Arrhythmia Suppression Trial (CAST),¹⁶ the drugs that significantly suppressed the surrogate end point of premature ventricular contractions led to an increased mortality. Similarly, new vasodilators that improved acute hemodynamics in congestive heart failure were later found to be associated with a higher death rate.^{7,8} In the field of percutaneous coronary revascularization, directional atherectomy led to improved coronary artery luminal dimensions compared with balloon angioplasty but a higher death rate or death and myocardial infarction rate.^{28,51} In the regression of coronary atherosclerosis trials with lipid-lowering therapies, an important 30% reduction of death or infarction was demonstrated, yet only a minimal change in arterial caliber occurred.⁵² Thus, a variety of surrogates, including cardiac rhythm, hemodynamics, and coronary arterial dimensions, can be misleading, even though each surrogate appears to be a logical marker of clinical outcome. On the other hand, selected surrogates have been prospectively validated to track with clinical outcome. As shown in the GUSTO-1 trial, early infarct vessel patency (at 90 minutes after therapy was initiated) was closely linked with 30-day mortality.⁵³ Although this does not obviate the need for large-scale trials of myocardial reperfusion, such a validated surrogate can provide direction for the development of future interventions.

Certain surrogate end points may have a complex relationship with clinical outcome. For left ventricular ejection fraction in patients with heart failure, a therapy that improves ejection fraction may worsen mortality, even though there is, in general, a clear-cut inverse relationship between left ventricular function and death. An important caveat for surrogate markers is that a treatment resulting in worse clinical outcomes is prone to lead to more patients

with missing end points and the artificial appearance of improved surrogate markers, since survivors in the group treated with the inferior treatment were less well at the outset. In light of all previous cardiovascular trials, however, surrogate end points cannot be considered authentic measures of true clinical efficacy and safety.

Subgroups

One of the most controversial aspects of clinical trials is dealing with subgroups. Key subgroups should be pre-specified as the important hypotheses for a trial are formulated. This approach assumes that there is a biological explanation and hence a rational scientific approach for testing a preformulated hypothesis. Because such subgroup analyses are usually underpowered, the number of subgroups evaluated should be limited.⁵⁴ These analyses are fraught with the hazard of obtaining spurious results; witness the classic Gemini and Libra analysis of the ISIS-2 data, in which, as a function of astrological birth sign, there was benefit or no survival benefit of aspirin for acute myocardial infarction.³ One should not look for statistical significance in a subgroup but rather for direction and consistency of the effect. Multiple overviews have now demonstrated that qualitative differences (treatments effective in one subgroup but detrimental in another) in treatment effects are rare but that quantitative differences are common. In general, given the relatively constant effects of treatments across subgroups, patients at higher risk in the absence of the effective therapy derive more benefit. Within this context, the issues of multiple comparisons that have been addressed with subgroup analyses are especially relevant and deserve careful consideration in interpreting subgroup analyses.³⁹

An alternative method of dealing with subgroups is to develop a basic statistical model from the randomized trial data, including treatment assignment and all relevant baseline characteristics. After adjustment for differences in baseline characteristics within subgroups, a test can be performed to determine whether a statistical interaction exists between the treatment assignment and the baseline characteristic of interest. This test for interactions is a conservative test and, if positive, should provide a basis for serious discussion of whether a true qualitative interaction is present.

Event Rates and Sample Size

The calculation and justification of sample size is at the crux of the design of a trial. Ideally, clinical trials should have adequate power, $\approx 90\%$, to detect a clinically relevant difference between the experimental and control therapies. Unfortunately, the power of clinical trials is frequently influenced by budgetary concerns as well as pure biostatistical principles. Yet an underpowered trial is, by definition, unlikely to demonstrate a difference between the interventions assessed and may ultimately be considered of little or no clinical value. From an ethical standpoint, an underpowered trial may put patients needlessly at risk of a new therapy without being able to come to a clear conclusion.

The actual control group event rate is a key parameter necessary for an accurate calculation of sample size, and in some instances a meaningful forecast of the true event rate is difficult to glean from the literature, often because of subtle differences in the baseline characteristics of patients entered into a trial compared with historical experience. The number of events rather than the number of

patients determines the power of a trial, leading to the recommendation that the number of events should be used to drive sample size rather than the conventional approach of assuming a proportionate reduction and recruiting to a fixed sample size. For example, in a trial that is intended to show a reduction of mortality, the sample size of the trial would be reached when the prespecified number of deaths had occurred. Although this approach has not often been used in the design of trials, it has particular utility when the event rate is not well characterized from previous studies.

