### Topics

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<th>Timing</th>
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<tr>
<td>Welcome / Introductions</td>
<td>10:00-10:10 AM</td>
<td>JPMA Mr. Inagaki</td>
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<tr>
<td>• Introduction: Harvard DSMB Program</td>
<td>10:10-11:10 AM</td>
<td>Barbara Bierer</td>
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<td>• Ethics Committees and DSMBs</td>
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<td>• When do you need a DSMB?</td>
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<td>• DSMB Membership and Responsibilities</td>
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<td>• US Regulatory Perspective on DSMBs</td>
<td>11:10am-12:10 PM</td>
<td>Bob O’Neil</td>
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<td>• MRCT Perspectives on DSMBs</td>
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<td>LUNCH</td>
<td>12:10pm - 1 PM</td>
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<td>• Japan Regulatory Perspective on DSMBs</td>
<td>1:00pm-1:30pm</td>
<td>Yuki Ando</td>
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<tr>
<td>• Monitoring for Safety &amp; Efficacy</td>
<td>1:30 – 2:30 PM</td>
<td>Yoko Tanaka, Toshi Tominaga</td>
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<td>• Monitoring for Futility</td>
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<td>• Japan Industry DMC Practices</td>
<td>2:30pm -3:00pm</td>
<td>Osamu Komiyama</td>
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<td>BREAK</td>
<td>3:00pm -3:15pm</td>
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<td>• EU Perspectives on DSMBs</td>
<td>3:15-4:00pm</td>
<td>Richard Kay</td>
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<tr>
<td>• Case Studies / Discussion</td>
<td>4:00pm – 4:55pm</td>
<td>Barbara Bierer, Toshi Tominaga, Yoko Tanaka, Participants</td>
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U.S. Regulatory Perspective on DSMB’s

Robert T. O’Neill Ph.D.
Senior Statistical Advisor
CDER, FDA

Japan Data Safety Monitoring Board (DSMB) Training,
Tokyo, Japan, April 4, 2014

Terminology: DSMB = DMC

Focus of talk is on Data Monitoring Committees
and their role in Multi-Regional clinical trials
Outline

◆ Some history of the DMC regulatory experience at FDA
◆ Relevant guidance dealing with DMC’s and MRCT’s
◆ Current gaps in DMC guidance
◆ The PLATO case study of MRCT
◆ Thoughts on future directions for DMC’s and training

Some DMC History

◆ ICH E3 and the Guidance on Format and Content of a Clinical Study (incorporates most of FDA’s 1988 guidance)
◆ FDA meeting on DMC’s and ‘administrative looks’
◆ The AIDS crisis and FDA’s interactions with DMC’s
◆ The FDA Guidance on DMC’s
◆ Division of Scientific Investigations – inspections and auditing of ongoing clinical trials with DMCs (new idea)
◆ Streamlining clinical trials – building quality into a trial
◆ Real time central monitoring of quality – risk based
Three FDA / ICH guidance documents deal with aspects of data monitoring committees and / or interim analysis. One deals with the MRCT.

- E3 deals with reporting results to FDA
- E9 deals with planning and study design
- FDA DMC guidance deals with operations and practices
- E5 deals with foreign data and the MRCT
Guideline for the Format and Content of the Clinical and Statistical Sections of New Drug Applications - July 1988

Interim analyses and data monitoring

...Therefore, all interim analyses, formal or informal, by any study participant, sponsor staff member, or data monitoring group should be described in full, even if the treatment groups were not identified. The need for statistical adjustment because of such analyses should be addressed. Minutes of meetings of a data monitoring group may be useful (and may be requested by the review division).

Thus, the issues of concern to FDA might be classified as planning of trials, reporting and documentation of completed trials, and operational issues such as:

1. Unreported interim analysis.
2. Planned or unplanned interim access to unblinded comparative study results for a variety of drug development reasons, some of which might be judged as non-inferential.  
3. Unplanned interim statistical analysis whose impact on study results is not assessed.
4. Unblinded access to study results which might bias the future conduct of that trial, for example, dropping of centres with poor relative efficacy results.
5. The recognition by all relevant parties of the regulatory implications of early termination of trials. These include the robustness of observed results to additional analyses that may be required; more importantly, there is the regulatory need for quick access to trial data so that major decisions, such as withdrawing a drug from the market or making a new drug available, can be accomplished in a timely manner.
6. Development of efficient, effective communication and information flow between DSMBs and the FDA, especially in areas of life-threatening disease and accelerated access to drugs.
7. Appropriate evaluation of exploratory trials (as opposed to confirmatory trials) in which the learning process must be accounted for by establishing specific decision points in the drug development process.
8. Planning trials not to stop early for efficacy reasons alone but to balance the need for safety data on longer term exposure with short term follow-up of early efficacy results.
9. Establishment of policies regarding access to ongoing data, access to unblinded data, and participation in the decision-making chain.
- Who maintains the study database, the randomization and assignment codes, and what sponsor staff, including statisticians charged with the data analysis given to the DMC, will be present at closed DMC meetings?
- What firewalls are in place to limit access to important trial comparative data?
- Whether the data analysis plan has appropriate stopping rules and planned interim analysis strategies.
- The plans and strategies for analyzing safety information, especially for events that are primary or secondary endpoints of the trial and any role the DMC has for evaluating serious unexpected events, or reporting their conclusions regarding such events.
- Whether there were differences between FDA and EMEA advice, and how they were resolved.

*Interactions between the DMC and sponsor, or DMC, sponsors and FDA, and potential changes in protocol depending on results.*

- What are appropriate interactions between CDER, sponsor, and study monitors; whether CDER should attend meetings of sponsors and their DMC [e.g. open vs. closed DMC / Steering Committee meetings].
- Addressing DMC recommendations and sponsor’s subsequent actions?
- Whether CDER should see interim data DMC reports.
- Whether any planned modifications to the study design are conditional on interim, unblinded results.
- Whether any mid-study protocol changes that were made were appropriate.
- Whether a decision to terminate was appropriate.
- Whether, prior to a sponsor reaching their decision, all identifiable important issues have been examined by the DMC when they make a recommendation for early study termination.
- What are potential difficulties that may arise in the clinical development program from an early termination that is being considered.

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*STATISTICS IN MEDICINE*


*Regulatory perspectives on data monitoring*[^1]

Robert T. O’Neill[^2]

In the early 1990s, most of the discussions in the statistical and clinical trial literature concerned models and methods for monitoring large publicly funded mortality and endpoint trials. Since there was little in the literature that concerned the process of data monitoring and interim analysis as carried out by the pharmaceutical industry, it was decided that these evolving issues needed broader input. On 24–25 February 1992, the FDA held a public workshop [4] in conjunction with the Pharmaceutical Manufacturer’s Association (PMA) on the topic of clinical trial monitoring and interim analysis in the pharmaceutical industry supported trials. This meeting was attended by over 1000 participants and it was the first time the FDA publicly addressed how the pharmaceutical industry was utilizing data monitoring strategies including the statistical methods in monitoring clinical trials and how the processes and procedure for monitoring trials sponsored by the pharmaceutical industry were implemented. A position paper from the industry, under the Writing Committee chairmanship of Ronald Kershner, reflected the issues and concerns at that time, and a meeting in 1993 at the National Institutes of Health on data monitoring covered some of the industry [5, 6] and regulatory concerns [7].
The Practice of ‘Administrative Looks’ was discouraged

The FDA learned from this workshop that many pharmaceutical sponsors had no written standard operating procedures for monitoring trials either for those monitored externally or those monitored internally. Even the application of statistical methods of interim analysis of the trials were not well understood among a broad sponsor population. Thus the workshop served the purpose to stimulate most large sponsors to develop these procedures and for the FDA to signal that they were expected to do so. There was also a confusion that the FDA was encouraging interim analysis of trials, and even perhaps early termination of trials. This was not the case. Rather, the FDA’s intention was to raise the level of understanding of when it may be appropriate to do interim analysis, and if it were done that it be planned in advance and statistically appropriate methods be employed. At the time there was a clear lack of communication between the statistical community and the clinical development community with a perception that monitoring was a statistical issue alone. In fact, data monitoring is a multidisciplinary effort.

FDA does not want to know about unblinded interim data results during the conduct of a RCT until it is completed (with rare exceptions)

ON COMMUNICATION BETWEEN DSMBS AND THE FDA

In a number of situations, particularly in life-threatening diseases, there is a blurring of trial ‘phases’ so that even early phase II studies may form the basis of a submission to the FDA. It is therefore important for the FDA to maintain an awareness of the progress of a study but at the same time not interfere with the decision makers regarding its progress or termination. Individual situations often dictate how the FDA should be involved with DSMBs but I believe a general consensus is that the FDA should not and does not want to be a routine observer nor a voting member in a DSMB. It may be useful, however, to identify a FDA representative as a liaison. For this relationship to function smoothly there needs to be some familiarity with the DSMBs organization and agenda. Routine actions and activities of a DSMB would not involve the FDA beyond communications and attendance at ‘open’ sessions and blinding of the FDA representative would be maintained. This arrangement in a liaison role would enable the FDA to be informed at appropriate times and be prepared for potential actions.

Much of the recent thinking on this matter has derived from involvement in the AIDS area, particularly with various National Institutes of Health trials and especially with the ACTG programme of the National Institute of Allergy and Infectious Diseases in which a very good yet protected information flow between the FDA and NIAID has occurred.
Published in 1998, ICH E9 addressed many issues

Table I. Key areas of discussion in the ICH E9 guidance.

- Group sequential designs – Section 3.4
- Trial monitoring and interim analysis – Section 4.1
- Interim analysis and early stopping – Section 4.5
- Role of independent data monitoring committee – Section 4.6

Table II. Key issues in E9 related to trial monitoring and interim analysis.

