Australian Clinical Trials Alliance

Report on the feasibility of the adoption of a proportionate approach to trial consent in Australia

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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.

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 ethics frameworks.

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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: International Policy Frameworks for Consent in Minimal-risk Pragmatic Trials

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 the process of consent to participate in research occurs as part of a clinical discussion. For this document, it includes the development of a paper or electronic information sheet that:

- is short - approximately 2 pages
- contains sufficient information to decide whether to participate
- provides links to additional information for participants who want it
- allows certain information* to be disclosed to participants verbally (if written consent to receive the intervention(s) is not normally required outside of the research context)
- has involved consumer input.

**The National Statement does not preclude fully verbal consent (3.1.25) but requires the participant's voluntary decision to be clearly established (2.2.7), thus, where written consent is not obtained, researchers should document the consent processes and the discussion with the patient.*

How should research risk be assessed?

Section 3.1.6 (a) of the National Statement 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.

International regulation [1] aligns with the National Statement. International guidance [2] [3] also clarifies that the off-label use of an intervention (if that use is established practice and supported by sufficient published evidence and/or guidelines) may also pose risks that are comparable to standard care.

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 consent in routine care, the common law requires disclosure of the purpose of a treatment, the material risks, benefits and reasonable alternatives [4] [5] [6]. In the research setting, there is a dual purpose for treatment (clinical care and obtaining generalisable knowledge to improve the care

[1] 45 Code of Federal Regulations 46. 111
[2] ADAMON: Risk analysis in clinical trials regarding the required amount of on-site Monitoring.
[3] MRC/DH/MHRA joint project: *Risk-adapted Approaches to the Management of Clinical Trials of Investigational Medicinal Products* and Clinical Trial Toolkit: Workstream Document C) Monitoring Procedures
[4] Australia High Court: Rogers v. Whitaker. Aust Law J 1993; 67: 47-55
[5] The Australian High Court also approved the Chatterton v Gerson [1981] 1 All ER 257 (UK)
[6] In 2015 the case of Montgomery v Lanarkshire Health Board [2015] UK High Court ruled that 'reasonable alternatives' should also be disclosed.

of future patients). Both should be disclosed [7]. This requires prospective participants to understand:

- 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 will alter their care

These elements closely align with the disclosures required by the National Statement (2.2.2 and 2.2.6 (a)). 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) 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 (usually industry trials) follow full ICH GCP so as not to jeopardise regulatory approval. However, as is the case in the US and UK, full compliance with ICH GCP in Australia is not mandated by law although the principles of GCP are generally adopted. Reflecting this in institutional policies and standard operating procedures would enable more concise consent documents to be crafted.

The National Statement 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 (TGA website).

Does the National Statement support integrated consent?

Yes, the National Statement 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 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

[7] Wendler, David, and Christine Grady. "What should research participants understand to understand they are participants in research?" Bioethics 22.4 (2008): 203–208.

states that each person's voluntary decision should be '*clearly established'* (2.7.7) but does not mandate written, signed and dated consent. However, informed consent for interventional trials often has two purposes:

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

For clinical trials, it is generally accepted that a consent document is signed by the participant.

However, US[8] regulation does not rule out an ethics committee considering a waiver of the requirement to document written consent and examples of trials using verbal consent exist[9].

As an intermediary step, UK Guidance encourages a 'simplified' approach to seeking consent for pragmatic trials [10]. Here, the routine clinical consultation about the treatments is provided verbally (as in clinical care) so that the written and signed information relating to the research component can be relatively short[11].

How should research risk be assessed?

Section 3.1.6 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,* 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.

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[12]. 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

[8] US 45 CFR 46.117(c) and CRF 21 56.109.c
[9] Sonny A et al: Deficit accumulation and phenotype assessments of frailty both poorly predict duration-of-hospitalization and serious complications after noncardiac surgery. Anesthesiology 2020; 132:82–9
[10] Wendler, David, and Wendler, David. "'Targeted' Consent for Pragmatic Clinical Trials." Journal of general internal medicine 30.5 (2015): 679–682. Web.
[11] HRA: Applying a proportionate approach to the process of seeking consent (2017)
[12] NHMRC PICF Templates for Interventional Trials

produced in 2016[13] and NT and ACT recommend their own templates. Only ACT offer a separate template for low risk research (although a few institutions elsewhere have developed their own).

What examples of international practice could be adopted in Australia?

Table 2 summarises some of the supportive mechanisms in the US and UK and clarifies that all these mechanisms are permitted by the National Statement (NS).

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)). **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) **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)	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 or not 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 (46.116(a)(5)(i)) **UK:** HRA Consent Guidance (2017) suggests that researchers separate the information needed to decide whether or not to take part from more detailed information. • First tier: Primary information needed to make a decision - that also explains how the further information may be accessed • Separate tier(s): Further practical/administrative information. Participant may choose to review only the first tier of information.	3.1.26 (b)
The use of mixed methods to deliver information	**UK:** For trials using routine treatments, the template for pragmatic trials recommend information disclosure to be both verbal (information provided during the clinical consultation) and written (disclosure of all additional research requirements).	5.2.17 (a)

[13] Participant Information & Consent Form - National PICF template (2016)

	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).	