Trial Oversight Committees

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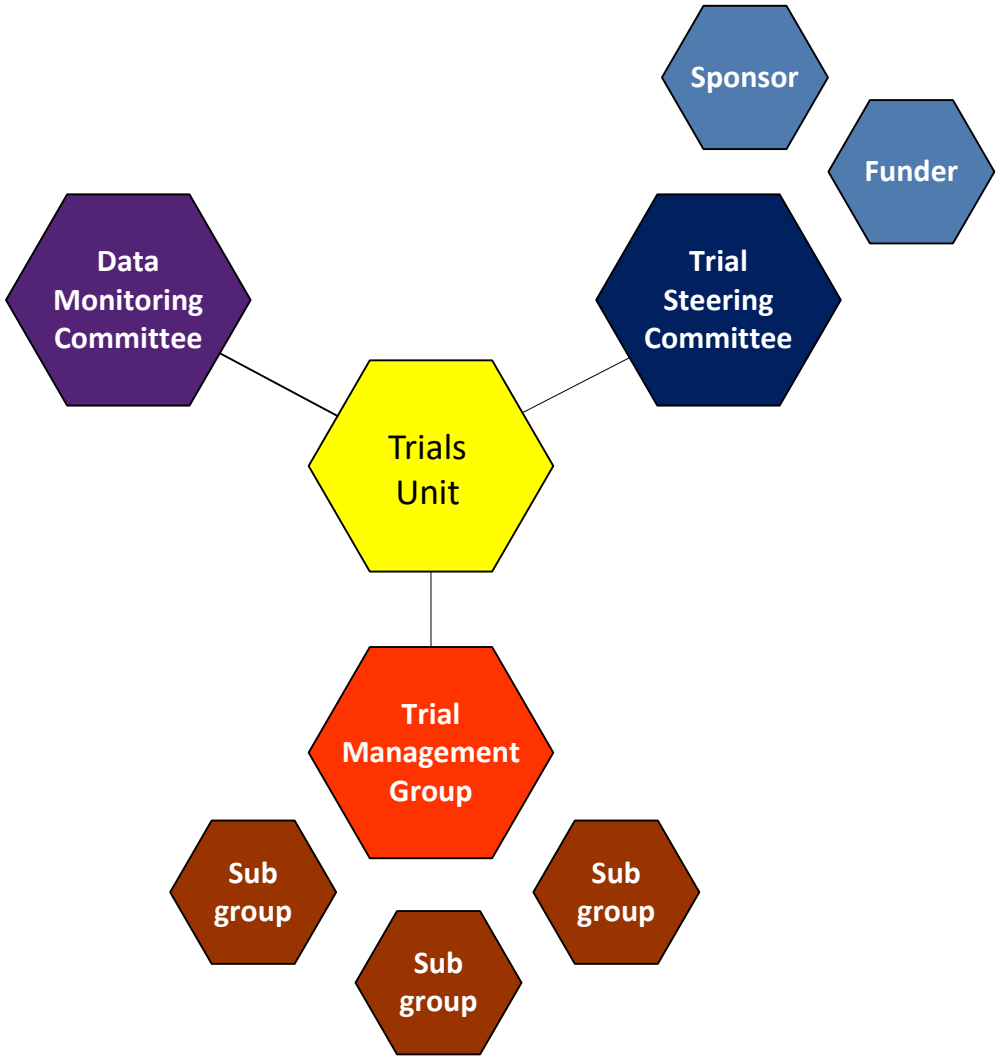
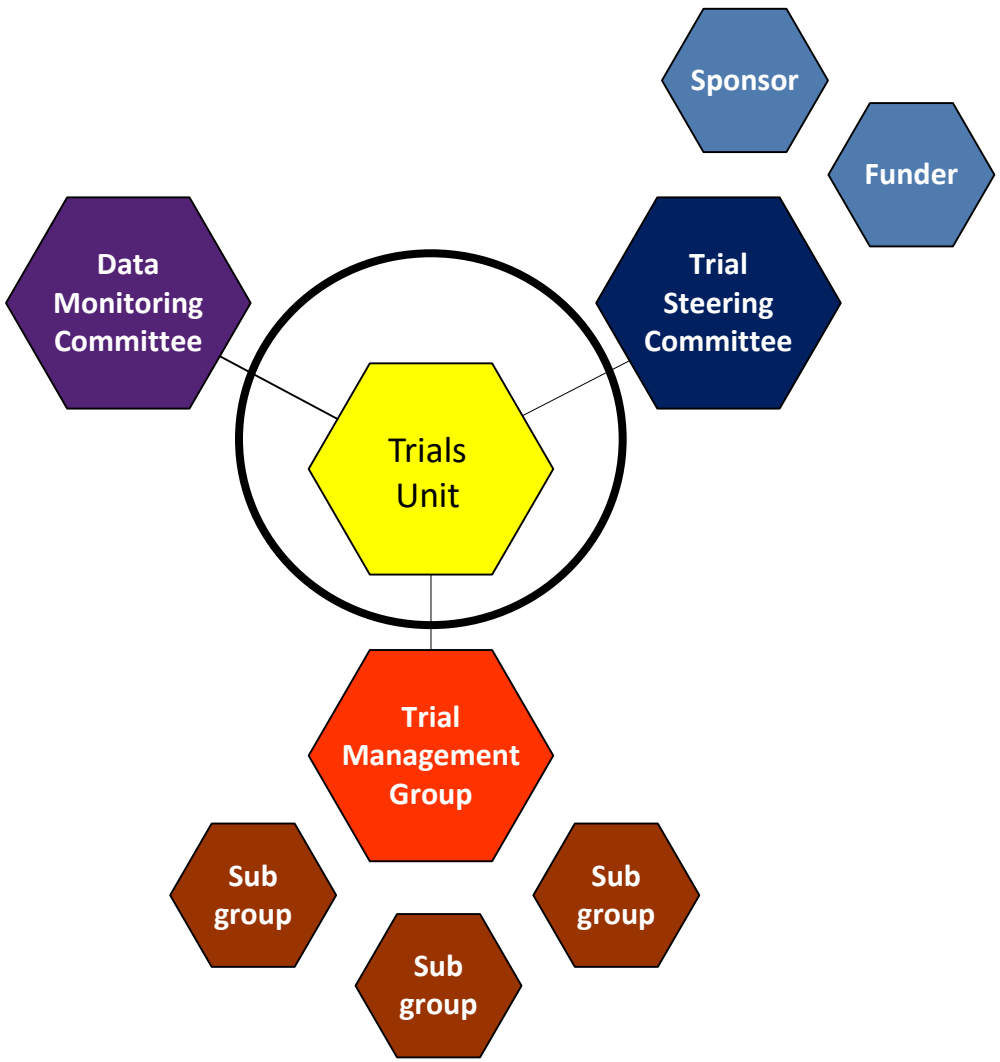
Oversight committees: who makes decisions



