DMCs in clinical trials

Part I: organizational aspects

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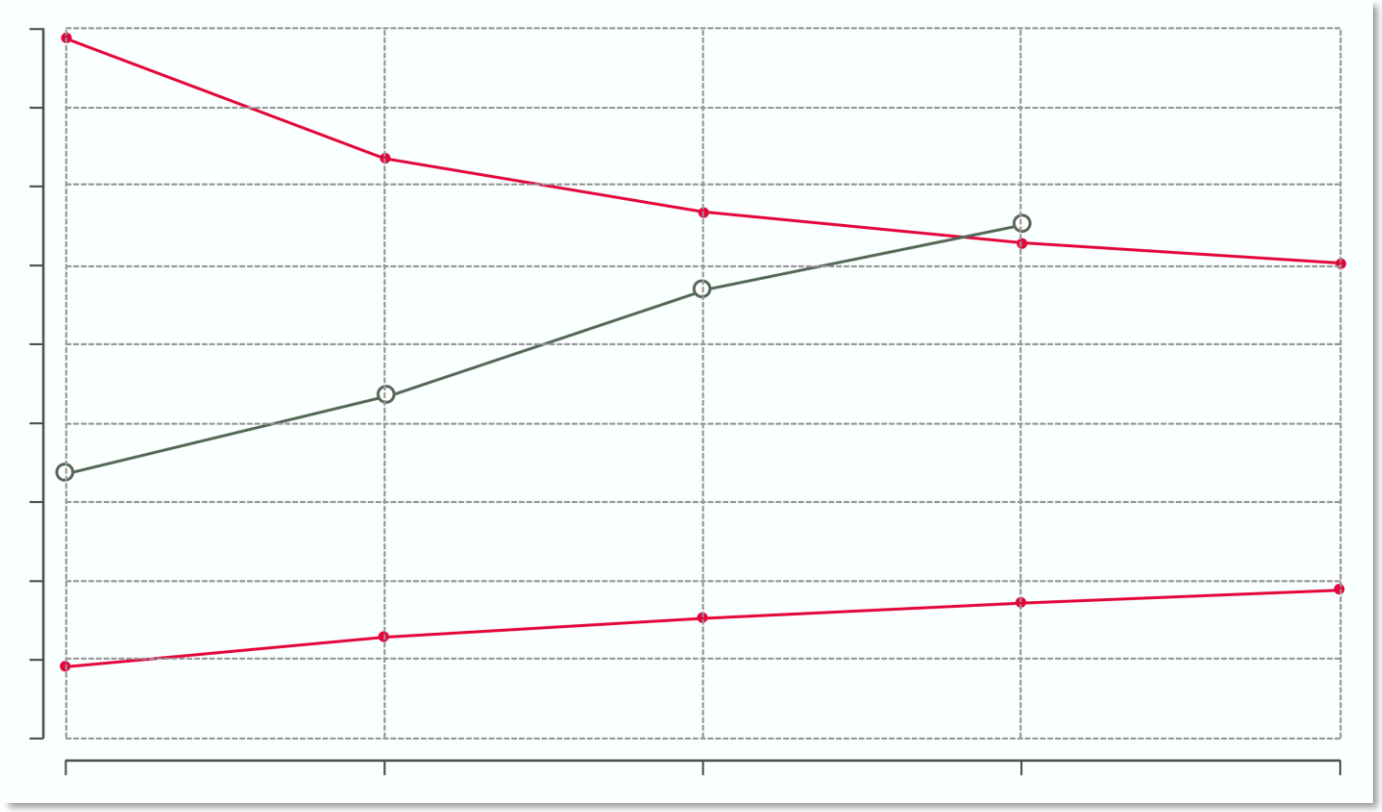
CTU Lecture, 25.01.2023



The next 30+ minutes

1. The what and why
2. Responsibilities
3. When do I need a (i)DMC?
4. Composition (qualifications and conflicts of interest)
5. Preparation/the charter
6. Meetings

Note: operational aspects regarding analysis and statistical aspects → part II

The what and why

Photo by Hadija Saidi on Unsplash

(independent) Data Monitoring Committee
Definition

- iDMC, DSMB, DSMC, …

A group of independent experts

Established by the sponsor of a clinical trial

To assess at intervals the progress of the trial

To recommend whether to continue, modify or stop the trial

Rationale

With some historical considerations

Assessment of interim results requires (value) judgements

Whether to modify or stop a trial is a (very) critical decision

The more we are engaged the more bias and preconceptions

Independent committee

History
The Greenberg Report

- The formal birth of independent Data Monitoring Committees
- Commissioned by the National Heart Institute (predecessor of NHLBI) to elaborate on organization, review, and administration of cooperative studies (1967) (Control Clin Trials 1988; 9: 137)
- Advisory Committee/Policy Board
  - Senior scientists or experts but not data-contributing
  - Review, make recommendations and advice; adjudicate controversies
  - Limited to offering substantive advice (not involved in funding operations)