- Oversight of the quality of the trial
- Breaking of the blind for treatment comparisons
- Each type involves different staff and access to different information
- Control of statistical and operational bias
- Plans in the protocols and/or amendments to prevent bias
- Distinguishes two types of monitoring
ICH E9 addressed many issues (cont)

Table III. Key issues in E9 related to interim analysis and early stopping.

- Definition of interim analysis and various goals of interim analysis
- Concepts of stopping boundaries and flexible alpha spending functions
- Interim analysis is a confidential process, staff involved in trial conduct should be blinded
- Most trials for efficacy should proceed to full completion of planned accrual
- Only subset of trials may need sequential monitoring of comparative treatment
- Need for external IDMC and special care for sponsor monitored trials to manage information
- Strong recommendation against unplanned interim analysis

Table IV. Key issues in E9 related to independent data monitoring committees.

- Written operating procedures and maintenance of records of all meetings and interim results available for review at trial completion
- Discussion of independence of external committee, sharing information and access
- Composition of the committee – clinical trial scientists including statistician
- Caution when pharmaceutical reps are on the IDMC – SOPs to control dissemination of information

Guidance for Clinical Trial Sponsors

Establishment and Operation of Clinical Trial Data Monitoring Committees

Issued in 2006

Did not anticipate MRCTs nor adaptive designs
3.2. Clinical Trial Steering Committees

In some clinical trials the sponsor may choose to appoint a steering committee; this committee may include investigators, other experts not otherwise involved in the trial, and, usually, representatives of the sponsor. A sponsor may delegate to a steering committee the primary responsibility for designing the study, maintaining the quality of study conduct, ongoing monitoring of individual toxicities and adverse events, and, in many cases, writing study publications. When there is a steering committee, the sponsor may elect to have the DMC communicate with this committee rather than directly with the sponsor. Interactions between the steering committee and the DMC consist primarily of discussions during "open sessions" (see Section 4.3) of DMC meetings and the communication of recommendations following each DMC review of the trial. More extensive interactions might occur when early termination is being considered, or when external forces (e.g., announcement of results of related studies) impact the ongoing trial.
4. DMC ESTABLISHMENT AND OPERATION

4.1. Committee Composition

The selection of DMC members is extremely important, as DMC responsibilities relate to the safety of trial participants. A poorly constituted DMC may fail to note problems that should be addressed, or may make recommendations that are unwarranted or whose consequences are inadequately considered, thereby undermining the safety of participants as well as the value of the trial. The ability of DMCs to provide the anticipated additional assurance of patient safety and trial integrity therefore depends on appropriate selection of DMC members.

The sponsor and/or trial steering committee generally appoint members of a DMC. Factors to consider in the selection of individuals to serve on a DMC typically include relevant expertise, experience in clinical trials and/or serving on other DMCs, and absence of serious conflicts of interest as discussed below. The objectives and design of the trial and the scope of the responsibilities given to the DMC determine the types of expertise needed for a particular DMC.

Most DMCs are composed of clinicians with expertise in relevant clinical specialties and at least one biostatistician knowledgeable about statistical methods for clinical trials and sequential analysis of trial data. For trials with unusually high risks or with broad public health implications, the DMC may include a medical ethicist knowledgeable about the design, conduct, and interpretation of clinical trials. Prior DMC experience is important when considering the committee as a whole; it is highly desirable that at least some members have prior DMC service. Prior DMC experience is particularly important for the statistical DMC member if there is only one statistician serving on the DMC.

Some trials may require participation of other types of scientists. Toxicologists, epidemiologists, and clinical pharmacologists, for example, could be included in particular cases when such expertise appears important for informed interpretation of interim results.

One or more individuals (often non-scientists) who may help bring to the DMC the perspectives of the population under study may be a useful addition in some settings. Generally, such a DMC member would not also be a participant in the trial, since awareness of the accumulating data could affect compliance or other aspects of trial participation. Rather, the member could be someone with the disease or condition under study or a close relative of such an individual, for example.

4.2. Confidentiality of Interim Data and Analyses

As described in 21 CFR 314.126(b)(5) (drugs) and 21 CFR 860.7(f)(1) (devices), sponsors of well-controlled studies should take appropriate measures to minimize bias. Knowledge of unblinded interim comparisons from a clinical trial is generally not necessary for those conducting or sponsoring the trial; further, such knowledge can bias the outcome of the study by inappropriately influencing its continuing conduct or the plan of analyses. Unblinded interim data and the results of comparative interim analyses, therefore, should generally not be accessible by anyone other than DMC members or the statistician(s) performing these analyses and presenting them to the DMC (see id.). Consistent with 21 CFR 314.126(b)(5) (drugs) and 21 CFR 860.7(f)(1) (devices), sponsors should establish written procedures, which may be included in the DMC charter, to ensure the minimization of bias, such as maintaining confidentiality of the interim data (see Section 4.3.1.4). Sponsors may, of course, also address such confidentiality issues in written agreements between the sponsor and members of the DMC as well as written agreements between the sponsor and investigators.
Concerns

◆ Firewalls and operational bias
◆ Autonomy of DMC
  ◆ Multi-regional clinical trials – not part of the DMC mandate – we hear that DMC’s should stick to what they were asked to do – DMC’s may say they don’t know if it is the sponsor’s request or the FDA’s request – confusion, clarification, disagreement may not be adjudicated – path to resolution
◆ Loose practices where firewalls break down and the importance of training of members
◆ Documenting the trust factor
The Trust Factor

The negative impact of not maintaining confidentiality - effects on study conduct and bias and trust in the results.

Quiet Doctor, Lavish Insider: A Parallel Life

Speaking in front of a packed convention hall in Chicago, a top Alzheimer's researcher, Sidney Gilman, presented the results of a drug trial that had the potential to change the fate of elderly patients everywhere.

But as he worked through the slides, it became clear to the audience on that day in July 2008 that the drug was not delivering and that its makers, Elan and Wyeth, could lose out on blockbuster profits. Along with other Wall Street analysts in the front rows, David Modowsky texted messages to clients to dump shares of the companies. "I can remember gasping" at the results, Mr. Modowsky said.

Little did anyone in the room know that 12 days earlier, Dr. Gilman had e-mailed a draft of the presentation to a trader at an affiliate of one of the nation's most prominent hedge funds, according to prosecutors, allowing the fund, SAC Capital, and its affiliate to sell over $500 million of Elan and Wyeth stock before Dr. Gilman's public talk.

Last month, the trader was arrested on insider trading charges after Dr. Gilman agreed to cooperate with prosecutors to avoid charges.

While he appeared a grandfatherly academic, Dr. Gilman, 80, was living a parallel life, one in which he regularly advised a wide network of Wall Street traders through a professional matchmaking system. Those relationships afforded him payment of $250,000 more a year — on top of his $250,000 pay from the University of Michigan — and travels with limousines, luxury hotels and private jets.

The riddle for Dr. Gilman's longtime friends and colleagues is why a nationally respected neurologist was pulled into the high-rolling life of a consultant to financiers and how he, by his own admission, arrived there less than 10 years before.

"My first reaction was, 'That can't possibly be right,'" said Dawn Kleinberger, a former student of Dr. Gilman's at Michigan.

What is clear is that Dr. Gilman made a sharp shift in his late 60s, from a life dedicated to academic research to one in which he accumulated a growing list of financial firms.

A Stock's Rise and Fall

Sidney Gilman, a top Alzheimer's researcher, oversaw the trials for a drug developed by Wyeth and Elan that had the potential to help Alzheimer's patients. Just days before publicly presenting disappointing results from the drug's trial in 2008, Dr. Gilman provided the data to Matthew Martoma, a trader affiliated with SAC Capital, prosecutors say, allowing Mr. Martoma to sell the stock and avoid big losses. Related Article.

Elan stock price

<table>
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<tr>
<th>Date</th>
<th>Event Description</th>
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<tbody>
<tr>
<td>JULY 17, 2008</td>
<td>Dr. Gilman provides Mr. Martoma with a PowerPoint file containing trial results for the Alzheimer's drug.</td>
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<tr>
<td>JULY 20</td>
<td>Dr. Gilman publicly presents the trial results at an event in Chicago.</td>
</tr>
<tr>
<td>JULY 20</td>
<td>Mr. Martoma's hedge fund finishes selling off its holdings of Elan and Wyeth stock.</td>
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Prosecutors allege that Martoma got "sneak peeks at drug data" before other investors via phone calls, e-mails and PowerPoint presentations from an 80-year-old neurology professor at the University of Michigan Medical School who was overseeing the drug's clinical trial, as well as providing consulting services to the hedge fund via a so-called expert networking firm, where he "moonlighted" for $1,000 an hour.

In announcing the criminal charges, Preet Bharara, the U.S. Attorney for the Southern District of New York, said Martoma and his hedge fund benefited from "what might be the most lucrative inside tip of all time." Also Tuesday, the SEC filed a parallel civil complaint, charging Martoma, CR Intrinsic, and the neurologist, Dr. Sidney Gilman, who is cooperating with prosecutors.

The complaint references Martoma speaking to the "hedge fund owner where he was employed" about his "recommendation" to sell shares of Elan and Wyeth after receiving the illegal inside information on July 17, 2008, that the Phase II trial of the drug did not go as well as Wall Street was expecting. The complaint alleges that on July 21, 2008, both Martoma and the "hedge fund owner" instructed a trader at the firm to sell its entire positions of Elan and Wyeth before the public dissemination of the trial results, scheduled for release on July 29, 2008.

The hedge fund ended up selling 10.5 million shares of Elan and 7 million shares of Wyeth. The hedge firm also placed a big trade that would allow it to profit if the stock fell in value once the bad news on the drug trial findings went public. And that's what happened. Shares of Elan plunged 42% and Wyeth fell 12% in the first trading day after the drug's poor trial results were made public.

