Australian Clinical Trials Alliance

# Comparative effectiveness trials: requirements for low risk ethics review

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## ACKNOWLEDGEMENTS

**Lead author:** Mrs Tanya Symons
**Chair of ACTA Reference Group:** Professor Nikolajs Zeps
**Project Manager:** Ms Nicola Straiton
**Developed by** the ACTA Embedding Clinical Trials in Routine Care National Reference Group.

## DISCLAIMER

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## BACKGROUND

One key focus of clinical trials networks is to conduct research that contributes to the evidence-base which underpins standard treatments and interventions. This type of research, known as comparative effectiveness research (CER), systematically evaluates the comparative merits of routinely used interventions to provide patients, clinicians and policy makers with better insights and evidence on what works best.[1]

## PURPOSE

The purpose of this document is to provide a brief overview of comparative effectiveness research, with a focus on comparative effectiveness trials (CETs). The document also discusses considerations for the review of CETs by Human Research Ethics Committees (HRECs) and examines the revisions in the National Statement (updated 2018)[2] that now offers the option of a low risk pathway for the ethics review of CETs.

The aim is to encourage wider use of the inherent flexibilities in the NHMRC National Statement2 that permits a proportionate approach to trial approval and conduct, based on the level of risk. Wider use of these flexibilities has the potential to make well-designed CETs easier and quicker to conduct, which in turn will enable researchers to accelerate the generation of evidence to guide optimal health care.

## COMPARATIVE EFFECTIVENESS RESEARCH

Comparative effectiveness research is a term that describes a diverse range of research (e.g. medical, behavioral, surgical)[3] that focuses on optimising health outcomes. It compares currently accepted/approved interventions to help improve the effectiveness and cost effectiveness of healthcare. There is no standard definition for CER, although several definitions and principles have been developed.[4] The definition in Box 1 illustrates the diversity of CER, both in terms of the type of intervention and the target of those interventions.

**Definition for Comparative Effective Research**

The generation and synthesis of evidence that compares the benefits and/or harms of:

a) alternative methods to prevent, diagnose, treat, and monitor a clinical condition, or to improve the delivery of care that are currently accepted, or

b) the same method(s) between different patient groups or clinical environments, or

c) a combination of the above.

**Box 1**

CER can use a broad range of methods, both experimental and non-experimental, but this document focuses on comparative effectiveness trials (CETs).

## COMPARATIVE EFFECTIVENESS TRIALS

The most effective way to resolve many treatment uncertainties is to embed large, comparative effectiveness trials (CETs) into clinical care. Also known as pragmatic trials or large simple trials, CETs often employ novel trial designs, such as adaptive or cluster designs, that can be embedded into routine clinical care. Most CETs are conducted by non-industry sponsors although commercial interest in pre-market use of pragmatic trials and real-world evidence is growing.[5]

CETs differ from traditional randomised controlled trials (RCTs) testing new interventions in several ways. These latter exploratory trials answer efficacy questions (i.e. the performance of an intervention under ideal and controlled circumstances), whereas CETs answer effectiveness questions, (i.e. the performance of an intervention under 'real-world' condition).[6]

To reflect real-world clinical practice, CETs are normally conducted with minimal exclusion criteria and recruit patients from a variety of practice settings. Participant follow-up mirrors normal care and endpoint data can be collected from electronic records or registries. These features not only enable the results of CETs to be more generalisable, but the burdens of trial participation (both for patients and clinicians) are also greatly reduced. Furthermore, when CETs are conducted using adaptive designs, they can compare multiple interventions across multiple patient subgroups to yield evidence that allows clinicians to better personalise treatments based on factors such as the severity of disease, genetics, and age.

To inform practice and policy, CETs can also be designed to incorporate cost effectiveness analyses and may use implementation science to address the challenges posed by translating evidence into practice. Figure 1 (overleaf) illustrates CETs in the context of RCTs and other types of research.

