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THE ROLE OF AN INDEPENDENT STATISTICAL ANALYSIS CENTER IN THE INDUSTRY-MODIFIED NATIONAL INSTITUTES OF HEALTH MODEL

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During the past four decades, the randomized clinical trial has evolved as a major research methodology for the rigorous evaluation of new medical interventions and therapies. The role of statistics in clinical trial methodology and the organizational structure of clinical trials have also evolved. More recently, there has been a shift in the funding of clinical trials, from the public (eg, National Institutes of Health, or NIH) to the private (pharmaceutical and device industries) sector. This paper describes an Industry-Modified NIH Model for the conduct of industry-sponsored clinical trials that involves a distinct statistical analysis center (SAC) and data management center, as opposed to the single unit, or coordinating center, utilized in most NIH-sponsored trials. The role of the SAC in support of the monitoring activities of an independent data monitoring committee (IDMC) is described in detail. Since the Greenberg Report was published in 1967, the number of multicenter confirmatory clinical trials that have an IDMC has steadily increased, and the recent International Conference on Harmonisation (ICH) E9 regulatory guideline on clinical trials supports this trend. This manuscript provides explicit guidance regarding the activities of an independent SAC for industry-sponsored clinical trials based on our experiences as a SAC for a number of such trials. Activities discussed include protocol development, drafting of written operating procedures for an IDMC and summary notes of its meetings, and preparation of an interim analysis plan and interim analysis reports.

Key Words: Randomized clinical trial; Organizational structure; NIH model; Industry-modified NIH model; Data and safety monitoring

INTRODUCTION

THE RANDOMIZED CLINICAL trial (RCT) has become the gold standard for evaluating the effectiveness of a new preventive, diagnostic, or therapeutic intervention (eg, drug, biologic, device, or procedure). In 1967, the National Heart Institute commissioned a task force to recommend an organizational structure for the conduct of multicenter clinical trials. The task force report, known as the Greenberg Report (1), outlined a model (Figure 1) that has served well for the past 30 years as the standard for many National Institutes of Health RCTs.

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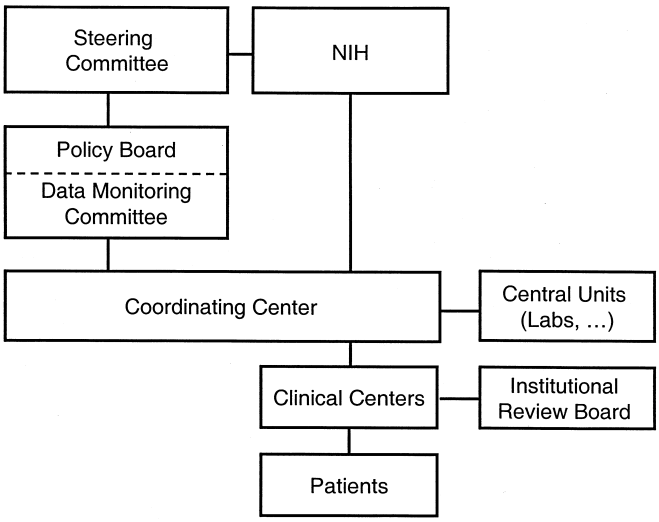

FIGURE 1. The NIH model.

Key components of the NIH model in the Greenberg Report include:

1. A steering or executive committee,
2. A coordinating center,
3. An independent policy or advisory board, and
4. The data-contributing participating units (eg, clinical centers, central laboratories).

The steering committee and its chair provide intellectual leadership for the RCT and ultimately advise the specific NIH institute director. The coordinating center has responsibility for data collection from the participating units, for data query and resolution, and for interim and final analyses of the data. The functions of the policy board were not specified in detail in the Greenberg Report, but in most NIH trials have included the monitoring of patient safety (2).

Since the Greenberg Report, recognition of the importance of monitoring safety in clinical trials, as well as trial conduct and early evidence of benefit, has steadily grown. The United States Food and Drug Administration (FDA) recently published a guideline, "E9 Statistical Principles for Clinical Trials" (3), which includes recommendations for data monitoring and the role of an independent data monitoring committee in conducting such activities. The guideline is based on recommendations of the International Conference on Harmonisation, a tripartite effort of the European Union, Japan, and the United States to promote international standardization of regulatory requirements for the approval of pharmaceuticals. Acceptance of this guideline is likely to lead to an even greater use of independent data monitoring committees in RCTs.

During the past three decades, there has been a gradual shift in funding for large RCTs in the United States from the NIH to the pharmaceutical industry (4). This has resulted in a need to adapt the NIH model to the particular needs of industry. In NIH-sponsored trials, the coordinating center is often located at an academic center, usually within a biostatistics unit (5). Although there have been a few successful industry-sponsored trials conducted in this way, industry has not generally contracted with an academic center to provide traditional coordinating center functions. Industry-sponsored RCTs are conducted within a broad framework of drug development for eventual marketing approval, and are subject to numerous

regulations concerning the collection and submission of data. Industry requires that the data for an RCT be collected and managed in a manner that is both regulatory-compliant and compatible with other work within the company that ultimately needs to be submitted with the RCT results for regulatory review. Integrated submission to regulatory agencies is facilitated if the industry sponsor utilizes its own staff, or a contract research organization (CRO) working according to detailed specifications, to collect and manage RCT data.

