Australian Clinical Trials Alliance

Applying a proportionate approach to consent in comparative effectiveness trials

Guidance for CTNs

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Concepts adapted from the National Health Service Research Authority consultation to develop a consent template for pragmatic trials*

ACTA workshop participants.

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 applying a proportionate approach to consent in comparative effectiveness trials for CTNs.

> '[Name of CTN] acknowledges the contribution of ACTA to the development of applying a proportionate approach to consent in comparative effectiveness trials within our network (reference: *Applying a proportionate approach to consent in comparative effectiveness trials*).'

DISCLAIMER

The information in this document is 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.

* National Health Service (NHS): Health Research Authority. (2017). *Template for pragmatic trials (v1.0)*. Accessed 12 May 2020 via http://www.hra-decisiontools.org.uk/consent/docs/Example%20PIS%20for%20pragmatic%20trial.pdf

KEY POINTS

- The Australian Government supports clinical research as a core business of the health system, embedded within routine care.
- While medical science advances have improved patient care and health outcomes, evidence of the comparative effectiveness of interventions in common use remains inadequate.
- Embedding comparative effectiveness trials (CETs) into routine care will accelerate the generation of this evidence.
- Traditional methods for the design and conduct of randomised controlled trials are ill suited to CETs. As a result, many socially valuable CETs are not even attempted. Transformational approaches are required.
- Consent should be commensurate to the risks and complexities of a trial. Long, legalistic consent documents are likely to reduce comprehension, increase anxiety, and may inadvertently subvert the consent process.
- Patients could be asked to participate in trials in a more satisfactory and straightforward manner that is aligned with clinical care and already supported by the Australian ethical and regulatory framework.

BACKGROUND

The Australian Clinical Trials Alliance (ACTA) is conducting work to maximise the ability of clinical trial networks to conduct efficient and timely research. These plans include initiatives to embed comparative effectiveness research into the health system by addressing the barriers that prevent this type of research from being conducted. The goal is for patients (in both primary and secondary care) to be recruited 'at point of care'. This would enable many more studies, particularly clinical trials, to be completed rapidly and at a fraction of the cost of traditional randomised controlled trials.[1]

Comparative effectiveness research is a broad term that is used to describe research that compares the benefits and harms of commonly used clinical or public health interventions. This type of research investigates methods to prevent, diagnose, treat, and monitor clinical conditions or to improve the delivery of care. This provides stakeholders; including patients, providers, and policymakers, with the evidence they need to make informed healthcare decisions. Many study designs are used to answer comparative effectiveness questions, but this document focuses on comparative effectiveness trials (CETs).

Consent is central to the ethical conduct of research, but over recent years the traditional informed consent process for clinical trials has become long and complex. Participant information sheets and consent forms (PICFs) are widely criticised for being written in ways that obscure important detail[2], reduce understanding and recall[3] and prioritise the needs of institutions to mitigate risk rather than the needs of participants[4].

The defining feature of CETs is that they involve interventions that are widely used in routine care, with risks comparable to standard care. CETs vary in the amount of burden placed on participants (e.g. from trial-specific tests, procedures, or data collection). However, most are designed to minimise disruption to clinical care, and as a result, participant burden is often low.

There is a growing consensus that traditional informed consent may poorly suit CETs.[5,6,7] For example, traditional consent causes levels of disruption to routine clinical workflows that make these trials impracticable. Patients may also be rejecting these trials because of an exaggerated and disproportionate perception of risk.[8] Moreover, the emphasis on the PICF ignores the context in which the consent process takes place, which involves discussion with health professionals, family and friends, and can often include obtaining additional information from external sources.

Recent advances, such as widespread use of electronic health records and the development of novel trial designs, motivate and enable the integration of research and clinical care. This has helped to increase the number of CETs conducted as an integral part of service delivery. However, to further enable the widespread embedding of CETs into routine care, many experts call for more pragmatic interpretations of ethical and regulatory frameworks or where necessary, revisions of those frameworks.[9,10,11,12]

This document summarises feedback from ACTA's Reference Group D and outcomes from a workshop (20 March 2020) involving consumers, HREC members, trialists, lawyers, and others, where risk-proportionate methods to obtain informed consent were discussed. Specifically, the workshop explored ways to enable **'integrated consent'**; a process where consent is obtained during the routine clinical encounter with the patient where treatment is offered. A similar consultation was held in the UK which culminated in a bespoke process and PICF template for low risk, pragmatic trials.[13]

Prior to the workshop, an analysis of the National Statement[14] was undertaken to determine whether its current provisions enable integrated consent. That analysis indicated that considerable flexibilities exist in the National Statement that potentially could be more widely used. The ACTA workshop ratified further work to underpin the adoption of practices to support the conduct of CETs in Australia while recognising the two distinct purposes for consent in interventional trials:

- to enable sufficiently informed participant choice
- to document legally effective authorisation.

The purpose of this document is to stimulate discussion between researchers, ethics committees and governance staff on the most effective ways to achieve both goals while also optimising the consent process for CETs. The Questions and Answers that follow provide information on the potential use of the flexibilities in the National Statement that support the use of integrated consent.

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.

WHAT IS MEANT BY 'SUFFICIENT INFORMATION TO DECIDE WHETHER TO PARTICIPATE'?