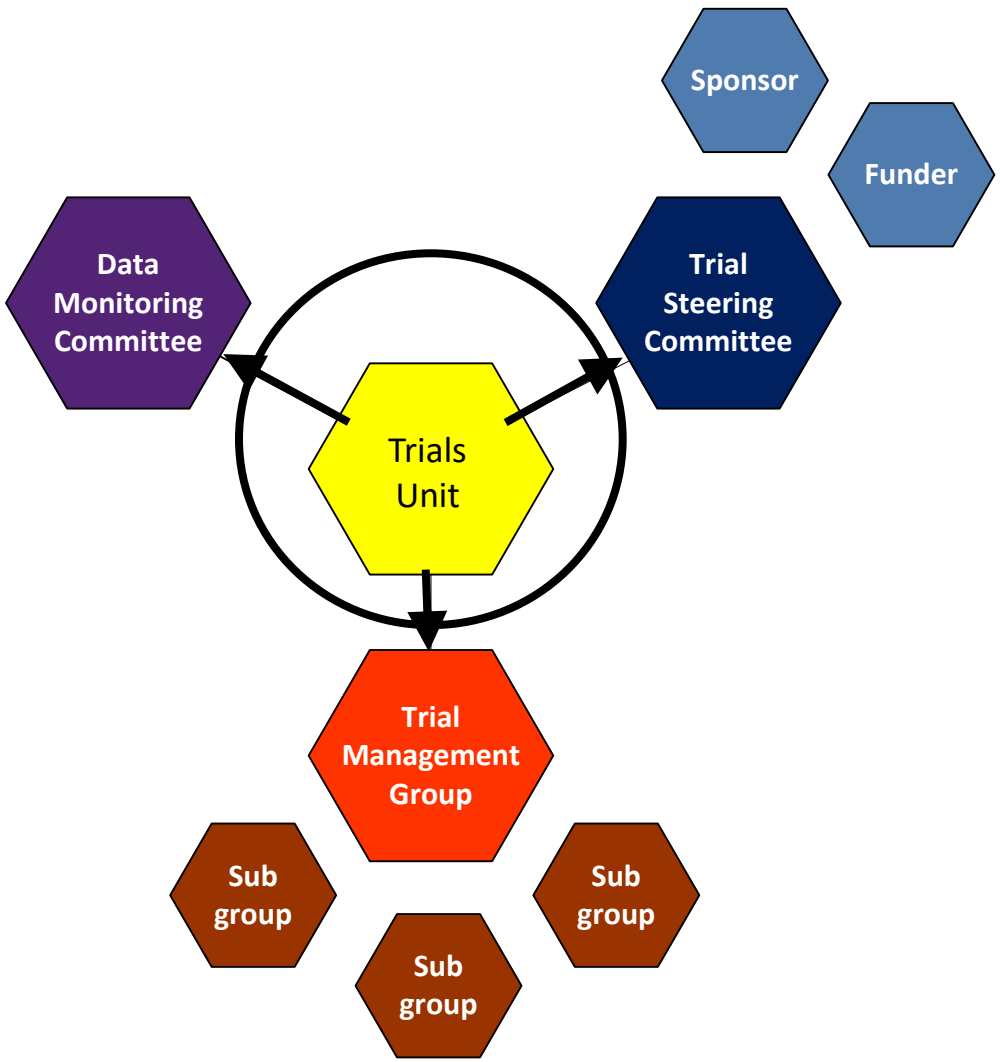
- MRC Good Clinical Practice model
- Many committees
- Variation across trials