The Q & A addendum to E5

Guidance for Industry

E5 – Ethnic Factors in the Acceptability of Foreign Clinical Data

Questions and Answers
Key Features of the Q & A’s

◆ Clarified some points of ambiguity in the initial guidance - indicated more experience needed and we would learn more

◆ Introduced the multi-regional trial concept for bridging - actually that design is very prevalent today - but also potentially problematic to interpret if not planned or conducted well

Guidance for Industry
E5 – Ethnic Factors in the Acceptability of Foreign Clinical Data
Questions and Answers

Q11: There seems to be an impression that the E5 bridging study would always be conducted after data in the original region is complete. Is this correct?

It may be desirable in certain situations to achieve the goal of bridging by conducting a multi-regional trial under a common protocol that includes sufficient numbers of patients from each of multiple regions to reach a conclusion about the effect of the drug in all regions. Please provide points to consider in designing, analyzing and evaluating such a multi-regional trial.

A11: Bridging data should allow for extrapolation of data from one region to another.
Although E5 speaks generally to extrapolation of data to a new region, E5 was not intended to suggest that the bridging study should necessarily follow development in another region. In the answer to Q1, it is made clear that it is also possible to include earlier studies conducted in several regions in a global drug development program so that bridging data might become available sooner. This can expedite completion of a global clinical development program and facilitate registration in all regions. A bridging study therefore can be done at the beginning, during or at the end of a global development program. For a multi-regional trial to serve as a bridging study for a particular region, it would need to have persuasive results in that region, because it is these regional results that can convince the regulators in that region that the drug is effective, and can “bridge” the results of trials in other regions in the registration application.
A multi-regional trial for the purpose of bridging could be conducted in the context of a global development program designed for near simultaneous world-wide registration. The objectives of such a study would be: (1) to show that the drug is effective in the region and (2) to compare the results of the study between the regions with the intent of establishing that the drug is not sensitive to ethnic factors. The primary endpoint(s) of the study should be defined and acceptable to the individual regions and data on all primary endpoints should be collected in all regions under a common protocol. In instances where the primary endpoints to be used by the regions are different, data for comparison purposes on all primary endpoints should be collected in all regions.

For a study intended to serve as a bridging study, the following points should be considered:

**Planning**

The multi-regional trial would have to satisfy requirements of the region where the application is to be filed with respect to design and analysis (see answer to Q1). In general, a multi-regional study should be designed with sufficient numbers of subjects so that there is adequate power to have a reasonable likelihood of showing an effect in each region of interest. Minor differences in design (e.g., age inclusion criteria, concomitant medication, etc.) may be acceptable and prior discussion with regulatory agencies is encouraged. For safety evaluation, it is important to make as uniform as possible the method for collection and assessment of safety information among regions.

**Analysis**

Given the goal of the multi-regional bridging study, it is critical to provide efficacy and safety results by region, with attention given to the usual analyses (e.g., demographic and baseline variables, patient disposition). It will be of interest also to examine consistency of effects across regions. In a dose response study, it will be especially important to analyze dose response relationships for efficacy and safety both within the regions and across the regions.

**Evaluation**

It is difficult to generalize about what study results would be judged persuasive, as this is clearly a regional determination, but a "hierarchy of persuasiveness" can be described.

1. **Stand Alone Regional Result**

   The most persuasive would be demonstration of the effect in the entire study, with the results of each region of interest also demonstrating a statistically significant result. It will also be important to compare results across regions.

2. **No Significant Regional Result But Similar Results Across Regions**

   With an effect demonstrated in the entire study, an analysis of results by region might not show a significant result in a region of interest but the data might nonetheless be persuasive to regulators in that region. Consistent trends in endpoint(s) intended for comparison across the regions or, in the case of a dose-response study, similar dose-response relationships across regions, might support an argument that the drug is not sensitive to intrinsic or extrinsic ethnic factors. Other data, for example, from approved drugs in the same class within region(s) could support such a bridging conclusion.
Regulatory oversight
Components

◆ The protocol, statistical analysis plan, DMC charter, firewall process and procedures
◆ The study report
  ◆ Compliance with stated plans
  ◆ Minutes
  ◆ Interim data set and/or analyses
◆ Regulatory audit, inspection, assurance of quality and integrity

Some suggestions for enhancing the trust in DMC infrastructure

◆ New paradigms for in trial oversight or regulatory inspections – not when the trial is completed but when it is ongoing – observe the process and/or the type of firewall in place – not intended to be punitive
  ◆ Perhaps to start with current confirmatory RCTs with DMCs for which FDA has oversight under the IND process – obtain experience with the DMC model first -
Possible future considerations

- Certification of DMC members just as current investigator regulations require
- Penalties for DMC members breaking confidentiality
- Taking a closer look at the constraints sponsors place on DMC’s
  - Who controls the action
- Modify and update the current guidance to address issues
- Auditing strategies –
- Monitoring multi-regional trials special considerations – quality assurance, agreements on auditing quality, dealing with and planning for heterogeneity

Interactions among sponsor, DMC and FDA

- The sponsor hires the DMC, its chair, and contributes to the charter
- Usually the DMC does not interact with FDA – sometimes the chair may seek FDA feedback but not about unblinded data decisions
- FDA reviews the protocol, the DMC charter, membership, along with the study design and interim analysis plans
- Sponsor may seek advice if DMC recommends changes to design
Challenging issues where there is no regulatory position or guidance

- Monitoring consistency of treatment effects in MRCT
- Composition of membership of MRCT – which regions are represented – all cannot feasibly be accommodated
- Qualifications of DMC member – not written in regulations such as investigator qualifications – DMC guidance addresses some issues
- Confusion regarding what is FDA’s position vs. sponsor’s interpretation to DMC

How might the EMA guidance on subgroups (heterogeneity - region) apply to the MRCT and to training of DMC members (and steering committees dealing with study design)

Guideline on the investigation of subgroups in confirmatory clinical trials
DRAFT

23 January 2014
EMA/CHMP/539146/2013
Committee for Medicinal Products for Human Use (CHMP)

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<tr>
<td>Draft Agreed by Biostatistics Working Party</td>
<td>September 2013</td>
</tr>
<tr>
<td>Adoption by CHMP for release for consultation</td>
<td>23 January 2014</td>
</tr>
<tr>
<td>Start of public consultation</td>
<td>03 February 2014</td>
</tr>
<tr>
<td>End of consultation (deadline for comments)</td>
<td>31 July 2014</td>
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Executive summary

1. Investigation into the effects of treatment in well-defined subsets of the trial population is an integral part of clinical trial planning, analysis and inference that follows the inspection of the primary outcome of the trial. The guideline should assist in the planning and presentation of these investigations and in the understanding of factors to be discussed when considering the credibility of findings.

2. The more homogeneous the population studied, in terms of baseline risk and in terms of response to treatment, the lower the importance of exploratory subgroup analyses for regulatory assessment. The more heterogeneous the study population, the greater the importance of subgroup analyses to check that the estimated overall effect is broadly applicable and supports assessment of risk-benefit across the breadth of the proposed indication. Exploration of heterogeneity should include covariate-adjusted analyses and subgroup analyses.

3. Methodological complications related to multiple analyses mean that exploratory investigations into effects in subsets of the trial population must proceed with caution taking into consideration all available evidence, not only the point estimates from individual subgroup analyses. Despite the statistical complications, not investigating, or ignoring results of subgroup analyses could also lead to incorrect decisions.
Case study based upon PLATO Study
A multi-regional clinical trial with differential treatment effects and what to make of it?
A several year effort in the evaluation process

Ticagrelor versus Clopidogrel in Patients with Acute Coronary Syndromes

This study and topic went before FDA’s Cardio-Renal Advisory Committee on July 28, 2010
The results regarding the primary end point did not show significant heterogeneity in analyses of the 33 subgroups, with three exceptions (Fig. 2 in the Supplementary Appendix). The benefit of ticagrelor appeared to be attenuated in patients weighing less than the median weight for their sex (P=0.04 for the interaction), those not taking lipid-lowering drugs at randomization (P=0.04 for the interaction), and those enrolled in North America (P=0.045 for the interaction).
The Advisory Committee is asked to opine on the approvability of ticagrelor to reduce thrombotic events in patients with acute coronary syndromes or myocardial infarction, whether treatment is intended to be medical management or percutaneous coronary intervention (PCI).

The support for this claim comes primarily from PLATO, a randomized, event-driven double-blind comparison of ticagrelor (180 mg loading dose plus 90 mg twice daily) and clopidogrel (300 or 600 mg loading dose plus 75 mg daily), on a background of aspirin (anywhere from 160 to 300 mg loading plus 75 to 325 mg daily). The primary end point was time to first event of cardiovascular mortality, myocardial infarction, or stroke, tested with α=0.05 (adjusted for one interim analysis). Overall results were as follows:

<table>
<thead>
<tr>
<th></th>
<th>Clopidogrel n=9291</th>
<th>Ticagrelor n=9233</th>
<th>HR</th>
</tr>
</thead>
<tbody>
<tr>
<td>CV death, MI, stroke</td>
<td>10.9%</td>
<td>9.3%</td>
<td>0.84 0.77-0.92</td>
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<tr>
<td>MI</td>
<td>6.4%</td>
<td>5.4%</td>
<td>0.84 0.75-0.95</td>
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<tr>
<td>CV death</td>
<td>4.8%</td>
<td>3.8%</td>
<td>0.79 0.69-0.91</td>
</tr>
<tr>
<td>Stroke</td>
<td>1.1%</td>
<td>1.3%</td>
<td>1.17 0.91-1.52</td>
</tr>
</tbody>
</table>

1. Please comment on the adequacy of the design and conduct of PLATO. In particular, was follow-up for end point events adequate?
2. Development programs for anti-platelet drugs have sometimes had separate studies for patients with similar characteristics and complications for UA/NSTEMI and STEMI.

