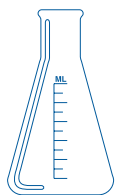


## Biopharmaceutical Section



American Statistical Association

# Biopharmaceutical Report

Volume 10, No. 1

Spring 2002

**Chair:** *Bob D. Small*

**Editors:** *Kannan Natarajan, Neal Thomas, and Kevin W. Anderson*

## Note from the Editors on the FDA Draft Guidance on Clinical Trial Data Monitoring Committees

**Kannan Natarajan**  
**Neal Thomas**  
**Kevin W. Anderson**

The purpose of this note is to highlight the recently published FDA draft guidance on Data Monitoring Committees (DMC). The document, titled "On the Establishment and Operation of Clinical Trial Data Monitoring Committees", was issued in November, 2001. This note also provides the readers with information on where to find presentations by FDA participants at the Workshop of FDA Guidance on Clinical Trial Data Monitoring Committees held on November 27, 2001 at Bethesda, Maryland. We give web sites and references for these documents. Finally, the primary intent of this note is to increase the awareness of this important proposed FDA draft guidance among the biopharmaceutical members. It is not intended to provide a comprehensive summary, critique, or endorsement of any or all of the proposed draft guidance.

### Background

The draft guidance discusses the roles, responsibilities and operating procedures of DMCs that carry out important aspects of clinical trial monitoring. The document discusses various models for DMCs and the FDA's viewpoint on some of the advantages and disadvantages of these models. As with all guidance documents, it is not intended to dictate the use of any particular approach but to ensure awareness of potential concerns that may arise with any specific model.

The draft guidance was published in *Federal Register* 11/20/2001, Docket #01D-0489. The 90 day public comment period began on 11/20/2001 and completed in mid-February. The draft guidance document can be accessed on the FDA web page [www.fda.gov/cber/gdlns/clindatmon.htm](http://www.fda.gov/cber/gdlns/clindatmon.htm) or the "What's New" section of [www.fda.gov/oc/gcp](http://www.fda.gov/oc/gcp).

A workshop on this draft guidance, sponsored by the FDA, was conducted on November 27, 2001 at Bethesda, Maryland. The FDA speakers in the workshop were Drs. Gregory Campbell, Susan Ellenberg, Mary Foulkes, Jay Siegel, and Robert Temple. The external speakers in this workshop

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included fifteen representatives from academia, industry, NIH, and the Veterans Administration. The public was invited to comment on the draft guidance at the meeting. The slides presented by the FDA speakers at this workshop can be found on the FDA web page [www.fda.gov/cber/summaries.htm](http://www.fda.gov/cber/summaries.htm).

## Content of the Draft Guidance

The draft guidance is divided into seven main sections:

- Introduction and Background covers the need for DMCs, provides a brief history of DMCs, and discusses some differences between government versus industry-sponsored trials.
- Determining Need for a DMC discusses when it is advisable to establish a DMC for a given trial. Such criteria as risk to trial participants, practicality of DMC review and assurance of scientific validity are discussed.
- DMC and Other Oversight Groups contrasts the responsibilities of other committees with regard to clinical monitoring and oversight to that of a DMC. The groups that are specifically mentioned are IRBs, clinical trial steering committees, endpoint assessment/adjudication committees, site/clinical monitoring, and others with monitoring responsibilities.
- DMC Establishment and Operation, by far the longest section of the document, covers many of the pragmatic aspects of a DMC's operation. This includes discussions on committee composition, confidentiality of interim data and analyses, establishment of standard operating procedures, and potential DMC responsibilities. To support the authors' recommendations, many of the underlying issues are discussed at length with reference to further discussion in the section on Independence of the DMC (see below).
- DMCs and Regulatory Reporting Requirements discusses the regulatory requirements for safety reporting to the FDA and interaction with the FDA on therapies considered for expedited development.
- Independence of the DMC outlines why it is desirable for a DMC to be independent from the sponsor and/or Steering Committee. It also discusses the value of sponsor interaction with the DMC, risks of sponsor exposure to interim comparative data, conduct of interim analyses, sponsor access to interim data for planning purposes and use of interim data in regulatory submissions.
- Sponsor Interaction with FDA Regarding Use and Operation of DMCs outlines when a sponsor should consult with the FDA on matters regarding the DMC. Specifically mentioned are planning the DMC, accessing interim data, and DMC recommendations for protocol changes.

