Australian Clinical Trials Alliance

Trial Endorsement and Review: Guidance for CTNs

September 2019

ACTA gratefully acknowledges operational funding from the Australian Government's Medical Research Future Fund

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PURPOSE OF THIS DOCUMENT

This document will assist Clinical Trial Networks (CTNs) in establishing trial endorsement policies/guidelines.

THE ROLE OF ACTA IN DEVELOPING ENDORSEMENT AND TRIAL REVIEW GUIDELINES

The Australian Clinical Trials Alliance (ACTA) is providing advice to assist CTNs in developing endorsement and trial review guidelines. The generic advice provided by ACTA should be considered and applied by each CTN taking into account the specific requirements of the CTN.

ACKNOWLEDGEMENTS

We acknowledge the contributions of ACTA CTN members and members of ACTA's Efficient and Effective CTNs Reference Group in the preparation, development and review of this document. We would like to thank Australian and New Zealand Intensive Care Research Centre (ANZIC-RC), Australian and New Zealand College of Anaesthetists Clinical Trials Network (ANZCA CTN) in sharing their policies that have been considered to develop this document.

USE OF THIS DOCUMENT

ACTA encourages the use of all materials listed on its website (www.clinicaltrialsalliance.org.au) in the pursuit of improving the clinical trials enterprise. ACTA requests that the following acknowledgement is included in any CTN authorship and publication guidelines that are developed and documented using knowledge gained from this document:

> '[Name of CTN] acknowledges the contribution of ACTA to the development of trial endorsement processes within our network (reference: *Trial Endorsement and Review: Guidance for CTNs*)'.

DISCLAIMER

The information in this document is for general guidance only. ACTA does not make any representations or warranties (expressed or implied) as to the accuracy, currency or authenticity of the information provided.

ABBREVIATIONS

ACTA	Australian Clinical Trials Alliance
CTN	Clinical Trial Network
NHMRC	National Health and Medical Research Council
PI	Principal Investigator
TSC	Trial Steering Committee
TMC	Trial Management Committee

RATIONALE FOR DEVELOPING A TRIAL ENDORSEMENT POLICY AND TRIAL REVIEW GUIDELINES

Endorsement of a proposed trial is undertaken by many CTNs and serves many purposes. These include evidence that the proposed trial has undergone peer-review by the CTN, that this is a shared commitment by the CTN to conduct and complete the trial, and that the track record of the CTN is available to support the proposed trial with respect to applications for funding and for recruitment of sites to participate. Additionally, endorsement can assist in prioritisation of possible trials and contribute to building the brand-value of the CTN. The stage of development of a proposal that is sufficient for consideration of endorsement is a decision for each CTN, but can be one or more of presentation of the proposal to a CTN meeting or Scientific Advisory Committee, a grant application, or a trial protocol. CTNs may also choose to endorse trials or endorse manuscripts resulting from trials or both.

CONSIDERATIONS WHEN DEVELOPING AN ENDORSEMENT AND TRIAL REVIEW POLICY/GUIDELINES

CTNs should consider explicit identification of the goals and purpose of an endorsement policy, including identification of relevant stakeholders and the benefits and responsibilities for each stakeholder. Stakeholders include, but are not limited to, the CTN, the investigators of the proposed trial, participants, consumers, healthcare system, and academic institutions. Several considerations should be taken into account when developing an endorsement policy including the process of endorsement, the requirements and considerations for endorsement, and the responsibilities of endorsement. The process, requirements for, and responsibilities should be set out in an endorsement policy document. The individual or group who have responsibility for the writing and review of the endorsement policy should be identified and a schedule for periodic review of the policy should be maintained.