The challenge is to preserve the essential features of the NIH clinical trial model, which has worked so successfully the past 30 years, within the clinical trial environment of the pharmaceutical industry. A key component of the NIH model, besides the steering committee, is the independent data monitoring committee, composed of members external to both the study and its sponsor. The independence of this committee is best maintained when the individuals responsible for the statistical analysis of interim data for the IDMC are also independent of the sponsor.

Another reason for using an external group for data analysis is to provide analytic support for academic clinician collaborators beyond the immediate needs of the sponsor. Clinician investigators participate in clinical trials to have access to newly developed therapies that improve patient care and to participate in medical research. Whether the RCT is industry or publicly sponsored, investigators want to maintain access to data after trial completion to conduct analyses for scholarly publication and presentation. If a therapeutic or preventive confirmatory RCT indicates a drug is successful, the industry sponsor has reporting responsibilities to regulatory agencies and has a strong financial incentive to complete these tasks as rapidly as possible. If such an RCT is neutral or negative (shows a harmful trend), the industry sponsor usually quickly reallocates its internal resources to more promising areas. Academic clinical investigators often have difficulty competing with these priorities.

A solution that satisfies the needs of both the industry sponsor and academic collaborators is the Industry-Modified NIH Model (Figure 2), first used to our knowledge in the Metoprolol in Acute Myocardial Infraction (MIAMI) trial (6). The model retains essential components of the NIH model by making one small modification: the data management and analysis responsibilities of the coordinating center are split between a data management center (DMgtC) and a statistical analysis center. The DMgtC has primary responsibility for data collection and management, and also participates in the preparation of reports required for regulatory approval. It may be either internal to the sponsor, or at a CRO. The SAC is primarily responsible for producing interim data analyses for the IDMC, and analyses of the final data set for publication in collaboration with the steering committee and the sponsor. It is external to, and independent of, the sponsor. Trial coordination and administration, generally the responsibility of the coordinating center in the NIH Model, is the responsibility of the industry sponsor in the Industry-Modified NIH Model. This role may be delegated to a CRO functioning as a DMgtC.

In this paper we describe in detail the role of a SAC in multicenter industry-sponsored clinical trials based on our experiences over the last decade as an independent SAC for the Prospective Randomized Milrinone Survival Evaluation (PROMISE) trial (7), the Prospective Randomized Amlodipine Survival Evaluation (PRAISE) trial (8), the Coumadin Aspirin Reinfarction Study (CARS) (9), the Vesnarinone Trial (VEST) (10), the Metoprolol CR/XL Randomized Intervention Trial (MERIT) (11), the Evaluation of Oral Xemilofiban in Controlling Thrombotic Events (EXCITE) (12) trial, and the Diaspirin Cross-Linked Hemoglobin Traumatic Hemorrhagic Shock (DCLHb-THS) trial (13). These experiences include RCTs with various industry sponsors, in several diseases, and with a range of results, for example, positive (MERIT), neutral (CARS), and negative (VEST).

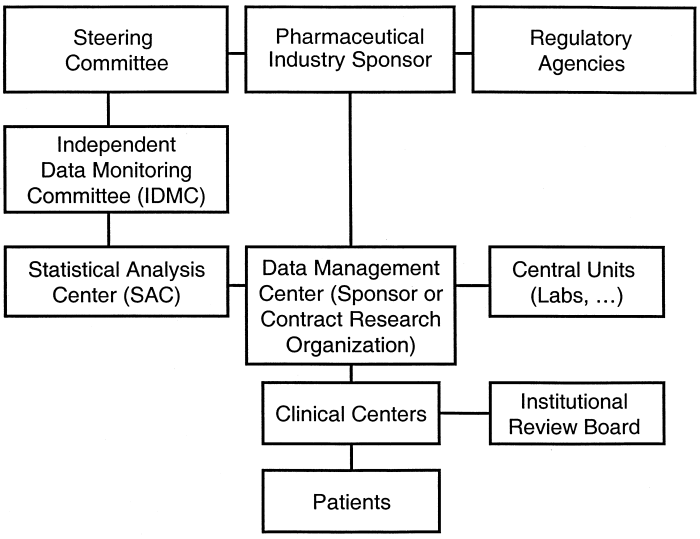

FIGURE 2. The Industry-Modified NIH Model.

