Data and safety monitoring and independent study review – regulatory and other practical issues

Sarah Brown
Institute of Clinical Trials Research,
University of Leeds, UK
Monitoring data vs interim data monitoring

- Monitoring data
  - Ongoing, regular, routine
  - Site visits, central statistical monitoring, etc

- Interim monitoring of data
  - Interim analyses
  - Analysis of accumulating, comparative data from trial before primary analysis
Who’s thought about who is going to monitor trial data?

• 1. I’ll let the trials unit do it
• 2. I’ve got all my monitoring committees sorted, thanks
• 3. I’m the PI I’ll look at the data
• 4. I’ll just look at the data at the end
• 5. I need to monitor data?!?!
Oversight committees in a trial

- MRC Good Clinical Practice model

Diagram:
- Data Monitoring Committee
- Trial Steering Committee
- Sponsor
- Funder
- Trials Unit
- Trial Management Group
- subgroup
- subgroup
- subgroup
- subgroup
MONITORING TRIAL DATA
EMEA and FDA Monitoring Guidance

- Effective monitoring of trials is critical to:
  - Human subject protection
  - Conduct of high-quality studies
- FDA Regulations:
  - Obligate sponsors to oversee their clinical trials
  - Are not specific about how sponsors are to conduct monitoring
Approaches to monitoring

• No single approach to monitoring is appropriate or necessary for every clinical trial
• Development of a risk-based approach encouraged
  • Identify critical study data and processes - what matters?
    • Safety
    • Interpretation of results
  • Tailored to specific risks of the trial
    • What could go wrong?
    • What would be the impact?
    • Could we detect it?
• Develop a risk-based monitoring plan
Monitoring Plan

• Describes monitoring methods

• Components:
  • Training and study-specific information
  • Communication of monitoring results
  • Management of non-compliance

• Types, frequency and intensity depend on:
  • Complexity of study design and types of endpoints
  • Clinical complexity of subjects
  • Quantity of data
  • Investigator experience
What data should we monitor?

• Errors that matter:
  • safety
  • interpretation of trial results
SAFETY DATA
Definition of an Adverse Event (AE)

An Adverse Event is defined as:

Any unfavorable and unintended sign including an abnormal laboratory finding, symptom or disease associated with the use of a medical treatment or procedure, regardless of whether it is considered related to the medical treatment or procedure, that occurs during the course of the study.
How do we categorize an adverse event in clinical trials?

**Seriousness**
- Death, life threatening, hospitalization, disability, congenital anomaly, event requires intervention to prevent permanent damage or impairment

**Severity**
- Intensity
- CTCAE grading

**Causality**
- Related to trial treatment?

**Expectedness**
- Reference to Investigator Brochure / Summary of Product Characteristics
Safety Terminology

- **Causality**
  - Expected
  - Unexpected

- **Expectedness**
  - Expected
  - Unexpected SUSAR

- **Seriousness**
  - Serious SAE
  - Non-serious

- **Adverse Event**
  - Related SADR
  - Unrelated
## Safety Reporting Responsibilities

**Investigator’s responsibilities**
- Causality of AEs
- Reporting all adverse events in the source documents and CRFs
- Reporting SAEs within time period specified in the protocol (usually 24 hours)
- Assessment of expectedness (SUSAR)
- Assessment of Dose Limiting Toxicities (phase I)

**Sponsor (CTU) responsibilities**
- Submission of SAEs as reported by the investigator
- Reporting SUSARs to Authorities
- Annual safety reports
- Notifying Ethics committee
Safety Monitoring

• On an individual patient basis
  • Never underestimate adverse event reporting
  • Ensure training of teams for data processing
  • Be alerted on adequate reference document (in clinical trials)
  • Ensure data timeliness

• Reviewing aggregate safety data by arm
  • Independent data monitoring committee
  • Identify trends, concerns, …
INDEPENDENT DATA MONITORING

• Interim monitoring of data
  • Reviewing aggregate, unblinded safety data
  • Interim analyses
  • Analysis of accumulating, comparative data from trial before primary analysis
Hypothetical trial

- Event-free survival
- 65% event-free at 4y
- Improve to 73% at 4y
- Absolute benefit = 8%
- Hazard ratio = 0.73
- 5% alpha (Type I error)
- 15% beta (Type II error)
- 85% power

→ ~437 events

- 5yr accrual
- 2yr min FU
- 7yr to answer

→ ~1430 patients
Hypothetical trial

What if something isn’t right?

