

Circulation

JOURNAL OF THE AMERICAN HEART ASSOCIATION



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Circulation 2004;110:3610-3614

DOI: 10.1161/01.CIR.0000148680.83392.50

Circulation is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 72514

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Lessons Learned From a Clinical Trial

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Remarkable advances in cardiovascular care have been substantially mediated by large-scale, randomized clinical trials. These trials not only have identified treatments resulting in major improvements in patient outcomes but also have enhanced our understanding of the natural history of contemporary disease and the impact of risk factors and complications.

The process by which phase III clinical trials in cardiovascular medicine are created, implemented, completed, analyzed, presented, and published has evolved dramatically over the past decade. Historically, government and academic alliances took center stage in this process because of their intellectual equity, opinion leadership, access to patients, and allocation of public interest-related research tax dollars. This axis has now shifted. Community practitioners and groups of physicians, often organized regionally, now provide the majority of subjects for clinical trials. Furthermore, substantial scientific expertise, at both the basic and clinical levels, resides within multinational pharmaceutical firms. Additionally, contract research organizations have seized the business opportunity afforded by the need for timely and efficient operational aspects of clinical trials. Although community-based trials, efficiency, and expertise are prerequisites for a major clinical trial, the extraordinary costs of completing them squarely places the sponsor in a dominant position.¹

Our participation in the failed large-scale attempt to develop a novel oral glycoprotein IIb/IIIa inhibitor, sibraxifiban, for secondary prevention of coronary heart disease has stimulated us to reflect on issues that arose in the design and conduct of this trial.^{2,3} Using the Sibraxifiban Versus Aspirin to Yield Maximum Protection From ischemic Heart Events Post-Acute Coronary Syndromes (SYMPHONY) and 2nd SYMPHONY trials as examples, we review issues here that should be of interest to investigators, clinical practitioners, participating institutions, sponsors, data and safety monitoring boards (DSMBs), and the patients whom we serve.⁴ Our purpose is to encourage discussion so that standards can be enhanced for this form of collaborative science.

The SYMPHONY Experience

The oral platelet glycoprotein IIb/IIIa inhibitor sibraxifiban met every criteria then known to qualify as a prototypical inhibitor of platelet aggregation.⁵ It seemed reasonable to assume that an agent with a more potent and predictable ability to inhibit platelet aggregation would have a more beneficial effect than aspirin on reducing cardiovascular events.^{6,7} This assumption was further buttressed by our generally favorable experience in the development of intravenous glycoprotein IIb/IIIa inhibitors for acute coronary syndromes.^{8,9} Extending this benefit with orally administered, longer-acting preparations was an obvious broadened paradigm.

Phase I and II studies demonstrated that doses accounting for creatinine clearance could reliably produce serum sibraxifiban levels within the range dictated by intestinal absorption with predictable inhibition of platelet aggregation and a dose-response relationship with bleeding sustainable in the acceptable range.^{5,10} Although the peak-to-trough ratio of ≈ 2 necessitated twice-daily dosing, this seemed acceptable, especially given the belief that a reversible platelet inhibitor would be beneficial. Hence, we undertook a large-scale phase III international trial of 9233 patients from 670 sites in 33 countries to define the effects of sibraxifiban on clinical outcomes.¹¹

After extensive discussions, the sponsor and the international Steering Committee initiated the protocol designed to evaluate the efficacy and safety of sibraxifiban. To explore potential interactions between aspirin and sibraxifiban, the Steering Committee preferred a 3-arm design of combination aspirin and sibraxifiban, aspirin alone, and sibraxifiban alone. However, the sponsor was concerned that an aspirin-sibraxifiban combination might demonstrate safety concerns that would be unfavorably linked to its novel compound and was hopeful that 1 of the sibraxifiban doses would demonstrate clear superiority. Thus, the sponsor mandated that trial funding would proceed only if there were 2 experimental arms, ie, low- and high-dose sibraxifiban (neither containing aspirin) and aspirin alone. Because the initial trial, 1st SYMPHONY, did not contain a combined aspirin-sibraxifiban

Received May 18, 2004; revision received June 21, 2004; accepted August 4, 2004.

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Consulting Editor for this article was Kim M. Fox, MD.

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(*Circulation*. 2004;110:3610-3614.)