OVERVIEW OF RESPONSIBILITIES

The primary role of the SAC is to produce interim analyses of the clinical trial data and prepare reports for the IDMC. The rationale for data monitoring and the role of the IDMC has been discussed in detail elsewhere (14–18). The primary responsibility of the IDMC is to ensure, throughout the duration of the RCT, that risks to patients in the trial are reasonable in relation to anticipated benefit. Trials may be terminated early if harm or treatment benefit has been adequately established. In some instances, trials may be terminated if no trend is apparent and continuation seems futile. In other instances, the IDMC may recommend modifications of trial design or conduct. To facilitate decisions of the IDMC, interim monitoring reports need to be both thorough and timely, and should include a broad range of information on study performance in addition to treatment efficacy and the occurrence of adverse events.

Additional responsibilities of the SAC should be clearly defined, preferably in writing as a component of the contract or agreement with the sponsor. The staff of the SAC will generally have a role in protocol development or review, especially with regard to the statistical aspects of study design and analysis. They may review the data collection instruments (eg, case report forms) and methods (eg, adverse event reporting), as these will both impact the timeliness and interpretation of interim data. When data collection and management are not independent of the industry sponsor, some form of direct verification by the SAC of key data items (randomization and primary endpoints) should also be considered.

The SAC provides a critical link between the IDMC and the RCT and/or sponsor, and will often take responsibility for various other functions that support the IDMC. The SAC may prepare draft written operating procedures for the IDMC (eg, IDMC charter), prepare agendas and summary notes of IDMC meetings, and provide general assistance in assuring that the IDMC functions smoothly, effectively, and confidentially. At the conclusion of the trial, the SAC should be involved in the preparation of final analyses and trial publication(s) in collaboration with the steering committee and sponsor.

PROTOCOL DEVELOPMENT

The SAC can be a valuable contributor to the study design and analysis plan during

protocol development, particularly if it is involved early in this process. As is well recognized, the study protocol is critical to the successful execution of a multicenter RCT. A draft protocol is often prepared by the sponsor, perhaps in collaboration with a few investigators, before the SAC has been identified. To effectively prepare the interim IDMC reports, the SAC needs to become familiar with all aspects of the study protocol including what data will be available and proposed statistical procedures. Including the SAC in the final stages of protocol development can serve this purpose, and at the same time make use of additional insight and expertise provided by members of the SAC.

In particular, the SAC should verify the sample size calculations, critically evaluate the likely quality of the primary endpoint information, and suggest or comment on the choice and appropriateness of any statistical analyses of the data. The SAC should also review the data collection procedures and forms prepared by the sponsor and/or CRO. In our experience, this review has often led to modifications that prevent problems from arising during interim data analysis.

Since interim monitoring requires repeated significance testing of evolving results, the protocol should indicate how the overall significance level of the trial will be protected. The SAC often plays a major role in developing statistical guidelines for interim monitoring, in collaboration with the sponsor and/or the IDMC, particularly if the methods to be employed are nonstandard or require further refinement. This potential for interesting new statistical problems or applications can be an additional incentive for the participation of academic statistical groups as a SAC in an RCT.

For example, the EXCITE Trial (12) protocol specified a primary outcome that was a composite of mortality and morbidity with a secondary outcome of mortality alone. Regulatory agency staff suggested to the sponsor that the trial not be stopped early for efficacy on the primary outcome unless there was also a significant benefit on total mortality. Discussions among the sponsor, SAC, and IDMC reflected concerns about continuing the trial with a compelling difference in the primary outcome and a consistent, albeit not statistically significant, mortality difference. There were also concerns about the possibility of ending the trial with a large difference in a secondary outcome and a nonsignificant difference in the primary outcome. These discussions eventually led to a protocol amendment adding a second primary endpoint, and interim monitoring guidelines for both primary endpoints (19), that satisfied all parties.

KEY ELEMENTS OF DATA FLOW

In the Industry-Modified NIH model, the DMgtC (with oversight by the sponsor if external to the sponsor) has responsibility for data collection, site monitoring, and data quality control and management, but remains blinded to treatment assignments. Datasets without treatment assignments, usually in the form of SAS transport files, are periodically transmitted from the DMgtC (either directly or via the sponsor) to the SAC for interim analyses. Serious adverse event information collected for regulatory purposes will often be separately managed by the sponsor, and may also be transmitted to the SAC for additional, or more up-to-date, analyses of safety. A one-time transmission of the study randomization code to the SAC should occur before the study starts.

It is important that a channel of communication for the discussion of data issues (eg, data collection procedures, timelines, data conventions, queries) be established between the SAC and DMgtC and/or sponsor before the trial begins. At a minimum, there will be frequent interactions via e-mail and telephone. In many trials there will be an initial meeting of representatives from each group, followed by a regular schedule of telephone conference calls to enable the SAC, DMgtC, and the sponsor to discuss issues of common concern. In our experience, the industry sponsor is extremely motivated to ensure both the quality and timeliness of RCT data (for reasons of safety, to comply with regula-

tory requirements, and to expedite drug marketing), and has the financial resources to do so.

