Australian
Clinical
Trials
Alliance

Report on the feasibility of a proportionate consent approach for comparative effectiveness research in Australia

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PURPOSE

The purpose of this document is to illustrate international consent policy that supports proportionate consent for comparative effectiveness trials and to clarify whether similar initiatives are permitted by the Australian regulatory and ethical frameworks.

USE OF THIS DOCUMENT

ACTA requests that the following acknowledgement is included in any documents that are developed using knowledge gained from this document. This will assist ACTA in identifying the usefulness and impact of this document in relation to the feasibility of a proportionate consent approach for comparative effectiveness research in Australia for CTNs.

> '[Name of CTN] acknowledges the contribution of ACTA to the feasibility of a proportionate consent approach for comparative effectiveness research in Australia (reference: *Report on the feasibility of a proportionate consent approach for comparative effectiveness research in Australia*).'

DISCLAIMER

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BACKGROUND

The Australian Clinical Trials Alliance, on behalf of the Clinical Trials Networks, are conducting initiatives to maximise the ability of the Networks to conduct efficient and timely clinical trials. These plans include work to embed clinical trials into the health system by addressing a range of barriers that prevent trials from being conducted. The one-size-fits-all approach to obtaining clinical trial consent is one such barrier and certain trial types, such as comparative effectiveness research, would benefit from a more proportionate and risk-adjusted approach to trial consent.

WHY IS TRADITIONAL CONSENT A BARRIER TO COMPARATIVE EFFECTIVENESS TRIALS?

Clinicians often do not know which of the many treatments used in routine care are best. The most effective way to resolve these treatment uncertainties is to embed large, comparative effectiveness trials (CETs) into clinical care. But CETs have characteristics that pose challenges when traditional consent is used.

Table 1: Challenges posed by traditional consent

CET feature	Challenge
Size: Large – to provide definitive results	Labour intensive, parallel systems for traditional consent (separate from clinical care) makes large trials infeasible without excessive use of public funds.
Study population: designed to be fully generalisable to the populations that they intend to treat (few exclusion criteria)	Traditional consent is a barrier to unselected participant recruitment. Differences between consenting and non-consenting groups may degrade trial validity and limit its ability to generate generalisable evidence.
Setting: conducted in routine care settings	The disruption to clinical workflows caused by traditional consent makes some CETs impracticable.
Risk: often minimal	An exaggerated and disproportionate perception of risk when traditional consent is used may increase consent bias.

Adapted from Symons et al. (2020). *International Policy Frameworks for Consent in Minimal-risk Pragmatic Trials*[1]

Internationally, efforts are underway to advance innovative trial designs to make them more effective and efficient. The United States, the United Kingdom and New Zealand are countries that encourage a more proportionate approach to consent. For some trial types, this enables the use of 'integrated consent' models that support the embedding of clinical trials into routine care settings.

WHAT IS MEANT BY INTEGRATED CONSENT?

Integrated consent is where patients provide consent at their point of care as part of the clinical discussion (or soon after). Integrated consent:

- Includes a short (paper or electronic) PICF – normally less than five pages
- Can link to additional information for participants who want it
- Permits some information to be disclosed to participants verbally (e.g. if written consent to receive the intervention(s) is not normally required outside of the research context)
- Provides sufficient information to decide whether to participate
- Includes consumer input, wherever possible.

HOW SHOULD RESEARCH RISK BE ASSESSED?

Section 3.1.6 (a) of the National Statement[2] requires the risk of research to be viewed *'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'*. In other words, the risks of the research are assessed as the risks that are incremental to those posed by standard care.

Both international regulation[3,4,5] and the National Statement regard the use of off label interventions (if that use is established practice and supported by sufficient published evidence and/or guidelines), as being no more risk than the use of the intervention in routine practice.

WHAT REQUIREMENTS ARE MANDATORY?

For consent to be legally valid, it must be voluntary (freely given without pressure or duress), given by a person with the necessary mental capacity who has been adequately informed. For participation to be adequately informed, the National Statement requires disclosure of *sufficient information* to enable an adequate understanding of the purpose, methods, demands, risks, and potential benefits of the research (2.2.2).[2] Knowledge of reasonable alternatives is also considered necessary for decision-making when other treatments or interventions are available.

For CETs, there is a dual purpose for treatment: 1) clinical care; and, 2) obtaining generalisable knowledge to improve the care of future patients. As well as understanding that they are being offered treatment for their disease condition, prospective participants must also understand:[6]

- that treatment is being offered in a research context, and that participation is voluntary
- the aims of the research – the use of data to obtain generalisable knowledge to benefit others
- the extent to which the research may alter their care.

These elements closely align with the disclosures required by the National Statement (2.2.2 and 2.2.6 (a)).[2] In the US, these elements are considered as the information that potential participants need in order to make a decision to participate (preamble in the US Common Rule).

IS COMPLIANCE WITH GOOD CLINICAL PRACTICE MANDATORY?

The status of the *Guideline for Good Clinical Practice* (ICH GCP)[7] is relevant to integrated consent as ICH GCP requires the written information to be provided to participants that include 20 elements for consent. In practice, all trials that submit data to regulatory authorities for marketing authorisation follow ICH to GCP so as not to jeopardise regulatory approval. However, the Guidelines themselves suggest (page 6) that the principles of GCP are generally adopted for 'other' research.