Anon 1989; Ellenberg 2019; Evans 2022

History
Coronary Drug Project

- 1965: Double-blind, placebo-controlled multi-arm trial (8341 patients, 53 sites)
  - Lipid-modifying drugs: low- & high-dose estrogene, dextrothyroxine, clofibrate, niacin
- Policy Advisory Board: review progress and conduct
- 1968: subgroup established (no outcome data to investigators and full Policy Advisory Board, only to subgroup)
  - 1970 → high-dose estrogen stopped for safety (CV events↑)
  - 1971 → dextrothyroxine stopped for safety (death↑)
  - 1973 → low-dose estrogen stopped for futility

Ellenberg 2019; Evans 2022

History
Establishment of DMCs

DMCs in federally funded (US) trials (National Institutes of Health, Veterans Affairs) became standard (1998: National Institutes of Health policy)

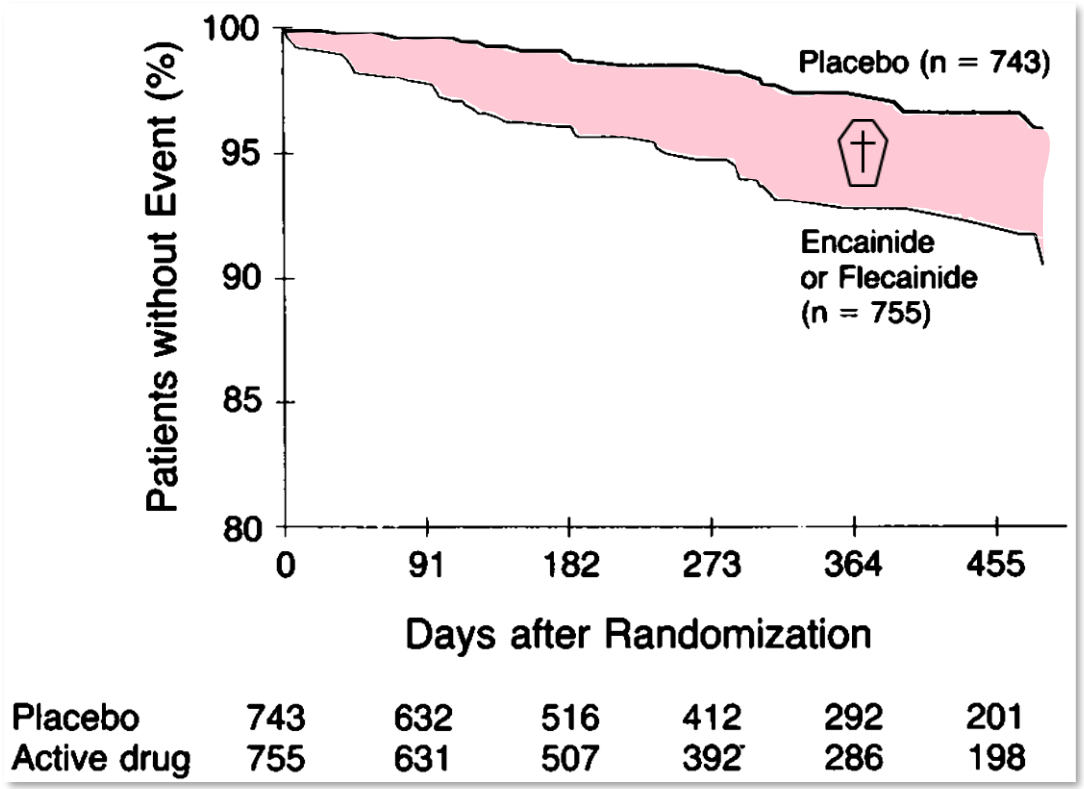
Europe: International Studies of Infarct Survival (ISIS) (1993: UK Medical Research Council policy)

1990ff: widespread implementation in industry (hesitancy to give access to data)

Cardiac Arrythmia Suppression Trial

CAST

- Randomized placebo-controlled trial to examine whether suppression of ventricular arrythmias with antiarrythmic drugs after myocardial infarction reduces death
- N=4,400 planned (encainide, flecainide, moricizine, placebo)
- Start in 1987 and 1989 prematurely stopped by DMC