For example, the Diaspirin Cross-Linked Hemoglobin Traumatic Hemorrhagic Shock (DCLHb-THS) trial (13) was the first large, multicenter industry-sponsored RCT to be conducted under the 1996 FDA rule (21 CFR §50.24) which allows an exception to the requirement for prospective informed consent for certain trials investigating therapies for acute, life-threatening conditions. The trial was conducted to assess whether an infusion of a hemoglobin-based solution during the initial resuscitation of severely injured adult trauma patients could reduce 28-day mortality. Very early in the trial, before the first planned interim analysis of the data and when only very limited data were available to the SAC, the SAC brought to the attention of the IDMC that there were more deaths among patients receiving DCLHb. Within 72 hours the sponsor, at the request of the IDMC, had contacted all sites requesting them to fax additional data to the CRO, and the CRO had entered the data and forwarded datasets to the SAC for analysis and review with the IDMC. Additional expedited data collection (over the holiday season) and in-depth analyses led to a suspension of patient enrollment 24 days later. Good communication among the IDMC, SAC, CRO, and sponsor, and the financial resources of the sponsor, were responsible for this rapid mobilization of effort and prompt response to a safety concern.

Because the industry sponsor may be involved in data collection or management, in whole or in part, some procedure should be implemented in industry-sponsored trials to provide for independent verification of a few key study data by the SAC. Key study data include information on the patients randomized to the study and reported primary endpoints, and may also include additional secondary endpoint information. For some trials, serious adverse events may also be included.

For example, in one RCT we received enrollment information directly from an independent contractor used to randomize patients to the trial through an interactive voice randomization system. Randomization information electronically generated by this system could be used to verify information obtained from case report forms in the clinical database and identify discrepancies. In several other trials, the study investigators were required to fax a randomization form and primary endpoint form(s) to both the SAC and the DMgtC (or industry sponsor). The SAC can compare these data to information available in the clinical database and alert the sponsor or steering committee to any inconsistencies. Also, because the processing of this limited amount of information by the SAC can be very rapid, this system can make possible more current interim analyses of the primary endpoint information as well as play a role in data validation.

SUPPORT OF THE IDMC

There are several ways that the SAC can facilitate the work of the IDMC and the interactions between the IDMC, sponsor, and steering committee, in addition to producing the interim monitoring reports (described separately below).

The IDMC Charter

For industry-sponsored RCTs, we suggest the SAC prepare a draft document (which we refer to as an IDMC charter) explicitly defining the roles and responsibilities of the IDMC and describing the official procedures to be used in carrying out its functions (eg, meeting frequency and format, voting procedures, etc.). The IDMC charter serves to delineate and make explicit the various responsibilities of the sponsor, DMgtC, and SAC to the IDMC, as well as those of the IDMC itself. This charter should be reviewed by the sponsor, the IDMC, and possibly the steering committee or relevant regulatory agencies, and should be formally approved by the IDMC.

Table 1 indicates the important components of an IDMC charter. The specific responsibilities and functions of the IDMC will vary for different trials. While not all trials

TABLE 1
Components of an IDMC Charter

Overview of IDMC Responsibilities:
- Ethical responsibilities to study participants to monitor safety and efficacy
- Scientific responsibilities to investigators and sponsor to monitor scientific integrity of the trial
- Economic responsibilities to the sponsor to monitor the trial for futility

Organization:
- Composition
- Selection of members

Specific Functions:
- Review the study protocol and any protocol amendments
- Review data collection methods and safety monitoring procedures
- Review and approve the IDMC charter
- Review and approve an interim analysis plan
- Review interim monitoring reports and make recommendations to the steering committee

Responsibilities of the Sponsor:
- Make resources and information, including study documents, available to the IDMC as required to carry out its designated functions
- Monitor the study conduct and the collection and quality control of study data
- Contract with the SAC for the preparation of interim monitoring reports
- Inform the IDMC of any potential safety concern that is idiosyncratic or previously unreported
- Provide analysis sets to the SAC containing data necessary for preparing IDMC reports
- Handle, financially and logistically, meeting arrangements of the IDMC
- Communicate regulatory information to relevant authorities

Responsibilities of the SAC:
- Prepare and distribute a draft IDMC charter
- Prepare and distribute a draft interim analysis plan
- Prepare and distribute study reports based on data received from the sponsor
- Prepare summary notes of each IDMC meeting or conference call

Conduct of IDMC Meetings:
- Meeting frequency and format (eg, open, closed, executive sessions)
- Definition of quorum and voting procedures
- Procedures for recommendations to the steering committee
- Summary notes
- Confidentiality requirements
- Conflict of interest guidelines

Appendix I–Statistical Interim Monitoring Guidelines

Appendix II–General Considerations for Early Termination

will be monitored for futility, we personally maintain that an RCT cannot be monitored for safety without also monitoring efficacy. The views of the sponsor and/or steering committee concerning early termination need to be made very clear to the IDMC, prior to any review of data by the IDMC.

