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**Title:** **A third trial oversight committee: functions, benefits and issues**

**Short title:** Third committee enhances trial oversight

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## **Abstract**

### *Background/aims*

Clinical trial oversight is central to the safety of participants and production of robust data. The United Kingdom Medical Research Council (UK MRC) originally set out an oversight structure comprising 3 committees in 1998. The first committee, led by the trial team, is hands-on with trial conduct/operations (“Trial Management Group”) and essential. The second committee (Data Monitoring Committee, (DMC)), usually completely independent of the trial, reviews accumulating trial evidence and is used by most later phase trials. The Independent (I)DMC makes recommendations to the third oversight committee. The third committee, (“Trial Steering Committee”), facilitates in-depth interactions of independent and non-independent trial members and gives broader oversight (blinded to comparative analysis). We investigated the roles and functioning of the third oversight committee with multiple research methods. We reflect upon these findings to standardise the committee’s remit and operation, and to potentially increase its usage.

### *Methods*

We utilised findings from our recent published suite of research on the third oversight committee to inform guideline revision. In brief, we conducted a survey of 38 UK-registered Clinical Trials Units, reviewed a cohort of 264 published trials, observed 8 third oversight committee meetings and interviewed 52 trialists. We

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convened an expert panel to discuss third oversight committees. Subsequently we interviewed 9 patient/lay third committee members and 8 committee Chairs.

### *Results*

In the survey most Clinical Trials Units required a third committee for all their trials (27/38, 71%) with independent members (ranging from 1-6). In the survey and interviews, the independence of the third committee was valued to make unbiased consideration of (I)DMC recommendations and to advise on trial progress, protocol changes and recruitment issues in conjunction with the trial leadership. The third committee also advised funders and sponsors about trial continuation and represented patients and the public by including lay members. Of the cohort of 264 published trials 144 reported a “steering” committee (55%) but the independence of these members was not described so these may have been internal Trial Management Groups. Around two thirds of papers (60%) reported having a (I)DMC and 26.9% neither a steering nor an (I)DMC committee. However, before revising the third committee Charter (Terms of Reference) greater standardisation is needed around defining members independence, composition, primacy of decision-making, interactions with other committees and the lifespan.

### *Conclusions*

A third oversight committee has benefits for trial oversight and conduct and a revised Charter will facilitate greater standardisation and wider adoption.

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**Keywords:** randomized controlled trials, trial oversight, Data Monitoring Committee, Trial Steering Committee, charter, patient advocacy

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## Introduction

Oversight is key to ensuring that randomized controlled trials are conducted according to Good Clinical Practice<sup>1</sup> thus protecting participant rights, well-being and safety and ensuring robust trial data. However, trial oversight varies considerably according to funders, trial type and between countries. The United Kingdom (UK) Medical Research Council's (MRC) guidelines for Good Clinical Practice, first published in 1998<sup>2</sup>, and updated in 2017<sup>3</sup> to include global trials, defines a tripartite trial oversight committee structure which is widely used in academic-led (investigator-led) trials (**Table 1 and Figure 1**) funded by UK government and charities. The first internal committee is responsible for trial development, day-to-day conduct, and dissemination. This is called a "Trial Management Group" in the MRC guidelines (sometimes referred to as a "Steering Committee" or operations group) and is led by the Chief Investigator. A second established oversight committee is the (Independent) Data Monitoring Committee ((I)DMC<sup>4</sup>) which monitors accumulating safety and, often, efficacy data, and is usually unblinded<sup>5</sup>. Research and discussion continues about (I)DMCs as their role and operation evolves over time which also highlights international differences since the third oversight committee (described below) is not often included in recent American publications about the (I)DMC.<sup>6-8</sup> In the USA, cardiovascular trials have a Steering Committee in a clinical trial model developed by the National Institute of Health which comprises the trial leadership who develop the protocol, lead the trial and publish the results.<sup>9</sup> One example is the MERIT-HF trial with an International Steering Committee

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comprising the International Executive Committee, national coordinators from each participating country and a non-voting sponsor representative.<sup>10</sup> A modified model has been used for industry-sponsored trials with company employees or a contract research organisation to oversee the trial, sometimes without a (I)DMC.<sup>9</sup>

The third trial oversight committee named “Trial Steering Committee” by the MRC Guidelines<sup>2,3</sup> comprises a Chair and a majority of independent members plus key trial personnel (roles and membership summarised in **Table 1**)<sup>2,3</sup>. This third committee reviews the (I)DMC recommendations blinded to outcome data by randomised treatment groups (unless required by an (I)DMC recommendation in exceptional circumstances). Here, we utilise our recent published research on the third oversight committee which identified benefits to trial conduct and by including patient advocacy to set out the arguments for its wider use. We also identify current challenges and deliberations in its operation.