Central role



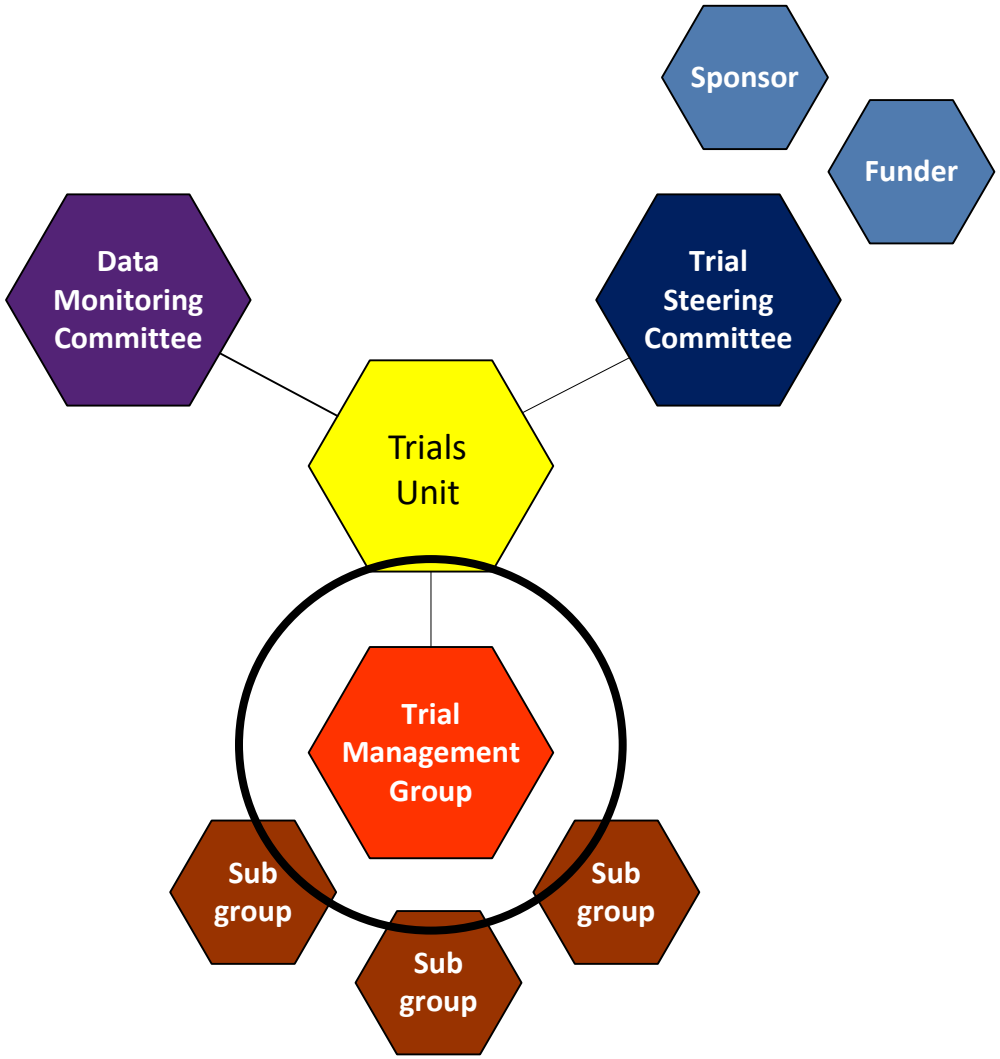
- Trial office central
- Conduit for inter-committee communications

Central role



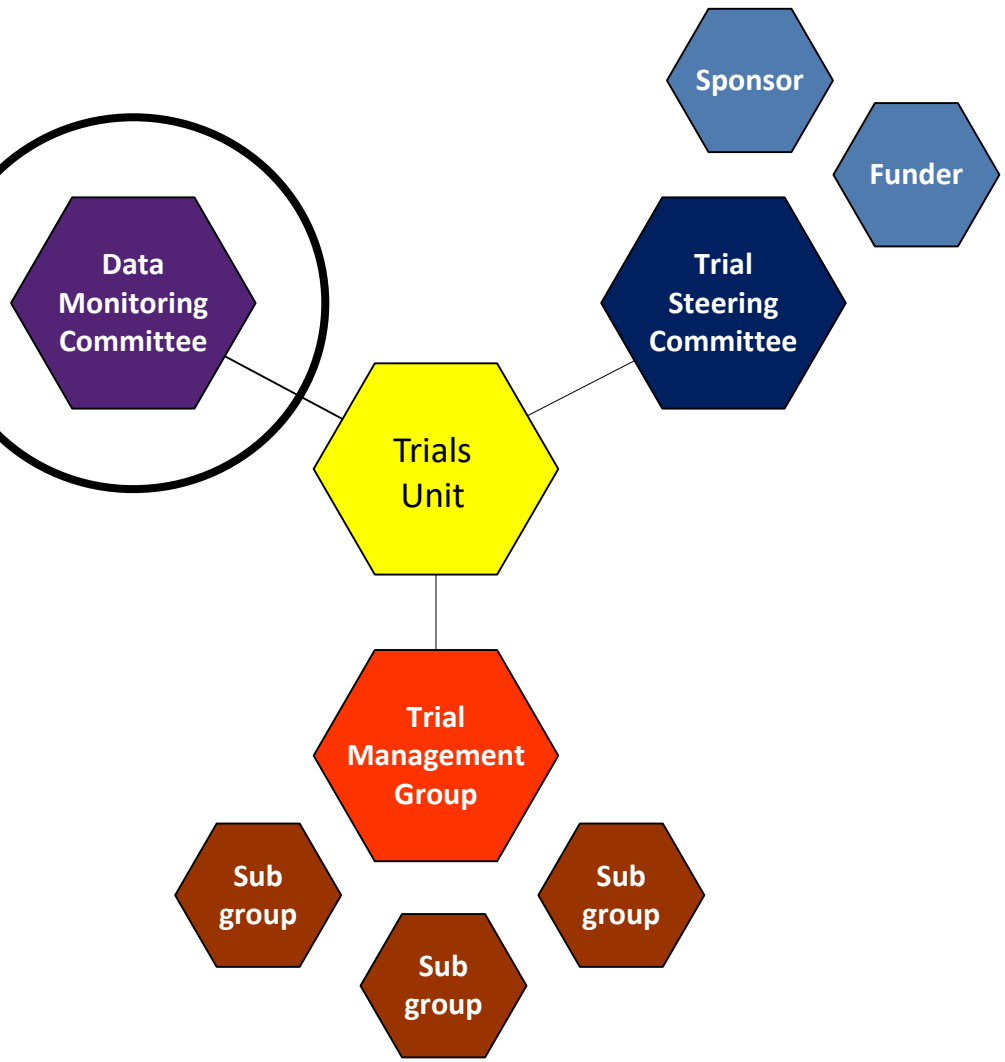
- Trial office central
- Conduit for inter-committee communications
- CTU produces reports
  - Not all staff see all reports