The monitoring of an RCT for scientific integrity is often a dual responsibility of the IDMC and the sponsor (with the steering committee). The scientific question is based on design assumptions in the study protocol, including the expected study population, the timeliness, type, and quality of data collection, expected rates of enrollment and of the primary outcome and adherence to assigned treatment. The ongoing scientific validity of the RCT depends upon whether these assumptions are being met in the RCT and on accumulating results of other related trials that may be conducted at the same time. Many design assumptions can be assessed

using aggregate data, which the sponsor can and should monitor. In fact, it is preferable if not necessary, whenever possible, to make midcourse design corrections without regard to treatment group differences. However, because design modifications can be costly for the sponsor, it is reassuring to study investigators to know that an independent body, the IDMC, is also monitoring study conduct in addition to safety and efficacy.

The composition of an IDMC has been discussed in numerous publications (14–18,20,21). For industry-sponsored trials it is especially important that the financial and intellectual independence of IDMC members be carefully considered. The charter should specify the IDMC appointment process, including possible replacement of members, and provide conflict of interest guidelines. Specific recommendations regarding financial independence of IDMC members are listed in Table 2.

There is no simple formula for how often the IDMC should meet. As is the tradition for NIH-sponsored trials, we strongly recommend that the IDMC members meet with the industry sponsor and the SAC before enrollment into the study begins to review protocol-related documents. This face-to-face meeting facilitates effective future interaction when difficult and complex issues must be considered and resolved. In our experience, most IDMCs choose to meet at approximately six-month intervals or at some prespecified fraction of observed enrollment or primary events, but they should meet at least once a year.

Generally, the rate at which data accumulate is much slower early in a trial than it will be later, when more patients have been enrolled, and data collection procedures are functioning efficiently. The IDMC can plan to meet at approximately regular intervals (in calendar time) and still have varying increments in information between meetings, with smaller increments early when safety issues are most critical and need to be responded to rapidly. In industry-sponsored trials, there is a strong business incentive, in addition to the scientific incentive, to enroll patients as

TABLE 2
Financial Independence of IDMC Members

IDMC members should be free of any actual or perceived financial conflicts of interest from the results of the RCT. Even after the results are public, the potential for a perceived conflict remains and should be considered in receiving funds from the sponsor.

We recommend an IDMC member:

- Receive a standard honorarium or consulting fees for performance of his/her responsibilities
- Be reimbursed for usual travel expenses
- Provide disclosure of external activities that may be perceived as a conflict of interest and annually update it
- Apply these recommendations to his/her spouse and dependents (21)

We recommend that an IDMC member *not*:

- Be directly dependent on study investigators for salary support, promotion, tenure, or similar decisions
- Buy, sell, or hold stock in the sponsor (this does not include investing in a mutual fund that may have stock in the sponsor)
- Be a paid consultant to the sponsor on the treatment being evaluated

We recommend that other situations be considered on a case by case basis. These situations include whether an IDMC member:

- Serves as a paid consultant to the sponsor on other research
- Participates in educational activities funded by the sponsor
- Receives funding from the sponsor for other research projects

quickly as possible. Thus, it is important for the sponsor, DMgtC, and SAC to consider, early in a trial, whether data collection procedures can provide sufficiently timely data to the IDMC to monitor safety effectively during the period of rapid enrollment.

A meeting format incorporating both open and closed sessions has proven to be useful [16,17,18,22]. The open session allows for interaction and discussion of study logistical matters between the IDMC and investigator representatives (such as the steering committee), the sponsor and DMgtC, the SAC, and if appropriate, regulatory agencies. The SAC should play a role in identifying topics of potential interest or concern to the DSMB, drafting an agenda, and coordinating participation. Issues that may be discussed include projected study timelines or enrollment, protocol adherence, event adjudication progress, status of amendments to the protocol, or data quality/flow, as appropriate. Apart from the specific information that is exchanged, it is important that the various groups involved in the trial have the opportunity to express their concerns and motivations to others. The presentation of information by treatment group is restricted to the closed session, which includes IDMC voting members and SAC staff only.

At the conclusion of any IDMC meeting or conference call, the IDMC should agree on what recommendations will be made. One of the following actions is generally recommended:

- Continue the RCT according to the protocol and any related amendments,
- Continue the RCT but modify the RCT protocol or data collection procedure (modifications may include, but are not limited to, changes in inclusion or exclusion criteria, frequency of safety monitoring, alterations in RCT procedures, adjustments in sample size, changes in duration of observation and follow-up), or
- Discontinue one or more of the treatment assignments (with provision for orderly discontinuation in accordance with good medical practice).