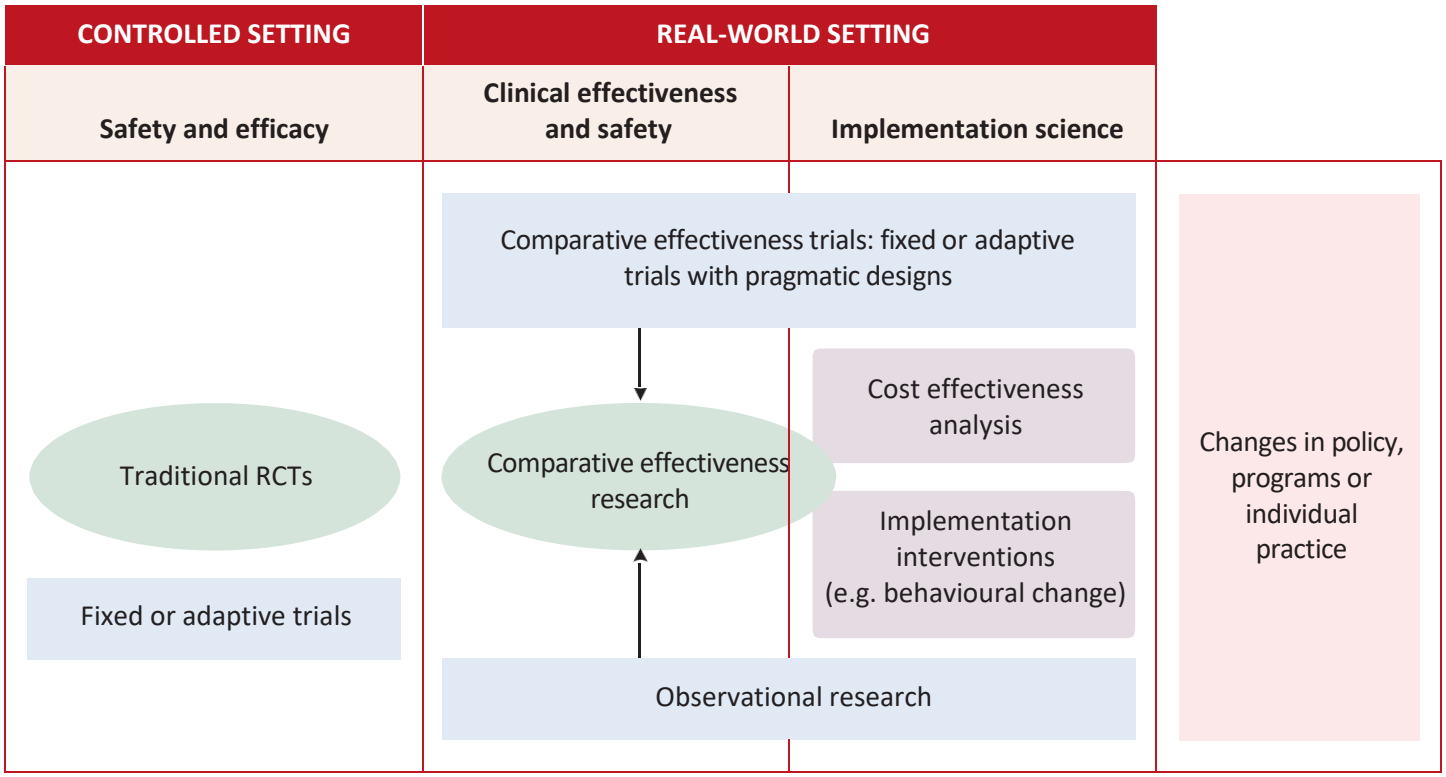



**Figure 1:** CETs in the context of RCTs and other types of research

# ETHICAL REVIEW OF COMPARATIVE EFFECTIVENESS TRIALS

## ASSESSMENT OF RESEARCH RISK

The 2018 update of the National Statement[2] includes a fully revised Section 3: Ethical considerations in the design, development, review, and conduct of research that clarifies how the risks of research should be assessed. Section 3.1.6 states: 'In health research involving an intervention, the risks of an intervention should be evaluated by researchers and reviewers in the context of the risks of the health condition and the treatment or treatment options that would otherwise be provided as part of usual care'. By confirming that the 'research risks' are risks that are incremental to standard care, the National Statement aligns with international guidelines adopted in many countries.[7]

The risks of the research should be assessed as the risks that are incremental to risks posed by standard care.

## TYPES OF CET THAT MAY BE ELIGIBLE FOR REVIEW BY A LOW RISK PATHWAY

Section 5.1.6 of the National Statement[2] lists the categories of research that must be reviewed by an HREC. Following the 2018 revision of the National Statement, the removal of Chapter 3.3 and revisions to Section 5 has created a low risk pathway for the ethics review of clinical trials. This permits *some*[†] CETs, with risks no greater than standard care, to be deemed suitable for review using a low risk pathway.