2.1. How many separate indications are there here?
2.2. Does the PLATO study, by design, support all of these indications? Is the delay in identifying whether the subject had NSTEMI/UA or STEMI until after randomization problematic?

Most of the documentation for PLATO considers effects in the whole population. If the Committee believes the several settings should be considered separately, then the following 2 questions will need to be considered for each.
3. Overall results for the clinical composite end point in the US differ qualitatively from the results in rest of the world. Considerable effort has gone into post hoc analyses to explain the regional differences. Are there also regional differences with respect to:
4. Do you believe the difference in clinical outcomes between the US and the rest of the world was attributable ...

4.1. the play of chance? There is only one country out of 43 whose results fall outside the 95% confidence limits for a region having the observed number of events. If you think that chance is the most likely explanation, are you sufficiently sure of that to make the overall results to be applicable to the US?

4.2. a difference in dosing of aspirin, which was generally higher in the US? If so ...
4.2.1. Aspirin dose was one factor among dozens explored. How do you adjust for such multiplicities?
4.2.2. How compelling are the external data that the dose of aspirin makes any difference in prevention of thrombotic events?
4.2.3. How do you explain the apparently different effect of aspirin dose on ticagrelor and clopidogrel?

4.2.4. If you think that aspirin dose is the most likely explanation for the discouraging results in the US, do you feel sufficiently sure that when administered with a low dose of aspirin, Brilinta will provide a clinical advantage over clopidogrel in the US population?
4.3. ... some other identifiable factor?
4.4. ... some unidentified set of population and care factors?
5. Please comment on the safety profile for ticagrelor compared with that of clopidogrel. In particular, please comment on ...

5.1. ... the incremental risk of bleeding.
5.2. ... dyspnea.
5.3. ... bradycardia and ventricular pauses.
5.4. ... hyperuricemia.

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**NDA 22-433 Brilinta® (ticagrelor) Efficacy Review**

Cardio-Renal Advisory Committee Meeting

July 28, 2010

Robert P. Fiorentino, MD, MPH

CDER, DCRP

**Outline**

- Regulatory context of PLATO
- Subgroups relevant to the proposed indication
  - Outcome by index ACS Event
  - Outcome by Medical vs. Invasive Management
  - Accrual & Timing of benefit compared to clopidogrel
- Regional Differences (US vs. non-US)
- ASA-ticagrelor treatment interaction hypothesis
NDA 22-433 Brilinta® (ticagrelor)
Cardio-Renal Advisory Committee Meeting
July 28, 2010
Jialu Zhang, Ph.D.

A Play of Chance?
- Total primary events: 1878 (151 in US)
- Treatment-by-US interaction is significant (p=0.0095)
- 3 countries had estimated HR ≥ 1.27
  - Australia (N=92), Taiwan (N=83) and US (N=1413)
  - P(HR≥1.27 in US | true HR=0.84) < 0.006

PLATO: No Factor Potentially Accounts for the Regional Interaction with the Exception of ASA Maintenance Dose During Therapy
The Vote

6. VOTE: Should ticagrelor be approved for reduction of thrombotic events in patients with UA/NSTEMI intended to be managed by PCI

The Committee Members suggested that the Voting questions (questions: 6, 7 and 9) be changed to the following. The FDA and the Chair agreed with the change.

6A Should ticagrelor be approved for reduction of thrombotic events in patients with non-ST-elevation and ST-elevation Acute Coronary Syndrome (ACS) intended to be managed by PCI?

7 people voted for approval 1 person voted against approval (there were no abstentions). Some members expressed the need to address the US versus non-US results and the ASA dose issues in a post-approval trial.

6B Should ticagrelor be approved for reduction of thrombotic events in patients with non-ST-elevation and ST-elevation, ACS intended to be managed medically?

7 people voted for approval 1 person voted against approval (there were no abstentions). Some members expressed the need to address the US versus non-US results and the ASA dose issues in a post-approval trial.

10.3. ... how the US results are to be described.

The majority of the committee members stated that there should be no limitations on its use with the caveat that language about US vs non-US results should be included.

Next steps

FDA requested that the sponsor retrospectively collect, as best as possible, the maintenance dose data on aspirin use over the entire duration of the PLATO trial.

Recall that aspirin use was not a stratified factor and that maintenance doses could vary within a subject, and may be missing in the records.
Issues dealt with in Dr. Temple’s decisional memo

- Addressing Dr. Stockbrige’s issues
- Addressing sponsor’s presentations and positions at the advisory committee
- Use of the statistical reviewer’s analysis and findings
Similar pattern of treatment effects in relation to ASA maintenance dose in US and Non-US

US results in the ≤ 100 mg ASA group are very similar to the OUS low dose results and results for ASA ≥ 300 mg are uniformly adverse, favoring clopidogrel both in the US and OUS. Results for the two components of the primary endpoint are shown in the following table.

<table>
<thead>
<tr>
<th></th>
<th>ASA ≤ 100</th>
<th>ASA ≥ 300</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>US</td>
<td>OUS</td>
</tr>
<tr>
<td>Primary</td>
<td></td>
<td></td>
</tr>
<tr>
<td>C</td>
<td>9.1% (24/263)</td>
<td>9.4% (699/7443)</td>
</tr>
<tr>
<td>T</td>
<td>6.7% (19/284)</td>
<td>7.3% (546/7449)</td>
</tr>
<tr>
<td>CV Death</td>
<td></td>
<td></td>
</tr>
<tr>
<td>C</td>
<td>2.7% (7/263)</td>
<td>4.1% (302/7443)</td>
</tr>
<tr>
<td>T</td>
<td>2.1% (6/284)</td>
<td>2.8% (209/7449)</td>
</tr>
<tr>
<td>NFMI</td>
<td></td>
<td></td>
</tr>
<tr>
<td>C</td>
<td>6.8% (18/263)</td>
<td>5.5% (413/7443)</td>
</tr>
<tr>
<td>T</td>
<td>4.6% (13/284)</td>
<td>4.5% (335/7449)</td>
</tr>
</tbody>
</table>

These results are very impressive on their face, showing great similarity for both components of the composite endpoint between US and OUS results once patients are divided into high and low aspirin

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Interpretation of the aspirin interaction

D. Effect of aspirin dose

The sponsor made a significant effort to establish the aspirin maintenance dose in the US and OUS (this was not easy because ASA dose was not recorded continuously) and in response to our CR letter explored a variety of ways of characterizing the aspirin maintenance dose for each patient. Results were similar for the methods that ignored the day 1 dose and used mean or median values. The sponsor’s conclusion was that the aspirin dose explained essentially all of the regional disparity.

The overall results of the study show a strong interaction with dose, with a graded relationship to dose that has a very high level of statistical significance (p=0.00006) in an analysis using a proportional hazards model with 3 terms: log median ASA dose, treatment, and the interaction between the 2 variables. Other interaction analyses are not as extreme but strongly indicate that higher aspirin doses led to a smaller effect of ticagrelor.
The Decision to Approve

- The advisory committee voted to approve the drug but were concerned about the dose of aspirin and that a second study in the US might be conducted - concern raised that it was not feasible, ethical, or practical, given the time to conduct it.

- If the US results were judged to be due to chance, then that is the basis for approval.

- If the US results were judged to be due to the aspirin dose, then the label should indicate that the drug not be used with higher doses of aspirin.

- While not contraindicated, the labeling describes the results and notes in several places, including a boxed warning, that maintenance doses of aspirin above 100mg appear to decrease effectiveness.

What the label states for indication and warning for aspirin dose

WARNING: BLEEDING RISK
- BRILINTA, like other antiplatelet agents, can cause significant, sometimes fatal, bleeding (5.1, 6.1).
- Do not use BRILINTA in patients with active pathological bleeding or a history of intracranial hemorrhage (4.1, 4.2).
- Do not start BRILINTA in patients planned to undergo urgent coronary artery bypass graft surgery (CABG). When possible, discontinue BRILINTA at least 5 days prior to any surgery (5.1).
- Suspect bleeding in any patient who is hypotensive and has recently undergone coronary angiography, percutaneous coronary intervention (PCI), CABG, or other surgical procedures in the setting of BRILINTA (5.1).
- If possible, manage bleeding without discontinuing BRILINTA. Stopping BRILINTA increases the risk of subsequent cardiovascular events (5.5).