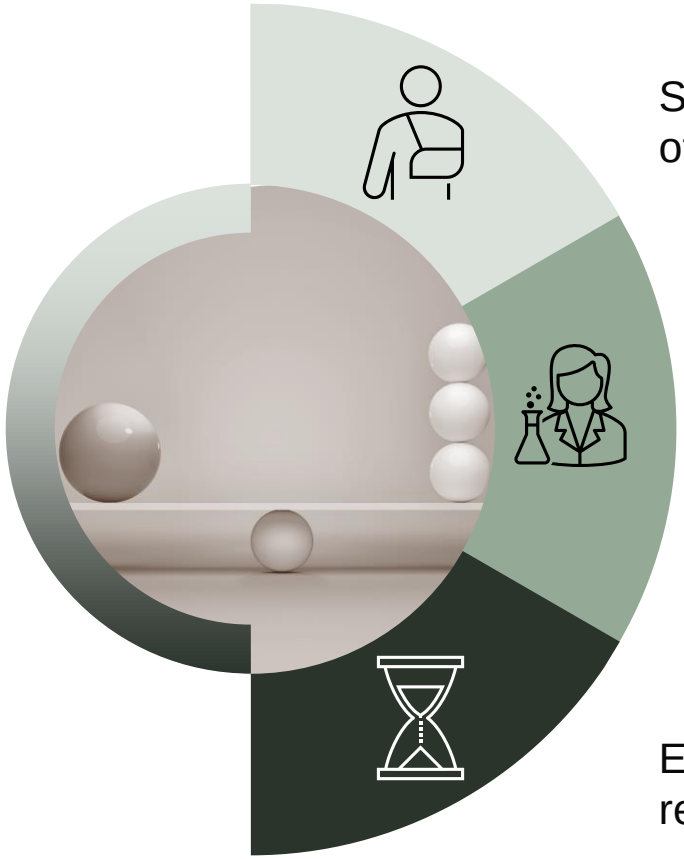


Responsibilities

Image by Pexels from Pixabay

Responsibilities
Principles

Recommendations
No decisions but recommendations to the sponsor (in reality, recommendations are rarely rejected)



Participants
Safeguard the interests of study participants

Science
Preserve integrity and credibility of the trial

Time
Ensure definitive and reliable results are available in a timely way

When do I need a DMC?

Determining the need for an iDMC

- When the risk of treatment is unknown
- When intervention(s) have known risks
- When formal interim analyses are to be conducted
- Trial is large enough to detect important effects (mortality)
- If important political ramifications exist
- Life-threatening conditions are studied
- When the regulator says so

Formal (risk) assessment

Table 9.1 Settings for an independent DMC or an internal monitoring committee

Type of setting[a]	Level of concern		Need for monitoring committees	
	Ethical	Credibility/ integrity	Independent DMC	Internal DMC
Setting 1				
Randomized trials (Ph 2b, 3, 4)	High	High	Yes	Likely
Randomized trials (Ph 1, 2a)	High	Moderate	Maybe	Likely[b]
Non-randomized trials	High	Lower	Maybe	Likely[b]
Setting 2				
Randomized (any phase trial)	Lower	Considerable	Maybe[c]	Likely[b]
Non-randomized	Lower	Lower	Unlikely	Maybe

[a]Setting 1 includes: life-threatening diseases (treatment, palliation, and prevention); diseases causing irreversible serious morbidity (treatment, palliation, and prevention); novel treatments for life-threatening diseases (treatment, palliation, and prevention) with potential for significant adverse events; vulnerable populations; trials intended to define optimal clinical practice. Setting 2 includes trials not included in setting 1.
[b]An internal monitoring committee would be advised if an independent DMC were not established.
[c]Integrity/credibility or quality of trial conduct issues could motivate the use of an independent DMC.