Trial Management Group (TMG)



- Responsibility
  - Day-to-day running
- Membership
  - 6 to 15
  - Chief Investigator
  - Lead clinicians
  - CTU's TMT
  - Other relevant people
- Meetings
  - Frequent

Data Monitoring Committee



- Responsibility
  - Review accumulating data
  - Safeguard interests of potential and actual participants, investigators and Sponsor
  - Assess safety and efficacy
  - Monitor overall conduct and ethics
  - Protect validity, credibility
- Membership
  - 3 to 5
  - Usually independent
- Meetings
  - Yearly or sooner

Advantages in stopping early (if convincing…)

Efficacy

- Earlier access to new treatment for future patients

Toxicity

- Fewer patients exposed to unsafe treatment

Lack-of-benefit

- Move away from insufficiently active treatments
- Focus limited trial resources towards more promising approaches

  → Not moving away early from insufficiently active treatments has a huge opportunity cost

Disadvantages in stopping early

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

- Do the stopping rules help?

Requirement for DMC

- No statutory requirement in Medicines for Human Use (Clinical Trials) Regulations 2004 for the sponsor to appoint a DMC
- Where a DMC is appointed it has no statutory role
- Research Ethics Committee and Competent Authority should be reassured when an IDMC will review data

DAMOCLES study: 23 questions about DMCs

→Examine DMC processes

→Identify how "right" decisions are made

Role of DMC
5 questions

Structure and organisation
5 questions

Information available to DMC
3 questions

Decision-making and reporting
10 questions

2 systematic reviews
- Literature on DMCs
- Small group decision-making processes

4 surveys
- DMC use in published RCT reports
- DMC use in recent RCTs
- DMC use in ongoing RCTs
- DMC policies of relevant organisations

2 in-depth qualitative work
- Case studies and examples of DMCs in action
- Interviews with experienced DMC members

DMC Charter

- Systematic and transparent approach to the structure and operation of DMCs
- Little explicit guidance before
- Highlights areas not routinely considered
- Provides guidelines based on multifactorial research
- Consistent structure useful
  - Even if guidance not accepted

DMC Charter

Free to download and widely used

Clinical Trials

A proposed charter for clinical trial data monitoring committees: helping them to do their job well

DAMOCLES Study Group*

Formal monitoring of data from randomised controlled trials (RCTs) is becoming more common. Wide variation exists in the structure and organisation of data monitoring committees (DMCs), with little guidance on how they should operate. We used various strategies to consider the behavioural, procedural, and organisational aspects of data monitoring in RCTs: systematic reviews of DMCs and small group processes in decision making; surveys of reports of RCTs, recently completed and ongoing RCTs, and the policies of major organisations connected with RCTs; detailed case studies of four DMCs that faced difficult decisions; and interviews with experienced DMC members. The findings aided the development of a template for a charter for DMCs. We summarise the findings and outline the key considerations at every stage of the data monitoring process. Widespread use of a charter for the structure and organisation of DMCs would promote a systematic and transparent approach, and enable them to operate more effectively and efficiently.

Lancet 2005; 365: 711–22

*Members listed at end of report

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Randomised controlled trials (RCTs) are widely accepted as the principal research method for assessment of the effectiveness of health-care interventions, and monitoring of trial data by data monitoring committees (DMCs) has become common.[1] There are inherent difficulties in decision making when uncertainty exists. Occasionally, DMCs are faced with difficult decisions about 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 commentators have suggested that any DMC would benefit from the development of a standard operating procedure or charter outlining its mode of operation and the responsibilities of different parties.[2–4] Little explicit guidance has been published on what should be included in such a charter, with the exception of a book by Ellenberg and colleagues.[5] 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 interim analyses. These are described fully elsewhere.[1] 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 set of 23 questions relating to DMCs, around which the study was structured.[1,5] These questions fell into four main sections: (1) the roles of DMCs; (2) their structure and organisation; (3) what information should be available to DMCs; and (4) 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 trials by members of the group and revised 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.[1,6] Here we present the proposed DMC charter (see end of article) with short summaries 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