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## Methods

The MRC Network of Hubs for Trial Methodology Research investigated the roles and function of this third oversight committee in trials within a suite of five published research studies. In brief, we conducted a survey of 38 UK Clinical Trials Units<sup>11</sup>, reviewed an international cohort of 264 published trials<sup>12</sup>, observed 8 UK Trial Steering Committee meetings and interviewed 52 trialists<sup>13</sup>. We convened an expert panel of trialists to review these results and existing guidance for the third oversight committee as the current charter had not prevented variance in operationalisation of this committee<sup>14</sup>. Concurrently, guidelines were produced from the National Institute for Health Research (UK funder) aimed at improving Patient and Public Involvement in trial oversight committees<sup>15</sup>. The key findings of these five components are summarised in Table 2 and underpin our recommendations below.



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## Results

### *Role and benefits of a third oversight committee*

The third committee's role is multi-faceted<sup>14</sup> and distinguished from other committees by its independent member majority, including the Chair, who are blind to comparative analyses (Table 1). This allows unbiased and informed considerations of (I)DMC recommendations on behalf of sponsors and/or funders and provision of advice directly to key trial personnel (e.g. Chief Investigator). The independent Chair and members should include clinical, statistical and other relevant experts.<sup>14</sup> Patient and Public Involvement contributors provide an important voice<sup>16</sup> valued by trialists, although more work is required to optimise their contributions.<sup>17</sup> A few of the Trial Management Group (including the Chief Investigator) should be included in third committee discussions, thus allowing direct interactions of the trial team with independent experts which is a unique feature of this committee (**Table 1**).

In our survey and interview research, trialists described this third committee as a valued "critical friend",<sup>16</sup> advising on data quality, trial eligibility, problematic recruitment, publications and on data release requests, also serving as a Data Access Committee (Table 2).<sup>11</sup>

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However, after viewing comparative data, there are situations where the (I)DMC should not comment on aspects of the trial, such as protocol amendments to change the primary outcome measure, target difference or analysis approach. In the EcLiPSE trial, an important competing risk was identified during the trial with implications for power.<sup>18</sup> The (I)DMC explicitly recognised that their knowledge of interim comparative data compromised their objectivity and the internal Trial Management Group may have had interests in continuing the trial which could have also compromised their recommendations. Therefore, any objective recommendations about the analysis plan required a third oversight committee which included independent members; critically, here, a statistician. The trial statistical team developed several analyses options which were reviewed by the third oversight committee which recommended retention of the original sample size calculation.

Input from independent experts is important to give objectivity but committees solely comprising independent members should only make recommendations, not decisions<sup>19</sup>, as was emphasised within recent (I)DMC recommendations from the Clinical Trials Transformation Initiative. A decision-making body was not proposed by the Initiative but this could be fulfilled by the third oversight committee which is not involved in the day-to-day conduct of the trial. The survey of UK Clinical Trials Units identified that this third committee is widely used for phase III trials (Table 2),<sup>11</sup> although the published cohort of trials showed that evidence of its influence and impact internationally is less clear, partly due to limited reporting of its use and

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variation in nomenclature, independence and membership (Table 2).<sup>12</sup> In contrast, interviews and the expert trialists panel endorsed the role of the third committee which is widely used in UK academic trials (70% of trials had a third committee in the survey, although not feasibility or pilot trials) (Table 2).

*Challenges and recommendations for operationalising the third oversight committee*

Revising the three-committee oversight structure guidance based on recent research and experience should encourage its wider and optimal use. Here we outline some current issues and logistical considerations upon which transparency and consistency are sought:

*Membership and independence of members.* Responsibility for appointing the committee may be taken by the sponsor or funder following recommendations from the trial team. Whoever determines membership might potentially infer accountability which could impact on the committees' perceived independence. The third committee provides a unique forum for trial team members with in-depth trial-specific knowledge to interact with expert independent members. However, the status, number and functions of the non-independent contributors (e.g. Chief Investigator, trial coordinator) requires clarification, particularly ahead of considering (I)DMC recommendations that may require the committee to access and review accumulating comparative results or potentially close the trial. The MRC<sup>3</sup> and National Institute for Health Research guidelines<sup>20</sup> recommend that the majority of

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members should be independent. However, some definitions of “independence” may be too restrictive or impede appointing relevant members.<sup>14,16</sup> Definitions used by journal editors<sup>21,22</sup> or previously derived for (I)DMCs<sup>19,23</sup> may be instructive. Independence between the third committee and (I)DMC members may also be important, e.g. if staff management responsibilities occur between members of committees<sup>14</sup>. Standardisation of mechanisms to document and help to define members’ independence could be a key development.