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Circulation is available at <http://www.circulationaha.org>

DOI: 10.1161/01.CIR.0000148680.83392.50

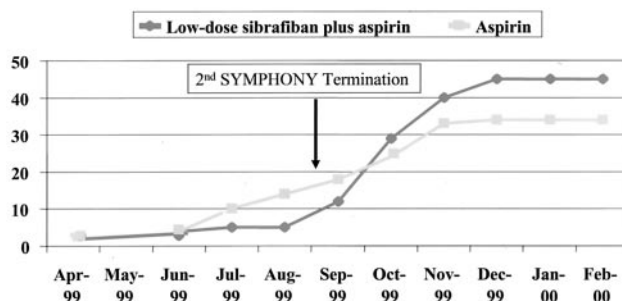
arm and because only a 3-month follow-up was planned, the 2nd SYMPHONY trial was designed and implemented before the outcome of 1st SYMPHONY was known to evaluate the impact of longer treatment (12 to 18 months) and to assess whether sibrافiban given in association with aspirin would be more effective than either sibrافiban or aspirin alone.^{2,3} Despite these differences of opinion, all partners agreed to proceed on a project that included massive sponsor investment, a major commitment of investigator time and energy, and the participation of thousands of acute coronary syndrome patients. For both SYMPHONY trials, the main databases were housed at the sponsor, and the databases, query rules, and operational reports run from the database were programmed by the sponsor under the direction of data management and project leadership at the main Coordinating Center at the Duke Clinical Research Institute. Data were entered and quality controlled via remote terminals at the Data Coordinating Centers. Statistical checks over the course of the trial were performed jointly by blinded statisticians from the main Data Coordinating Center at the Duke Clinical Research Institute and the sponsor. Access to the database was restricted by function of the user and was password protected. Access to the database other than for specified reports and data management activities was restricted and carefully documented.

When the Steering Committee met after 28 months to review the results of the 1st SYMPHONY trial, no difference was evident between groups in the rates of the primary composite end point of death, nonfatal (re)infarction, or severe recurrent ischemia at 90 days.² The myocardial (re)infarction rate was slightly higher in the high-dose sibrافiban group and severe recurrent ischemia was modestly lower in both sibrافiban arms compared with aspirin alone. Because a dose-response relationship with bleeding was evident with sibrافiban, biological activity was presumed.

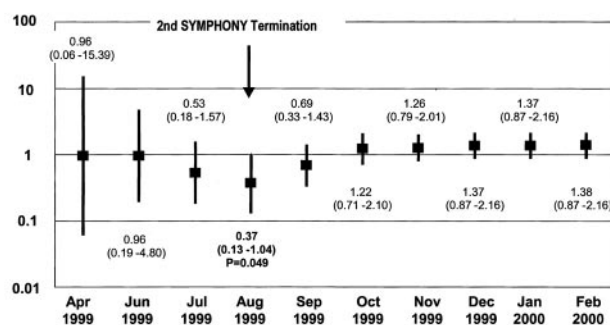
At about this time, other oral glycoprotein IIb/IIIa data emerged, including lack of efficacy with xemilofiban and concern about an increased hazard with orbofiban, a third agent in this same class.^{12,13} After reflecting on these developments, the future commercial prospects for development of sibrافiban, and the costs associated with continuing the trial through the planned 12- to 18-month follow-up, the sponsor summarily terminated the 2nd SYMPHONY trial, thereby resulting in shorter and more variable follow-up, a reduced sample size (6671 versus the originally intended 8400 patients), and a substantial reduction in the final statistical power.

At this juncture, options included (1) terminating the high-dose sibrافiban arm and continuing enrollment in the low-dose sibrافiban plus aspirin and aspirin alone arms and (2) ceasing all enrollment, terminating the high-dose treatment, but continuing treatment in the aspirin and aspirin plus low-dose sibrافiban arms with follow-up in all patients. Despite vigorous protestation from the Steering Committee about overlooking a potential benefit in the combined aspirin-sibrافiban arm and diminishing the likelihood of understanding mechanisms associated with the results, the sponsor decided not to pursue further investigation. Interestingly, an unplanned preliminary analysis based on 2nd SYMPHONY data then available conducted by the Steering Committee and

A Absolute number of deaths by treatment



B



Time course of mortality in aspirin and low-dose sibrافiban plus aspirin arms of 2nd SYMPHONY. A, Change in absolute number of deaths. B, OR for mortality over time. Note that when 2nd SYMPHONY was terminated in August 1999, there was favorable trend toward mortality reduction for low-dose sibrافiban plus aspirin, whereas when complete follow-up and final data were cleaned and locked, this trend reversed, indicating excess hazard of low-dose sibrافiban plus aspirin.

