Data Monitoring Committees, interim analysis and early termination in paediatric trials a systematic review

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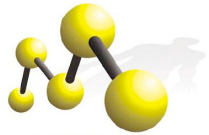

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A systematic review of the reporting of Data Monitoring Committees' roles, interim analysis and early termination in pediatric clinical trials

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REGULAR ARTICLE

Data monitoring committees, interim analysis and early termination in paediatric trials

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ABSTRACT

Aim: To evaluate whether paediatric randomized clinical trials (RCTs) adopt recent guidance on Data Monitoring Committees (DMCs), interim analysis and early termination.
Methods: We reviewed paediatric RCTs that reported on DMCs, interim analysis or early termination, published in eight general medical and paediatric journals (2005–2007). We searched full-text databases for eligible trials and recorded predefined parameters on each item. Reported activities were compared with current scientific guidance.
Results: A total of 110 of 648 paediatric trials (17%) reported on DMC, interim analysis or early stopping. Various approaches for convening a DMC were identified; information on DMC composition and independence was limited. Strict predefined statistical

Data Monitoring Committees recommendations, Interim Analysis results and Early Termination decisions…

- Can influence study validity
- Adequate reporting necessary

Data Monitoring Committees

- Roles:
  - protect the interests of study participants
  - safeguard the scientific integrity of trials

- Tasks:
  - interim monitoring of safety/efficacy outcomes
  - vigilance over study conduct and safety aspects
  - recommendations regarding trial continuation (e.g. early stop for efficacy, harm or futility)

DMCs in Pediatric Trials

"DMCs should be considered for vulnerable populations, such as children"

… but no specific guidance

FDA (2006), EMA (2005)

Only 2% of trials 1996-2002 reported to have a safety committee

Sammons et al. Acta Paediatr. 2008

Objectives

1. Frequency of reported use of DMC, interim analysis and early stopping
2. Quality of the reporting on these parameters
3. How were DMC tasks performed

in pediatric trials published in peer-reviewed journals

Methods (1)

- Included journals (2005-2007):
  - *BMJ, JAMA, Lancet, N Engl J Med*
  - *Arch Dis Child, Arch Ped Adolesc Med, J Pediatr, Pediatrics*

- Included trial reports:
  - RCTs
  - including participants 0-18 years
  - DMC or interim analysis or early termination reported

Methods (2)

- Full-text searching and selection

- Collected data
  - General trial characteristics
  - Risk of bias
  - *A priori* a set of parameters on DMC characteristics, interim analysis and early termination