Composition and qualifications

Members
Qualifications

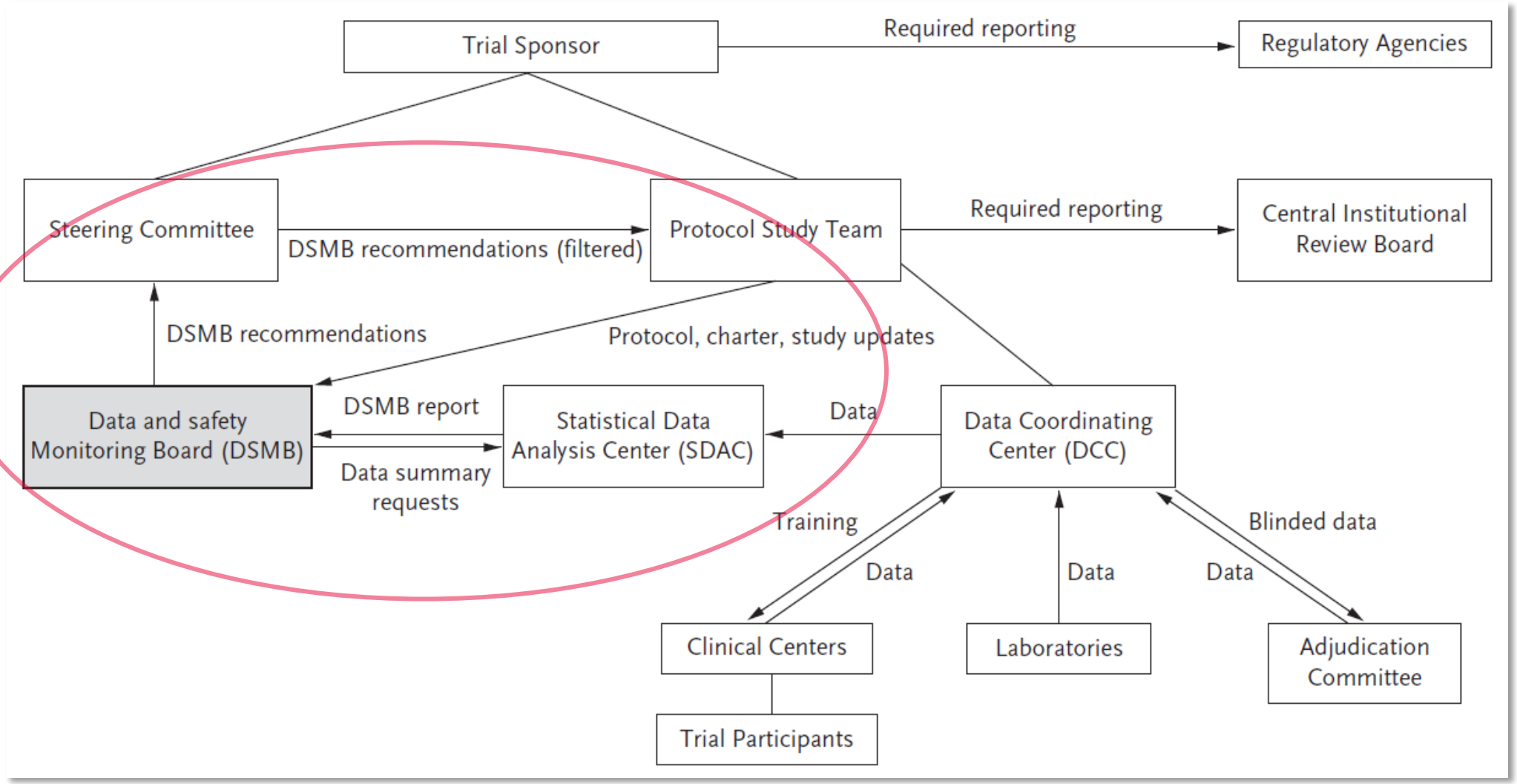
- Ca. 5 members (3-12)
  - Clinicians (in and near the field of the trial) and statistician(s) (,patient(s), epidemiologist, ethicist, scientists, …)
    - Independent of sponsor and trial (conflict of interest!)
    - Integrity
    - Experience in clinical trials
    - Knowledge of statistical principles
    - At least some: experience in Data Monitoring Committees
- DMC statistician (unblinded) member without voting right