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). 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:

- **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.**

The information in **bold** is considered the *key information* that a prospective participant (or their authorised representative) should be given to decide whether or not to participate.* Any written information should be presented in a concise and focussed manner, using plain language principles and ideally, should be co-produced with/tested by consumers.

* As a general principle, the more comparative effectiveness trials deviate from established practice, the greater the amount of information required.

WHY SEPARATE THE KEY INFORMATION FROM OTHER INFORMATION?

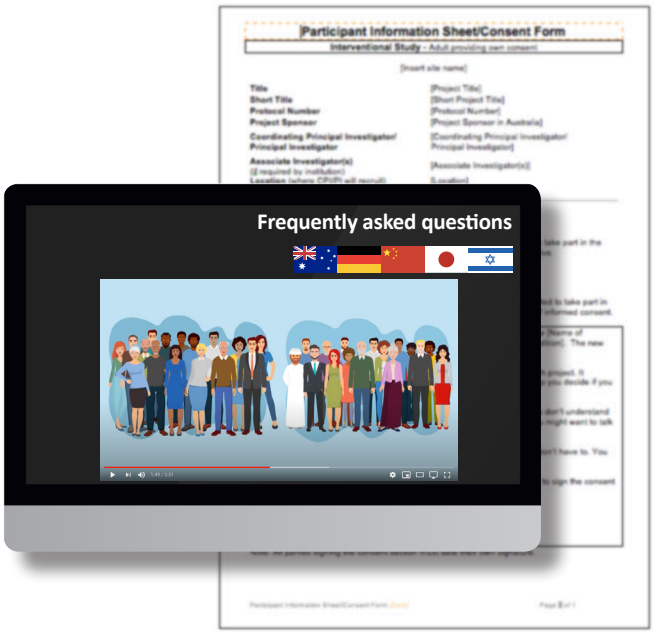
The National Statement recommends that trial information is *presented in ways suitable to each participant* (2.2.3). Some studies show that patients are often happy to make decisions on much less information than is currently provided in a traditional PICF.[15] Other studies suggest some patients would have liked more information than was provided.[16] For more complex studies, exercising choice is challenging when all trial information is contained within a single document; particularly as potential participants are expected to sign to confirm that they have read and understood all information. Even if PICFs are sectioned into 'general and trial-specific' or 'key and supplementary', patients are still overwhelmed when presented with an information sheet that runs to many pages. Providing patients with the option to access further information is one way to avoid this.* For some CETs, this approach could include:

1) A concise PICF, supplemented by the verbal discussion during the clinical consultation when treatment is offered, which together, provide sufficient information to make an informed decision about participation (Tier 1).
2) Separate, user-friendly methods to access additional study information (e.g. from a trial website or a separate leaflet) (Tier 2).

The primary information should clearly explain how additional information is accessed.

INTEGRATED CONSENT

Tier 1: Key information



Tier 2: Extra information

Integrated consent differs from traditional consent in two ways: 1) the use of a tiered approach, and 2) the use of mixed methods for information provision.

1) **A tiered approach to proving information:** The National Statement appears to permit the use of a tiered approach by requiring prospective participants to 'understand' the trial's key information (2.2.2) and for additional information that is *'not deemed necessary for a person's voluntary decision'* to be 'communicated' (2.2.6). This suggests that prospective participants can sign a consent form without having to read the additional information about the trial - in the knowledge that more comprehensive information can be accessed at any time.
2) **The use of mixed methods to provide information:** The National Statement allows consent to be expressed orally (2.2.5) but requires researchers first to consider the *'nature, complexity, and level of risk of the research'* (2.2.5 a). For lower risk trials, this suggests that the information provided during the clinical consultation (expressed orally) may not need to be duplicated in the PICF. Instead, the PICF could refer to the conversation and encourage participants to ask questions. Guidelines for pragmatic trials in other countries support this approach.[13]

*For simple trials, all information should be able to be accommodated in a short PICF.

HOW SHOULD RESEARCH RISK BE ASSESSED?

Section 3.1.6 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 risk of the research should be assessed as the risks that are incremental to those posed by standard care**. This interpretation aligns with international guidance.[17,18,19] For example, the use of an off-label intervention, if that use is established practice in the population and supported by sufficient published evidence and/or guidelines, may well pose little or no incremental risk when compared to standard care. Similarly, many CETs involve approved therapeutic goods or interventions supported by evidence from prior randomised trials or systematic reviews, but others may involve interventions or treatment strategies that have entered routine practice with little evidence of effectiveness. In both cases, where these interventions or treatments are in common use, the risks of the intervention(s) are comparable to standard care.

ARE THERE ANY PRE-CONDITIONS FOR THE USE OF INTEGRATED CONSENT?

In addition to the usual ethical requirements for clinical trials, the following pre-conditions should be met before the use of integrated consent is considered for CETs:

- There should be a properly informed uncertainty about the comparative merits of the treatments or interventions being tested.
- There should be sufficient evidence that the treatments or interventions are the best available standard care for the condition under study and the proposed trial population.*
- The trial's risks should be low (comparable to standard care for the study population).

* The burden of proof rests on the study team or sponsor to satisfactorily demonstrate that the proposed trial arms involve intervention(s) that are considered the best available standard of care.

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