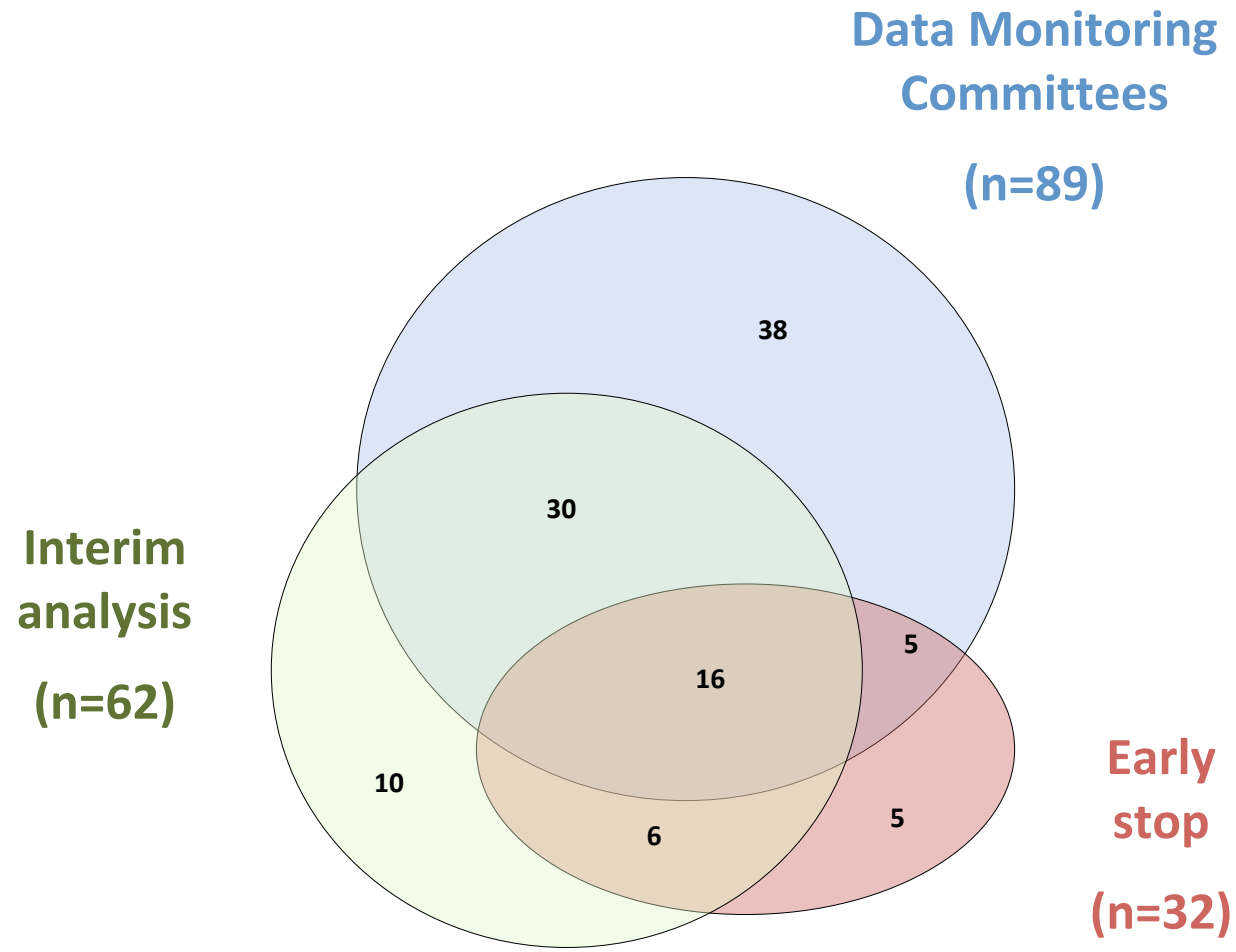
Grant AM et al. Health Technol Assess. 2005
Ellenberg et al. *Data Monitoring Committees in Clinical Trials. 2*002

Results

- Of 648 pediatric trials, 110 (17%) reported on DMC or Interim or Early Termination

	general	pediatric
DMC or IA	68/249 (27%)	37/399 (9%)
ET	14/249 (6%)	18/399 (5%)

Overlap of DMC / Interim / Early Termination



Trial Characteristics

- 47/110 (43%) were parallel, superiority, 2 arm, drug treatment, with placebo control
- Population
    - *Pediatric journals:* neonatal conditions (52%), median 136 participants
    - *General Journals:* infections (44%), median 601 participants
- Outcomes included mortality in 51%
- Risk of bias low

DMCs

- Inconsistent nomenclature (16 expressions)
- Reporting & Conduct
  - Members' identity (61%)
  - Independence (37%)
  - Monitored outcomes (56%)
    - Of which 48% included were safety + efficacy
  - Predefined stopping guidelines (26%)
    - Of which 43% used exclusively statistical rules
  - No paper reported all DMC parameters

Interim Analyses

- Reporting & Conduct
  - Number of interim analyses performed (84%)
  - Whether interim analyses were pre-planned (50%)
  - Statistical monitoring methods (53%)
    - "Traditional" frequentist methods (e.g. O'Brien Fleming rule) 17/33 (52%)
    - No adjustment for type I error: 12/33 (36%)
    - No adjustment of results: 19/33 (58%)

