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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)

Regulation and Policy

CLINICAL TRIALS

Clinical Trials
2015, Vol. 12(6) 664–676

DOI: 10.1177/1740774515589959
ctj.sagepub.com
SAGE

Trial Steering Committees in randomised controlled trials: A survey of registered clinical trials units to establish current practice and experiences

Elizabeth J Conroy[1], Nicola L Harman[2], J Athene Lane[3], Steff C Lewis[4], Gordon Murray[4], John Norrie[5], Matt R Sydes[6,7] and Carrol Gamble[2]

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

Harman *et al. Trials* (2015) 16:597
DOI 10.1186/s13063-015-1125-z

Trials

RESEARCH Open Access

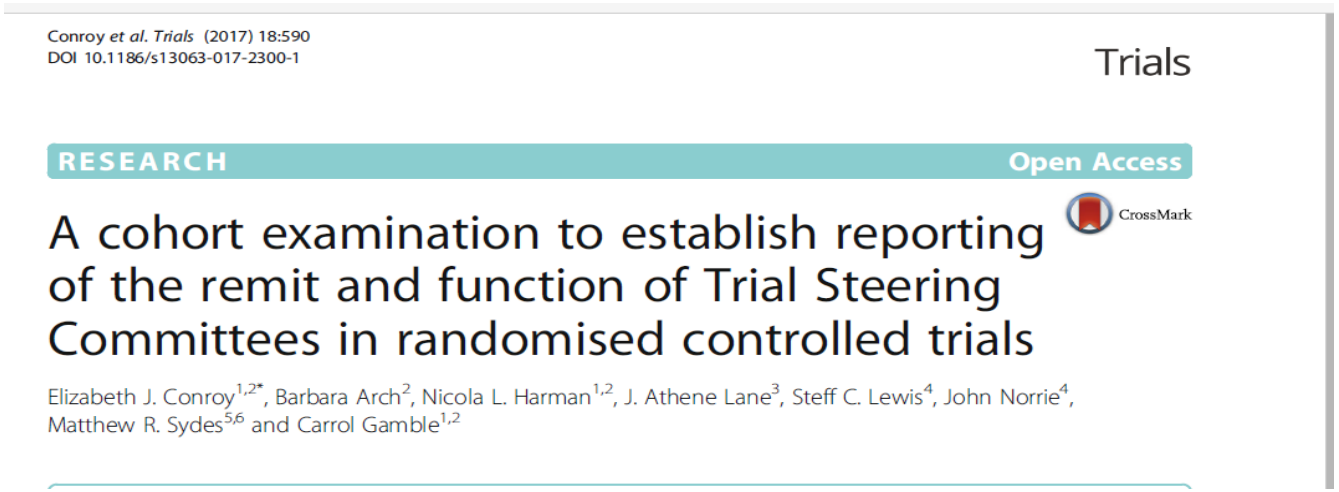
Exploring the role and function of trial steering committees: results of an expert panel meeting

Nicola L. Harman[1*], Elizabeth J. Conroy[2], Steff C. Lewis[3], Gordon Murray[3], John Norrie[4], Matt R. Sydes[5,6], J. Athene Lane[7], Douglas G. Altman[8], Colin Baigent[9], Judith M. Bliss[10], Marion K. Campbell[11], Diana Elbourne[12], Stephen Evans[13], Peter Sandercock[14] and Carrol Gamble[1]

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



Conroy et al. Trials (2017) 18:590
DOI 10.1186/s13063-017-2300-1

Trials

RESEARCH Open Access

A cohort examination to establish reporting of the remit and function of Trial Steering Committees in randomised controlled trials

Elizabeth J. Conroy[1,2*], Barbara Arch[2], Nicola L. Harman[1,2], J. Athene Lane[3], Steff C. Lewis[4], John Norrie[4], Matthew R. Sydes[5,6] and Carrol Gamble[1,2]

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

Daykin *et al. Trials* (2016) 17:307
DOI 10.1186/s13063-016-1425-y

Trials

RESEARCH Open Access

What are the roles and valued attributes of a Trial Steering Committee? Ethnographic study of eight clinical trials facing challenges

Anne Daykin[1*], Lucy E. Selman[1], Helen Cramer[1], Sharon McCann[2], Gillian W. Shorter[3,4], Matthew R. Sydes[5,6], Carrol Gamble[7], Rhiannon Macefield[1], J. Athene Lane[1] and Alison Shaw[1]

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

Daykin *et al. Trials* (2017) 18:612
DOI 10.1186/s13063-017-2305-9

Trials

RESEARCH Open Access

'We all want to succeed, but we've also got to be realistic about what is happening': an ethnographic study of relationships in trial oversight and their impact

Anne Daykin[1*†], Lucy E. Selman[1,2†], Helen Cramer[1], Sharon McCann[3], Gillian W. Shorter[4,5], Matthew R. Sydes[6,7], Carrol Gamble[8], Rhiannon Macefield[1], J. Athene Lane[1,2†] and Alison Shaw[1†]

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

Nicholson et al. Trials 2015, 16(Suppl 2):P78
http://www.trialsjournal.com/content/16/S2/P78

TRIALS

POSTER PRESENTATION Open Access

Enhancing public involvement in trial oversight committees through qualitative research with eight trials facing challenges

A Nicholson[1], A Daykin[1], R Macefield[1], S McCann[2], G Shorter[3], M Sydes[4], C Gamble[5], A Shaw[1], JA Lane[1*]

From 3rd International Clinical Trials Methodology Conference
Glasgow, UK. 16-17 November 2015

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ISSN 2050-4349

An evidence base to optimise methods for involving patient and public contributors in clinical trials: a mixed-methods study

Carrol Gamble, Louise Dudley, Alison Allam, Philip Bell, Deborah Buck, Heather Goodare, Bec Hanley, Jennifer Preston, Alison Walker, Paula R Williamson and Bridget Young

P25

Developing good practice guidance for the involvement of public members in project oversight groups (Trial Steering Committees, Study Steering Groups)

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Research Involvement and Engagement 2017, **3(Suppl 1):**P25

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" [CI]

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
  - Particular baseline values
  - Overall event rates or control group event rates
- Information from DMC: enough to inform, not enough to unblind
  - DMC must express its recommendations and their rationale clearly and in enough detail to allow the 3rd Committee to form its opinion
  - 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