WARNING: ASPIRIN DOSE AND BRILINTA EFFECTIVENESS
- Maintenance doses of aspirin above 100 mg reduce the effectiveness of BRILINTA and should be avoided. After any initial dose, use with aspirin 75-100 mg per day (5.2, 14).
安全性評価に主眼をおいたデータモニタリング委員会の特別研修会

Japan Regulatory Perspective on DSMBs

独立行政法人 医薬品医療機器総合機構
スペシャリスト（生物統計担当）
安藤 友紀

本日の内容

• DSMBに関連する本邦の状況
  – DMCガイドライン作成の背景
• DMCガイドラインの内容
  – 各章の内容と関連する話題
DSMBに関連する本邦の状況

- 以前は、本邦においては欧米と比較して、死亡等のイベントを評価変数とした大規模かつ長期にわたる臨床試験が、それほど多く実施されてきていなかった
  - 中間解析の実施も抗がん剤等の一部の医薬品の開発に限られていた
  - DSMB/DMCが設置される臨床試験も限られていた
- 近年、このような状況が急速に変化し、本邦においてもDMCに関するガイドラインが作成された

DMCガイドライン作成の背景

- 臨床試験をとりまく状況の変化
  - IT技術の発達による迅速なデータ収集
    - Electronic Data Capture（EDC）の利用
  - 中間解析の積極的な実施に関する議論
    - 開発の効率化
    - アダプティブ・デザインの利用
  - 医薬品開発の国際化
    - 大規模国際共同治験への参加
DMCガイドライン作成の背景

• 審査・相談における経験
  – アダプティブ・デザインの利用
  – 適切な安全性データモニタリングの必要性
  – DMC設置の必要性
  – DMC運営の適切性
  – DMCと治験依頼者の関係
  – 統計家の独立性

  DMCの設置、運営の基本的な点に関するガイドラインが必要

DMCガイドライン

• 平成23年度より検討を開始し、2年程度をかけて作成
  – 「データモニタリング委員会のガイドラインについて」（平成25年4月4日薬食審査発0404第1号）
ガイドラインの構成

1. 緒言及び背景
2. DMCの必要性と役割
   1. DMC設置の必要性の判断
   2. DMCの役割と責務
   3. DMC委員の役割と責務
   4. DMCの業務
   5. 臨床試験に関連する他の組織との関係
3. DMCの設置と運営
   1. DMCの構成
   2. 中間データの取扱い
   3. データモニタリング及び勧告の手順と留意すべき点
4. DMCの独立性
   1. DMCの独立性
   2. 治験依頼者との関係
   3. 中間解析を実施する統計家の独立性
   4. 中間解析に伴う統計的留意事項
1. 緒言及び背景

・ガイドラインの目的
  - 治験依頼者（自ら治験を実施する者も含む）により実施される医薬品又は医療機器の臨床試験（治験）における、DMCの必要性、役割、設置と運営に関して現時点での一般的な指針を与える

・経緯
  - 早期の意思決定やデザイン変更に関する議論
  - 医薬品開発の国際化、国際共同治験への参加

  本邦においても、試験途中の判断において重要な役割を担うDMCに関するガイドラインが必要

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1. 緒言及び背景

・「独立データモニタリング委員会」ではない？
  - データモニタリング委員会（DMC: Data Monitoring Committee）
  - 独立データモニタリング委員会（IDMC: Independent Data Monitoring Committee）
  - 効果安全性評価委員会（DSMB: Data and Safety Monitoring Board）

  - DMCは試験実施側と別の立場から実施中の試験データの評価をする。必ずしも治験依頼者から独立している必要はない組織として提案されている

  - 安全性評価が重要となる早期の試験等を含む、広い範囲でのDMC設置も視野に入れ、DMCとした
1. 緒言及び背景

「データモニタリング」
  - モニタリング
    - 臨床試験全体の実施状況の確認
    - 試験実施中の有効性及び安全性データの評価
  - 本ガイドラインでは後者を「データモニタリング」とした

「中間解析」
  - 本ガイドラインでは、群間比較試験におけるデータモニタリングに伴い試験途中で実施される、有効性又は安全性に関する群間比較を意図した、割り付けを明らかにして行う解析、を指す

2.1 DMC設置の必要性の判断

- 全ての臨床試験でDMCによるデータモニタリングが必要となるわけではない
- 必要性について十分に検討するべき
  - 設置には一定の資源が必要、試験管理も複雑化
  - 臨床試験の目的、デザイン、評価変数、試験期間、対象患者集団等を考慮
- 設置される状況の例
  - 中立的な立場からのデータモニタリングが必要とされる、
    - 死亡又は重篤な転帰を評価変数とした比較対照試験
    - 大規模かつ長期にわたる臨床試験
    - 安全性に関する事前情報の少ない初期の臨床試験
    - 医薬品等及び被験者の特徴からリスクが高いと想定される試験
2.2 DMCの役割と責務

- DMCは
  - 被験者の安全性を確保し、
  - 臨床試験の完全性を可能な限り保証するため、
    実施中の試験データを評価し、治験依頼者に対して適切な
    助言・勧告を中立的な立場から行う
- 様々な影響を考慮
  - 社会的な影響、組織的な影響
  - 関係者の知的興味や市場の影響
  - 中止や計画の変更により得られる又は失われるであろう
    知見
- 事前に規定された中止／継続等の意思決定の基準
  以外にも様々な観点から十分に問題を考慮し議論するべき

2.3 DMC委員の役割と責務

- DMC委員に必要とされる点
  - 臨床試験の方法論及びDMCの役割に関する知識
  - 責務を負うに十分な能力
  - 治験依頼者との間に重大な利益相反がない等中立的な
    意見を述べられる立場
- 各自がDMCの役割と責務を十分に理解
  - DMCの判断に及ぼす可能性のある影響
  - 中立的な立場からの議論の必要性
  - 中間解析の結果を知りうる立場であること
    - 情報の漏洩、個別の利益のための利用をしてはならない
- 異なる専門性を持つ複数のDMC委員による、根拠に
  基づく意見、互いの専門性を尊重した議論が重要
2.4 DMCの業務

・安全性モニタリング
  – 安全性上の理由による試験の早期中止の勧告
  – 有害事象発現率の比較
  – 重要な有害事象に関する詳細な検討
  – 有害事象のリスク軽減のための治験実施計画書の変更の勧告

・事前に規定された中間解析に基づく評価
  – 有効性による早期中止
  – 無益性による早期中止

2014/04/04 DMC training

2.4 DMCの業務

・試験実施状況のモニタリング
  – 被験者の登録状況、対象被験者の妥当性、脱落例の発現状況、治験実施計画書の遵守状況等

・外部情報の利用
  – 関連試験の結果等の外部データに基づいた、実施中の試験に対する中立的な立場からの検討
  – 関連試験のDMCとの情報交換の可能性
  – 第一種の過誤の増大や、試験結果の信頼性の確保については留意する必要がある
2.5 臨床試験に関連する他の組織との関係

- 治験依頼者
  - 臨床試験を計画し、その全てに責任を持つ
  - DMCの設置、運営、及びDMCの助言・勧告を受けて試験の中止、計画の変更を決定する責任を持つ
  - 治験運営委員会（Steering Committee又はClinical Trial Steering Committee）を設置できる

- 治験審査委員会（IRB：Institutional Review Board）
  - 臨床試験の各実施施設において、当該施設の被験者の安全性の確保の適切性、臨床試験実施に関する科学的妥当性を審査
  - DMCの設置、役割、勧告を踏まえた試験実施の適切性を検討することができる

- イベント評価（判定）委員会
  - イベント評価の一貫性と客観性の確保のため、イベントが治験実施計画書の基準を満たしているかを、通常、盲検下で評価する
  - DMCによるデータモニタリングとは別

3.1 DMCの構成

- DMC委員の選定
  - 治験依頼者が指名
  - 多くの場合、臨床医と1名以上の統計家の計3名以上で構成
  - 各委員の経験（臨床試験、DMC）、利益相反を考える

- 利益相反の考慮
  - DMCが中立的な立場から正当に意見を述べること、またそれを保証するために利益相反を適切に管理
    - 利益相反の開示
    - DMCが結論に至った過程を事後的に第三者が確認できること
  - 重大な利益相反のある個人を委員にするのは避ける
  - 委員に潜在的な利益相反がある場合、その内容をDMC等に対して開示する
  - 問題とすべき利益相反の程度、委員選定の手順、利益相反に関する情報開示の方法は事前に決定しておくことが望ましい
3.1 DMCの構成

・国際共同治験における留意点
  （後述）
・運営のサポート
  • 事務局の設置
  • 中間解析作業を実際に担う統計家（プログラマー等も含む）
  第三者機関として開発業務受託機関（CRO：Contract Research Organization）等の利用も可能
  CRO等選定の責任は治験依頼者にある

国際共同治験における留意点

• 背景
  日本を含む国際共同治験の実施数が増加
  開発のどの段階の国際共同治験にも日本人が含まれることがあり得る
• 治験相談等で議論となった点
  日本からの国際共同治験参加時点で、日本人における安全性情報が必ずしも十分ではない場合がある
  安全性に関して民族間の差異の可能性がある場合がある
  試験中の安全性評価を慎重に行うべきではないか？
  地域間で何らかの差異が生じた場合に気づくことができるべきではないか？
国際共同治験における留意点

• 「3.1 DMCの構成」における記載
  ー 本来、参加する各地域又は一部地域から委員を選択することが適切
  ー 本邦の専門家がDMC委員として参加することが望ましい
  ー それが困難な場合にも日本人被験者の安全性に関する検討方法等をあらかじめ考慮するべき

• 可能な限りということではあるが、少なくとも地域間の差異の可能性も踏まえ有効性、安全性の評価ができる委員が必要ではないか

3.2 中間データの取扱い

• 臨床実施中に割り付けが明らかにされた結果を知ることによる影響の懸念
  ー 試験実施や結果の解析等への影響、試験成績にバイアスが生じる可能性

• 盲検解除された中間データ、中間解析結果を閲覧できる関係者を制限する必要がある
  ー DMC及び中間解析を実施しDMCに提出する統計家に限定

• 治験依頼者は情報の漏洩を防ぐため、適切な方策を講じる
3.3 データモニタリング及び勧告の手順と留意すべき点

3.3.1 手順書の整備
- DMCは、治験依頼者及びDMCにより合意されたDMCの手順書（DMC charter）に従って活動する
- 手順書の内容
  - DMCの設置目的
  - DMCの構成委員、利益相反の管理、他の試験関係者との関係
  - 会議のスケジュール、会議の形式、出席者
  - 検討対象となるデータ、中間データの解析手順、盲検解除に関する手順
  - 盲検解除された中間データを閲覧できる者
  - 治験依頼者への勧告の手順と治験依頼者の対応
  - 記録の作成と保存
  - 緊急的な会議の開催要件、実施手順