*Patient and Public Involvement contributors.* Although highly valued, there is a lack of clarity currently about the roles of patient and public contributors. To enhance Patient and Public Involvement contributions there should be role descriptions prior to appointment, systematic recruitment, initial training and ongoing support<sup>15</sup> both before to inform and prepare patient and public contributors, during, to facilitate involvement in what could be complex scientific discussions, and after meetings to allow for further feedback and comment. Committee members may also benefit from awareness of recommended good practice from advisory organisations for Patient and Public Involvement and engagement.<sup>15,24</sup>

*Primacy in decision-making and relationship with (I)DMCs.* The third oversight committee was originally established as the decision-making committee<sup>2</sup> but many trialists currently view it as being advisory to funders and sponsors.<sup>13</sup> It is unclear

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how much authority the committee really has because funders and sponsors can withdraw support without reference to, or in contradiction of, third committee recommendations.<sup>13</sup> At least one UK funder has recently constituted a fourth oversight committee, with independent members, to oversee trial progress;<sup>25</sup> other funders may have similar structures. Opinions vary among stakeholders<sup>13,14</sup> as to whom the third oversight committee reports, and with which groups they communicate, including whether this is determined by the nature of their recommendations or requests. Clinical Trials Units, which coordinate most UK academic/investigator-led government or charity-funded trials<sup>26</sup> (similar to USA data management/coordinating centres) can facilitate reporting between oversight committees. A clearly defined process should also exist for managing rare disagreements between the (I)DMC and the third committee. This process, which should be documented early in the trial, should ensure appropriate and timely decision-making, protect the interests of the trial and prevent unnecessary exposure of third committee members to blinded comparative outcome data.<sup>19</sup>

*Organisation, including 'umbrella' committee structures.* The third committee is usually formed prior to recruitment, may inform protocol development, and usually finishes at publication of main results. If the committee assumes data access responsibilities (a more recent role<sup>14</sup>) or oversight of access to biological samples it would potentially have to continue indefinitely because requests are more likely

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after the main publications. Long-term committee maintenance may become impractical so requires further consideration and clarity of duration in the charter.

The third committee's initial meeting is preferably held face-to-face early in the trial for members to become familiar with each other and the trial and to facilitate future communications; this meeting can be joint with the (I)DMC to build trust and working relationships. Subsequently, remote meeting methods (e.g. videoconference) may enable frequent, quorate meetings, especially with international membership, although this may reduce members' ability to contribute effectively, especially Patient and Public Involvement members.<sup>17</sup> The meeting mode may be also informed by the nature of the (I)DMC recommendations and further work is needed on understanding the impact of the mode on member input and function.

Reports from the (I)DMC and their rationale must be sufficiently detailed to allow the third committee to consider them effectively. Excessive detail, however, may expose the third committee members to blinded, undisclosed or inappropriate information which may compromise their role going forward. Standardised inter-committee reporting methods (e.g. template documents) would reduce these potential pitfalls. Updating relevant external evidence for the committee underpins the third committee's ability to provide an informed broader view of a trial's

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continued legitimacy. Literature reviewing methods should be transparent to guard against potential bias, e.g. a documented search strategy.

Membership is usually voluntary and trialists report difficulties getting experienced members.<sup>11</sup> Convening a third committee that oversees multiple trials in a clinical area (“umbrella committee”) could be time- and resource-efficient, but might be challenged by time constraints to give adequate oversight of complex trials or those in difficulties.<sup>16</sup> A wider variety of trials, requiring further expertise, may also be difficult to encompass in one committee. Umbrella committees may reduce scheduling issues but have increased risk of (future) conflicts of interest. Agreeing independent membership may also be difficult across multiple funders and sponsors. This promising approach to trial research efficiency requires more formal evaluation.

## **Conclusions**

Robust clinical trial oversight is critical to the validity and safety of trials but some roles are less suited to internal management groups or an independent DMC. We identified that a third oversight committee gives additional independent guidance and an expert interface between independent and trial members, is valued by trialists, and incorporates patient and public contributors. This third committee is used widely in UK academic-led trials and prevents recommendations from the (I)DMC being considered solely by the trial team. Some issues still exist for

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operationalising this third committee optimally and their resolution through wider engagement could result in internationally recognised trial oversight standards.