The IDMC charter should specify the reporting procedure for IDMC recommendations. In some trials, the IDMC reports only to the chair of the steering committee, and not directly to the sponsor, while in other trials it may report to both. In either case, we suggest that recommendations be transmitted in writing within a week of the meeting, and that there be a formal written response to the recommendations.

Absolute confidentiality is of utmost importance to the work of the IDMC to prevent evolving trial results from impacting the execution of the trial. The IDMC charter should note that IDMC members and SAC staff must treat IDMC reports, discussions, and summary notes as strictly confidential. To assist in maintaining confidentiality, the SAC should collect IDMC reports at the conclusion of a meeting and inspect the meeting room for any remaining confidential material.

Because the IDMC charter is an officially approved document, the statistical interim monitoring guidelines used to control the type I error of the primary endpoint(s) analysis should be included as an appendix to the charter, if not previously detailed in the protocol. A discussion of more general considerations for early termination of the trial (summarized in Table 3) is included as a second appendix to the charter and can be tailored to the specific trial. A separate, more complete, interim analysis plan should be prepared by the SAC to describe in detail the types of analyses to be included in the interim analysis reports.

The Interim Analysis Plan

The interim analysis plan addresses the concerns of the industry sponsor and the IDMC about the amount, timeliness, and types of analyses to be performed. It also serves as an important planning tool for the SAC. Development of the interim analysis plan requires careful consideration of the RCT design and protocol, case report forms, and the data collection process. An interim analysis plan should include:

TABLE 3
General Considerations for Early Termination of an RCT

1. Strength of the evidence
2. Baseline comparability of the treatment groups
3. Unbiased evaluation
4. Impact of missing data
5. Compliance with the treatment regimen
6. Consistency of the treatment effect for various outcomes
7. Consistency of the treatment effect for various subgroups
8. Length of follow-up
9. Whether benefits outweigh risks
10. Impact of differential use of concomitant therapy
11. Whether current trends can be reversed if trial is continued
12. Sponsor and regulatory perspective on early termination
13. External consistency
14. Public impact
15. Repeated testing
16. Multiple comparisons

- A brief overview of the trial protocol and procedures,
- An overview of the plan for interim analyses and monitoring boundaries,
- A description of report style and analysis conventions, and
- An enumeration of the specific graphics and analyses to be included in each report.

The overview of the trial protocol and procedures briefly summarizes the treatment arms, primary and secondary outcome measures, study procedures, enrollment plan if available, and data management/flow issues of relevance to the IDMC (eg, influencing the quality and timeliness of interim data). The overview of the interim analysis plan describes the types of reports that will be prepared for the IDMC, and their approximate frequency. The statistical guidelines for the interim monitoring of the primary endpoint(s) need to be described in sufficient detail that it is clear to both the IDMC and the SAC how to proceed.

The final component of the interim analysis plan is a detailed listing of the specific graphics and analyses to be included in a report. For each display, the information generally included is the data source, the type of graphic, specific categorizations (if appropriate), denominator or risk set definitions, censoring conventions, and whether the display will be for treatment groups combined or individually. The analysis of the primary and secondary endpoints of the trial receives particular attention. Analyses by subgroups are specified and the use of any endpoint adjudication information is also considered.

Review of an interim analysis plan by the sponsor statistician and the IDMC can help to clarify varying ideas about exactly what information will be available during the RCT versus what information the IDMC wants to see, how it should be presented, and what assumptions will need to be made. However, it is important to emphasize that the specific structure or content of interim analysis reports need not be fixed and may change during the course of the trial. Many factors (eg, the stage of the trial, the nature of the accumulating data, the focus of an IDMC meeting, and requests by IDMC members) will influence report content or how specific data items are analyzed and presented.

IDMC Meeting Arrangements

In our view, both the financial and the logistical aspects of arranging scheduled IDMC meetings (eg, transportation, lodging, and meeting room) should usually be the responsibility of the sponsor, with input from the SAC and the IDMC regarding scheduling and specific requirements. An emergency

IDMC meeting that needs to happen quickly or without informing the sponsor may be arranged by the IDMC chair or the SAC, with some provision made for financial reimbursement by the sponsor.

The chair of the IDMC should lead an IDMC meeting, with the participation of the SAC. A draft agenda for the meeting should be prepared, including particular issues needing to be discussed in addition to report review, for prior approval by the chair and distribution to IDMC members with the report. In our experience, the SAC generally leads discussion of the interim analysis report, summarizing for the IDMC key elements of the report, assumptions used, or data problems encountered. The SAC, along with any statistician members of the IDMC, also serve as important resources to the IDMC on the statistical methods employed in the trial.

IDMC Summary Notes

Summary notes should be prepared after each IDMC meeting or conference call. They should be approved by all IDMC members at their next meeting, and serve as a permanent record of IDMC deliberations. Summary notes can be drafted by the SAC or by the IDMC chair; our experience is that the IDMC chair is very willing to let the SAC assume this responsibility. Draft summary notes may go first to the IDMC chair for review and comment, usually within a week of the meeting, and can then be distributed to the other IDMC members. A draft letter to the chair of the steering committee from the IDMC chair with the IDMC approved recommendations, carefully worded so as to avoid any indication of evolving treatment differences, is prepared in conjunction with the summary notes.