Preparation and charter

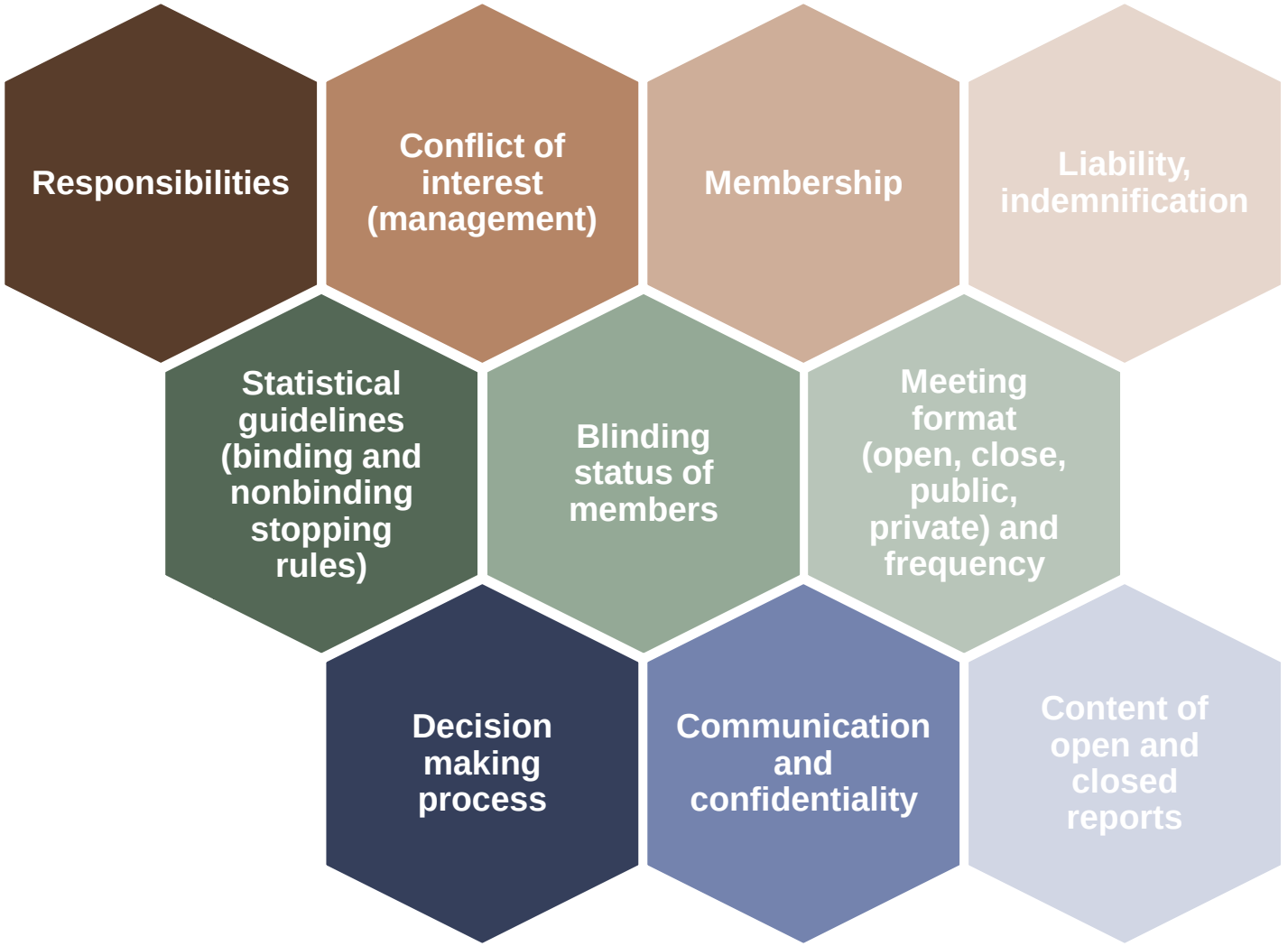
Preparation
Selecting members

- Before study starts
  - Allows the review of study protocol (↔ independence …)
  - Discussion and agreement on charter (to be signed by all members) and reports
- Responsibility of sponsor (with Trial Steering Committee)
- Chair of DMC a critical role (often a senior clinician in the clinical field)

Interactions



The charter


Responsibilities
Conflict of interest (management)
Membership
Liability, indemnification
Statistical guidelines (binding and nonbinding stopping rules)
Blinding status of members
Meeting format (open, close, public, private) and frequency
Decision making process
Communication and confidentiality
Content of open and closed reports

Meetings

Process

1. Inform DMC about upcoming meeting and find date/time
2. Statistical analysis (open and closed report)
3. Provide agenda and reports (1-2 weeks in advance)
4. Meeting
   - Open session
   - Closed session
5. Recommendation
   - Call (chair)
   - Written statement (signed by all members)

Content of report(s)

- Recruitment, quality and other operational aspects, …
- Baseline characteristics
  - Eligibility
  - Population
- Compliance
- Outcome data
- Safety parameters
- Line listings
- Subgroups

- Closed report by trial arm ↔ open report

The open session

- DMC & sponsor representatives (coordinator, statistician, …)

1. Review action items from last meeting
2. Study updates (recruitment, progress, …)
3. Clinical updates including external evidence
4. Safety updates
5. Statistical updates
6. Next steps

The closed session

- DMC (including DMC statistician)

1. Conflict of interest declarations
2. Review of closed report with discussion
3. Recommendation(s)
4. Reminder about material handling (usually: destruction)

Recommendations

- Aim for consensus (not majority voting)


Continue study unmodified


Adapt protocol/study


Terminate study

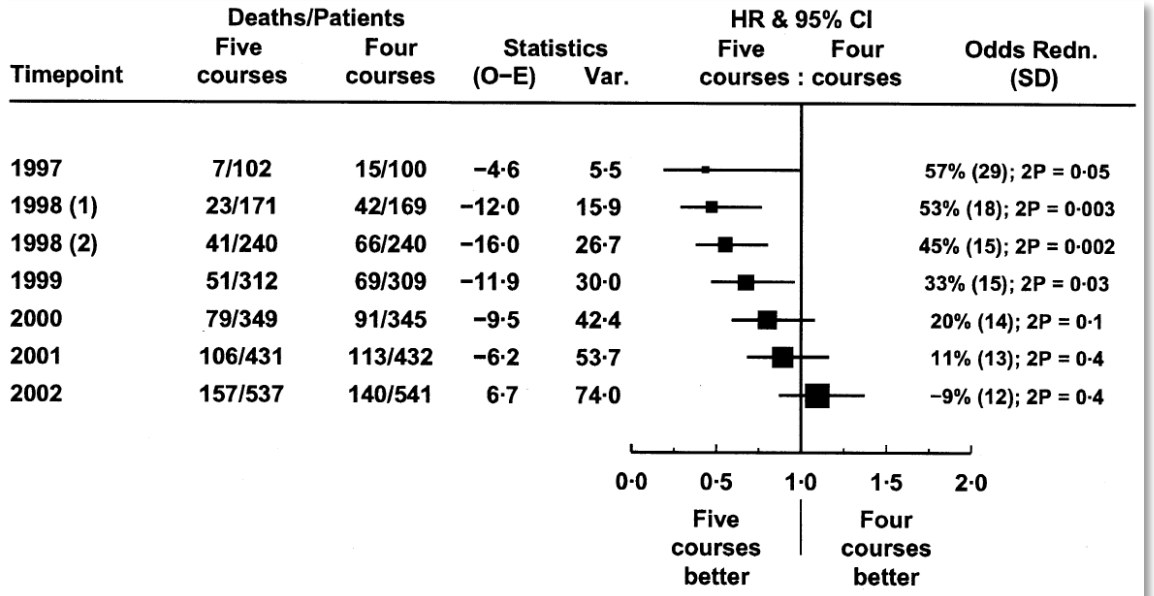
- (Serious) harm
- Benefit established
- Too low chance of showing effect (futility)
- Study conduct too problematic (quality)