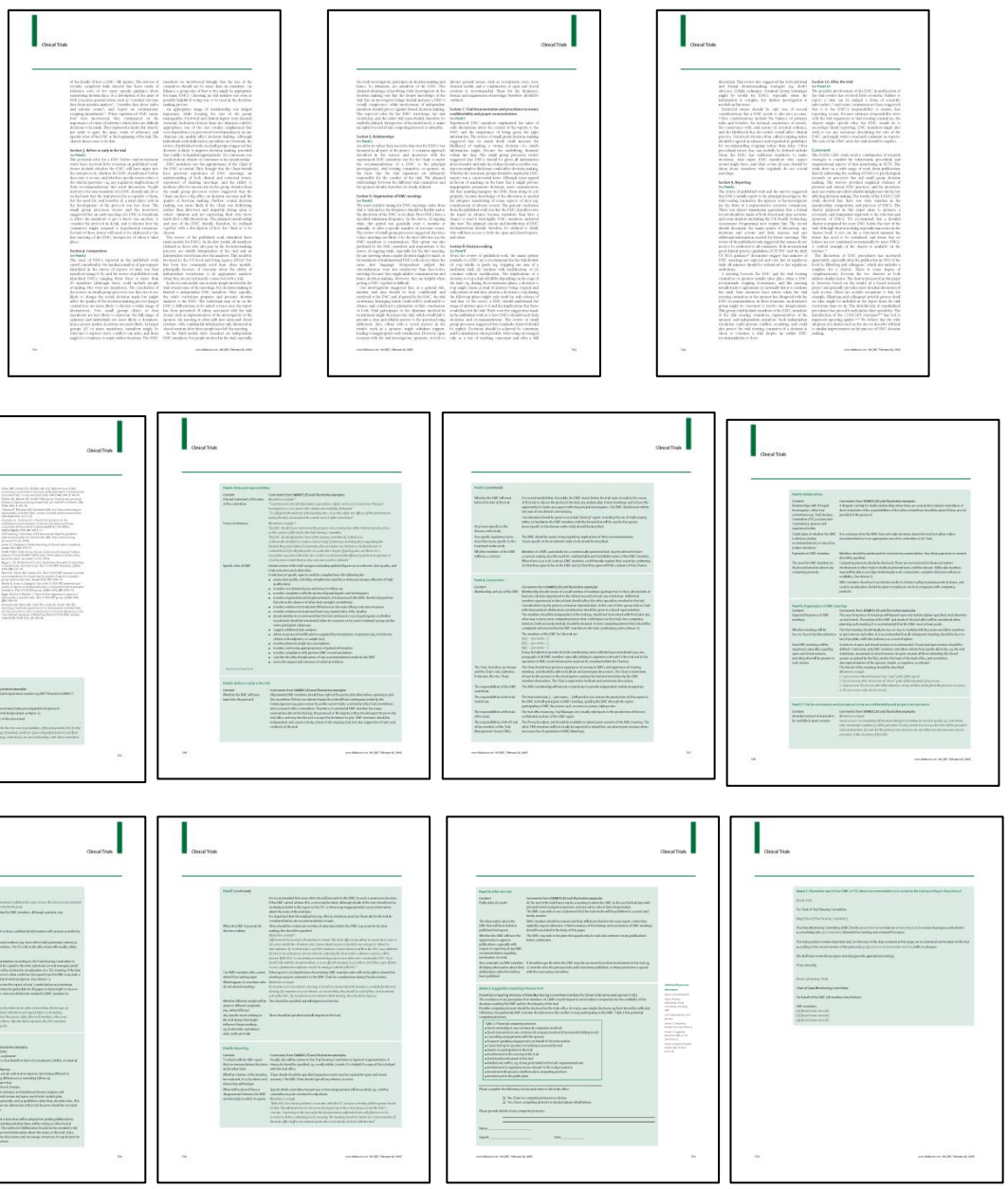
See *Panel 1*

The introduction should include the identifying details (eg, trial number) and objectives of the trial, and an outline of the scope of the charter to frame the charter for each specific DMC. A flow diagram of the trial design could also usefully be included (see additional figures and information at end of article).

Section 2. Roles and responsibilities

See *Panel 2*

From the reviews and the interviews, there was consensus that all parties—DMC members, investigators, and sponsors or funders—can usefully agree in advance many