PROCESS FOR ENDORSEMENT

Issues for consideration in relation to process for endorsement include:

- What information, and in what format, is it required for submission (for example, presentation, grant application, protocol)
- Whether presentation to a CTN meeting or Scientific Advisory Committee is part of the process
- Whether endorsement is a single- or multi-stage process
- Whether internal or external peer-review will occur and who will undertake that peer-review, including whether review by a site-level research coordinator and/ or a consumer is required
- Who is responsible for the decision regarding endorsement and what the process is for reaching a decision
- How conflicts of interests among those who undertake the endorsement decision will be identified and managed
- Will the CTN charge for endorsement
- Deadlines and timelines for the endorsement process
- Eligibility requirements to submit an application for endorsement, including in relation to commercially sponsored or funded studies, studies led by overseas investigators, external collaborators who are not members of the network and whether joint endorsement with one or more other CTNs is possible
- Process for appeal and dispute resolution, if appropriate
- What post-endorsement quality assurance measures are required to ensure the research is conducted as proposed (for example, mandated peer-review of final protocol and protocol changes).

REQUIREMENTS FOR ENDORSEMENT

Issues that may be relevant and incorporated into a policy with regard to requirements for endorsement include:

- Meeting the requirements of the National Statement on Ethical Conduct in Human Research, including sufficient clinical equipoise
- Commitment to adhere to trial regulatory requirements including, where appropriate, one or more of Good Clinical Practice, The Australian Clinical Trials Handbook, NHMRC Code of Conduct for Research, SPIRIT guidelines for protocol development, CONSORT and equivalent statements for reporting of trial results
- Scientific quality including sufficient preliminary evidence, if appropriate results of systematic reviews, evidence of context such as surveys or observational studies of current practice or equipoise or both, a planned sample size that is sufficient for a plausible effect size, and appropriate statistical methods
- Feasibility including pilot studies, support from sites, availability of placebo, sufficient funding or a feasible plan to obtain sufficient funding
- Consumer involvement and/or review
- Support from clinicians for the relevance of the question
- Alignment with mission and vision of the CTN, including CTN priority areas
- Budget and site payment budgets/process
- Involvement of categories of personnel such as earlier career investigators and trial coordinators in trial management
- Contribution from additional sub-studies
- Potential for implementation of the results into clinical practice or policy including implementation plan
- Data sharing and access to data for sub-studies
- Access to the intervention including novel drug or PBS-approved supply
- Access to investigations including MBS items
- Availability of central trial coordination including project management, data management, statistical support, and health economics
- Agreement from an appropriate legal entity to act as Sponsor and data custodian
- Publication and dissemination plans.

RESPONSIBILITIES OF ENDORSEMENT

The responsibilities of the investigators of endorsed studies should be outlined clearly. Considerations in this regard include:

- Compliance with authorship and publication policies, presentation policies, competing studies policies, co-enrolment policies, requirements regarding progress reports
- Requirements related to the choice of participating sites
- Manuscript endorsement process
- Use of logos and CTN branding
- Any requirements around implementation or measurement of implementation and impact.

DEVELOPING A TRIAL ENDORSEMENT POLICY/GUIDELINE AND TRIAL REVIEW GUIDELINES

WHO IS RESPONSIBLE FOR DEVELOPING THE GUIDELINES?

The development of the trial endorsement policy and review of applications for endorsement would often be managed by the most senior committee within the governance structure of the CTN (Executive or Steering Committee), although it may be devolved, in part or in whole, to a group such as Scientific Advisory Committee or a designated Trial Endorsement Working Group/Committee. For the remainder of this document, the committee responsible for endorsement is referred to as the Network Executive Committee.

REVIEW AND ENDORSEMENT OF THE GUIDELINES

All Network Executive Committee members should be given the opportunity to review the guidelines and discuss it at a suitable meeting. The endorsement policy should outline the process by which endorsement decisions are made, for example, whether a majority vote is sufficient. The endorsement guidelines should be reviewed at regular intervals by the Committee to adapt to the evolving clinical trials landscape and the experience of the network.

AIMS OF TRIAL ENDORSEMENT

When developing an endorsement policy, a background to the network and clear aims of trial endorsement should be clearly outlined. The network may elect to align these aims with the mission and vision of the CTN.