## Selected Highlights

### *Determining the Need for a DMC*

The draft guidance suggests that there are several factors

relevant to determine the need for a DMC and these factors relate primarily to "safety, practicality, and scientific validity". With regards to the safety, it suggests several possible considerations where there could be potential risk to trial participants. In terms of practicality, it elaborates on specific cases when the trial duration may be short and a DMC might not have adequate opportunity to contribute.

### *Composition of DMC*

As the draft guidance states—"A DMC may have as few as three members, but may need to be larger when representation of multiple scientific and other disciplines, or a wider range of perspectives generally, is desirable". The guidance describes the issue of conflicts of interest in choosing individuals to serve on a DMC. In this regard, it calls for the sponsors to have established procedures in place to assess potential conflicts of interest of proposed DMC members and to provide disclosure to all DMC members of any minor conflicts that are not thought to impede objectivity. With regards to individual members, the draft guidance suggests that the study sponsor usually appoints the DMC chair, with more importance placed on requirement of prior experience for the DMC chair so that other members will look to the chair for leadership on administrative and scientific issues. It also recommends that if the DMC has only one statistician, then the statistician have prior DMC experience as well.

### *Format of Interim Reports to the DMC and Potential DMC responsibilities*

The guidance suggests that the DMC should have access to the actual treatment assignments for each study group. It argues against the use of only coded assignment information that permits the DMC to compare data between study arms but does not reveal the actual treatment assignments. For the sake of protecting against inadvertent unblinding, the guidance recommends that the DMC receive unblinded treatment codes separately when needed and the interim reports should present results using codes.

### *Independence of the DMC*

The draft guidance emphasizes the independence of the DMC from the sponsor by providing several advantages of having an independent DMC. It argues the risk of further unblinding and hence a substantial risk to the integrity of the trial when the sponsor is exposed to unblinded interim data, whether it be a small group or a single individual within the sponsoring organization. It further cautions against the use of the sponsor's statistician to perform the unblinded interim analyses for the DMC and recommends that the "integrity of the trial is best protected when the statistician preparing unblinded data for the DMC is external to the sponsor, especially for critical studies intended to provide definitive evidence of effectiveness."

*(continued)*

If the sponsor requires access to interim data, while FDA permission is not required, the draft guidance recommends a discussion with the FDA regarding the potential risks and implications of that action, and of methods to limit the risks may contribute to informed decision making.

#### ***Presentations by FDA members at the DMC Workshop***

As mentioned before, some members of the FDA presented excerpts of the draft guidance at the DMC workshop held in November 27, 2001. All of these presentations can be obtained from the FDA CBER web site previously mentioned above.

Of specific note is Dr. Jay Siegel's presentation on the "Independence of the DMC". It provides case examples that illustrate the risks of sponsor exposure to interim comparative data.

#### **Related Reading**

The subject of DMCs and their role in clinical trial monitoring has been discussed in a number of recent publica-

tions (such as those given below). Many additional references are given in their bibliographies.

The 23rd Annual Meeting of Society for Clinical Trials was held on May 12-15, 2002. This meeting had a session titled "Data Monitoring Committees: Composition and Independence" that featured speakers and discussants from academia, industry and the FDA. More information on this meeting could be obtained from the web site <http://www.sctweb.org>.

#### **References**

Fisher, M.R., Roecker, E.B., and DeMets, D.L., *The Role of an Independent Statistical Analysis Center in the Industry-Modified National Institutes of Health Model*. Drug Information Journal, Vol. 35 pp. 115-129, 2001.

Wittes, J., *Data Safety Monitoring Boards: A Brief Introduction*. Biopharmaceutical Report, American Statistical Association, Vol. 8, No. 1, pp. 1-7, 2000.

## Section News

### Letter from the Chair

**Bob Small**

This is my first letter to the Section and it comes at a very interesting time for us. The Section has grown a great deal and has had a number of significant successes. It is also faced with a number of problems and issues that will require difficult decisions and hard work to allow the Section to continue to prosper.

I will begin by reviewing some of the major proceedings and accomplishments of the recent past and highlighting some upcoming events of the Section. I will not make the effort in this space to thank and recognize all of the people who have made significant contributions to the Section in the recent past. That will take a lot of ink and I will do it in a future letter. I will mention just a few who have done some outstanding things for us.