We anticipate that a clearer oversight structure should benefit academic-led and industry-led trials, especially later-phase trials. We propose “PICTO: Partly-Independent Committee for Trial Oversight” or “SITOC: Semi-Independent Trial Oversight Committee” to emphasise the independence of the Chair and some members and to distinguish it from the internal Trial Management Group (sometimes called a “steering committee”). We also propose that (I)DMCs should make recommendations directly to the third committee.<sup>23</sup> There is widespread utilisation of data monitoring charters<sup>19</sup> for the (I)DMC and agreement on a third oversight committee charter would delineate the committee purpose and functions more clearly and potentially increase its uptake and value.



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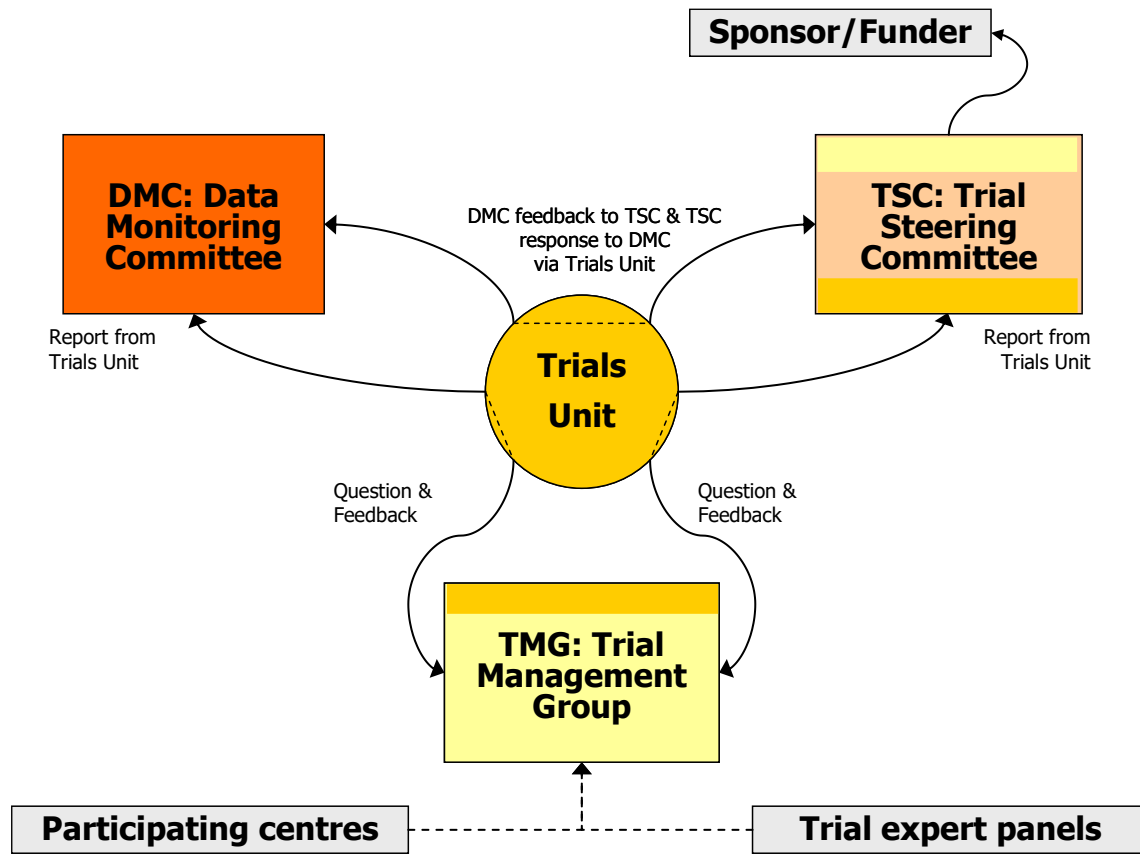
## **Declaration of conflicting interests**

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Figure 1 Oversight committee structures including third committee (Trial Steering Committee