before final query resolution, end-point adjudication, and data lock were complete revealed a marginally significant ($P=0.049$) result favoring reduced mortality for the combination of aspirin plus low-dose sibrافiban arm. As in the 1st SYMPHONY study, we found marginally significant reductions in severe recurrent ischemia in 2nd SYMPHONY.^{1,2} However, when all the data were tallied, this apparent benefit of sibrافiban was not evident, and the final results confirmed the excess hazard of sibrافiban on both death and death or myocardial (re)infarction. The Figure shows the mortality pattern as increasing amounts of data were available over the course of the trial. These results underscore the potential hazards of reliance on putative surrogate end points and early looks at efficacy before all data are compiled and cleaned and the end points adjudicated. In aggregate, all programs with orally administered glycoprotein IIb/IIIa inhibitors showed the same excess hazard.^{14,15} Notwithstanding the many positive lessons learned from the SYMPHONY trials, we remain concerned about how the 2nd SYMPHONY trial was terminated and believe it may not have been in the best interests of patients, investigators, and participating institutions. Moreover, the unexpectedly abrupt cessation of a major trial highlighted an important lack of clarity regarding the relative roles, responsibilities, and authority resting between the

academic partners and sponsor. Hence, we believe that future trials should anticipate this potential and have a management plan for such contingencies.

Protecting the Welfare of Human Subjects

The commonly used term “drug development” may serve to dissociate some trial partners from the realization that the process relies on human experiments for which patients volunteer and their medical care providers devote substantial time and energy. We believe that these elements should be developed in an ethical framework and recognized by all who design, conduct, fund, and regulate human experiments.¹⁶

Patients should be ensured that their participation will contribute to a clear answer to a meaningful clinical question. They have the right to be appropriately informed and to be ensured that a balanced system of monitoring their involvement in a trial exists. If they are participating in a trial that is terminated prematurely for commercial reasons, investigators and institutions may fall short of fulfilling their ethical obligations. On the other hand, trials that are unduly prolonged because of the scientific interest of the investigators may present an ethical dilemma. When trials are terminated prematurely because of concern over treatment futility and lack of commercial viability of a therapy, an inconclusive answer can potentially leave the door open for additional unnecessary investigation of the same or a related agent from a different sponsor. This has the potential to put even more patients at untoward and needless risk to address a question that might have been answered definitively had the original trial been carried to its natural conclusion. So, in this context, institutional review boards need to be satisfied that the proposed research is ethical, the risks are acceptable, adequate explanation is provided to human subjects, and appropriate informed consent is acquired.

A well-constructed, independent, and informed DSMB also plays a key role in ensuring the protection of human subjects and providing advice on the ongoing study conduct.¹⁷ The DSMB’s opinion should be solicited by both the steering committee and sponsor at appropriate stages of the trial, and its involvement is pivotal in the final decision making regarding the wisdom of continuation.¹⁸ In the case of early termination of 2nd SYMPHONY, the sponsor’s decision to cease enrollment and follow-up was made without consulting the DSMB, leading to significant concerns by the Steering Committee about the sponsor’s motives and wisdom of the unilateral decision. Subsequently, meaningful DSMB involvement was undertaken and was instrumental in creating an orderly process of trial closure through which care was taken to ensure that patients were on standard therapy and that data were collected during therapy withdrawal. Ultimately, the ethical obligations of both the investigators and sponsors to patients who had consented to this human experiment were fulfilled. This included sponsor support for completing data collection and analysis for all enrolled patients and presentation and publication of the trial results.

Communication Across Trials

The experience with the oral glycoprotein IIb/IIIa inhibitors also highlights the need for communication between DSMBs

of parallel trials of similar agents from different sponsors and investigative groups, realizing that the subtle differences in trial design and compounds tested necessitate caution in interpreting comparisons across trials. Interestingly, although both the 2nd SYMPHONY and Orbofiban in Patients With Unstable Coronary Syndromes (OPUS) trials of oral glycoprotein IIb/IIIa antagonists had been prematurely terminated, investigation of yet another oral glycoprotein IIb/IIIa agent [Ilotrafiban in Blockade of the Glycoprotein IIb/IIIa Receptor to Avoid Vascular Occlusion (BRAVO)] continued despite collective evidence of harm amassed from the 3 prior agents studied.¹⁹ However, in contrast to the SYMPHONY trials, the BRAVO effort encouraged frequent discussions between the DSMB, the sponsor, and the investigators. Its further study was subsequently terminated early on recommendation of its DSMB because of excess hazard. The final trial results, reported nearly 2 years later, confirmed patterns of excess hazard similar to those in previous trials.¹⁹