Statistical Analysis

A vital component of the study design is a detailed and comprehensive plan for the analysis of study data. Of major importance is an adequately detailed specification of the methods that will be used for statistically comparing treatment arms with respect to the primary study end point. Also important, however, are the methods to be used for analyzing the major secondary outcomes and the salient safety and laboratory parameters. Treatment comparisons should be performed according to the principle of "intention-to-treat," that is, subjects are analyzed (and end points attributed) in the treatment arm to which they are randomized regardless of subsequent crossover and regardless of whether the randomly assigned treatment is actually administered. For the most part, analyses on an actual treatment basis should be considered supplemental and interpreted with appropriate cautions. The analysis plan for large-scale trials should also include an acceptable approach for interim analysis and monitoring of the data, including the guidelines or boundaries that will be used for interpreting the significance of treatment differences as the study is progressing. A summary of the key features of the data analysis plan should be included as an integral part of the study protocol: major technical details can be included as an appendix or supplement. The analysis plan should be approved by the Data and Safety Monitoring Board (DSMB) and also by appropriate regulatory authorities in cases in which data will be submitted for regulatory approval and product registration.

Recently, the Bayesian approach to the analysis of clinical trial data has become popular among some clinical trialists.⁵⁵ This approach is an outgrowth of Reverend Bayes' theorem that to pick a winner in a horse race, we intuitively use all of the horses' previous track records to integrate the likelihood of winning.⁵⁶ Applying this theorem to clinical trials simplistically means factoring in all previous comparisons of the intervention being tested to the result of the proposed project. The debate with the biostatistical traditional frequentist approach to trial design and the proponents of Bayesian analysis is currently unsettled, but it is likely that Bayesian approaches will be increasingly applied to the analysis of clinical trial data sample size in the years ahead.

Role of the Steering Committee

Concerns about the design or conduct of a trial can be overcome by the selection of an appropriate Steering Committee, which serves as the "building committee" or management group throughout the design, execution, and dissemination of a trial. The committee should include a balance of scientific knowledge about the therapy being tested, clinical expertise in the management of patients with the disease in question, experience with clinical trials

methodology, and geographic and political diversity. Since many of the issues that will arise in a clinical trial cannot be predicted, the Steering Committee must be viewed as an unbiased deliberative and policy-making body. In the design phase of the trial, the Steering Committee is responsible for the writing of a protocol that integrates all of the items discussed above. The Committee is the final clearinghouse for the protocol and the case report form, for the main and ancillary hypotheses, for the end points, dosage selection, entry criteria, sample size justification, and the analysis plan. Members of the Steering Committee should be particularly active in the construction phase of the project, because it is the experience and insight of this group that serves as the intellectual foundation for the trial. With multicenter and multinational trials, it is important that the Steering Committee represent the investigator constituents of a given country or region. For example, if a trial involves a complex task that cannot be accomplished in a particular country, the protocol may need to be adapted. The appointment of a national coordinator for each country, who is automatically a member of the Steering Committee, has proved to be a very important method of improving communications between the Steering Committee and the local investigators in a particular country. Examples from our group are summarized in Table 3.

Conduct

The conduct of the trial integrates enrollment and the operating functions of the key committees including the Steering Committee, the Coordinating Center, the DSMB, the Clinical Event Committee, governmental regulatory agencies such as the Food and Drug Administration, and the sponsors (Fig 2).

Because the Steering Committee represents the collective wisdom of the many constituents of a trial, we believe that it should have final authority in making decisions about the conduct of the trial. For example, if the DSMB believes that the trial should be prematurely terminated or that a major change in design is required, the Steering Committee needs to carefully consider the recommendation; however, a final decision as to whether action, and specifically what action, should be taken depends on a variety of factors requiring balanced consideration. In addition to the decision-making process, the Steering Committee is fully responsible for the smooth conduct of the trial with respect to enrollment that conforms with the planned time line, and this can be facilitated by close communication with all the trial participants and committees.