3.3.2 会議の開催
- 公開審議（Open session）
  - DMC委員、治験依頼者の代表者、治験運営委員会、その他の治験関係者等が参加
  - DMCに対し主に試験の実施状況に関する情報を提供
  - 治験依頼者とDMCが試験に関連した外部データを共有する機会
- 非公開審議（Closed session）
  - DMC委員及び中間解析を担当する統計家、DMC事務局が参加
  - 中間解析を担当する統計家から提出された（盲検解除を含む）データについて議論
  - 治験依頼者に提示する勧告内容の検討
3.3 データモニタリング及び勧告の手順と留意すべき点

• 3.3.3 勧告
  - 書面により勧告を行う
    • 試験の継続（計画の修正・変更あり／なし）
    • 試験の一時中断、試験の中止、等
  - 勧告時には盲検性の維持に注意
  - 原則として詳細な試験結果については伝達しない
  - 治験依頼者はDMCから受けた勧告に基づき判断
    • 必要に応じ、治験審査委員会、治験運営委員会、治験責任
      医師等に伝達
  - 勧告を受けて試験の中止、計画の変更等を決定する
    責任は治験依頼者にあるが、その判断による影響について
    検討するにあたり、事前に規制当局に確認することは可能

DMCと規制当局との関係

• DMCによる個々の試験の中止、計画の変更等の勧告に関して、基本的には規制当局が関与することはない
• DMCの勧告を受けて試験の中止、計画の変更等を決定する責任は治験依頼者にある
• ただし、関連する薬剤の臨床試験が実施中である際等、理由によっては個々の試験の中止等の影響が大きい場合もある
• 中止等の判断による影響について検討する際に、治験依頼者が事前に規制当局に確認することは可能
  - 実際の中止に関する情報は規制当局に報告される
3.3 データモニタリング及び勧告の手順と留意すべき点

• 3.3.4 必要な記録
  - DMCに関わる全ての会議の議事録の作成、保管が必要
    • 公開審議の議事録
    • 非公開審議の議事録
      - 事務局及びDMC委員で作成、試験終了後までDMC委員以外には開示されていない
      - 結論に至った過程を事後的に第三者が確認できるよう作成
  - 臨床試験に関する記録におけるDMC
    • 治験実施計画書
      - DMCの役割、少なくともDMC委員長を記載し、詳細は手順書を参照
    • 総括報告書
      - DMC委員の構成
      - データモニタリングの実施内容、勧告内容、治験依頼者の判断
      - 付録としてDMCの手順書、議事録、勧告書面等を添付

審査におけるDMC議事録の確認

• 一部の試験では、DMCの運営、判断が評価の際に重要な位置づけとなる
  - 安全性データモニタリングが重要な試験
  - IDMCによる試験の中止／継続／デザイン変更の判断が予定された試験
• 承認審査において議事録を確認し、適切に運営されていたか確認する場合がある
  - その時点で得られた情報に基づき適切なプロセスを経て結論に至ったか
  - 特にIDMCの運営の適切性が問題になることがある
• 結論に至った過程を事後的に第三者が確認できるよう議事録を作成することが重要


4.1 DMCの独立性

- 治験依頼者から独立したDMC
  - 客観性の高いデータモニタリング
  - 試験成績に対するバイアスの混入を抑え、試験の信頼性を向上させる
  - 被験者の安全性が適切に確保される
- 独立性の確保
  - DMC委員がDMCとしての役割以外で試験デザインや実施に関与しない
  - 治験依頼者との間で重大な利益相反がない
- 独立性を高めるとともに、DMCが詳細な情報に基づき十分な議論ができるよう配慮する必要がある
  - 治験依頼者や治験責任医師等とDMCの間で、一定の制限の下で必要な情報のやりとりが可能とする、等
- 試験の特徴により求められる独立性は異なる

4.2 治験依頼者との関係

- 治験依頼者の役割
  - DMC委員の選定と任命
  - DMCが円滑に機能するための環境を整える
  - DMCの意思決定の独立性を確保
- 勧告を踏まえた判断は治験依頼者の責任
4.3 中間解析を実施する統計家の独立性

- 中間解析を実施する統計家
  - DMC委員以外で盲検解除されたデータが閲覧可能
  - 中間解析の実施において他の関係者がデータを閲覧しないよう適切な管理が必要

- 中間解析を実施する統計家の独立性
  - 試験デザインの設計及び変更についての意思決定や試験の運営管理に関与させないことが適切
    - 中間解析に基づく意思決定に混入するバイアスの最小化
    - 盲検解除された中間データに関する秘密保全
  - 基本的には中間解析を担当する統計家とDMCの統計家は兼任するべきではない

5. 中間解析に伴う統計的留意事項

- DMCの統計家に必要なこと
  - 中間解析特有の問題点の認識
    - 複数回の統計学的検定による第一種の過誤確率の上昇
    - 中間データによる治療効果の過大推定
  - 事前の規定の確認
    - 統計解析計画（中間解析の実施時期、実施回数、統計解析手法等）の妥当性の吟味と、必要な勧告
    - DMCに報告される中間データの有効性及び安全性の解析結果やその提示方法

- DMCの統計家以外の委員も中間解析特有の統計的諸問題を理解しておく必要がある
まとめ

- 一部の臨床試験では、DMCの設置が重要な位置づけとなり、必要に応じて設置を検討するべきである
- 適切な委員を指名し、利益相反は適切に管理することが重要である
- DMC委員は臨床試験、DMCに関する知識、責務をうに十分な能力を持ち、実施中の試験データに基づいて治験依頼者に対して適切な助言・勧告を中立的な立場から行う
- 治験依頼者はDMCを設定、環境整備を行い、DMCの勧告を受けた判断を行う
- DMCが適切に運営され、結論を導くことができたかどうか、議事録等から第三者にも明確になるように配慮する必要がある

おわりに

- 本邦のDMCガイドラインでは基本的な点を記載している
- 臨床試験デザイン、DMCを含む臨床試験実施体制が今後多様化していく可能性がある
- ガイドライン内容も踏まえ、被験者の安全性及び臨床試験の完全性の確保のため、継続的に議論していくことが重要
  - 個々の試験デザインに対し最適な体制
  - デザイン変更を伴う臨床試験の実施
Japan Industry Perspective

Osamu Komiyama
Chairman, Data Science Expert Committee, Drug Evaluation Committee, JPMA

DMC/DSMB: Not common in Japan

• Experiences of DMC/DSMB have been limited in Japan. Because...
  – Historically, few long-term clinical trials addressing mortality and important morbidity have been conducted
    • In most cases, long-term clinical trials = Open label Extension studies (under ICH-E1A)
  – Thanks to the “Drug-lag”, there have been very limited cases, such that the tight situation of having to choose between “continue the study” and “stop the study”.
  – The use of Adaptive Design clinical trials is also limited
Q: Does your company have an experience of **interim analysis**?

<table>
<thead>
<tr>
<th>Year</th>
<th>Yes</th>
<th>No</th>
</tr>
</thead>
<tbody>
<tr>
<td>2009</td>
<td>26</td>
<td>37</td>
</tr>
<tr>
<td>2010</td>
<td>23</td>
<td>39</td>
</tr>
</tbody>
</table>

Q: Does your company have an experience of **Adaptive Design**?

<table>
<thead>
<tr>
<th>Year</th>
<th>Yes, experienced an adaptive design with unblinding.</th>
<th>Yes, only an adaptive design under blinded manner.</th>
<th>No experience</th>
</tr>
</thead>
<tbody>
<tr>
<td>2009</td>
<td>11</td>
<td>2</td>
<td>50</td>
</tr>
<tr>
<td>2010</td>
<td>14</td>
<td>6</td>
<td>39</td>
</tr>
</tbody>
</table>
J-DMC Guideline (issued April 4, 2013)

- 7 years behind US’s and EU’s
- However, best practices were cherry picked from FDA and EMA guidelines to create Japanese DMC guideline
- Added perspective: independence of DMC member
  - Conflict of Interest
  - Importance of documentation, enabling reconstruction of “What DMC did”

To tell you the truth,…

- This added perspective was proposed through public comment by JPMA (based on my experience)
- In my company, I have several experiences of DSMB member or chairman. I had thought…..

COI is clear. I’m an employee.
I will behave honorably
Global Development has become popular

- The settlement reports from 26 JPMA member companies (listed on the first section of the Tokyo Stock Exchange), FY2013 2Q&3Q
  - They boost international sales
  - 42% of total amount of sales is oversees sales

Safety Review in MRCT

J-guideline,
Section 4.1 Committee Composition

When a sponsor establish a DMC in a large MRCT, the DMC should, wherever possible, include representatives from a subset of participating countries or regions. When J-patients are included in such a MRCT, it is preferable that J-expert participates in the DMC as a member, in consideration of J-healthcare environment or known safety profile of the test drug. If not feasible, the sponsor should consider how to evaluate safety of J-subjects prospectively. The value of J-DMC member will be enhanced when special safety monitoring of J-subjects is needed (e.g., J-use experience or safety information is poorer than the other regions).

FDA guideline,
Section 3.1 Committee Composition

Appropriate representation of gender and ethnic groups may be of particular importance for some trials. DMCs for international trials will usually include representatives from at least a subset of participating countries or regions; however, it is often not feasible to have every participating country represented on the DMC. For the reasons discussed at the beginning of Section 4.1, we recommend that the primary criterion for selecting all appointees should be their respective expertise and experience.
**Viewpoints**

<table>
<thead>
<tr>
<th>Monitor</th>
<th>Individual Data</th>
<th>Accumulated (aggregated) Data</th>
</tr>
</thead>
<tbody>
<tr>
<td>Data validation</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Data verification</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Corroboration</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**DSMB**
- To determine the evidence level of causality
- To ensure the safety of the study subjects
- To determine whether there is any value to continuing the trial

**Important safety information**

- **SAE or**
  - It put the patient at risk for developing a clinically significant outcome.