**Table 1 Three committee trial oversight structure, composition, independence and responsibilities**

Name	Typical composition	Independence in membership	Primary responsibilities
Trial Management Group (TMG) (referred to by some as "Steering Committee")	Chair: Chief Investigator (trial leadership) Key clinical input Trial team (including operations, statistics, programmers) Patient and Public Involvement contributors	No	Ongoing trial conduct and day-to-day operations
Data Monitoring Committee (DMC) OR Independent Data Monitoring Committee (I)DMC <sup>1</sup>	<i>Chair: Independent member*</i> <i>Statistician*</i> <i>Clinician(s)*</i> <i>Additional expertise as required *</i>	Yes, usually all, and reflected in committee name	Review accumulating unblinded comparative safety, efficacy and other outcome data
Third Oversight Committee (Trial Steering Committee)  Suggested titles: PICTO ("Partially-Independent Committee for Trial Oversight") or SITOC ("Semi-Independent Oversight Committee)	<i>Chair: Independent member *</i> <i>Clinician(s)*</i> <i>Statistician*</i> <i>Patient and Public Involvement contributors *</i> Chief Investigator Trial statistician Sponsor and/or funding	Partial: majority of independent members, including Chair and those marked *	Oversee trial conduct and progress Ensure scientific integrity Advise on protocol, recruitment progress, adherence/contamination, follow up/attrition and data quality Advise funders and sponsors on trial continuation Review (I)DMC recommendations blind to comparative data Facilitate patient/public advocacy Review new external evidence relating to trial Review primary trial publications Review data access requests (in some cases)

\* Independent members

**Table 2 Research on third trial oversight committees**

<b>Research focus</b>	<b>Methods</b>	<b>Sample</b>	<b>Main results</b>
Current UK practice and experience <sup>9</sup>	Survey	38 Clinical Trials Units	<p>27 Units required a TSC<sup>1</sup> for all trials (71%)</p> <p>9 Units used one TSC for multiple trials (27%), most one per trial (29)</p> <p>33 Units used Terms of Reference (87%), 30 based on MRC Guidance</p> <p>Independent members ranged from 1-6, usually statistician (24 Units), clinicians (35 Units) and PPI (28 Units)</p> <p>Variation in operation e.g. voting rights, quoracy, duration</p> <p>TSC reviewed protocol changes, main trial publications, analysis plan, publication policy (data sharing at 16 Units)</p> <p>TSC decided on trial continuation for sponsors/funders</p>
Reporting of remit and function <sup>10</sup>	Literature review of trials cohort	<p>264 trials published in 6 months in 2012 in British Medical Journal, The Lancet and New England Journal of Medicine</p> <p>UK (161) and USA (50) trials</p>	<p>TSCs reported in 144 trials (55%), 61 called TSC, 42 Steering Committee, Steering Group (14) or Executive Committee (10)</p> <p>109 of trials with TSC also had (i)DMC (76%)</p> <p>84 TSCs specified Chair, clinical (46), statistics (29), PPI (39) members but independence could not be determined</p> <p>Low reporting standards of constitution, activity make evaluation and impact on trials impossible to assess</p>
Roles, relationships and attributes <sup>11,14</sup>	Observation and interviews	<p>8 trials TSCs and TMG<sup>2</sup>s</p> <p>52 interviewees with trialists</p>	<p>Independence valued, difficult to operationalise and define</p> <p>Patient advocacy role important including through PPI</p> <p>Quality assurance role a “critical friend” valued highly</p> <p>Chair is critical to success with experienced members</p> <p>Lack of clarity around roles and accountability</p> <p>Changes over time in roles of funders, sponsors and TSC</p>

<b>Research focus</b>	<b>Methods</b>	<b>Sample</b>	<b>Main results</b>
Review existing guidance, role and functions <sup>12</sup>	Expert panel at two meetings	7 clinicians, statisticians and trial methodologists	Supported third committee role, need for revision and expansion of MRC <sup>4</sup> guidelines. Complex, challenging, real-life examples needed to ensure comprehensive development. Importance of experienced members and development of training resources Issues to clarify: indemnity, lifespan, operationalisation, data sharing role, primacy with funders and sponsors
Develop PPI <sup>3</sup> guidance in oversight roles <sup>13</sup>	Interviews	9 PPI TSC committee members and 8 TSC Chairs	TSC good for PPI to provide fresh perspective Role and responsibilities need clarity and role descriptions Chair to encourage PPI involvement which teleconferences may hinder Ongoing support to PPI members needed No training provided but could help avoid 'tokenism'

<sup>1</sup>Trial Steering Committee (TSC), <sup>2</sup> Trial Management Group (TMG, sometimes called "Steering Committee"), <sup>3</sup>Patient and Public Involvement,

<sup>4</sup>Medical Research Council.