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COOPERATIVE STUDIES

Confronting the Issues of Patient Safety and Investigator Conflict of Interest in an International Clinical Trial of Myocardial Reperfusion

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ROBERT M. CALIFF, MD, FACC, ON BEHALF OF THE GLOBAL UTILIZATION OF STREPTOKINASE AND TISSUE PLASMINOGEN ACTIVATOR FOR OCCLUDED CORONARY ARTERIES (GUSTO) STEERING COMMITTEE*

The Global Utilization of Streptokinase and Tissue Plasminogen Activator for Occluded Coronary Arteries (GUSTO) trial is a large scale international trial of new myocardial reperfusion strategies. The primary hypothesis is that early and sustained coronary artery recanalization will be associated with a significant reduction in mortality. The four regimens that are being tested are 1) streptokinase with subcutaneous heparin; 2) streptokinase with intravenous heparin; 3) accelerated recombinant tissue-type plasminogen activator (rt-PA) with intravenous heparin; and 4) combination streptokinase, rt-PA and intravenous heparin. The planned recruitment of 41,600 patients in 1,500 sites from 15 countries is expected to be completed by December 1992 and will enable detection of a 15% reduction or 1% absolute difference in mortality compared with that associated with standard therapy (streptokinase and subcutaneous heparin).

In designing the trial, two important issues were directly addressed. First, a strategy was developed to provide assurance of patient safety during large scale investigational use of an aggressive thrombolytic regimen. This includes fascimile transmission of a one-page safety summary form to the Data Coordinating Center within 24 h of death or discharge, acceptance of the concept of "net clinical benefit" and close surveillance of the trial's progress by the independent Data and Safety Monitoring Committee. Second, to avoid potential conflict of interest beyond elimination of any position of financial equity, the Steering Committee unanimously voted to prohibit any honoraria for speaking engagements, payment for consultancy or travel or reimbursement of any kind from any of the five corporate sponsors until 1 year after publication of the results. Incorporation of these approaches may facilitate the design of future large scale randomized trials in cardiovascular medicine.

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Few areas in medicine have witnessed as radical a change in the past decade as that of the management of acute myocardial infarction, in which thrombolytic therapy has emerged as a central focus of cardiovascular therapeutics. Although intravenous thrombolytic therapy was rarely used until the mid-1980s, it has become the standard of care for appropriately eligible patients in the past 3 years (1). In concert with an acceptance of this more aggressive therapeutic intervention was the willingness of clinicians to exchange an incidence of intracerebral hemorrhage of approximately 0.5% for a 30% relative reduction in mortality (2). Despite this major advance, recent large trials of thrombolytic therapy point to a persistently high 30-day mortality rate of 10% irrespective of which thrombolytic agent is administered (3,4). Moreover, significant residual left ventricular dysfunction despite thrombolytic therapy suggests that additional therapeutic strategies are needed.

However, as the opportunity for further major reduction in mortality becomes attenuated, it behooves investigators to pay particular attention to any incremental risk associated with new therapy. In the course of designing a large scale clinical trial of different thrombolytic regimens, we, the Steering Committee, became acutely aware of the need to ensure patient safety if more aggressive pharmacologic regimens, which pose a potentially higher risk for serious bleeding complications (5–8), were contemplated.

The second major issue that the committee faced was the need for industrial sponsorship in the design, execution, publication and presentation of the study's results (9–11). It is the purpose of this report to communicate the guidelines and safeguards that address the important issues of patient safety and investigator conflict of interest in a large scale international clinical trial of myocardial reperfusion.

*The members of the Committee are listed in the Appendix.