The 2018 revision of the National Statement has enabled a low risk pathway for clinical trial ethics review.

**Note: Multicentre CETs**
As low risk ethics applications differ greatly between states and territories, the Human Research Ethics Application (HREA) is used under the National Mutual Acceptance model for both multi-centre applications and for applications that have the potential to become multi-centre.

[†] Appendix 1 provides a flow diagram to help determine whether review by low risk pathway is possible. Box 1 and Box 2 list activities and trial populations that trigger the requirement for 'full' HREC review.

## CONSIDERATIONS FOR CETS

The ethical requirements laid down in the National Statement[2] apply to all trials, including CETs. For example, there is always a requirement for clinical equipoise – defined as a genuine uncertainty within the expert clinical community about the comparative merits of the alternatives to be tested.[8] To take part in a trial, investigators must be committed to resolving that 'treatment uncertainty'.

Research is often considered as inherently risky. This might be attributed to the widely held view that researchers have dual loyalties – to patients and to the trial protocol, whereas the sole focus of the clinician in a clinical care context is the wellbeing and best interests of the patient.[9] But for CETs, this assumption is of little relevance as the goal of CETs is therapeutic and they are performed with the intention to benefit the trial participant (by standardising that particular standard of care) as well as future patients.[10] However, other factors require additional consideration to ensure that the risks of CETs remain low, and these are outlined below.

### a) Determining standard of care and choice of comparators

CETs must compare treatments that are widely believed to be the best available standard care†. Determining standard care (also termed usual care) can be challenging when there are a range of different approaches that are each accepted by medical experts as proper practice for a certain type of condition. In the absence of definitive evidence for the best treatment, variation in medical practice is commonplace – with everyday choices made based on a range of factors including clinician knowledge, patient preferences, habit, socioeconomic or cultural factors, marketing campaigns and cost. The outcome is haphazard (random) care in place of evidence-informed care.

The choice of appropriate comparators is, therefore, a central issue in CETs. The optimal comparators are those that relate to the primary research question.[11] Inappropriate or sub-optimal choices[12] can adversely affect the inferences drawn from a trial and its ethical acceptability. Investigators must systemically and transparently justify their selection of the comparator arm(s) by providing the reviewing HREC with robust evidence supporting their choices.

> The optimal comparator(s) is one that will provide the clearest answer to the primary research question. Investigators should clearly explain their choice of comparator, disclose any alternatives that were considered, explain why they were rejected and acknowledge any limitations associated with their choice.[11]

Many factors can complicate comparator choice, including substantial variability in practice between centres or countries. Complications also arise when standard care is difficult to describe or is inconsistent.[13] This is particularly the case in trials investigating ranges of doses (e.g. oxygen saturations, ventilator tidal volumes). Although one solution would be to include a study arm representing 'physician's choice', this must be weighed again the impact on generalisability (and therefore value) of the trial – i.e. if the usual care arm was shown to be inferior or superior in the trial, it may be impossible to ever know why. This highlights the importance of pre-trial preparation as described in a case study in an article by Thompson *et al*.[13]

When available, comparator choice should be based on the recommendations from up-to-date, high-quality clinical practice guidelines. If no such guidelines exist, researchers must demonstrate a well-developed understanding of current practice (e.g. through the review and synthesis of current literature) which would include evidence that the chosen comparator intervention is routinely used in clinical practice. This evidence could come from several sources including[14,15,16,17]

- Point prevalence surveys
- Observational studies
- Meta-analyses
- National reimbursement lists
- Prescription statistics (if appropriate)
- Registries.

† The term standard care is the care provided within the bounds of accepted practice rather than the individual care a patient would have received at the healthcare institution had they not opted to take part in research.