The biggest section event was the moving of our Fall workshop due to the September 11th tragedy. We had actually considered canceling it but Greg Enas and Anna Nevius pulled their Program team together and managed to move the whole meeting to January with out one change in the Program. This proved to be a truly amazing accomplishment. The Program was one of the most ambitious so far with a number of parallel sessions and a very diverse set of speakers. In the end, the move of date proved successful, as we did not lose a single speaker and we had over 400 attendees, making it the best attended workshop so far.

In addition to the workshop, we have had a number of other program successes. The Spring ENAR meeting in Alexandria featured three sessions sponsored by the Section. This is the most we have ever had at an ENAR meeting. Len Oppenheimer has also done an outstanding job as

Program Chair for the upcoming JSM in New York. We have four sponsored invited sessions and a large number of Topic Contributed and Contributed sessions. We also have three courses and I urge you to look on the ASA Web page to review the description of the courses. This year all registration is online and there is some concern that members will miss the various ancillary events at the JSM.

The workshop did highlight a problem in the section finances, however. For a number of reasons we ended up losing over ten thousand dollars on the event. This is a devastating blow since the original idea was to make money on the event to finance other projects of the section. It comes at a time when we lost revenue because of other changes. We used to make money on the sale of the Proceedings from the Section's sessions at the JSM but now the ASA has decided to put all Proceedings on a CD and offer it at registration. This is an appropriate idea and takes advantage of technology to more easily distribute the work of the ASA. We do end up losing income though.

We also suffered a second unexpected loss of income. We had had a number of corporate members in the Section. Recently the ASA prohibited Corporate Members in the Sections. This resulted in the loss of several thousand dollars in income.

Among the changes that we are instituting this year to address these financial problems are a delay in the Industry FDA workshop until the fall of 2003. We felt that the Fall was, for a number of reasons, by far the best time of the year to have the meeting. At the same time we did not believe that we could put together an acceptable meeting in

*(continued)*

the shortened time caused by the move of this past year's event. Delaying until 2003 will give us a chance to put together a great meeting with an acceptable budget. We have also begun exploration of a Corporate Sponsor program, which is allowed as a replacement for the Section Corporate membership program. We are also reviewing possibilities for reduction in costs. One thing that we are considering is making the Biopharmaceutical Report an exclusively electronic document. This would save several thousand dollars in mailing and printing costs. Though I dislike mentioning it we will also be reviewing the dues for the section. We still have very low dues compared to other sections and they are still lower than they were a number of years ago when we cut them. Even a substantial increase would not get them to the level of six or seven years ago.

I want to thank all of the officers and committee members for the tremendous work they have been doing and also would like to thank the members of the Section who contribute in numerous ways for making this one of the most active and successful Sections of the Association.

## Volunteers Needed ENAR/ASA 2003

Want to be a part of the invited Biopharm program in 2003? This might seem like a long way away, but deadlines for drafts of invited programs are due in only a few months. Volunteer yourself or recommend a colleague. We need topics for invited sessions along with suggested speakers and potential organizers. We also need suggestions for short courses (suggested speakers appreciated!)

Please email your ideas ASAP to Stacy David at [David\\_Stacy@Lilly.com](mailto:David_Stacy@Lilly.com).



**WWW.**

**URL for ASA  
Biopharmaceutical Section**

**Nandita Biswas**

*Web Master for Biopharmaceutical Section*

The url for ASA Biopharmaceutical Section webpage has changed from: <http://asabp.best.vwh.net/index.htm>

To: <http://www.amstat.org/sections/SBIOF/>.

Old page now forwards to new address after 5 seconds.

