Trial Steering Committees

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Overview

- Background
- Evidence base
- Current challenges
- Way forward
BACKGROUND

➢ DAMOCLES (2005)
  - Established Data Monitoring Charter which has been widely used for RCTs since 2005.
  - No equivalent Charter exists for TSCs establishing role and functionality in RCTs

➢ MRC Guidelines for Good Clinical Practice (1998)
  - Provides brief Terms of Reference for TSCs representing first guidance on TSC remit and structure
  - Not known how extensively used to inform TSC roles and practice
  - Acknowledged variation in practice (nationally and internationally)
RESULTS IN BRIEF

• 38 of 47 CTUs responded to survey
• 21 of 33 units using a Terms of Reference provided a copy

• Identified:
  • widespread adoption of the MRC Guideline
  • More than half identified components in need of improvement

• Conclusion: ToR useful but limitations in existing provision need to be addressed

• Network collaboration- UKCRC registered CTUs

• Survey covering TSC role, requirements and experience for membership, methods to identify members, meeting frequency

• Request to supply document covering remit, objectives and functionality for their TSCs if one existed
METHODS

• Expert panel selected based on prior TSC experience and roles as statisticians, clinicians, and methodologists

• 12 questions set and discussed by the panel at two full day meetings

RESULTS IN BRIEF

• Agreement on the role of the TSC, to which it was accountable, the membership, the definition of independence, and the experience and training needed.

• More difficult to answer without examples:
  • Management of ethical issues, difficult/complex situations and issues the TSC should not ask the DMC to make recommendations on
  • Additional topics: review of data sharing requests, indemnity, lifespan of the TSC, general TSC administration, and the roles of both the funder and the sponsor, but did not include PPI
  • Uncertainty in areas due to absence of real-life examples, need to consider PPI
METHODS

• RCTs identified reported in BMJ, The Lancet, NEJM in 6 months in 2012 & full NIHR HTA Monograph series

• Details of TSC constitution and impact were extracted from main publication and published supplements

RESULTS IN BRIEF

• Cohort of 264 trials established, TSC in approx. half of trials
• Funder role in oversight committee selection unclear
• Variation in naming conventions, number of members (median 7, range 2 to 52), reporting unclear with regards to membership and independence
• Reporting transparency about role and decision making low
• Understanding benefits and impacts of the TSC role using literature is challenging
• A need to develop reporting guidelines to aid transparency of clinical trials and allow understanding of stake-holder involvement in decision making
METHODS

- 8 TSC and 6 TMG meetings observed, and audio recorded
- 65 Interviews with 51 independent and non-independent TSC members, sponsor and funder reps and chief investigators

RESULTS IN BRIEF

- Key roles: quality assurance and patient advocacy
- Difficulty in operationalising the definition of independence used by some funders
- Valued attributes: Experience of running a trial and prior oversight committee membership
- Independence valued for impartiality and considered critical
- Funder selection of TSC members thought to inhibit TSC patient advocacy role
RESULTS IN BRIEF

- TSC decision making utilised DMC guidance, but could differ in recommendations
- Clear communication lines essential between all oversight committees
- CTUs could potentially arbitrate rare DMC and TSC disagreements, agree early on in trial
- Primacy of TSC potentially reduced by greater accountability to funders and sponsors
Enhancing public involvement in trial oversight committees through qualitative research with eight trials facing challenges

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Developing good practice guidance for the involvement of public members in project oversight groups (Trial Steering Committees, Study Steering Groups)
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Current issues in operationalising the 3rd oversight committee

- **Who should determine membership?**
  - Whoever determines membership may potentially infer accountability impacting on perceived independence of the 3rd Committee.
  - Ability to appoint and terminate involvement if necessary implies that the 3rd Committee are answerable to, or work for, those making such appointments.

- Expert panel ideal: the 3rd Committee does not work for one particular stakeholder of the trial.

- **Primacy in decision-making, including trial closure?**
  - Decision making or advisory to funder/sponsor?
  - Unclear how much authority the committee really has because funders and sponsors can withdraw support without reference to or in contradiction of third committee recommendations.

“so they’re there to advise the [funder], who then makes the decision” [Cl]

making them much more a tool of the funder rather than a source of independent scientific advice ... the TSC to my mind has become almost a puppet.” [CTU Statistician]

“The TSC guides the sponsor, and ultimately the decision to move forward or not with the study sits with the sponsor” [Sponsor]
Membership

- A unique forum for TMG members to interact with expert independent members

- Non independent members
  - Who should the non-independent members be?
  - Ratio of independent to dependent members
    - Sufficient to stipulate a majority?

- Independent members- who should they be and how should independence be defined?
  - Clinical and statistical inputs and an independent Chair
  - Importance of the Chair in success of the 3rd Committee
  - Expert panel: previous trials experience and acting as a non-independent member or as an observer for part of a wider trial team
  - Patient and Public Involvement (PPI) contributors
    - Unsystematic and opportunistic recruitment has produced an over reliance on a small number of experienced public contributors.
Capacity and training

- Expert panel: experienced trialists
- CTU surveys highlighted key difficulties in appointing statisticians and public contributors
- Single vs umbrella committees
- Initial development of SOS found that within UKCRC registered CTUs
  - 359 Statisticians
    - 213 able to sit as a DMC independent member, 116 no current appointments
    - 36 statisticians on 5 or more committees
    - Most committees sat on by one statistician is 14
- Observer opportunities should be promoted- funder role for this?
Communication

- Debate around who the 3rd Committee should communicate its advice on IDMC recommendations to

- Impacted by
  - who they are considered to ‘work for’
  - presence or absence of funder/sponsor representation

- Lines of communication should be clear throughout

“We were careful to clarify that the route of communication was between us and the TSC to the DMC... They advise TSC, not us...The trouble originally was DMC badgering us.” [CI]

“low-level minimum bureaucracy...The fundamental thing that the funder wants to know is, I would say, “is our money in trouble” [TSC]; Several suggested a short TSC T/C debrief with the funder or standard form”
Mode of meeting

- Face to face versus remote
- Remote may be more practical and better attended
- Remote meetings can affect a members ability to contribute
- Greater difficulties in establishing good relationships
  - Particular concern for public contributors
- Importance of interpersonal chairing skills
Information provided to TSC

➢ Should any level of data split by treatment group be provided?

➢ Variation in practice
  o Particular baseline values
  o Overall event rates or control group event rates

➢ Information from DMC: enough to inform, not enough to unblind
  o DMC must express its recommendations and their rationale clearly and in enough detail to allow the 3rd Committee to form its opinion
  o Standardised inter-committee reporting methods (e.g. template documents) may help avoid these potential pitfalls.

➢ Standard DMC-to-3rd Committee reporting methods may help achieve a suitable compromise

➢ Provision of external evidence. – how well/systematically is this done?
  ▪ Updating relevant external evidence is time-consuming
  ▪ Literature reviewing methods should be transparent to guard against potential bias, e.g. a documented search strategy.
Lifespan

- Formed during pre-trial stage
- Often limited input to protocol
  - Defined within grant application
  - Agreeing to be a member=level of acceptance of design
- 74% CTU survey felt 3rd Committee lifespan should end when the final results draft is available
- Role in data sharing?
  - Impact end date
  - Good decisions become more challenging with dwindling knowledge of long closed trials
What next?

- Draft commentary prepared to submit to Clinical Trials journal
- Workshop-to consider commentary points
- Charter
- Tackle international variation