Changes in biological investigation have moved us into an “industrial age” in which many corporate entities can scale up quickly to approach a biological system once it is described in the scientific literature. Although confidentiality during discovery is a critical element of therapeutic development, the ethics of “cross talk” among companies and study organizations needs further discussion. In the case of the glycoprotein IIb/IIIa receptor, more than a dozen companies launched major discovery programs during the same time frame. From a purely commercial perspective, sharing information during early development is obviously very risky and makes little sense. In contrast, there is ample reason to be concerned that failure to share some early and critical information could lead to unnecessary, or even hazardous, human experimentation. We see few options for solving this problem other than facilitating rapid public dissemination of findings from clinical trials when there is a possibility that the knowledge gained could have major implications for other ongoing development efforts.

Academic Interactions

The world of clinical academic medicine thrives on a complex mixture of an altruistic desire to improve medicine, a fascination with science, financial gain, and personal or professional enhancement. In cardiovascular medicine, this mix has led to the formation of groups of academic thought leaders who have a major influence on the direction of research and the translation of that research into practice. These groups are typically organized in an informal manner that is influenced by geography, links to common training, friendships, technical skills, and allegiances to institutions, themes, and ideas.²⁰ The rules of engagement of the academic side of the collaboration are much less codified than the role definition of industry sponsors.

As beneficiaries of these interactions, we endorse and encourage the use of academic-industrial partnerships in the conduct of clinical trials. Indeed, these partnerships have spawned the success of multinational clinical trials designed to answer questions requiring population samples too large for success in a single country. Although we would oppose efforts to alter this balance if they inhibited this highly successful approach to international collaboration, constructive examination of the process seems desirable.

Clinical trials have now evolved into a structure that includes a principal investigator or study chair, a sponsor, steering and executive committees, a DSMB, a data-coordinating center, and various core laboratories. These entities often have overlapping responsibilities and function,^{18,21} and better definition of roles and responsibilities is desirable.

The process by which steering committees function during a trial is more an art than a defined process or science. Typically, substantial efforts are made to function through consensus rather than by vote. In many current cases, the steering committee plays an insignificant role in trial decisions, and the principal investigator is often closer to the sponsor than the steering committee, especially if appointed by the sponsor. Beyond this, tensions may arise from national and international differences in economic support, operational procedures and responsibilities, enrollment, and other expected time-sensitive deliverables.

Most trials continue to rely on the sponsor or a contract research organization to manage data collection and analysis. In the SYMPHONY trials, the databases were managed through a collaboration of academic centers and the sponsor. Although we believe that management of the databases by academic collaborators is preferable because it ensures independence of data analysis and the capability of the investigators to access the database for appropriate interpretation, this alternative may be satisfactory as long as the data are promptly transferred at the conclusion of the trial to a central academic repository to permit independent analysis.²²

Academia has thrived on a “marketplace” of innovative ideas in peer-reviewed journals in which investigator originality is of fundamental importance. On the other hand, large multicenter international clinical trials usually require consensus development among a writing group and/or steering committee and the sponsor that is not conducive to domination of the message by a single individual. Decisions about which ideas lead to manuscripts and who the authors will be remain key issues ideally defined at the outset to avoid multiple interpretations of the same data set published in separate articles. In the case of the SYMPHONY trials, publication of incorrect trial results in a systematic overview before the publication of the main trial manuscript that was neither verified from the primary trial database nor endorsed by the Steering Committee was an issue.²³ Although in this case the overall message was similar to that in a later publication, such a practice reflects inappropriate use of data generated by a community effort; could lead to erroneous conclusions about treatment effect, associations, or risk; and thereby could diminish the impact of the analysis sanctioned by the steering committee. Establishing a publications committee charged with review and approval of requests for data for publication and adhering to its policies is a solution.

The principles that outline qualification for authorship are well outlined by others, and we embrace them.²⁴ For the SYMPHONY trials, the primary manuscripts were crafted by a writing group, vetted by the steering committee, and published under the name of all participating investigators. All investigators were informed of these important tenets when the database was opened for secondary manuscripts. We highly encourage a systematic approach to manuscripts

that is governed by a publications committee with routine input from the steering committee using electronic media for rapid turnaround of information.