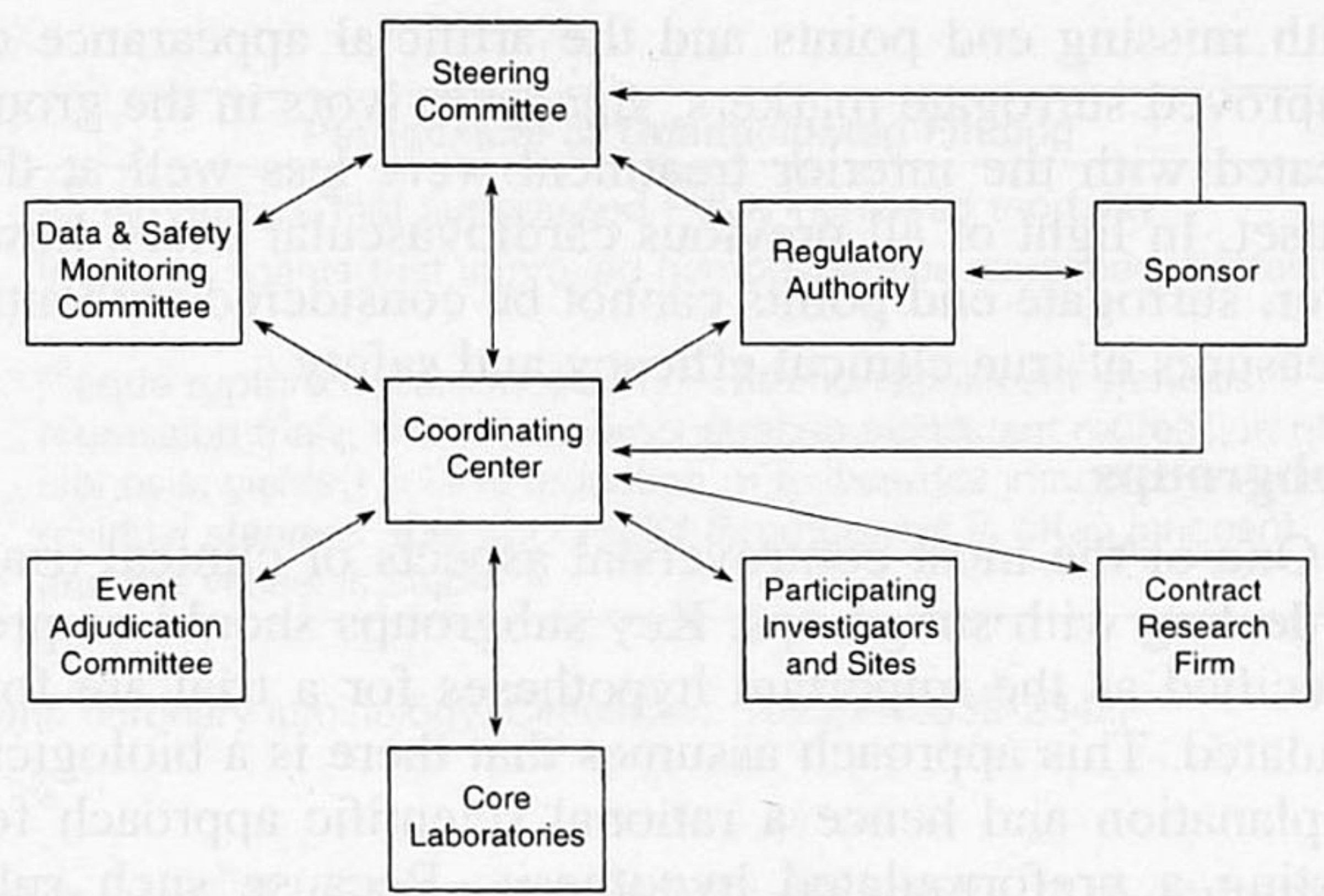


FIG 2. Interrelationships of the major groups and components of a large-scale clinical trial.