- **Discontinuation due to adverse event**
  - It was severe in intensity.
  - It was sustained rather than transient.
  - The drug effect was large
    - (e.g., a 10 mm Hg mean increase in diastolic blood pressure versus a mean increase of 0.5 mm Hg).
  - The outcome of the drug effect was permanent (caused total blindness) or resulted in sequelae (e.g., decreased visual acuity).
  - The drug effect could not be prevented or minimized (e.g., by reducing the dose).
Basic way of thinking

“You need to be a detective and gather as many *clues* as the data permit. The clues that point to where the evidence might be are *safety signals*.”

“The more clues pointing in the same direction, the greater the likelihood the safety finding is real and not a red herring (false signal).”

Michael J. Klepper and Barton Cobert, Drug Safety Data (2011)
New risk should be tried to find globally. “Find it out from our nation” does not make sense.

Our nation has never experienced such a SAE

- **DO NOT sit on the sidelines**「対岸の火事」と思うな
  – [No!] “It is easy to bear the misfortunes of others”
- **Feel as serious as ever our nation had experienced**
Safety Review in MRCT

“Why does Asia/Japan have high risk?”

After data is accumulated, such a research question arises.

Well-known important risks in Asia/Japan

- the risk of developing **Stevens-Johnson syndrome** is increased in Asians taking the anticonvulsant drugs carbamazepine and phenytoin
- In some anti-cancer drugs or antirheumatic drugs, **interstitial pneumonia** has been more reported in Japan than in the rest of the world
  - It may be true...
  - Excess reporting, because well-known in Japan?
The other DSMB use cases (1)

- Prior to joining MRCT, Japanese phase I study needed?
  - Limited number of Japanese subjects is powerless to identify Japan specific risk or to draw safety profile
  - Skip such a J-Phase I study, and carefully oversee “What occur?” by using DSMB

The other DSMB use cases (2)

- Accommodate a request from FDA’s Final Rule

![FDA](U.S. Food and Drug Administration Logo)
Summary

- Experiences are limited in Japan.
  - We must familiarize people in Japanese community.
- DSMB is not for “sexy” design clinical trials (e.g., adaptive design), but for any clinical trials where subject safety and justification of continuing the trial should be carefully watched
  - Very useful to carefully oversee subjects’ safety during the progression of clinical trials
- In some cases, e.g., exploratory stage, (open-level) long term, internal DSMB may be acceptable
- In MRCT setting, DO NOT treat only Japanese differently, without evidence of high risk in Japanese patients
EU Perspectives on DMCs

Professor Richard Kay, PhD
RK Statistics Ltd
&
School of Pharmacy, Cardiff University

Regulatory Guidance

Guidance for Clinical Trial Sponsors
Establishment and Operation of Clinical Trial Data Monitoring Committees

For questions on the content of this guidance, contact the Office of Communication, Thrombus and Manufacturing Assurance (OTMA) at 020 3755-7570 or 020 3755-1080

U.S. Department of Health and Human Services
Food and Drug Administration
Center for Biologic Evaluation and Research (CBER)
Center for Drug Evaluation and Research (CDER)
Center for Devices and Radiological Health (CDRH)
March 2006

DRAFT AGREED BY THE EFFICACY WORKING PARTY
October 2003 - September 2004

ADPTION BY COMMITTEE FOR RELEASE FOR CONSULTATION
November 2004

END OF CONSULTATION (HEADLINE FOR COMMENTS)
July 2005

AGREED BY WORKING PARTY
June 2005

ADPTION BY COMMITTEE
July 2006

DATE FOR COMING INTO EFFECT
January 2007

See additional PFS statement in Section 8 of this guidance
Regulatory Guidance

- FDA and CHMP guidance in line on major points
- Difference in emphasis on some issues
- FDA guidance more detailed

- Presentation will raise issues from my experience in being involved in set-up and conduct of DSMBs/DMCs
  - In a ten-year period involved in over 50 such committees in mainly drug but also some device trials – 30% based in US, 70% based in EU
  - Link back to regulatory documents as appropriate

Setting up a DMC - 1

- Involve DMC members at the protocol stage
  - Before finalisation, to obtain buy-in
  - Essential that members are comfortable with rationale for study, main design features, stopping rules
  - Must be fully operational before study starts – then responsive to early safety signals

- FDA 'Scheduling the initial meeting of a DMC before the study is initiated has many advantages. At this meeting, the DMC can discuss the protocol and analytic plan, model informed consent form ...’

- CHMP ‘A DMC has to be fully functional before enrolment into the study starts to enable it to respond to any safety signal.’
Setting up a DMC - 2

- Members (or at least most of them) should have prior DMC experience
  - Essential for the chairperson, and the statistician (particularly if there are formal stopping rules)
  - How to gain that experience? Recommend that inexperienced members work alongside experienced members
- FDA ‘Prior DMC experience is more important for the chair than for other DMC members, as members will look to the chair for leadership on administrative as well as scientific issues’
- CHMP ‘In order to facilitate the work of a DMC it is helpful that some of the members, at least the DMC chair, have served on a DMC earlier’

Setting up a DMC - 3

- Other aspects of membership
  - Chairperson should be clinical expert in therapeutic area – guide discussions/communicate accurately to those outside of committee
  - Ideally include Drug Safety specialist – familiar with MedDRA coding and regulatory implications of various decisions
- Duration of involvement
  - In oncology trials, study duration will be several years
  - At what point should the committee be disbanded?
  - DMC will be the only group who see unblinded aggregate information
  - Committee should remain in place until all patients are off treatment or at the point when the database is locked and the sponsor unblinded
Stopping for Efficacy - 1

- Stopping for efficacy, limits overall data
  - Invoking stopping rules for efficacy (usually based on p-value for primary endpoint) limits data available for other considerations
  - Secondary endpoints, efficacy data in subgroups, safety data
  - Important at planning stage to recognise this; if stopping potentially compromises these other issues building in an interim analysis for efficacy may be undesirable
- FDA ‘For trials that may be terminated early because a substantial benefit has been observed, however, consideration may still need to be given to the adequacy of data with regard to other issues such as safety, duration of benefit, outcomes in important subgroups and important secondary endpoints’

Case Study 1 – EGF100151

- Open-label study of Lapatinib (Tykerb) as add-on to capecitabine in advanced or metastatic breast cancer in patients who have received prior therapy which included anthracyclines, taxanes and trastuzumab
- Primary endpoint – TTP (time to progression or death due to breast cancer); OS (overall survival) was an important secondary endpoint
- Sample size 528, two interims planned based on 133 and 266 TTP events (as identified by investigator)
- O’Brien-Fleming type boundaries, $\alpha = 0.0014$ at first IA
Case Study 1 – EGF100151

- First IA (03 April 2006) at 146 TTP events (324 patients recruited) gave \( p = 0.00013 \), factor of 10 below \( \alpha \) cut-off
- DMC recommended stopping further recruitment
- Sponsor adopted recommendation offering Tykerb to patients in the control arm (cross-over)
- Regulatory authorities uncomfortable
  - Subjectivity in progression declared by investigator (open-label study)
  - Lack of mature OS data – cross-over preventing these data being collected

Case Study 1 – EGF100151

- Tykerb approved but with some delays
- FDA *The survival data are not mature for evaluation. As of 03 April 2006, there were 119 deaths occurred. The difference in median survival between the two treatment groups was only 1 week (67.7 versus 66.6 weeks for combination arm vs. capecitabine alone arm; two-sided p-value: 0.177)*
- TTP based on independent assessment gave \( p=0.0076 \)
- Safety profile of Tykerb acceptable
Stopping for Efficacy - 2

- Stopping when boundary not crossed
  - Usually very stringent $\alpha$ boundary (e.g. 0.001) at interim analysis
  - Important that trial not stopped unless this boundary is crossed - can happen when p-value ‘impressive’ compared to conventional 0.05 significance level – destroys control of type I error and will usually destroy the trial as well
- FDA ‘If the DMC recommends early termination for efficacy before a boundary is crossed, however, and this recommendation is implemented, the Type I error cannot be preserved and the study results may be difficult to interpret’

Stopping for Efficacy - 3

- Not stopping when boundary crossed
  - Evidence at interim in terms of $p \leq \alpha$ may be borderline
  - Recognition that data will not be 100% clean and also ‘out of date’
  - Judgement needed in order to make recommendation
- FDA ‘The DMC will usually recommend termination when these thresholds are crossed, but it is not obligated to do so, since other aspects of the interim data may complicate the issue’
Case Study 2 - EMBRACE

- E7389 versus TPC (treatment of physician’s choice) in patients with locally recurrent or metastatic breast cancer previously treated with between 2 and 5 prior chemotherapy regimens including an anthracycline and a taxane
- Primary endpoint – overall survival (OS)
- Sample size based on requiring 412 events, single interim planned at 206 events
- O’Brien-Fleming type boundaries with adjusted α level of 0.003 at interim and 0.049 at final analysis

07/04/2014

Case Study 2 - EMBRACE

- IA using Cox PH model (adjusting for stratification factors) gave p=0.0018 – borderline significant
- Data on which analysis based approximately 8 weeks out of date – Interactive Voice Recognition System (IVRS) provided up-to-date information on numbers of deaths
  - IVRS data gave less separation between groups than seen in association with formal IA
  - Potential that p-value for up-to-date data would not achieve required level for stopping
- No safety concerns – decision taken to continue study
- Final analysis, HR=0.81, p=0.041
- Regulatory approval granted

07/04/2014
Sto\p{pp}ing for Efficacy - 4

- Stopping with a Time to Event endpoint
  - Shape of Kaplan-Meier curves may change over time
  - Differences early in the time scale may diminish later in time
  - Logrank test for treatment differences not optimal in these circumstances
  - Important to see complete Kaplan-Meier curves for full interpretation
  - Stopping at an IA prevents this full interpretation