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Protocol Design

The primary objective of the Global Utilization of Streptokinase and Tissue Plasminogen Activator for Occluded Coronary Arteries (GUSTO) trial is to establish whether rapid restoration of infarct vessel patency and sustained reperfusion favorably affect survival outcome. Initially, three intravenous thrombolytic strategies were selected for comparison: 1) accelerated dosing of recombinant tissue-type plasminogen activator (rt-PA), which is associated with 75% patency of the infarct-related vessel at 60 min and 85% patency of this artery at 90 min (7,12,13); 2) combination rt-PA and streptokinase therapy, which has been demonstrated to avoid reocclusion in 95% of patients who have successful reperfusion (14–16); and 3) streptokinase therapy, which is the confirmed reference therapy from previous large scale trials (4,17,18). All three thrombolytic regimens include oral aspirin and intravenous heparin, the latter adjusted to maintain a 2- to 2.5-fold elevation of the activated partial thromboplastin time for at least 48 h.

Impact of ISIS-3. At the American College of Cardiology meetings in March 1991, preliminary results from the largest myocardial reperfusion trial performed to date, the Third International Study of Infarct Survival (ISIS-3), were reported (4). In this trial of 46,115 patients who were randomly assigned to receive one of three alternative thrombolytic drugs (streptokinase, duteplase or anistreplase), a secondary randomization was used to allocate patients to receive either subcutaneous or no heparin. There was no significant difference in 35-day mortality among the thrombolytic agents or with the use of subcutaneous heparin. However, when the preliminary data from ISIS-3 were combined with data from the Gruppo Italiano per lo Studio Della Sopravivenza nell'Infarto Miocardico (GISSI-2) (17) and the International Study Group (18), there was a reduction in mortality from 10% for no heparin (32,573 patients) to 9.5% for subcutaneous heparin (32,544 patients) ($p < 0.05$) (4). Although a higher rate of probable intracerebral hemorrhage and transfusion was noted in patients receiving subcutaneous heparin than in control patients in both trials, the overall outcomes favored the use of subcutaneous heparin. To date there have been no large scale, controlled, mortality reduction trials of intravenous heparin coupled with thrombolytic therapy.

As a result of these findings, we modified the GUSTO trial to incorporate a fourth arm of intravenous streptokinase with subcutaneous heparin. This regimen was perceived to be the best reference standard because it had been evaluated in >20,000 patients (3,4,18). Thus, this fourth arm is intended to provide an authentic and contemporary reference with which the other three experimental arms can be compared in order to appropriately test the probability of lower mortality without an undue increase in the risk of intracerebral hemorrhage.

Entry criteria and sample size. In GUSTO, as in the other large scale trials, the patient entry criteria are broad in scope, with no upper age or blood pressure limit or exclusion for many of the reasons patients are often deemed ineligible for thrombolytic therapy (1). Only active bleeding, history of stroke or central nervous system disease, noncompressible punctures, recent trauma or surgical treatment and previous streptokinase or anistreplase therapy represent absolute contraindications for enrollment. Patients with other relative contraindications to thrombolytic therapy can be entered or withheld at the discretion of the investigators. The primary end point is 30-day mortality and the sample size of 41,600 patients is adequate to detect a 15% reduction or 1% absolute difference in mortality, whichever is smaller, for any of the experimental therapies (alpha 0.05, beta 0.20, two-tailed). The trial is being conducted in 14 countries in four continents (see Appendix) with the randomization center and data coordination at Duke University and intermediate coordinating center in Leuven, Belgium. Although the trial design had input from the sponsor in the planning phase, the protocol was approved by the Steering Committee independently of the sponsor, and the fourth arm was conceived and ratified by vote of the Steering Committee.

Investigator-Patient Relations

With the intravenous thrombolytic regimens that are being assessed, it is clear that the potential for serious bleeding complications is increased compared with that of standard therapy. Although the use of combination or accelerated rt-PA therapy has not been associated with an apparent increase in intracerebral hemorrhage, the most dreaded untoward consequence of such therapy, only 500 and 1,000 patients, respectively, have been studied with each regimen. This is far short of the number of patients needed to reliably exclude a modest increase in bleeding risk. In GUSTO, the large number of patients (anticipated up to 100) who may be treated on any particular day mandates very close and contemporary surveillance of safety data and advance specification of boundaries or guidelines for stopping an arm of the trial (19).