The DSMB is charged with ensuring the safety of the trial and overseeing the interim analyses.⁵⁷ This committee consists of at least 3 senior clinicians experienced in the conduct of clinical trials and clinical procedures, at least 1 or 2 biostatisticians, and 1 bioethicist. It is crucial that confidentiality of the data be maintained by the Committee members, since this group will be the only individuals who are privy to the results before they are disseminated. Even though the data that the Committee reviews are sometimes blinded (ie, presented by treatment, with treatment identity blinded), it is imperative that their deliberations and actual data be kept strictly confidential. Predefined stopping rules of the trial are to be established by the Steering Committee, included in the protocol, and viewed as acceptable to the DSMB before initiation of the trial.⁵⁸ If any concerns arise regarding issues of safety or lack of proper execution of the trial in any manner, the concerns should be expressed to the Steering Committee.

The Steering Committee's relationship with industry sponsors is critical to its optimal function. No one affiliated with the sponsor should be a member of the Steering Committee, because this committee should be free of conflict of interest. It is vital that everything be done to maximize the autonomy of the Steering Committee and thus minimize the potential bias that can arise in the decision-making process of the multifaceted operations of the trial. As we expressed in a previous publication, it is essential that no member of the Steering Committee have any financial interest in the industry sponsor, including not only equity but also payment of honoraria, consulting fees, or even travel reimbursement.⁵⁹ These provisions also apply to the

TABLE 3. Trials of the VIGOUR Group in Acute Coronary Syndromes

Trial	Design	Treatments	Size	Feature*
GUSTO I	Open label, randomized	Streptokinase, alteplase, heparin (intravenous, subcutaneous)	41 021	Angiographic; substudy to link to mortality outcomes
GUSTO IIa	Double blind	Heparin, hirudin	2651	
GUSTO IIb	Double blind	Heparin, hirudin	12 142	Angioplasty substudy
PARAGON	Double blind, placebo controlled	Lamifiban±heparin	2282	"Pick the winner" approach
PURSUIT	Double blind, placebo controlled	Integrilin	10 750	Timing of intervention substudy
GUSTO III	Open label, randomized	Retepase, alteplase	15 000	Genetics of plaque rupture and coronary atherosclerosis

GUSTO I indicates Global Utilization of Streptokinase and Tissue Plasminogen Activator for Occluded Coronary Arteries; GUSTO II and III, Global Use of Strategies to Open Occluded Coronary Arteries; PARAGON, Platelet IIb/IIIa Antagonist for the Reduction of Acute Coronary Syndrome Events in a Global Organization Network; and PURSUIT, Platelet GP IIb/IIIa Underpinning the Receptor of Suppression of Unstable Ischemic Trial.

*All of the trials have included prospective cost-effectiveness studies, hemostatic studies, and the primary end point of death (GUSTO I and III) or death and myocardial infarction (other trials).

families of Steering Committee members. Reimbursement for activity in the project, such as travel to an investigator meeting, should be defrayed by the project budget, without the potential for any financial transaction between a company and an investigator. Although this strategy is more rigorous than many contemporary trials demand,⁵⁹ it helps to ensure maximal distance between industry and investigators during the trial and in the period when major results of the trial are disseminated.

Freedom from conflict on the part of the Steering Committee should not inhibit meaningful input to the trial by the industry in any respect. Representatives from the industry frequently know more about the new drug or device being tested than any member of the Steering Committee. The company's perspectives about the trial design and conduct may be especially valuable, and eventually industry will need to gain the approval of regulatory authorities to make the product available. Therefore, for some Steering Committee meetings, it may be worthwhile for a sponsor representative to be present. However, such representatives do not have voting rights, and importantly, when key decisions about trial conduct and primary interpretation of the trial results are made, industry representatives should be absent. In such situations, the presence of the sponsor can have an inhibitory or restraining effect on free discussion.

It is understandable that industry has difficulty accepting a more limited role in the clinical trial design and execution, particularly when a substantial amount of capital is being invested in a new drug and the large-scale project is the definitive test for commercialization, therefore representing much of the cumulative cost of the research program. Whereas industry clearly has a need to be assured that the project is being properly designed and conducted, autonomy of the investigators and integrity of the trial will greatly augment the authenticity and value of the trial's findings. Thus, although many companies currently reject the notion that large-scale trials should be performed independently from industry, we believe that such a template is highly desirable for the future. Academia, clinical practitioners, industry, and patients have a common desire to bring effective medical therapies into clinical practice as efficiently as possible. We believe that rigorous efforts to ensure the unbiased conduct and interpretation of critical efficacy trials will ultimately achieve the mutual goals most successfully.