Issues and difficulties

- Apparently clear signal at beginning (low number of events)

→ MRC AML12 trial

- 4 versus 5 courses of chemotherapy for AML
- 90% power to detect 20% improvement in 5 year overall survival (50% → 60%)
- No fixed stopping rules, p≈0.00



Timepoint	Deaths/Patients Five courses	Four courses	Statistics (O−E)	Var.	HR & 95% CI Five courses : Four courses	Odds Redn. (SD)
1997	7/102	15/100	−4·6	5·5		57% (29); 2P = 0·05
1998 (1)	23/171	42/169	−12·0	15·9		53% (18); 2P = 0·003
1998 (2)	41/240	66/240	−16·0	26·7		45% (15); 2P = 0·002
1999	51/312	69/309	−11·9	30·0		33% (15); 2P = 0·03
2000	79/349	91/345	−9·5	42·4		20% (14); 2P = 0·1
2001	106/431	113/432	−6·2	53·7		11% (13); 2P = 0·4
2002	157/537	140/541	6·7	74·0		−9% (12); 2P = 0·4

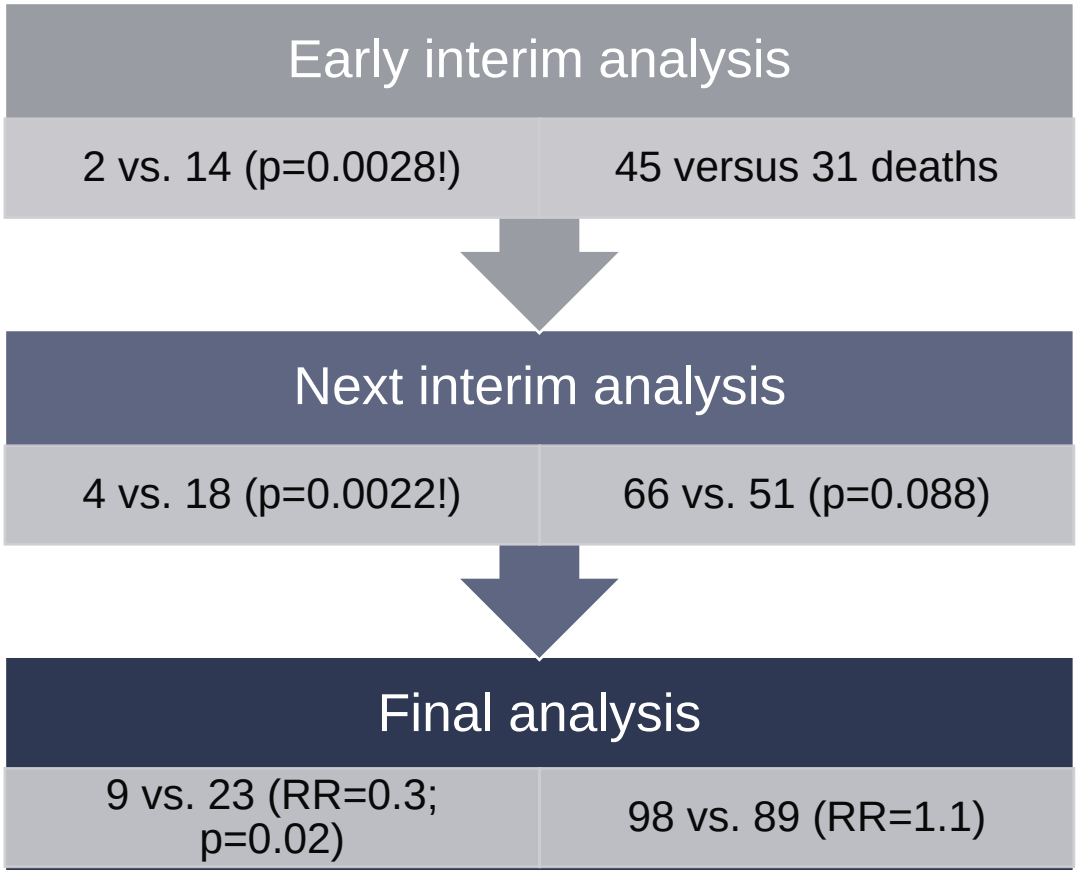
Fig. 1. Hazard ratio plot of mortality in the five versus four courses randomization in the MRC AML12 trials. O–E=observed minus expected, Var.=variance, HR=hazard ratio, CI=confidence interval, Odds redn.=odds reduction, SD=standard deviation.