7 years = long
1400 patients = many

Check safety
Unacceptable toxicity?

Check efficacy
Convincing results?
Advantages in interim monitoring

Interim analysis
Safety and/or efficacy

Reassurance
Continue as planned

Action
Efficacy
Early access to treatment?

Toxicity
Fewer pts exposed to harm

Lack-of-benefit
Resources focused to alternatives
Disadvantages in interim monitoring

- Repeated looks increase chance of false findings
- Stop too early?

- Help from “Early Stopping Rules”
Group sequential & alpha-spending methods

- Focus on Type I error (false positives)
  - More looks $\rightarrow$ more chances to stop in error

- Control overall alpha by penalising interim looks
  - Alpha is ‘spent’ across the interim looks
  - Differing statistical approaches in how to ‘spend’ alpha

- Translates to formal stopping boundaries
Some stopping rules

![Graph showing some stopping rules](image)

- **O'Brien & Fleming**
- **Haybittle-Peto**
- **Pocock**

Classical standardised test statistic $Z$ vs. Proportion of trial completed (%) (EFS events)

- **Z = 1.96**

Values:
- None
- 87
- 174
- 262
- 350
- 437

In the graph, the classical standardised test statistic $Z$ is plotted against the proportion of the trial completed (%) and the number of Endpoints-Free Survival (EFS) events. The stopping rules represented by O'Brien & Fleming, Haybittle-Peto, and Pocock are shown with distinct lines and critical values for different stages of the trial.
Some problems with stopping rules

1. Tend to focus on stopping early for efficacy
   • Convincing efficacy not a common problem
   • New generally not better than standard

2. Boundaries often symmetric
   • Should as much evidence *against* new treatment be needed to stop trial?

3. Unidimensional
   • Don’t capture totality of data
Informal approach

• Stop trial early if:
  Data would convince people with a range of prior opinions

• Consider:
  • Totality of the data
  • Maturity of the data
  • What is already known from elsewhere

• Convincing data might be $P<0.001$
  • Rather like Haybittle-Peto method
  • “Informal Bayesian” approach to thinking
Points to consider when considering interim analyses

1. Dramatic treatment differences are unlikely
2. Trial stopped on random high?
3. Lack of long-term data
   • Early advantage vs long-term detriment
   • Early toxicity vs long-term benefit
   • Non-proportional hazards (hazard changes with time)
4. Imprecise, wide confidence intervals
5. Unconvincing results
   → Not credible
   → Not able to change practice

• Who monitors all this data?
Data Monitoring Committee (aka DMC/DMEC/DSMB)

- **Responsibility**
  - Review accumulating data
  - Assess safety and efficacy
  - Protect validity, credibility
  - Only group to see interim comparisons by arm

- **Membership**
  - 3 to 5
  - Commonly independent

- **Meetings**
  - Yearly or sooner

- **Advisory**
  - Sees data in a format that is not normally widely shared beyond the core statistical team
  - Privileged position
# Need for independent DMC

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<thead>
<tr>
<th>Independent DMC needed</th>
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<tbody>
<tr>
<td>Life-threatening illnesses</td>
</tr>
<tr>
<td>Vulnerable populations</td>
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<tr>
<td>Significant potential risk of harm</td>
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<tr>
<td>Unknown or uncertain risks</td>
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<tr>
<td>Long-term follow-up</td>
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<td>Survival-based outcome measures</td>
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Practically every cancer trial will need an IDMC, or equivalent
A proposed charter for clinical trial data monitoring committees: helping them to do their job well