Source: The Lancet 2011; 377:914-923 (DOI:10.1016/S0140-6736(11)60070-6)

Case Study 2 - EMBRACE

Hazard ratio 0.81 (95% CI 0.66-0.99), p=0.041

ErboAn (n=508)
TPC (n=254)

Deaths: 274 (54%), ErboAn: 148 (58%), TPC

Number at risk
ErboAn
TPC

0 2 4 6 8 10 12 14 16 18 20 22 24 26 28
Time (months)

Overall survival (%)
Functioning of a DMC - 1

14

- Responsibilities for scientific integrity of the study
  - Recruitment rates – in line with expectations?
  - Protocol violations, dropouts, non-compliance, missing data
  - Any differences by site/region in the above?
  - Distribution of baseline factors; are patients representative of targeted study population?
  - Poor quality will also make it more difficult for the DMC to do its job

- FDA ‘A DMC will generally review data related to the conduct of the study (that is, the quality of the study and its ultimate ability to address the scientific questions of interest), in addition to data on effectiveness and safety outcomes’

- CHMP ‘Quality of study conduct is essential to allow a DMC to reach valid conclusions. Thus in performing its task a DMC should consider essential parts of study conduct like e.g. protocol adherence and patient withdrawal’

07/04/2014

Functioning of a DMC - 1

15

- Sponsor will also be looking at these issues
  - Sponsor may have different objectives
  - Issue – recruitment too rapid/number of patients per site too small/difficult to control quality
  - Independent review by DMC gives different perspective

- In EU recruitment in Eastern Europe often rapid
  - Trial gives patients access to treatments otherwise not available
  - Patients may be sicker at time of entry
  - Less access to supportive care
  - May be more tolerant of side effects
  - May wish to recommend a cap on recruitment in certain regions – potential different benefit/risk balance in Eastern Europe

- FDA mentions baseline balance for important prognostic factors
  - Little DMC can do about this
  - But may help to put differences in efficacy/safety profiles into context

07/04/2014
Functioning of a DMC - 2

- Tables/Listings
  - Data to be reviewed may cover several thousand pages
  - Inexperienced DMC members can find this daunting
  - Members should start by reviewing tables – go to listings only if specific patient data needed
- Important Tables
  - Those dealing with Interim Analyses for efficacy
  - AEs/SAEs – MedDRA coding – although tend to be sceptical about tables that focus on ‘AEs related to study medication’ as judged by the investigator
  - Important laboratory parameters (such as the liver transaminases)
  - Tables relating to QTc prolongation
  - Dose Administration tables

Functioning of a DMC - 2

- Tables will be separated by treatment group (coded)
  - Some misunderstanding – both FDA and CHMP recommend viewing completely unblinded data
  - Tables with groups combined of little value
  - Tables which separate out treatment groups but are not decoded can mislead – will certainly waste time
- FDA ‘We recommend that a DMC have access to the actual treatment assignments for each study group’
- Graphs
  - Extremely useful – can reveal much more than tables
  - Especially useful for SAEs, laboratory and QTc data
  - Following examples taken from Amit, et al. (2008)
Most frequent AEs ordered by relative risk

Graphs - 2

Figure 4. Distribution of ASAT by time and treatment.
**Functioning of a DMC - 3**

- **p-Values for safety**
  - Should these be produced?
  - Unless there is a specific pre-specified safety hypothesis, not useful
  - Problems with multiplicity and an excess of false positives
  - Also non-significant p-values may hide differences that could be important clinically – rare events/low power

- **Balancing benefit/risk**
  - If DMC considering stopping for safety concerns may need to review efficacy in order to assess benefit/risk
  - Is there a price to pay for \( \alpha \) under these ‘unplanned’ efficacy analyses and if so, what impact will this have on the final \( \alpha \)?
  - Some sponsors impose a stringent \( \alpha = 0.001 \) for such ‘looks’

**Functioning of a DMC - 4**

- **Data being reviewed will not be 100% clean**
  - Some data cleaning will have taken place
  - DMC need to be aware that data discrepancies will exist in the data they review
  - Some adverse events will be miscoded or not coded at all
  - If data too ‘dirty’ however, DMC cannot do it’s job

- **Data being reviewed will be out-of-date**
  - Data could be up to 2 months out-of-date
  - Often compromise between clean data and timely data – must decide what level of cleaning is acceptable
Functioning of a DMC - 5

- Clinical database versus Safety database
  - Case Report Forms will generate clinical database
  - Sponsors pharmacovigilance department will generate safety database based on reported SAEs
  - Clinical database will be out-of-date, safety database should be up-to-date (maybe only a few days old)
  - There will be discrepancies because of time lag but also cleaning issues
  - Safety database extremely useful – should always be provided

Functioning of a DMC - 6

- Independent statistician providing data for DMC should attend closed meetings
  - Is on hand to provide information when data questions arise
  - Can also take meeting minutes – a good model – frees up the chairperson to chair the meeting
  - Can also have responsibility for archiving meeting reports and minutes to pass over to sponsor once trial complete

- FDA ‘We recommend that the DMC keep minutes of all meetings’
Functioning of a DMC - 7

- Control dissemination of information based on unblinded data
  - Essential to protect integrity of study and avoid bias
  - Independent statistician (preferably external to the sponsor) in place to provide unblinded information
  - Important that recommendation passed back to sponsor at the end of closed session does not reveal unblinded information
  - If recommendation is to stop/modify study then additional information communicated; needs to be managed carefully
- FDA ‘Sponsor exposure to unblinded interim data, through the DMC or otherwise, can present substantial risk to the integrity of the trial’
- CHMP ‘(Such) operating procedures should also describe how the integrity of the study with respect to preventing dissemination of unblinded study information is ensured’

Functioning of a DMC - 7

- Dissemination of regulatory concern
  - Can cause bias and destroy integrity of study
    - Shift in population under study
    - Changes in methods of assessment
    - Changes in recruitment patterns
  - Not uncommon for regulators to compare data before and after an interim analysis (or design change) to assess consistency
  - Responsibility is on the sponsor to demonstrate consistency of treatment effect
Case Study 3 – 2NN Study

- Open-label, randomised trial in patients with chronic HIV-1 infection - investigator initiated study
- Primary endpoint - treatment failure – composite endpoint (virology, disease progression, therapy change)
- Initial design, patients randomised (1-1-1) to
  - nevirapine (once daily) – N1
  - efavirenz – E
  - combination of N1 and E
- Primary comparison N1 vs E
- Nevirapine is the experimental drug, objective to show non-inferior (similarity) to efavirenz
- DSMB – involved in monitoring study, 2 interim analyses

Five months into the trial (388 randomised) another study (comparing N1 (once daily) with nevirapine twice daily) showed effectiveness of nevirapine related to minimum concentration

- 4th arm, nevirapine twice daily (N2), added
- Randomisation from this point on
  - N1, E, N1+E and N2 in ratio 1:2:1:2
- New primary comparison
  - N2 vs E
  - Other comparisons; N1 vs E and N1 vs N2
- Final sample size n=1216
Case Study 3 – 2NN Study

Failure rates before and after design change

Results before and after change different – undermines data for study as a whole

Functioning of a DMC - 8

- Disagreements within DMC
  - Always best to reach consensus
  - Can go to a vote, but only if absolutely necessary
  - Before that, often useful to schedule early re-examination and set down some ‘rules’ on what decisions can then be taken
  - This may involve new/additional analyses – can result in alerting/unblinding sponsor
  - Ideal if independent statistician has pre-approval from sponsor to provide those new analyses (within reason)
Functioning of a DMC - 9

- Problems if sponsor disagrees with DMC recommendation
  - Sponsor can choose to ignore recommendations in relation to efficacy – hopefully with sound arguments
  - Recommendations to stop in relation to safety more problematic – DMC may feel patients at undue risk
  - No clear route for DMC members to take if their recommendations are not followed – grey area
  - Members covered by confidentiality so difficulties in alerting regulators for example
  - FDA only require reporting relating to SAEs be sent on to them
- Recommendation: Safety concerns expressed by DMC should be routinely reported to regulatory authorities (and in a timely manner) – add this statement to guidance documents. Responsibility for actions to be taken then lies with the sponsor

Functioning of a DMC - 10

- Indemnity insurance
  - DMC members could potentially be held legally liable for their recommendations if patients have suffered harm
  - DMC members must have adequate professional indemnity insurance and sponsor should contribute in some way to this
  - Alternatively sponsors, in their contracts with members, should indemnify them against claims from third parties
Summary

DMC Set-up
- Involve members early
- Experience important
- Define duration of involvement

Stopping Rules
- Follow them to avoid destroying the control of α
- Take sensible decisions based on data that is not current nor clean

DMC Functioning
- Some responsibility for trial integrity
- Role of independent statistician
- Dissemination of unblinded data – avoid
- Data presented in graphs in addition to tables/listings
- Issues if sponsor disagrees with recommendations
- Legal protection

References

- EGF100151: Geyer, Forster et al. (2006) NEJM, 355, 2733-2743
Question for the essay for Harvard MRCT Center’s certificate

• ケース・スタディで紹介された事例において、DSMBがどのような検討をもっとすべきだったでしょうか？
  – In the example shown in Case Studies, what kind of consideration/review should the DSMB have done more?

• DSMBをもっと積極的に利用するために、あなたの組織における課題と課題に対する方策を考えてください
  – To use DSMB more actively, what is a challenge in your organization? And how do you tackle with the challenge?

• 日本においてDSMB委員の経験者を増やすためにどのように取り組みが必要でしょうか？
  – To increase the number of people with experience of DSMB member (in Japan), what kind of approach should we take?