Issues and difficulties

- Apparently clear signal at beginning (low number of events)
- Primary versus secondary endpoint e.g., primary endpoint shows efficacy for experimental intervention but safety endpoint shows harm
- Statistical boundaries crossed but overall picture not convincing

→ ACTG 081 Trial

- Prevention of serious fungal infection in 424 AIDS patients
- Fluconazole versus clotrimazole
- 10% → 2.5% (25 events)



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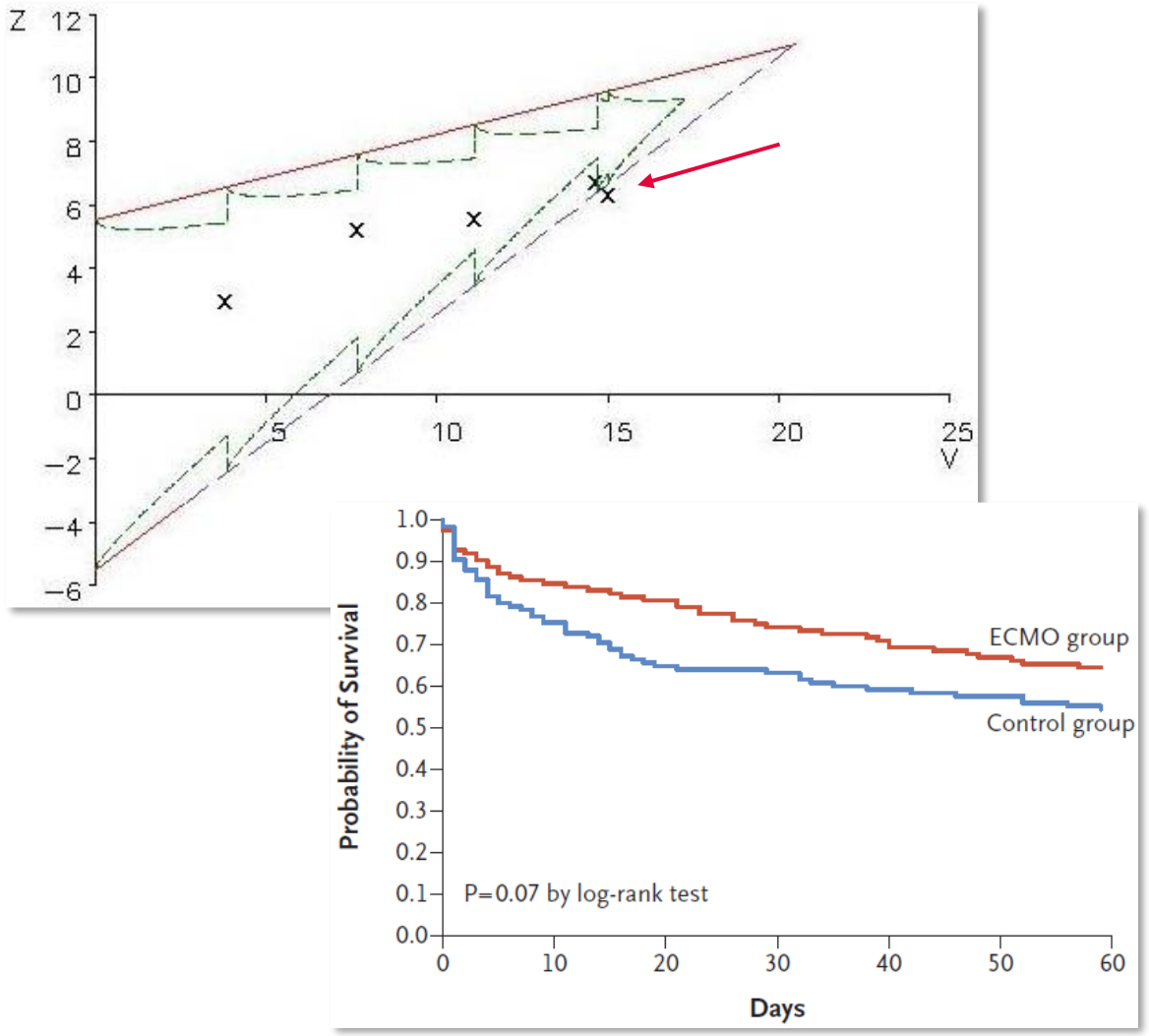
- Futility stopping