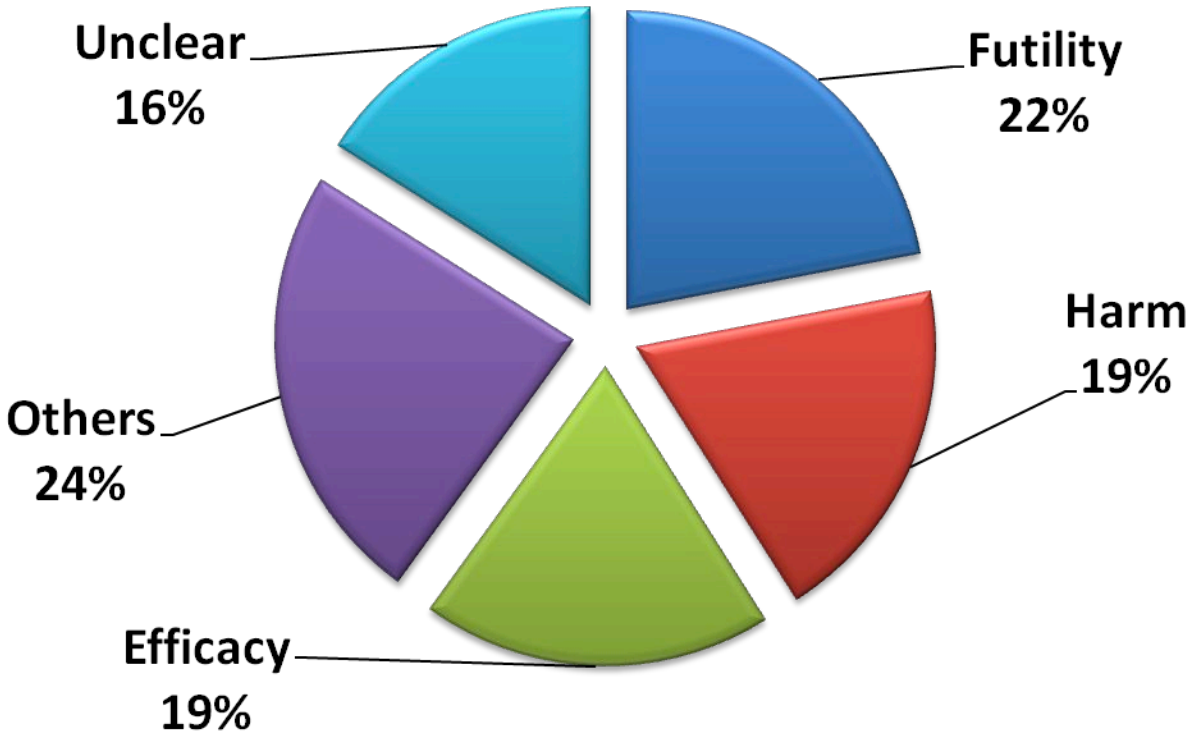
Early Termination

- DMCs reported in 66%
- Not reported
  - Predefined stopping rules (69%)
  - Statistical monitoring methods (47%)
    - When reported 41% did not adjust for type I error
  - Timing (41%)
  - Outcomes under monitoring or analysis (44%)
- Only two papers reported all relevant methodological parameters

Early Termination

- 4 trials terminated only 1 or 2 arms
- 9/25 (36%) included <50% of planned sample size

Motives for termination



Discussion

- Reporting incomplete and heterogeneous
  - Adherence to reporting standards (CONSORT-statement)
- Decision-making by DMCs shows limitations
  - Need for training and charters
- Need for standards for the establishment, roles and conduct of DMCs in pediatric trials

Problem & Impact

- Issues re. whether or not installing a DMC ("vulnerable populations")
- Pediatric trials should be adequately monitored
  - for safety
  - for efficacy
  - conduct, progress
- Many pediatric researchers are not aware of existing guidelines

Guidance on the following topics:

When is a DMC necessary?

Who should serve on a DMC?

Scope and responsibilities of a DMC

Operation of DMCs

Reporting

General recommendations for installation of a DMC in pediatric RCTs

- Clinical criteria
  - new interventions with few safety data available
  - major morbidity or mortality endpoints
  - high-risk populations
- Methodological criteria
  - sequential design - early stopping
  - large sample size
  - multicenter trials