Aims of endorsement may include:

- Promoting a high standard of research design, conduct, analysis and reporting
- Enhancing chances of success and competitiveness on grant applications
- Strengthening the brand and reputation of the CTN
- Encouraging participation of CTN sites and investigators in the trial
- Improving the track record of the CTN in delivering high quality studies
- Enhancing attractiveness of the completed study to journal editors
- Developing transparent processes for allocating finite network resources to high quality trials (e.g., central coordination resource, sites, site PIs etc)
- Raising the profile of the network and ensuring use of logo name, branding and style is only used on suitable high-quality studies
- Benefitting investigators (especially early career investigators) through the CTN track record, in competitive funding applications.

TYPES OF STUDIES THAT MAY BE CONSIDERED FOR ENDORSEMENT

It is important for the Network Executive Committee to clearly define in the endorsement policy what type of studies will be considered for endorsement. This may be restricted to clinical trials or multicentre studies that fulfil the aims of the CTN's mission or vision, or it could be a study that specifically addresses a pre-defined research priority area of the network. The CTN may also consider endorsing other types of studies, for example, pilot and feasibility studies, national audits, single centre studies, quality studies, surveys etc. Nonetheless, clear definitions of the types of studies should be provided in the policy document to manage expectations of the network and to limit the endorsement policy/guidelines to the core aims/ business of the CTN.

Example wording for policy

Applications that will be considered for CTN endorsement are:

- Multicentre clinical trials related in the field of [insert specialty or disease area] that will involve the [insert network name] of trial investigators, sites and coordinators. A clinical trial as defined by the World Health Organization (WHO) is "any research that prospectively assigns human participants or groups of humans to one or more health-related interventions to evaluate the effects on health outcomes".
- Single or multicentre feasibility or pilot studies that may lead to a future [insert network name] endorsed large multicentre clinical trials.

CATEGORIES OF TRIAL ENDORSEMENT

The CTN may want to consider offering levels/categories of endorsement. These categories may include:

1. **Trial endorsement only**
   Endorsement of studies/trials run by the network investigators, however, no central support or resources are provided to coordinate or facilitate the trial.
2. **Trial endorsement and support**
   Endorsement of studies/trials run by the network investigators (or eligible investigators), and the investigators draw on central support or resources to coordinate/facilitate the trial.
3. **Endorsement of trials led by external groups or international networks**
   Endorsement of studies/trials only run by external groups or international networks where there is no central support or resources required to coordinate/facilitate the trial.

If different categories of endorsement are offered by the network, it is important to delineate the application criteria and conditions of endorsement for each category. It is also important to state what is offered to the investigators for each of the categories and if there are any associated costs. The Network Executive Committee should also consider the publication and authorship guidelines that apply for each category.

APPLICANTS

The guidelines should stipulate who is eligible to apply for CTN endorsement under each of the categories of trial endorsement (if applicable). Applicants may include:

Member of the network

A formal member of the network, affiliate, honorary member etc. who is listed as an investigator on the protocol and/or trial management committee.

External collaborators

It is common for the CTN to recruit participants to a study led by collaborators in another discipline. The Network Executive Committee should consider if applications will be accepted by external collaborators and what the conditions are of endorsement. For example, this may include if a member of the CTN should be listed among the investigators in the protocol, be on the trial management committee, and/or listed as an intended author on the main manuscript.

International networks

It is common for some CTNs to recruit participants to internationally-led trials. The Network Executive Committee may consider applications from international networks if they foster collaboration between the networks. The CTN may consider that it is a requirement for the trial to be endorsed by the CTN if the study draws on the CTNs pool of sites and investigators, and if so, whether a member of the CTN should be assigned as the national leader.

Higher-degree students

The CTN may accept applications from students. If so, does their supervisor need to be listed as an investigator in the protocol or trial management committee.

THE APPLICATION PROCESS

This section outlines the application process. It may be beneficial for the CTN to ask the applicants to submit an initial application form to enable the Network Executive Committee to discuss the proposal and endorsement policy with the applicant (see Appendix A).