Randomised controlled trials (RCTs) are widely accepted as the principal research method for assessment of the effectiveness of healthcare interventions, and monitoring of trial data by data monitoring committees (DMCs) has become common. There are inherent difficulties in decision making when uncertainty exists. Occasionally, DMCs are faced with difficult decisions after the continuation of a major trial, which, in turn, will affect the future evidence base available to guide policy and practice for that clinical setting. Practices in such committees vary widely, however, and no standard approach exists. The UK NHS Health Technology Assessment Programme commissioned the DAMOCLES (Data Monitoring Committees Lessons, Ethics, Statistics Study Group) to investigate the processes of monitoring accumulating trial data and to identify ways of increasing the likelihood that DMCs make good decisions. Several committees have suggested that any DMC would benefit from the development of a standardised operating procedure or charter outlining its mode of operations and the responsibilities of different stakeholders. While explicit guidance has been published on what should be included in such a charter, with the exception of a book by Ellenberg and colleagues, one main aim of the DAMOCLES study was, therefore, to develop a template for a charter to systematically describe the operating practices and procedures of a DMC.

Research strategy

The DAMOCLES study used several complementary strategies to study behavioural and organisational aspects of DMCs and procedural issues of decision makers. These are described fully elsewhere. In brief, we used systematic reviews of published work on DMCs and on small group processes in decision-making surveys of reports of RCTs, of recently completed and ongoing RCTs, and of the policies of major organisations connected with RCTs. Detailed case studies of four DMCs in which difficult decisions were faced (including interviews and interviews with experienced DMC members. At the beginning of the project, we developed a list of 23 questions relating to DMCs, around which the study was structured. These questions fell into three main sections: (i) the role of DMCs, (ii) their structure and organisation, (iii) what information should be available to DMCs and in what form, and (iv) their decision making and reporting in DMCs.

On the basis of the results, we formulated a list of considerations that would be valuable for a DMC to address at the start of a trial. We developed these into a draft charter following the same broad lines as the 23 questions. The draft was piloted on a small number of DMCs by members of the group and refined in view of this experience.

The charter

Full details of the systematic review, the results of the surveys, and the systematic review of small group processes in decision making have been reported elsewhere. Here we present the proposed DMC charter in Appendix A, with short summations of the key points contributing to each of the charter’s ten sections. From the review of published work and the cross-sectional surveys, we could see that various names and descriptors are used to describe the data monitoring process. We propose that groups responsible for data monitoring be given the standard name, Data Monitoring Committee (DMC).

Section 1. Introduction

Section 2. Roles and responsibilities

Section 3. Decision-making

Section 4. Reporting

Section 5. After the trial

Trial details

Roles and responsibilities

Before or early into trial

Composition: membership and independence

Relationships

Organisation of meetings

Documentation, confidentiality and communication
Decision-making

- Agree in advance how “decisions” reached
- “Stopping rules” vs “stopping guidelines”
- IDMC should understand full range of options
  - Consider implications of any recommendations
- Consensus always preferable
- Can non-attending members input?
In summary

• Monitoring data
  • ongoing, regular, routine
  • Safety assessments on individual patient basis
  • PIs / trials unit / trial management group
• Interim monitoring and early stopping rules
  • Check on accumulating, aggregate, interim safety and/or efficacy data
  • Stop trial early for conclusive finding
  • Many statistical guidelines available
• Data Monitoring Committee
  • Independent members
  • DAMOCLES DMC charter
Reading - DAMOCLES


Reading - Websites

• European Medicines Agency. Guideline on Data Monitoring Committees (2005)

• Food and Drug Administration. Guidance for Clinical Trial Sponsors Establishment and Operation of Clinical Trial Data Monitoring Committees (2006)

• National Research Ethics Service Guidelines on Data Monitoring Committees (2010)
Reading - Books