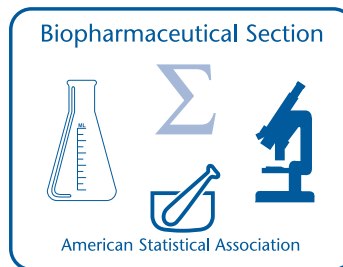
Please update your bookmark

## Announcements



### 10th Merck-Temple Conference November 22, 2002

The 10th Merck-Temple Conference, November 22, 2002, will be held in the Greater Philadelphia Area. Buffet lunch, parking, and breaks included with registration. Speakers are: David DeMets (Univ. of Wisconsin); Ingram Olkin (Stanford Univ.); Sanat Sarkar (Temple Univ.); Keith Soper (Merck); Anastasios Tsiatis (North Carolina State Univ.); and Scott Zeger (Johns Hopkins Univ.). Charges: \$80; \$25 for full time graduate Students; \$40 from Merck; \$60 from AstraZeneca, Janssen, and Wyeth. For further information contact Boris Iglewicz, telephone (215) 204-8637, or website starting in June [www.sbm.temple.edu/~bio-stat](http://www.sbm.temple.edu/~bio-stat). Send registration check, address, e-mail address, telephone, fax number to: Boris Iglewicz, Biostatistics Research Center, Department of Statistics, Temple University, 1810 North 13th Street, Philadelphia, PA 19122.



### Short Courses Sponsored by the Biopharmaceutical Section at the August 2002 JSM Meeting in NYC—Sign Up Early To Insure Seat.

**Saturday: August 10th 8 AM–4 PM**

Design and Analysis of Quality of Life Studies in Clinical Trials: Diane Fairclough  
(University of Colorado Health Sciences Center).

**Monday: August 12th 1 PM–5 PM**

Introduction to Molecular Biology and Bioinformatics Studies for Analysts: Emmanuel Lazarides (IARC)

**Tuesday: August 13th 1 PM–5PM**

Statistical Methods for Microarray Studies: Emmanuel Lazarides (IARC)

# ASA CONTINUING EDUCATION

## Continuing Education Program Seeks Student Monitors for Continuing Education Courses at JSM

The 2002 Joint Statistical Meetings—Continuing Education Program seeks student monitors for its educational presentations. CE presentations will be held at the Sheraton New York Hotel and the New York Hilton and Towers—in New York City, New York from Saturday, August 10 to Tuesday, August 13.

Student monitors are expected to:

- Attend a brief mandatory monitor training session on-site where important and last minute information will be explained.
- Be available for the entire presentation.
- Pick up materials, textbooks, etc. for presentation.
- Process registrants—check them into the course, hand out required materials and respond to inquiries
- Distribute, collect, and tabulate evaluations.
- Insure registrants requesting continuing education units complete mandatory time requirements.

Student monitors will be allowed to audit one course of equal length for every course he/she monitors (Note: the course being monitored must be a different course from the one being audited).

If you are interested in participating, provide your name, current and summer mailing addresses, email and phone number to Madge Haven, Education Manager. Send your information either by email to [madge@amstat.org](mailto:madge@amstat.org) or by fax to 703-684-3768.

Monitors will be sent notification of acceptance. They will also be asked to select the presentation to monitor and the course he/she wishes to audit.



## Joint Statistical Meetings August 11–15, 2002 New York City, New York

### Key Dates for JSM 2002:

**June 1, 2002**—Draft manuscripts due to session chairs for all regular and topic contributed papers and any invited papers with discussants

**July 5, 2002**—Last day for early bird registration forms to arrive at the office

**July 6, 2002**—Advanced registration fees apply

**July 19, 2002**—Hotel reservations and advanced registration deadlines

**July 20, 2002**—On site registration fees apply

For details, see: [www.amstat.org/meetings/jsm/2002](http://www.amstat.org/meetings/jsm/2002)