Interactions Between the Sponsor and the Investigators

Many industry-funded clinical research studies testing medical products pay investigators to enroll patients and to follow the protocol. There is seldom an independent steering committee in these cases, and only recently have independent DSMBs become routine. However, in the world of large cardiovascular trials, the standard of an independent steering committee has been accepted.^{18,21}

The rules under which the steering committee operates are determined by a legal contract and by the protocol. We appreciate that the contracts governing most trials are not in synchrony with the current science of multicenter studies.²⁵ They rarely require transfer of the database to the primary authors and often give each individual site the right to publish the data from its own patients. While recognizing that a major commercial interest in a medical product may make it difficult to objectively assess the value of that product, we encourage all physicians enrolling patients in clinical trials to include both a commitment to publish and a process to ensure that the trial is interpreted independently of the sponsor in their contracts.

However, this requirement for independence should imply no lack of respect for or responsibility to produce trial results that meet the level of scrutiny required by global regulatory authorities. The medical products industry is replete with outstanding investigators who have much to contribute to the design, analysis, and interpretation of clinical research, and those who contributed to the original components of the trial should be recognized for their effort with authorship.

Revisiting the Interplay of Fundamental Science and Clinical Trials

We are surely now at a turning point in the history of clinical trials. Based on good intentions, a paradigm of mechanistic proof of principle has guided clinical medicine. The belief was that understanding the mechanism by which a treatment worked practically guaranteed a rational approach to therapeutic benefit. We now know that in most cases this simplistic notion is not sufficient to protect the public from potential harm from unrecognized toxicity or from failure to recognize the benefit of a discarded drug. Moreover, unexpected results from trials can generate new hypotheses, thereby stimulating new scientific discovery about mechanisms and unintended targets (eg, ACE inhibitors and statins).

In the case of the oral glycoprotein IIb/IIIa inhibitors, the initial belief was that simply blocking the receptor would lead to benefit through a prevention of thrombosis. Only when these drugs failed did further research show that significant biological effects may result from differential occupancy of the receptor. Thus, as the drug cycles from 50% to 90% inhibition of platelet activation and back, glycoprotein IIb/IIIa receptors are left in activated and unoccupied states,²⁶ and packets of CD40 ligand are released into the circulation, causing a proinflammatory state. In contrast, ticlopidine and clopidogrel were developed as antiplatelet drugs when their

Lessons Learned

1. Establish an academic steering committee and independent DSMB with clear terms of reference and lines of communication.
2. Create ongoing inventory of investigative studies related to current project and provide opportunity for selected intertrial communication on key issues as appropriate.
3. Define potential circumstances for early trial termination and consultation process by which such judgments are to be made and communicated.
4. Ensure prompt transfer of database to academic steering committee and data analysis independent from the sponsor.
5. Establish, communicate, and adhere to clear and fair publication policies and procedures at the outset.

receptor was unknown. Although the thienopyridines were considered to be suboptimal platelet inhibitors compared with glycoprotein IIb/IIIa inhibitors on the basis of platelet aggregation measures, other (still unknown) factors have led to a broad benefit of these drugs.^{7,27,28}

Early termination of clinical trials may have other unintended consequences. Interrogation of patient pharmacokinetic, pharmacodynamic, and genetic samples in such studies is often planned but may not be executed if further compound development is precluded. Such decisions do a disservice to the overall scientific endeavor and the opportunity to understand the fundamental causes of failure that might inform therapeutic development efforts of the future. We believe that fidelity to the construct of creating generalizable scientific findings should be an essential part of the clinical research enterprise when humans have volunteered for an experiment. To the credit of the industrial sponsor of the SYMPHONY studies, the research contract ensured that the database was interrogated and that timely publications ensued.

Conclusions

Progress in the treatment and prevention of disease will continue to depend in part on the conduct of large-scale collaborative clinical trials. We believe that the lessons discussed here and summarized in the Table will assist in its optimal evolution.

Disclosure

Drs Armstrong and Newby have received research support from Hoffmann-La Roche Ltd. Dr Van de Werf has received research grants and speaker's bureau funding from Hoffmann-La Roche Ltd, Boehringer Ingelheim GmbH, Genentech Inc, Aventis Pharmaceuticals Inc, Servier, and Proctor and Gamble. Dr Califf has a research contract with Hoffmann-La Roche Ltd.

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KEY WORDS: trials, clinical ■ multicenter studies ■ biomedical research ■ ethics, research