FULL APPLICATION

The application may include the following documents:

- Cover letter addressed to the Chair of the network explaining why their trial should be considered for endorsement
- Applicant CV
- Completed initial application checklist (see Appendix A)
- Contact details (name, position, department, hospital, contact email, contact mobile, membership status)
- Full or partial research protocol (see below) – this should be developed in accordance with SPIRIT checklist
- Grant application
- Any letters of support for the study from site investigators to support feasibility of the trial
- Trial budget
- Any secured funding for the trial
- List of funding applications submitted to funding bodies
- List of workshops and dates that the protocol has been presented/discussed to CTN members
- A register of declared interests signed by all members of the trial management committee.

Other requirements that may be considered as a condition of endorsement:

- Evidence of consumer involvement, or a consumer member on the trial management committee
- Trial coordinator on the trial management committee
- Early career researcher on the trial management committee.

Ensure all items included in the criteria for endorsement are provided in the full application.

APPLICATION DEADLINES AND PROCESSING TIMEFRAMES

The endorsement policy should outline any application deadlines and processing timeframes. The Network Executive Committee may wish to set endorsement application deadlines well ahead of major funding deadlines to allow for ample processing timeframes. This allows for the CTN to manage risk (real and perceived) ahead of funding application deadlines, which is particularly important for managing competing studies where there are similarities in the eligibility criteria.

REVIEWERS

Independent expert reviewers are highly valuable to the endorsement process. They should have clinical expertise in the field and/or have expertise in trial design and conduct, and should be free of conflict of interest. The Network Executive Committee should outline in the endorsement policy how many reviewers will be sought to review the endorsement application and where they will be sought from. This may include within the Network Executive Committee, the members of the network who have clinical expertise in the topic of interest, or external collaborators with clinical expertise in the topic of interest. The CTN may consider that at least one reviewer is from the Network Executive Committee. The CTN may consider that at least one reviewer is a site trial coordinator, as these individuals can bring substantial expertise regarding feasibility and capacity to operationalise a trial concept. The CTN may consider review by a consumer or consumer representative.

The Network Executive Chair may be responsible for assigning/sourcing appropriate reviewers with the help of the rest of the committee if required.

CONFIDENTIALITY

Expert reviewers who are provided with the application and protocol will treat the protocol as confidential and will not forward the protocol to peers. If there are any concerns about the application, including any conflict of interest, this should be raised with the Network Executive Chair in the first instance.

REVIEW PROCESS

The reviewers may opt to meet to discuss applications and to come to a consensus about the outcomes of the application. The Network Executive should consider how it will manage any inconsistent decisions among reviewers. The reviewers should provide a written report with questions, comments and concerns they have about the protocol. The turnaround time for this report should be specified to provide clarity to applicants (a period of two to three weeks is common). If applicants will be provided with opportunity for rebuttal the time available for the applicant to respond should also be specified.

COMMUNICATIONS, DISPUTE AND APPEALS PROCESS

The applicant should be informed whether they have been successful or unsuccessful in their application by a formal letter from the Chair of the Network Executive Committee. If successful, the letter should list the conditions and requirements of endorsement that must be accepted by the applicant. If the CTN permits appeals for an unsuccessful application, the process for such appeals should be clearly defined in the endorsement policy.

CONDITIONS OF ENDORSEMENT

CONSIDERATIONS FOR CONDITIONS OF ENDORSEMENT

The network should consider the ongoing obligation from the trial investigations for the duration of the trial. These may include:

- That the investigators are required to carry out the endorsed study in compliance with appropriate regulatory requirements including ethical review committees
- Timely set up, recruitment, analysis and publication
- Adherence to network processes. For example:
  - Authorship and publication policies
  - Safety oversight/trial oversight procedures
  - Conflict of interest
  - Competing study and co-enrolment policies
  - Manuscript endorsement requirements
  - First public release requirements
- Investigators are required to obtain funding and the resources they need to carry out the study.
- Annual reporting (written progress updates and final reports)
- Presentations (for example, the investigator should be given the opportunity, or may be required, to present findings at the CTN meeting)
- Use of the CTN branding and styles guides for presentations and publications
- Acknowledgement of the CTN in all presentations and publications
- The right for the Network Executive Committee to review and approval for first public release of trial results
- Trial registration
- Feedback of results to participating sites and the timing of such feedback.