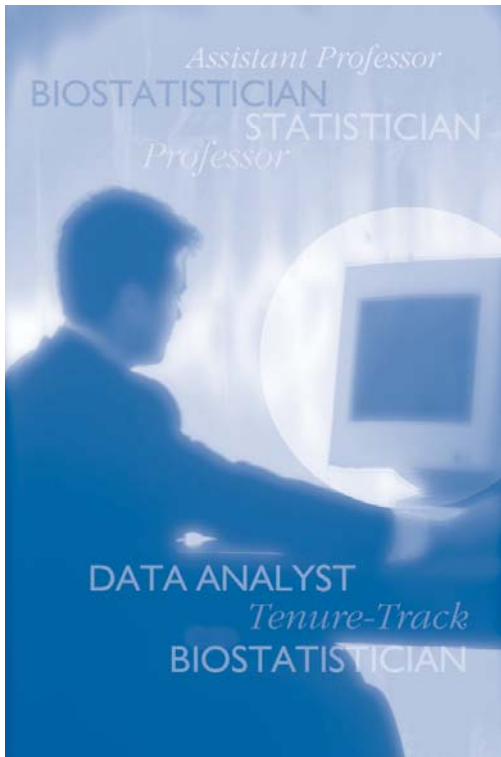


# ONLINE ADVERTISING

## The ASA JOB WEB

### *ASA's New Online Career Center!*

Searching for a quality employee? Now there is a virtually instant way to reach qualified potential employees with your employment opportunities. The ASA JOBWEB will give employers access to an extensive online database of resumes from quality individuals looking for careers in the statistical field. You will be able to locate great candidates without leaving your desk. Post your job openings in the database to reach many qualified job seekers specializing in various areas of statistical practice.



- **Advertise Your Job Openings** through ASA JOBWEB.
- **Create and Maintain Your Company Account** to post and manage your job listings.
- **Utilize Enhanced Job Detail Screens** to include your company logo, profile, and a link to your Web site.
- **Search the Resumes of Qualified Statisticians**...our resume database consists of registered job seekers that submitted their resume to the resume database. (This database will be available but will take time to become populated with resumes, as this service is new to both employees and job seekers).
- **Use Application Delivery to automatically receive job seeker applications** via email including skills ranking data, a cover letter, text resume, and any other documents the candidate chooses to submit.
- **Resume Search Agent...employers can set up and save different sets of search criteria** and they can be notified by email when new resumes are put into the system that match their criteria.
- **Job Management Reports...employer accounts offer job management information** including the number of times a job has been viewed and the number of online applications they received for a job, as well as job posting and closing dates.

The pricing structure is kept simple to streamline the posting process. The costs are as follows for each calendar month of appearance. Any ads that meet the deadline requirement for *Amstat News* will appear both online and in print for the regular classified advertising rate below. Please note that there is no limit to words used in your online ad, however your print ad must not exceed 65 words including contact information but not your EOE statement.

Non-Profit Organizations (with proof of status)..... \$440 per month

For-Profit Organizations..... \$650 per month

Job Seekers will be able to View Your Jobs...searching by keyword, job category, type of job, job level, state/country location, job posting date, and date range of job posting.



**SIGN UP STARTING MAY 1<sup>ST</sup> at <http://jobs.amstat.org/>**

Monthly costs for online ads are determined by how many calendar months the ad appears (not necessarily 30 days). For example, an ad submitted by a non-profit organization on October 10 to be posted online from October 15 through November 15 will be charged \$880 (\$440 x 2), since the ad appeared in two calendar months. Online ads are not commissionable and member discounts are not given.

# Chapters & Sections

Visit the joint Chapter & Section information booth at JSM in New York for their latest information. Chapter and Section members will be available to answer your questions, distribute pamphlets and brochures, display sample Section newsletters and past issues of the Council of Chapters' quarterly newsletter LINK which are displayed on the Internet, exhibit Chapter and Sections membership applications to join, as well as a short COC Careers in Statistics PowerPoint presentation online. Officer rosters will be available for viewing as well as updating information.



All Chapter and Section officers may pick up a new officer ribbon for their name badge at the booth as well. In addition, there will be free prizes for the first 25 visitors to the information booth, as well as some chocolates for everyone.

ASA has 79 Chapters that are the geographical groups of members spread throughout the U.S. and Canada. Twenty-one Sections of the ASA represent a common interest area of members from all over the world.



# JSM 2002

## Let's Hear from You!

If you have any comments or contributions, contact Editor Neal Thomas, Principal Statistician, Biostatistics, Bristol-Myers Squibb PRI, 5, Research Parkway, Wallingford, CT 06492; Phone 203-677-7270; email: [neal.thomas@bms.com](mailto:neal.thomas@bms.com); Associate Editor Kevin W. Anderson, Director of Biostatistics, Axio Research Corporation, 2601 4th Avenue, Suite 200, Seattle, WA 98121; Phone 206-577-0238; email: [kevina@axioresearch.com](mailto:kevina@axioresearch.com); or Past Editor Kannan Natarajan, Director, Biostatistics, Bristol-Myers Squibb PRI, P.O. Box 5400, Princeton, NJ 08543; Phone 609-818-4299; email: [kannan.natarajan@bms.com](mailto:kannan.natarajan@bms.com).

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