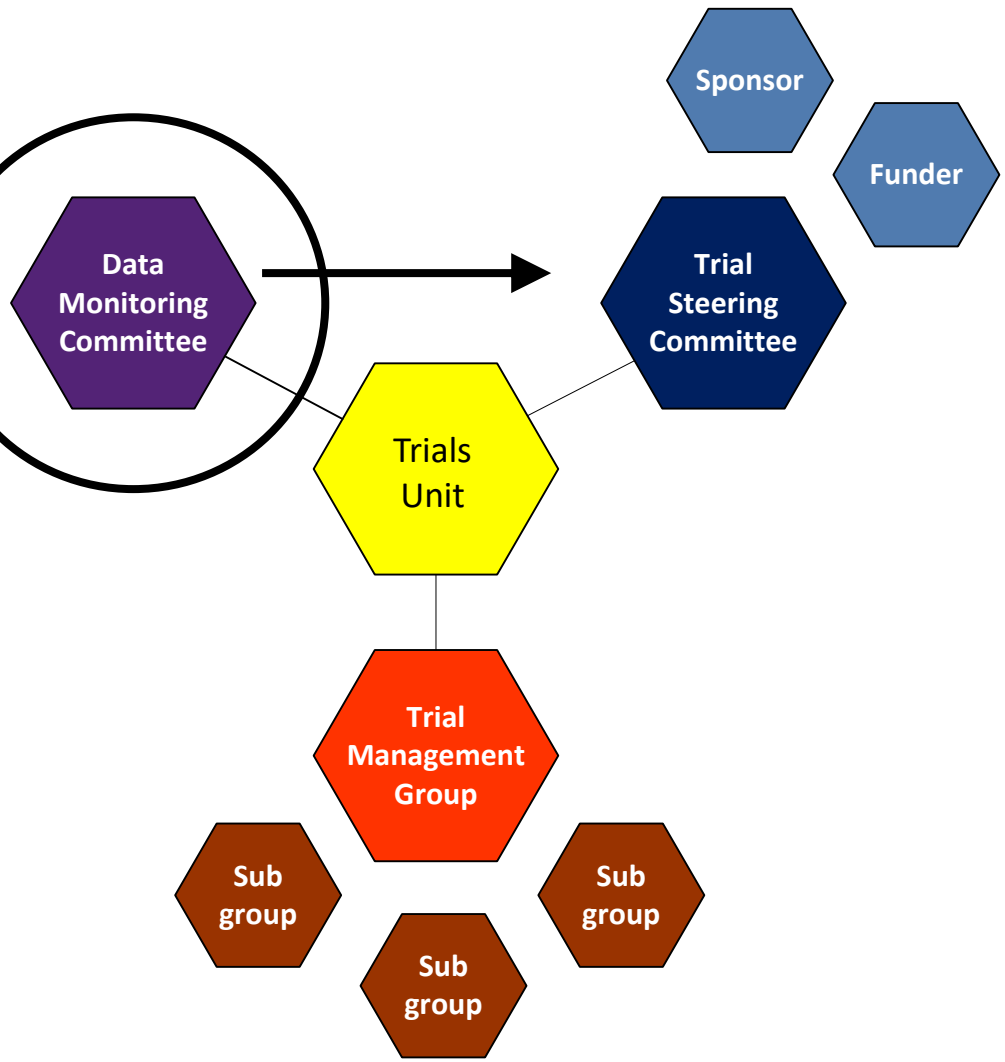


http://bit.ly/DAMOCLES_charter

S6: Organisation of DMC meetings

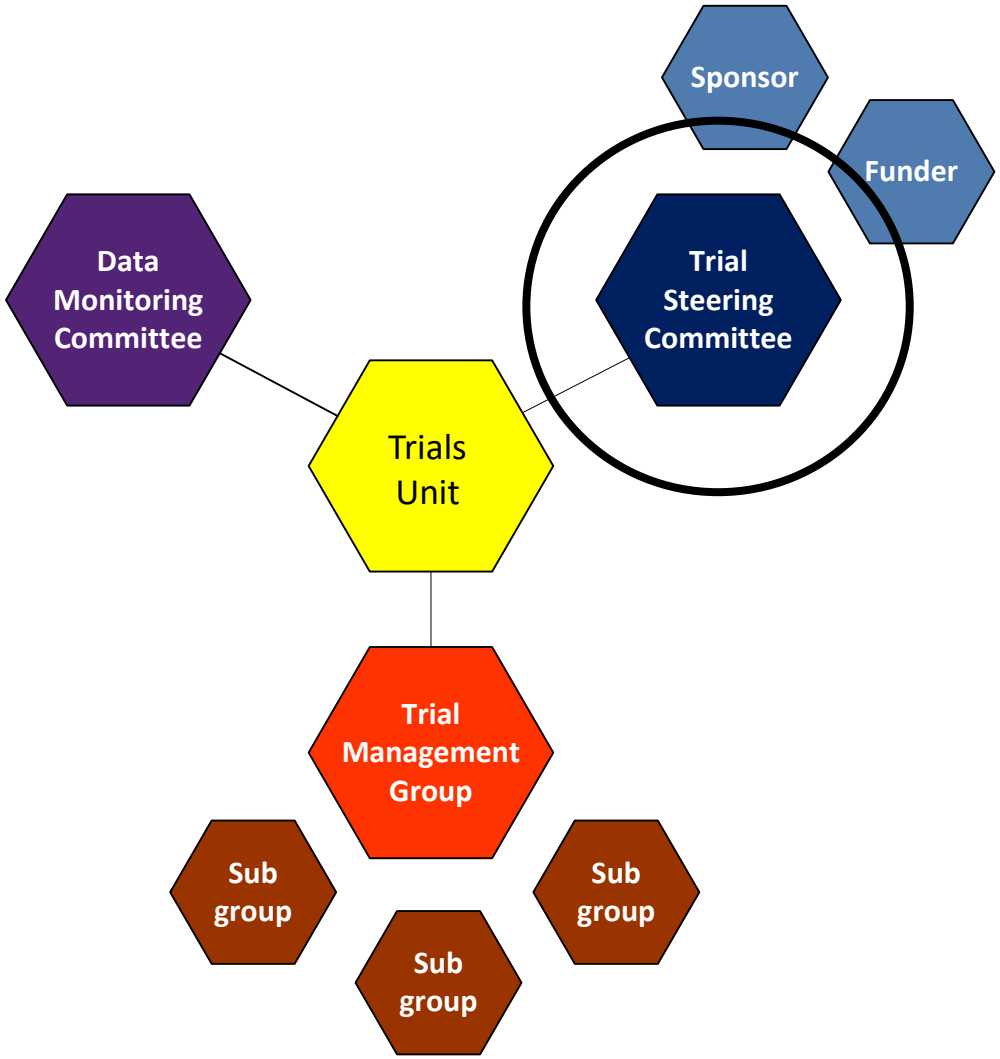
#	Session	Data	IDMC	Trial Statistician	Chief Invg Trial team
1	Open	Introductions Trial updates Accrual Baseline characteristics Common treatments	Yes	Yes	Yes
2	Closed	Specific treatments Toxicity Activity and efficacy	Yes	Yes	No
3	Executive	Discussion	Yes	No	No
4	Closed	Feedback & questions	Yes	Yes	No
5	Open	Feedback & questions	Yes	Yes	Yes