A similar theme can be developed within the trial at the level of participating sites and investigators. Financial disbursements for the research effort can be made through the Coordinating Center, obviating the need for direct financial linkage between the sponsor and the investigators. This also reinforces the concept that the management operates through a peer review system rather than being orchestrated by industry. Monitoring of the data obtained in the trial is an integral part of quality assurance. An $\approx 10\%$ audit rate, with cases selected on a random basis, will ensure representative sampling of primary data. Each site should undergo on-site monitoring, with comparison of the case report form and source medical documents. All of the deaths and major end points of a particular trial should be verified by the audit process, such that if the event rate is $>6\%$ or 7% , the actual requirement for on-site audits will turn out to be $\approx 15\%$ in order for all sites to be monitored and all major end points to be confirmed by source document review. Such an undertaking is an expensive com-

ponent of the large-scale trial, but if it is not performed, it leaves open the vagaries of the findings. Only in a random auditing and source medical record documentation can the findings of a trial be considered authentic.

The governmental control agency, such as the Food and Drug Administration in the United States, should be considered an active, pivotal collaborator in the project. Input from the primary and secondary regulatory agency reviewers is an excellent source of peer review. Discussions about the appropriateness and extent of auditing and adverse reporting are essential before the project begins and in the event of safety concerns or unanticipated results. The governmental agency clearly has the need to determine whether the data validate a claim for safety and efficacy of a novel intervention and to provide assurance of patient safety. Furthermore, a thorough understanding by the governmental agency of the specific disease and the therapy being tested is vital, and this can be promoted by frequent cross talk and dialogue throughout the trial and at the end of the analysis phase.

Dissemination of the Results

The primary mechanism for reporting data from a large-scale trial is via a peer-reviewed article. This process needs to be pursued on a timely basis, because the results of a trial may have a substantial impact on clinical practice. Two recent trials of HMG-CoA reductase inhibitors for cholesterol lowering have been disseminated in an exemplary fashion—the Scandinavian Simvastatin Survival Study (4S)²⁵ and the West of Scotland trials.²⁶ In both cases, the first presentations were at a major scientific session (the 67th and 68th Scientific Sessions of the American Heart Association in 1994 and 1995), with publication during the same week in the *Lancet* and the *New England Journal of Medicine*, respectively. This necessitates highly orchestrated responsibilities of locking the cleaned database, drafting the manuscript, finalizing the manuscript with approval of all members of the Steering Committee, submission and peer review of the paper, and coordination of the dates of presentation with the editors of the medical journal in which the article is to be published. For all this to converge in synchrony, considerable forethought is necessary at the outset of the project, with reassessment of time lines during the course of the trial. These two examples are exceptional; typical delays from presentation of the results to actual publication are ≥ 12 months.⁶

Ideally, the data would be in final form when there is first dissemination in a public forum. However, given the large data sets that frequently require months to query missing data, make corrections via the monitoring of the trial, and perform final analyses, it is unlikely that all aspects of a trial will be complete at the time a presentation is made.⁶⁰

At the major national and international meetings, first-time presentation of clinical trial results have become increasingly popular and are often regarded as the high point of the scientific program. However, there is little or no opportunity for discussion of the results with the investigators at these meetings, and the limited time available for presentation inherently compromises full disclosure of the results, often with an emphasis on the positive components. Furthermore, these meetings are covered by a large number of reporters, and the data are frequently presented in the lay press and media. Such reports are typically encapsulated, based on a trial that has not undergone peer

review, and can be misleading. One frequently used approach to promote improved quality and completeness of the public dissemination has been for the investigators or the national program to organize a press conference. During such a conference, reporters and journalists are free to ask questions to better understand the methods or results of the trial or even the underlying disease state or intervention that is being studied. In theory, such a news conference can promote a more accurate message for the public. However, the process is quite unpredictable and may engender more confusion or misinformation. Since controversy facilitates bringing a medical news story to a high level of public attention, there is sometimes undue emphasis on this aspect of the story. Each finding typically is presented as more definitive in a video or newspaper medium, because the sound or video "bites" are selected to be brief and can easily be taken out of context. Often, little time is allotted from the press conference to the "story" being told to the public, which precludes checks for accuracy. Accordingly, we believe that a new challenge for clinical trialists is to consciously prepare for an organized simultaneous dissemination to both the scientific, medical community and the public. This involves the drafting of a press release that should be approved by all members of the Steering Committee before a meeting with key representatives of the media to ensure, as far as possible, complete understanding of the major findings of the trial. The message therefore has to be simplified and synthesized so that it will be easily understood by the lay public. Uncertainties about the results and need for confirmation and caution should receive appropriate emphasis, given the tendency of the public to react very strongly to new findings.