→ EOLIA trial

- Extracorporeal Membrane Oxygenation for severe acute respiratory distress syndrome



Issues and difficulties

- Apparently clear signal at beginning (low number of events)
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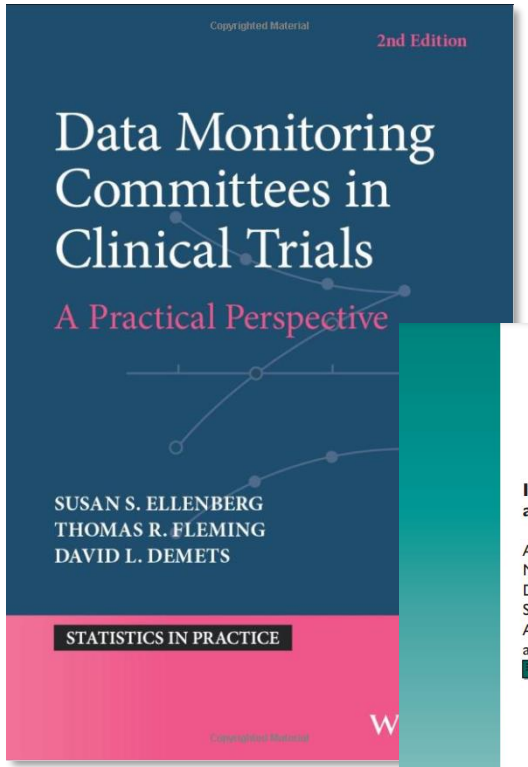
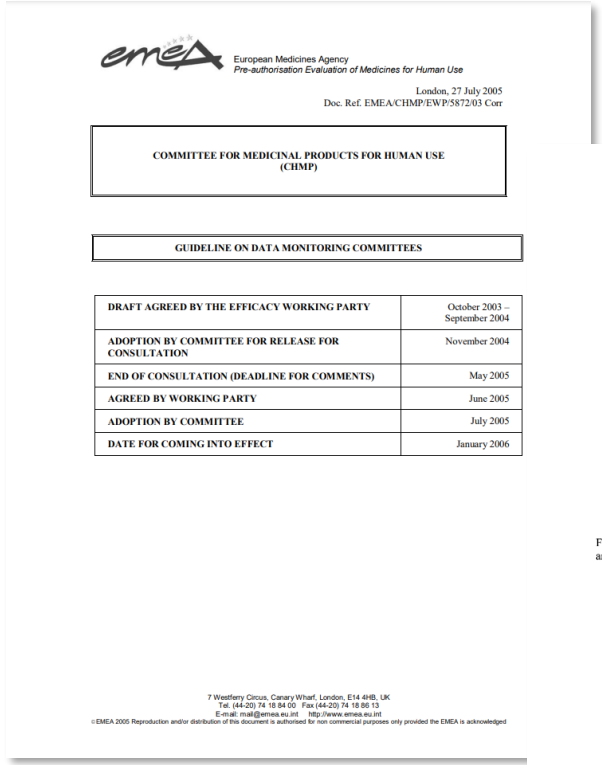
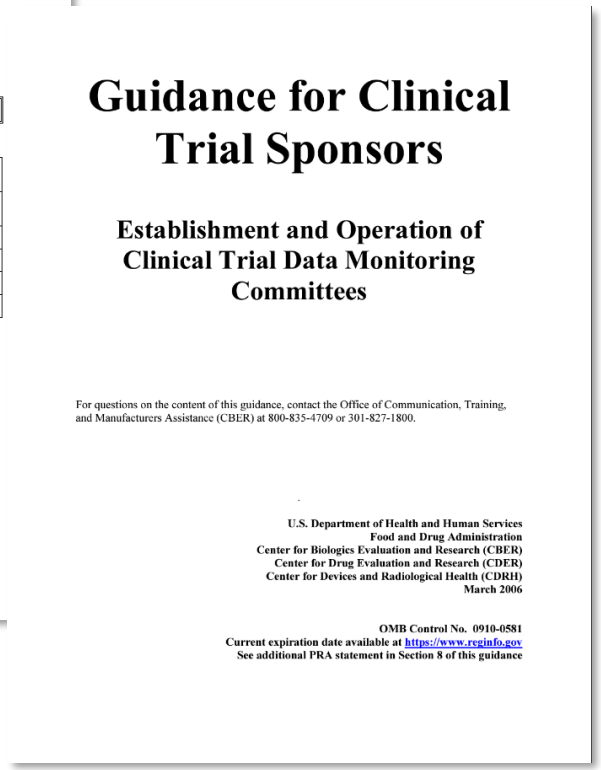
- Futility stopping
- Subgroup effects (heterogeneity)

Resources







SCT
CLINICAL TRIALS TRANSFORMATION INITIATIVE

[Online training (lectures)]

[CTTI recommendations]

Thank you
for your attention!

References

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