The following case study from the Australian and New Zealand Intensive Care Network illustrates how comparator arms could be justified.

| Case Study: The BLING III Trial[18] | |
|---|---|
| **Trial objective** | To compare the use of continuous infusion of β-Lactams with intermittent infusion in critically ill patients with sepsis on all-cause mortality within 90 days. |
| **Rationale** | β-Lactam antibiotics are the most common class of antibiotics used to treat life-threatening infections in the intensive care unit (ICU) setting. Despite improved maintenance of plasma antibiotic concentrations with continuous infusion, there is current uncertainty about survival benefits compared with standard intermittent infusion in critically ill patients with sepsis admitted to the ICU. This trial aims to resolve this important treatment uncertainty. |
| **Activity to determine comparators** | Review of literature to confirm β-Lactams are the most common class of antibiotics and how they are delivered – including a systematic review, and two-point prevalence studies (collection of data at a specific point in time), one of which was conducted in 37 ANZ ICUs. |
| **Comparators** | Continuous infusion or intermittent infusion of β-Lactam (piperacillin–tazobactam or meropenem) over 30 minutes. |

### b) The competence of the clinician-investigator

When trials are conducted with novel interventions, risks relating to the delivery of those interventions are mitigated through sufficient training for clinicians to appropriately follow the protocol. Although CETs involve established treatments, participants may be assigned to treatments that the clinician does not routinely use or may not be familiar with. Thus, it is important to ensure such ensuing risks are mitigated through sufficient training to adequately deliver the relevant intervention to which the patient is randomised.

### c) When current treatments have little evidence for their use

Many treatments routinely used have never been shown to be effective in clinical trials. As a result, some CETs are conducted specifically because there is an absence of evidence of effectiveness or cost-effectiveness. The outcome of such trials is often the removal of ineffective or harmful treatments or interventions from routine practice.[19,20] What differentiates CETs from traditional trials is that the comparators are 'established care' rather than novel care. The risks of this research then are no different and are indeed comparable to standard care.

### d) The use of randomisation in place of clinician choice

When compared with normal care, the key added feature in CETs is *randomisation*, with few other additional activities that could interfere with routine care workflows or that could pose additional risk or burden to participants. Notwithstanding this observation, there is growing recognition that randomisation triggers disproportionate levels of oversight and lengthy and rigid consent processes for trials. The underlying rationale for this *research exceptionalism*[21] is that patients are at more risk when treatment is chosen by randomisation. Evidence from systematic reviews refutes this.[22,23] Randomisation may alter an individual patient's exposure to potential benefits and harms (the study arm may lead to harm or it may lead to benefit, or it may lead to identical outcomes relative to the alternative arm) but, in itself, randomisation does not increase risk as both arms represent acceptable standards of care. The key factor is that patients are adequately informed of the implications of trial treatments and can evaluate the ways in which their trial treatment might differ from usual care – knowing that they are free to refuse trial participation if they prefer one treatment's risk/benefit profile over another. Notably, many experts have highlighted that patients are much less informed about risks when receiving the same treatment outside the trial setting. The fact that trial participants may be better informed could be viewed as a collateral benefit of participation.[24]

### e) Disclosing uncertainty

The consent discussion for CETs includes the disclosure of uncertainty. Although there is a belief that disclosure of uncertainty may cause discomfort or anxiety in prospective participants, it has also been argued that good practice outside the trial setting would require clinicians to share these uncertainties about care as relevant information before patients make decisions about that care.[25] Fuller disclosure to patients about the uncertainty associated with the interventions being studied could foster greater understanding and ultimately improve trust in routine care as well as the clinical research process.[26]

### f) Cluster trials

Many CETs adopt cluster designs where the units of allocation are 'clusters' of individuals (e.g. medical practices, hospital wards, care homes). These trials raise questions and specific ethical issues that are unique to this design. For example, because cluster randomised trials may have consequences for groups as well as for individuals, the assessments of benefits and harms are more challenging.[27]