Currently, thrombolytic therapy for acute myocardial infarction results in an approximate 1 in 200 (0.5%) event rate of intracerebral hemorrhage. In Table 1, using this rate as a standard of reference for 1,000 patients receiving a thrombolytic regimen, the 95% confidence interval data are presented for expected versus observed stroke rates. If the observed rate of hemorrhagic stroke significantly exceeds the accepted standard (eg, five hemorrhagic strokes among 1,000 patients), the Data and Safety Monitoring Committee will be responsible for adjudicating the data and making a recommendation to the Steering Committee. If a safety problem is evident, possible recommendations would include either changing the treatment regimen or discontinuing one arm of the trial. Ultimately, the Steering Committee will decide to accept or modify such a recommendation.

Most important in this process is the rapid and efficient on-site acquisition of data concerning any untoward clinical events. Within 24 h of death or discharge, a one-page safety

Table 1. Probabilities and Confidence Intervals for the Incidence of Stroke Based on an Expected Hemorrhagic Stroke Rate of 0.5% in 1,000 Patients Receiving Thrombolytic Therapy

No. of Strokes Observed	95% Confidence Intervals	Probability of Having >1 Stroke If True Rate Is 0.5%	Probability of Having <1 Stroke If True Rate Is 0.5%
1 (0.1%)	0–0.29	0.96	0.04
5 (0.5%)	0.06–0.94	0.38	0.62
10 (1.0%)	0.38–1.62	0.014	0.97
15 (1.5%)	0.7–2.3	0.0001	0.99

summary form is transmitted by facsimile to the Data Coordinating Center detailing whether the patient had a stroke or a life-threatening bleeding event. The hemorrhagic stroke rate will be ascertained on a biweekly basis and if clear-cut trends emerge in comparing observed rates with representative data from Table 1, discussion with the Data and Safety Monitoring Committee may become necessary.

Two key issues will require judgment on the part of the Data and Safety Monitoring Committee. First, the concept of "net clinical benefit" will be considered. If the observed rate of intracranial bleeding complications is higher than the expected rate, it must be interpreted in the context of the overall effect of treatment on mortality. Because >50% of patients who experience intracranial hemorrhage ultimately die, these patients are assigned to the mortality rather than to the morbidity category. Hence, a therapy that simultaneously increased intracranial hemorrhage but decreased total mortality might on balance be considered beneficial. Second, the extensive quality assurance methods and the inclusion of mandatory efforts for computer tomographic or nuclear magnetic resonance imaging should a neurologic event occur in GUSTO could lead to greater reporting of strokes than in previous megatrials. The reference streptokinase plus subcutaneous heparin arm should provide important perspective on this issue.

Investigator-Industry Relations

The sheer size of this trial, involving more than 1,500 hospitals and several thousand investigators, reduces the potential impact of biases attributed to a single investigator; however, important potential conflicts of interest still exist. In *Webster's Third New International Dictionary*, a conflict of interest is defined as a "conflict between the private interests and official responsibilities of a person in a position of trust." Although it usually implies the potential for direct financial gain, such a conflict might subtly or even subconsciously affect an investigator's objectivity. Careful review of the guidelines adopted by three large, multicenter, randomized trials in cardiovascular medicine reveals some potential gaps in procedures for avoiding unnecessary financial ties between clinical investigators and industry sponsors (11,20) (Table 2). To avoid any financial linkage, it is clearly desirable that the investigator have no equity interest such as stock or stock options in a company sponsor and that there be no remuneration for a consultancy arrangement, expertise or service during the course of the trial. Such guidelines apply not only to the investigator but to his or her spouse, dependents and family. This "freedom from equity or employment" rule, adopted by several designers of clinical trials and organizations such as the American Medical Association (10) and the American Federation for Clinical Research and institutions such as Harvard Medical School (9), appears to represent an emerging consensus. There is continued debate, however, exemplified by the subsequent rejection as draconian of the draft guidelines from September 1989 of the National Institutes of Health and the Alcohol, Drug Abuse and Mental Health Administration (21–25). On the other hand, the limitations of simple disclosure are well recognized (26).