Summary notes should list the date, location (if a meeting), and attendees. The notes should present a brief overview of the items considered rather than a transcript of the discussion or a reiteration of the report contents. Majority and minority opinions can be stated without identifying individual members. IDMC members should recognize the potential for scrutiny of the summary notes at the conclusion of the RCT by all interested parties, including regulatory agencies.

INTERIM MONITORING REPORTS

The preparation of interim monitoring reports is not unique to industry-sponsored RCTs, but becomes the principal focus of the SAC in the Industy-Modifed NIH model. Despite the importance of interim monitoring reports to the activities of the IDMC, there is limited guidance available on the format or content of IDMC reports (5), so these are discussed in some detail here.

The University of Wisconsin Department of Biostatistics and Medical Informatics employs a system of clinical trial reporting that relies on graphical presentation without sacrificing any of the detailed information contained in tabular reports. The graphical style enables large amounts of information to be communicated in a manner that is both maximally informative and easy to review in a short period of time. Treatment comparisons, both at baseline and over time, are easily examined, as are time-related trends in the data.

Key features of the reporting system are listed in Table 4. The report is produced using an integrated combination of software tools, including SAS, S-Plus, and $L^{A}T_{E}X$, providing both flexibility and standardization. The majority of figures present categorical data as bar charts representing the percent of patients in a particular category, continuous data represented as boxplots, or time-to event data as Kaplan-Meier estimates of survival curves. Subgroup analyses of the treatment group difference are summarized in a relative risk graphic that displays hazard or risk ratios and their nominal 95% confidence intervals. Customized graphics can be inserted as desired, for example, to display interim analysis boundaries and observed results or conditional power calculations.

Graphical displays are annotated with the number of patients included, p-values (where appropriate), and detailed captions. The report also includes backup tables of univariate

TABLE 4
Features of the University of Wisconsin Reporting System

Integrated software:
- SAS for data processing, summarization of large data sets, most statistical analyses
- S-Plus to produce graphical displays
- L^AT_EX and PERL for text, tables and listings, report compilation

Graphical Presentation:
- Boxplots
- Bar charts (simple, multiple, stacked)
- Kaplan-Meier plots
- Relative risk graphic
- Additional custom graphics (eg, cumulative accrual, interim monitoring boundaries)

Annotations:
- Denominators, risk sets, percentages
- P-values (multiple contrasts)
- Legends
- Detailed captions (source and vintage of data, key assumptions or definitions)
- Figure identifier (mnemonic label, index, auto-referencing, cross-referencing to supporting tables)

Supporting Material:
- Backup tables of univariate statistics and frequency counts for graphical displays

Two report versions produced in parallel:
- Open session aggregate report
- Closed session report by treatment group

statistics and detailed frequency counts corresponding to all graphical displays, generally in a separate section with cross-referencing. A sample report produced from the Beta-Blocker Heart Attack Trial (BHAT) is available in Adobe Acrobat format via our Web site (http://www.biostat.wisc.edu/biostat/sdac/sdacpdf.html). Other report formats are possible and may be equally satisfactory.

An additional feature of the reporting system is that both open and closed session reports can be produced simultaneously with minimal additional time or effort. The open session report summarizes the data without regard to assigned treatment and is intended for use in an open session or by anyone involved in the conduct of the study at the discretion of the sponsor. The closed session report includes comparisons by assigned treatment and is viewed only by the IDMC, SAC, or others determined by the IDMC. Certain types of analyses are not appropriate for inclusion in an open session report (eg, relative risk or conditional power graphics) and can be selectively omitted.

It is important that interim monitoring reports provide the IDMC with the information necessary to:

- Monitor the occurrence of adverse events with the goal of ensuring patient safety,
- Monitor performance of the study (eg, recruitment and baseline characteristics, adherence to protocol) to assess whether modifications of the design and/or the study protocol might be appropriate to increase the likelihood of the trial's success, and
- Monitor evolving evidence regarding treatment efficacy to allow the IDMC to consider recommendations for early study termination for either efficacy or futility.