The Network Executive Committee may opt to reserve the right to withdraw endorsement at any stage should the study not progress adequately, if it is not being conducted in accordance with these conditions, or if irresolvable conflicts of interest arise.

AUTHORSHIP AND PUBLICATION POLICY

The CTN should carefully consider whether conditions of endorsement are linked to the CTN's publication and authorship policy for each of the endorsement categories (if applicable). For example, the first and third category of endorsement: *Trial endorsement only*, and *Endorsement of trials run by external groups or international networks* where there is no further involvement from the CTN, it may only require the CTN to be recognised in the acknowledgements section of the final manuscript, whereas the second category, *Endorsed and supported trials*, it may require the CTN group name to be by-lined in the main manuscript as a condition of endorsement.

See ACTA's *Authorship and Publication Policy: Guidance for CTNs* for more information.

TRIAL FUNDING CONSIDERATIONS

The Network Executive Committee may wish to consider if they will offer endorsement for both publicly-funded and commercially-funded trials, and the conditions under which they will accept the application. A distinction may be made between endorsement of a commercial study in which the commercial entity is the sponsor (and has control over trial planning, design, conduct, and reporting) and commercial funding in which independent academic researchers retain control over the trial. Where a commercial entity is the sponsor or is providing funding, the responsibilities of the CTN, the commercial entity, and other parties should be set out clearly in an executed contract.

THE RIGHT TO RETRACT ENDORSEMENT

The Network Executive may want to reserve the right to retract endorsement. This may result from the following:

- Research misconduct
- Failure to get ethics approval
- Failure to obtain funding
- Failure to recruit at a sufficient rate
- Failure to adhere to the requirements of endorsement.

MANAGING COMPETING STUDIES

Competing studies endorsed by the same network may compromise trial recruitment and risk the reputation of the network and therefore the CTN brand, in particular for studies where co-enrolment is not possible. This may include the same study drug or indication being studied, or overlap in eligibility criteria. Competing studies run by the same network may jeopardise potential funding opportunities and coherence among network members. It is important for the Network Executive Committee to consider how it will manage competing studies, preferably by a formal competing studies policy.

Some considerations include:

- Requesting that the investigators provide evidence of feasibility (for example, site investigators indicating that they support the study or plan to recruit to the study).
- Facilitation of co-enrolment wherever possible
- A clear process for prioritisation of potentially competing studies, for example, priority for already funded studies or a temporal sequence of endorsement.

APPENDIX A: INITIAL APPLICATION FOR ENDORSEMENT

[INSERT NAME] CLINICAL TRIALS NETWORK
APPLICATION FOR ENDORSEMENT

Please complete, scan and email your completed application to the [admin officer]

APPLICANT DETAILS

NAME	
POSITION	
DEPARTMENT	
HOSPITAL / UNIVERSITY	
CONTACT EMAIL	
CONTACT PHONE	
MEMBERSHIP STATUS	☐ Member of network ☐ Non-member
ROLE IN STUDY	[Principal Investigator]

APPLICATION DETAILS

TITLE	
SYNOPSIS (200 WORDS)	

APPLICATION CHECKLIST ***include all items in endorsement criteria***

ITEM	YES	NO
Protocol		
Steering committee membership		
Administering institution		
Aims and hypotheses		
Background with references		
Detailed research plan		
Sample size calculation or other justification for sample size		
Proposed analyses		
Proposed budget		
Proposed coordinating centre		
Funding strategy		
In-principle support from sites		
Consideration of ethical issues		
PRESENTATION AT WORKSHOP OR SCIENTIFIC MEETING		
Workshops and date(s)		
Future workshop and dates		

CONFIRMATION AND SIGNATURE OF APPLICANT

I confirm that, in the event of successful endorsement, I take responsibility for compliance with all the conditions of endorsement as outlined in the [name of network] Guidelines for Endorsement [version number]

Signature

Date

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