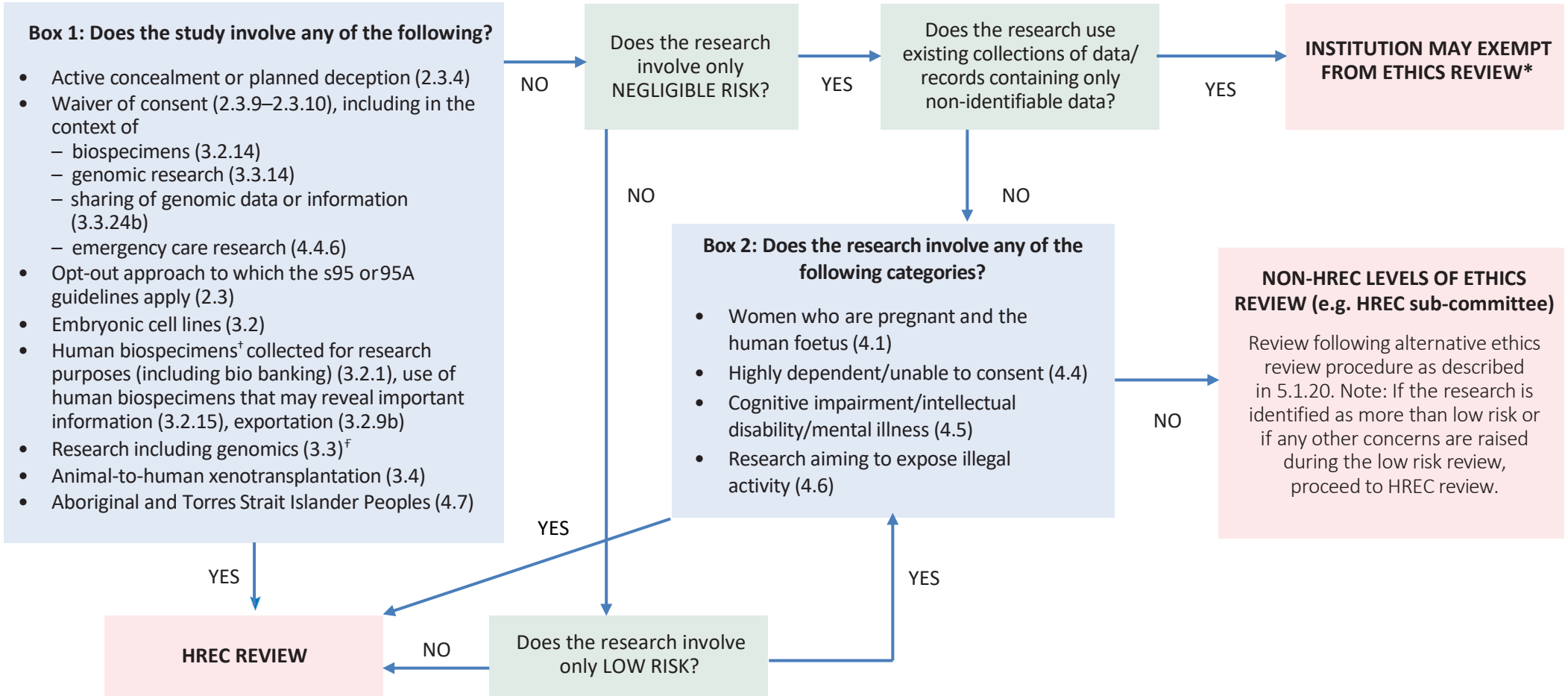
*The Ottawa Statement on the Ethical Design and Conduct of Cluster Randomised Trials*[27] provides detailed guidance on the ethical design and conduct of cluster randomised trials and addresses the ethical issues that may arise in cluster randomised trials.

## CONCLUSION

The NHMRC's National Statement[2] provides a pathway for the review of clinical trials by low risk pathways. This document clarifies how researchers and ethics committees can establish whether a CET is eligible for review as low risk. It also illustrates the typical ethical issues posed by CETs and how these issues (and any associated risks) can be mitigated through careful planning and preparation during trial design.

The Australian ethics and regulatory framework for clinical trials permits a proportionate approach to trial conduct even when a trial cannot be categorised as low risk. Researchers should demonstrate to the reviewing HREC that any relevant ethical issues have been addressed so that the HREC is able to support a proportionate approach to trial conduct – such as the use of integrated consent processes[28], and a risk-adapted approach to the management and monitoring of the trial[29].

# APPENDIX 1: FLOWCHART TO DETERMINE A STUDY'S RISK LEVEL




* Institutions that do not have separate procedures for reviewing research that is exempt from ethics review would review this sub-set of research under their established LNR review processes.
† Research involving the use of human biospecimens that still meets the definition of low risk after 3.2.2–3.2.3 are considered, may qualify for a non-HREC level of ethics review.
‡ As a general principle, research including genomics will require review by an HREC; however, if no information that can identify an individual is used and no linkage of data is planned, the research may be determined to carry low risk (3.3).

**Adapted from** Office for Health and Medical Research (2018) Guidelines for low and negligible risk (LNR) research review processes or exemption from ethical review, Sydney.

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