The National Statement[2] contains a single reference to ICH GCP (5.2.6) that requires compliance *'for relevant research'*. As ICH GCP was not intended to be fully applied to non-regulatory trials, this type of trial could be considered as falling outside the definition of 'relevant research'.

WHAT ABOUT CETs THAT INVOLVE THERAPEUTIC GOODS?

Most CETs fall outside the *Therapeutic Good Regulations (1990)* because they involve the use of registered goods within their marketing authorisation. However, some may involve the routine use of off-label treatments. For these trials, the *Therapeutic Goods Regulations* require compliance with the Therapeutic Goods Administration's (TGA's) version of ICH GCP and with the National Statement. In some areas, ICH GCP conflicts with the National Statement. In this instance, the TGA permit the National Statement to be the default document (refer to TGA ICH GCP webpage).

DOES THE NATIONAL STATEMENT SUPPORT INTEGRATED CONSENT?

Yes, the National Statement[2] permits a flexible approach, encouraging researchers to consider the *nature, complexity and level of risk of the research* (2.2.5 (a)). It states that information must be *presented in ways suitable to each participant* (2.2.3), *'should not be unnecessarily long or detailed, even for complex interventional research'* (3.1.26) and recommends researchers consider strategies to provide information that is *'staged or tiered'* (3.1.26 (b)).

IS WRITTEN CONSENT MANDATORY?

The National Statement[2] encourages researchers to consider whether information is *'best communicated through speech, writing, some other way, or a combination of both'* (5.2.17 (a)). It states that each person's voluntary decision should be *'clearly established'* (2.7.7) but does not explicitly require written, signed, and dated consent for clinical trials.* However, informed consent for interventional trials often has two purposes:

1. To enable sufficiently informed participant choice
2. To document legally effective authorisation.

HOW SHOULD RESEARCH RISK BE ASSESSED?

Section 3.1.6[2] states that *'the risks of an intervention should be evaluated … 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'*. This helps clarify that *'research risks'* are risks that are incremental to standard care. The NHMRC's *Guidance, Risk-based Management and Monitoring of Clinical Trials involving Therapeutic Goods*[10], provides further advice, suggesting that the risks of a medicinal product may be deemed as comparable to standard care if the medicinal product:

- is used within its registered indication, or
- is routinely used off-label (i.e. established practice supported by published evidence and/or guidelines).

WHAT TYPE OF TRIALS CAN USE THIS MODEL?

All trials can (and should) adopt approaches to make PICFs concise and readable. The tiering of information is recommended internationally (see Table 2). However, the more research deviates from established practice, the greater the amount of information required. Nevertheless consent is process that uses a PICF but also involves comprehensive discussions with participants and additional sources of information as needed.

WHAT TEMPLATES ARE USED IN AUSTRALIA?

In 2012, the NHMRC published PICF templates for: 1) self; 2) parent or guardian; or 3) person responsible for interventional trials.[11] These templates are recommended for all trials, irrespective of risk. A review of individual States and Territory DOH websites indicates that most jurisdictions (VIC, QLD, SA, WA) recommend the 2012 NHMRC templates. NSW recommends the National PICF produced in 2016[12] and NT and ACT recommend their own templates. Only ACT offers a separate template for low risk research.

* Other countries, such as the US, allow ethics committees to consider 'verbal consent' (i.e. no requirement for a signed consent form)[8] and examples of its use exist[9].

WHAT EXAMPLES OF INTERNATIONAL PRACTICE COULD BE ADOPTED IN AUSTRALIA?

Table 2 summarises some of the supportive mechanisms in the US and UK and New Zealand, and that similar advice can be found within the National Statement (NS).

Table 2

Supportive policy		
Policy	**Extracts from National Guidance/Regulation**	**NS reference**
Discourages the use of templates with a one-size-fits-all approach for interventional research	**US:** Requires investigators to consider on a trial-by-trial basis, what information; 'a reasonable person would want to have in order to make an informed decision about whether to participate' (45 CFR 46.116(a)(4)).[13] **UK:** States that 'the closer the research is to standard practice, the less need there is to provide patients and service users with detailed and lengthy information' (UK Policy Framework 2017).[14] **NZ:** Recommend information is delivered in a form appropriate to the individual concerned; tailored patient information sheets and consent forms that researchers have trialled with a group of people who are similar to the potential study participants (NEAC National Ethical Standards).[15]	2.2.3 2.2.5 2.1.8 3.1.26 5.2.17
Requires or recommends a 'tiered approach' that begins with the information deemed most likely to enable a person to decide whether to participate.	**US:** Requires PICFs to begin with a concise and focused presentation of the key information that is most likely to assist in understanding the reason one might or might not want to participate in the research (45 CFR 46:116(a)(5)(i)).[13] **UK:** Suggests pragmatic trial template16 allows researchers to separate the information needed to decide whether to take part from more detailed information.	3.1.26 (b)
The use of mixed methods to deliver information	**UK:** For trials using routine treatments, Health Research Authority Guidance[17] recommends information disclosure to be both verbal (information provided during the clinical consultation) and written (disclosure of all additional research requirements). **NZ:** Explicitly describes integrated consent as a process where consent to participate in research can occur as part of a clinical discussion (NEAC National Ethical Standards).[15]	5.2.17 (a)

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