A standard report should include the basic components listed in Table 5. An introduction should summarize key features of the study protocol, including treatment groups, outcome measures, follow-up procedures, and data flow pertinent to the interpretation of interim data. The interim analysis plan for the primary endpoint analyses should be described along with a brief history of previous IDMC meetings. The introduction should

TABLE 5
Components of an IDMC Interim Analysis Report

Introduction:
- Overview of trial protocol and procedures (treatment arms, outcome measures, study procedures and data flow, interim analysis plan)
- Overview of report (purpose of report, report outline, list of abbreviations, sources of data)
- Report structure and graphical conventions
- Notes on chapter contents (patient sets, definitions, assumptions)
- List of key participants (names and contact information for IDMC, sponsor, SAC, steering committee chair)

Main Material:
- Accrual and study status
- Baseline characteristics (eg, demographics, medical history)
- Primary and secondary endpoint analyses
- Adverse events
- Other safety measures (eg, follow-up physical exam, laboratory data)
- Additional analytical considerations (eg, comparison of observed to expected event rate, sample size, power or conditional power calculations)

Ancillary Material:
- Detailed lists of accrual by center or serious adverse events, case report forms, etc.

describe the sources of data included in the report and transfer dates, as well as the graphical, statistical, or data conventions used. It is useful to provide contact information (eg, address, phone, fax, e-mail) for IDMC members and other key study personnel.

Following the introduction, the study data are displayed, usually with minimal interpretation. The SAC should provide the IDMC with impartial data analyses, not conclusions. The types of study data collected generally fall within the categories listed in Table 5 (accrual and study status, baseline characteristics, etc.). These may be standard chapter headings in IDMC reports, although for many studies we often include additional chapters describing an index event (eg, hospitalization or revascularization) or special safety concern (eg, bleeding event) in greater detail. Any specialized statistical analyses (eg, analyses of the observed versus expected event rate and implications for sample size, power or duration; conditional power calculations; multiple regression modeling) will generally be presented in a separate section that includes more textual motivation for these analyses. Detailed tabular information or listings can be included in a separate section of the report to promote easy review of the main material.

In many industry-sponsored clinical trials there is a separate mechanism for expedited reporting and data management of serious adverse events for regulatory purposes, with a later reporting of the event on a case report form. Because of the difficulty of merging interim data from different sources, information obtained from a separate database would usually be displayed in a separate section.

Alternatively, for other sponsor or regulatory needs, we frequently prepare two distinct reports, an abbreviated safety report based on serious adverse event (SAE) and accrual information, and a more detailed meeting report based on all of the data submitted on case report forms. The safety report may be produced more frequently and be reviewed by only a subset of IDMC members, for example, the chair. A meeting report would be prepared for any scheduled meeting involving the entire IDMC. Information on the occurrence of SAEs is generally an important component of interim monitoring reports because of its greater clinical significance, and timeliness for the purpose of monitoring safety. Having a separate, more limited, safety report also facilitates rapid

report production and contributes to greater timeliness of important safety information.

Interim analysis reports should be distributed for review approximately one week prior to the meeting or conference call so that members have sufficient time to review them. This will require that IDMC members be contacted first, to assure that they will be available to receive the report. A secure and expedited delivery system should be used.

FINAL ANALYSIS AND PUBLICATIONS

At the conclusion of the RCT, we suggest that the SAC prepare a final report based on the final locked data set. This serves a number of purposes. First, the SAC has a lot of experience understanding the study data and has tested programs in place to generate a thorough, well-documented report based on its experience with interim monitoring reports. If the RCT is successful, the resources of the sponsor will be dedicated to producing documents necessary for the regulatory process and rapid drug approval. In the meantime, the SAC-generated report can be distributed to study investigators for their use in preparing a final report for publication. Second, the IDMC and SAC have each made an important contribution to the RCT, and together have insights gained during monitoring that can be shared with the sponsor and the study investigators. We have found it quite useful to have a final joint meeting with the IDMC, SAC, sponsor, and steering committee, during which the updated SAC report based on the final data is reviewed and discussed. Lastly, it has been our experience that the SAC-generated final report can easily become the centerpiece of material sent by the sponsor to regulatory authorities for review. This serves as an independent documentation of the interim monitoring process, as well as an independent validation of final analyses by the sponsor.

During a large RCT a rich body of information is collected. At the conclusion of the trial the industry sponsor will be focused on questions relating to the commercial use of the product, for example, its efficacy, safety profile, and specific labeling issues, while study investigators will usually have many additional questions of more academic interest. If a trial is neutral or negative, an industry sponsor will reallocate its internal resources to other projects. An independent, academically-based SAC can serve to provide the study investigators with greater access to trial data by collaborating with them on additional analyses and publications of lower priority to the sponsor. This has been standard practice for NIH-sponsored trials and is an important incentive and reward to academic investigators that involves relatively little additional cost to the sponsor.

SUMMARY

This paper has described a model for the conduct of industry-sponsored clinical trials and the role of an independent statistical analysis center within this model based on our experiences over the last decade. An independent statistical analysis center can be responsible for a broad range of activities in support of an IDMC and good clinical trial conduct, preserving essential features of the well-established NIH clinical trial model. These include a role in protocol development, drafting of written operating procedures for an IDMC and summary notes of its meetings, preparation of an interim analysis plan and interim analysis reports, and collaboration in publications. To provide guidance for industry sponsors of clinical trials and academic statistical groups involved in similar activities, we have described these functions or documents in some detail.

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