Over the years, the public has demonstrated their "need to know" and exercised their "right to know" the results of clinical trials. As clinical investigators, it is imperative that we be mindful of this tendency and entitlement. There has been an unfortunate erosion of the public trust in clinical trials, usually as a result of lack of timely disclosure of important data. For example, in the breast cancer research trial by Fisher and colleagues,⁶¹ there was a delay before the problem of scientific misconduct within the trial was unveiled. This temporarily resulted in undermining of the validity of the results and ultimately Congressional hearings, with subsequent publication of the data after reanalysis that reaffirmed the validity of the original findings.⁶² In the GUSTO IIa trial, we found that intravenous heparin or hirudin was associated with a heightened rate of intracerebral hemorrhage, leading to cessation of the trial and reinitiation at different dosages of the agents.³⁸ The trial was stopped in April 1994, and analysis was promptly begun to determine which factors were associated with the hemorrhagic strokes. Within 2 months, it was determined that a number of baseline clinical factors contributed to the bleeding complications, including age, sex, and systolic blood pressure at the time of entry. Since hirudin was investigational and not available for use and the dosage of heparin was not conventional, nor was the effect on death or myocardial infarction statistically significant for heparin, a manuscript was submitted to *Circulation* and published in October 1994 via the Rapid Communication mechanism (2 months from submission to actual publication). Nevertheless, at the time of the publication, a news reporter accused the trialists of having intentionally withheld important data from the public.⁶³ The reporter sug-

gested that a press conference should have been conducted as soon as the analysis was complete and that peer review by a medical journal was unnecessary, with attendant unacceptable and unethical delays.^{63,64} This experience has increased our sensitivity to what may be considered expectations of some of the lay media.

Besides reporting the results via the peer-reviewed article, at scientific sessions at national meetings, and to the public, a fourth dimension of the release is to the financial community. This can be extremely delicate, because the results may have a pivotal influence on the value of a company and the stock price. The Securities and Exchange Commission of the New York Stock Exchange has specific guidelines for companies involved in medical devices, pharmaceuticals, and biotechnology regarding the timeliness and completeness of clinical trial data. Once the results are known by representatives of the company, only a limited amount of time (24 to 48 hours) is permitted before the data are provided to the financial community and the public. Therefore, it is essential to devise a strategy at the outset of a trial so that representatives of the company are informed of the results at a time that will not result in the need for disclosure because of such financial obligations. Typically, this results in informing the sponsor of a trial only 1 or 2 days before the public dissemination is planned. Otherwise, the first report of the data from an important trial may be via the financial section of a newspaper rather than directed to the medical community.

By the same token, it is incumbent on the Steering Committee to inform the investigators, who have put forth considerable work throughout the project, of the principal findings of the study before any public meeting. The first access to the data and ample time for discussion with members of the Steering Committee are essential steps in what should be considered an entitlement of the investigators by virtue of their participating in the project. Although there may be a current ebb in the public trust in clinical investigation, clinical trialists have a cardinal goal to fully restore such confidence in the future. The principal reason that large-scale trials are undertaken is to improve health. It can only be considered a paradox if such efforts are not perceived as genuine and important.

Cardiovascular clinical trials have made enormous contributions to the advancement of state-of-the-art therapy for patients. As society attempts to come to grips with rapidly advancing biotechnology and escalating costs, a rational system is essential to provide patients, payers, and providers with evidence on which to base decisions about which therapies will be recommended and which should be eschewed. The blueprints for such a system will continue to evolve, but the fundamental structure outlined here should help to provide an effective foundation balancing the interests and needs of the various constituents who consume and deliver medical care. Recent collective experience has clearly established that large-scale, rigorously conducted trials with mechanistic ancillary projects will be a useful template for advances in cardiovascular medicine, and most likely other medical disciplines, in the next millennium.

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