Data Monitoring Committee



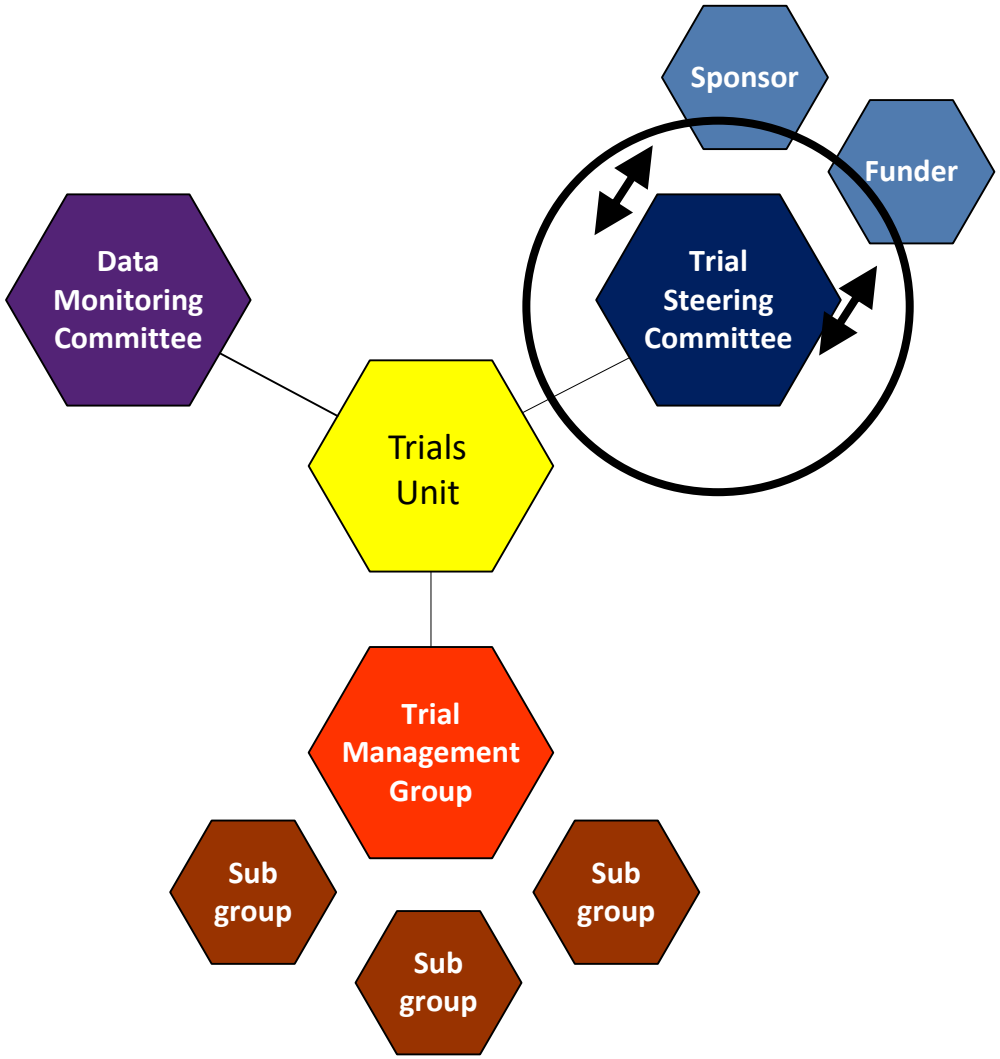
- Recommendations to TSC
- TSC makes decisions

Trial Steering Committee



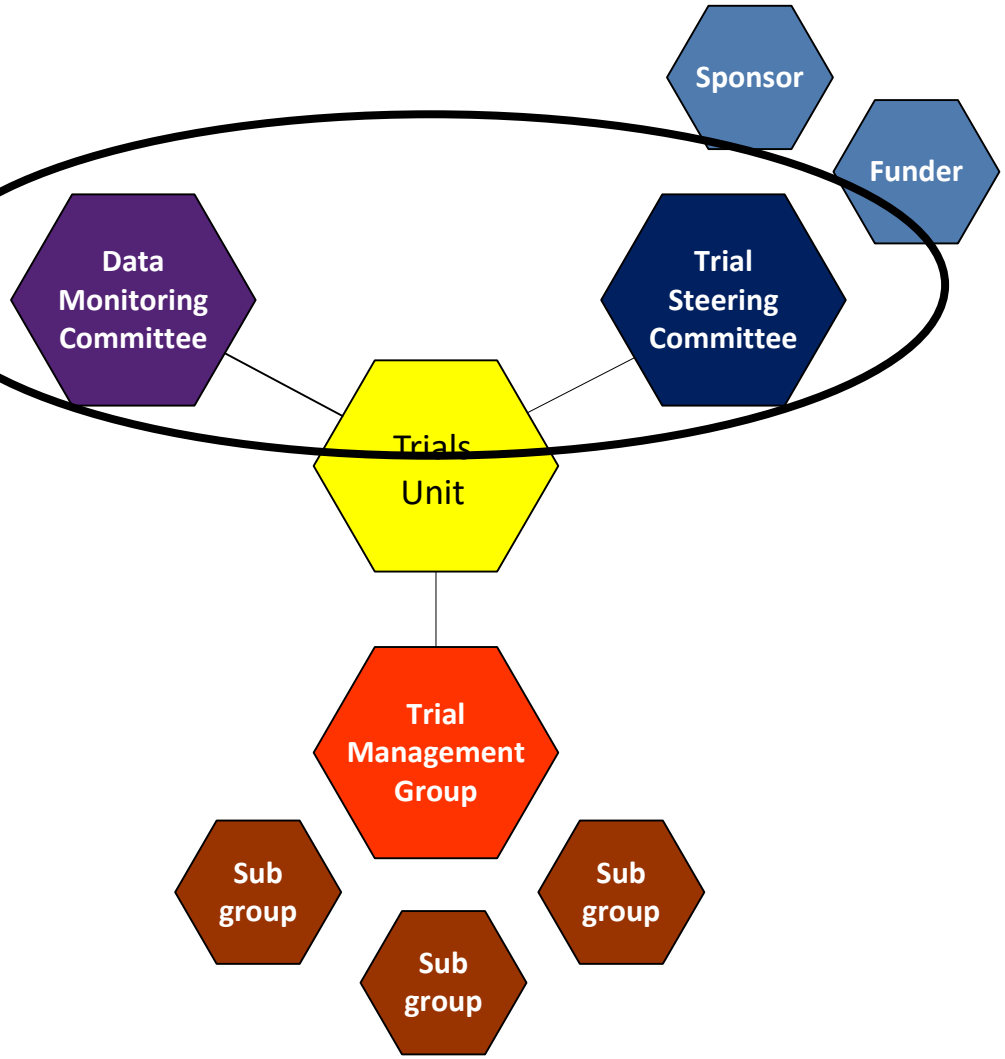
- Responsibility
  - Provide overall supervision
  - Provide advice on all aspects of the trial
- Membership
  - 5 to 10
  - Some independent members inc Chair
  - Some TMG members inc CI and CTU lead
- Meetings
  - At least yearly