The GUSTO Steering Committee decided to significantly extend the standard criteria. By unanimous vote, it banned honoraria paid by the trial sponsors for educational activities or lectures and reimbursement for travel expenses. Investigator travel related to the research project is being reimbursed from the study's budget. In recognition of the critical time period after completion of the trial and dissemination of the data, along with the possibility that any financial ties during the phase of presentation of data might delicately affect the tone or interpretation of a lecture, the Steering Committee also extended the period for avoidance of *any* financial ties to 1 year after formal publication of the trial's primary results. In contrast, many other trials either have not specified the duration of potential conflict of interest or have ceased applying guidelines as soon as the data have been publicized (Table 2).

The guidelines are applicable to all of the sponsors, which in this trial include Bayer (New York, New York); CIBA-Corning Diagnostics (Medfield, Massachusetts); Genentech (South San Francisco, California); ICI Pharmaceuticals (Wilmington, Delaware) and Sanofi Pharmaceuticals (Paris, France). In addition, these safeguards were adopted by the Steering Committee and the Data Safety and Monitoring Committee and all members of the Data Coordinating Center. At the level of participating site principal investigators, written documentation is required that acknowledges the lack of any equity interest in the sponsors. We believe that such stringent guidelines, albeit not absolutely necessary, are important to ensure the highest level of integrity for the project throughout its execution and dissemination phases.

Table 2. Conflict of Interest Guidelines in Cardiovascular Clinical Trials and Medical Organizations

	Source (ref. no.)	Stock, Equity, Interest	Consultancy	Honoraria, Educational Program Payments	Travel Expenses	Financial "Time Window"
Multicenter cardiovascular trials						
Post-CABG	Healy et al. (11)	No	No	Not addressed	Not addressed	Until date of publication
BARI	Protocol (32)	No	No	Not addressed	Not addressed	Not addressed
TIMI phases III–V	Holden (20)	No	No	Not addressed	Not addressed	1 yr after presentation
GUSTO	Current study	No	No	No	No	1 yr after publication
Medical organizations						
American Medical Association	(33)	No	Disclosure	Disclosure	Not addressed	
NIH/ADAMHA (rejected)*	(34)	No	No	No	Not addressed	
American College of Cardiology (ACC)	(35)	Disclosure to ACC if >$10,000	Disclosure to ACC if >$10,000	Disclosure to ACC if >$10,000	Not addressed	
Harvard Medical School	(36)	No	No	Not addressed	Not addressed	
British Cardiac Society	(37)	Disclosure with publication	Disclosure with publication	Disclosure with publication	Not addressed	
American Federation for Clinical Research	(22)	No	Disclosure with lectures	Disclosure with lectures	Not addressed	
American Heart Association	(38)	Disclosure if invited speaker, Committee	Disclosure if invited speaker, Committee	Not permitted when representing AHA	Not addressed	

*Proposed guidelines September 1989. BARI = Bypass Angioplasty Revascularization Investigation; CABG = coronary artery bypass graft; GUSTO = Global Utilization of Streptokinase and rt-PA for Occluded Coronary Arteries; NIH/ADAMHA = National Institutes of Health and Alcohol, Drug Abuse, and Mental Health Administration; No = not permitted; ref. = reference; TIMI = Thrombolysis in Myocardial Infarction.