Trial Steering Committee



- Executive committee
- Acts for Sponsor and Funder
  - Doesn't necessarily report to
- Some TSCs include reps from Sponsor and funder

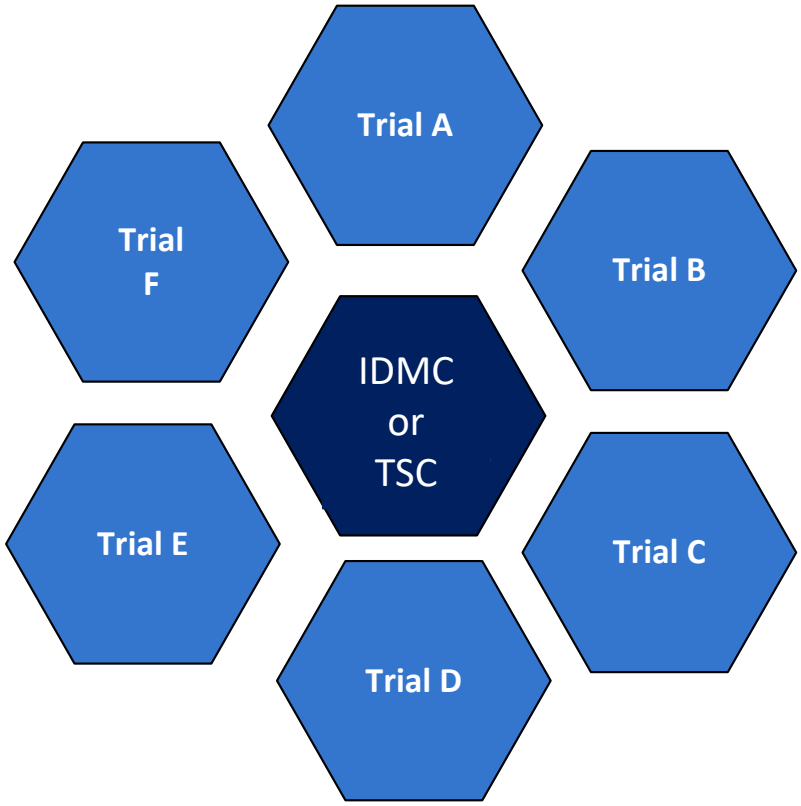
Variations



- Combined roles
  - DMC
  - TSC
- Executive committee sees interim data

→ Some N.American trials group

Umbrella Committees



- Committee covers many trials
  - Efficient use of resources
  - Logistic issues

Trial Oversight Committees

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Dec-2014

Reading - DAMOCLES

1. Grant AM et al. Issues in data monitoring and interim analysis of trials. Health Technology Assessment monograph series 2005, 9:1-238

2. The DAMOCLES study group. A proposed charter for clinical trial Data Monitoring Committees: helping them to do their job well. Lancet 2005, 365:711-722

Reading - DAMOCLES

3. Sydes MR et al. Reported use of data monitoring committees in the main published reports of randomised controlled trials: a cross-sectional study. Clinical Trials; 2004, 1(1):48-59

4. Sydes MR et al. Systematic qualitative review of the literature on data monitoring committees for randomized controlled trials. Clinical Trials; 2004, 1(1):60-79

5. Walker AE et al. Small group processes relevant to data monitoring committees: an overview of reviews. Clinical Trials; 2004, 1:282-296

6. Clemens F et al. Monitoring accumulating data in randomised controlled trials: surveys of practice in recent trials, of practice in ongoing trials, and of policies of relevant organisations. Clinical Trials; 2005, 2:22-33

Reading - Websites

- European Medicines Agency. Guideline on Data Monitoring Committees. 2005 www.emea.europa.eu/pdfs/human/ewp/587203en.pdf

- Food and Drug Administration. Guidance for Clinical Trial Sponsors Establishment and Operation of Clinical Trial Data Monitoring Committees. 2006 www.fda.gov/downloads/RegulatoryInformation/Guidances/ucm127073.pdf

Reading - Books

- Ellenberg S, Fleming T, DeMets D. Data monitoring committees in clinical trials: A practical perspective. Chichester: John Wiley & Sons Ltd, 2004.

- Herson J. Data and Safety Monitoring Committees in Clinical Trials. CRC Press, 2009.