Investigation-Industry Relation

The freedom of design of the GUSTO protocol was the first step of many to secure autonomy during the execution of the trial. The processes for data collection, quality assurance, management, access and analysis were all considered in depth. The data are collected by study nurses at each of the participating sites and quality assurance of these data is achieved by source medical record documentation in a randomly determined 10% of patients, as well as in all patients with a major untoward event, such as intracerebral hemorrhage or stroke. The monitoring is performed by an independently contracted research organization (Clinical Research International). After verification locally, all of the data are forwarded to the Data Coordinating Center. Throughout the trial, none of the sponsors or Steering Committee members will have access to the data unless a change in trial design is required. The Data and Safety Monitoring Committee, comprising five cardiologists, two biostatisticians and one ethicist, will periodically review the data at recruitment milestones of 3,000, 12,500 and 24,000 patients and of approximately 41,600 patients at the trial's completion. However, even this independent committee will interpret the safety and mortality data in a blinded fashion. For example, data will be labeled as treatment A, B, C or D at one meeting and treatment W, X, Y or Z at another. A similar set of guidelines is in place for the Food and Drug Administration, which will receive regular reports of the trial's progress. The only exceptions to blinding of data will be that two biostatisticians at the Data Coordinating Center will know the code, and, for example, if there is an apparent excess of intracerebral hemorrhage in one treatment arm, then decoding the regimen may become necessary. The sponsors will not have any knowledge of data unless there has been a clear-cut safety problem that involves a possible change in protocol, as described earlier. At the time of the trial's completion, the primary data will be analyzed by the Steering Committee and fully interpreted and discussed as a group before any scientific or public presentation.

Conclusions

GUSTO represents the first United States-based large scale myocardial reperfusion trial. Although such population studies of tens of thousands of patients are considered simple owing to the design and lack of comprehensive data collection (the case report form is only three pages), the process of reaching consensus about conflict of interest policy and patient safety standards is complex. We clearly recognize the pivotal need for dialogue and interaction between industry and clinical investigators (20,27,28). Such relations are essential for scientific and clinical development as well as medical education. Extra care has been exercised to maintain an arm's length relation between the industrial

sponsors and the trialists of GUSTO during the project's execution and dissemination phases. This will enhance unbiased data acquisition and interpretation (29). Furthermore, this large scale effort is quite unique from the standpoint of the Food and Drug Administration, which conventionally requires complete medical research source documentation, stringent participating site documentation and full characterization of every adverse event. Although our first priority is assuring patient safety (30,31), we have established some special allowances with random auditing and rapid communication mechanisms that enable us to proceed with confidence to test aggressive thrombolytic regimens. Incorporation of some of the novel approaches adopted in the GUSTO trial may facilitate the planning of other large scale randomized clinical trials in the future.

Appendix

GUSTO Steering Committee

Eric J. Topol, MD, Chairman (Cleveland, Ohio); Paul Armstrong, MD (Toronto, Ontario, Canada); Phil Aylward, MD (Bedford Park, Australia); Gabriel Barbash, MD (Tel-Hashomer, Israel); Eric R. Bates, MD (Ann Arbor, Michigan); Jean-Pierre Boissel, MD (Lyons, France); Robert M. Califf, MD (Durham, North Carolina); James Chesebro, MD (Rochester, Minnesota); Jacques J. Col, MD (Brussells, Belgium); David de Bono, MD (Leicester, England); Joel M. Gore, MD (Worcester, Massachusetts); Alan D. Guerci, MD (Baltimore, Maryland); John Hampton, MD (Nottingham, England); Jack Hirsh, MD (Hamilton, Ontario, Canada); David R. Holmes, MD (Rochester, Minnesota); John Horgan, MD (Dublin, Ireland); Neal Kleiman, MD (Houston, Texas); Victor Marder, MD (Rochester, New York); Douglas Morris, MD (Atlanta, Georgia); E. Magnus Ohman, MD (Durham, North Carolina); Allan Ross, MD (Washington, D.C.); Wolfgang Rutsch, MD (Berlin, Germany); John Sines, MD (Sydney, Australia); Maarten L. Simoons, MD (Rotterdam, The Netherlands); Alec Vahanian, MD (Paris, France); Frans Van de Werf, MD (Louvain, Belgium); W. Douglas Weaver, MD (Seattle, Washington); Harvey White, MD (Auckland, New Zealand); Robert Wilcox, MD (Nottingham, England)

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