Australian Clinical Trials Alliance

Guidance on Implementability

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TABLE OF CONTENTS

ABBREVIATIONS

ACTA	Australian Clinical Trials Alliance
IMP	Investigational Medical Product
GRADE	Grading of Recommendations Assessment, Development and Evaluation
PRECIS-2	Pragmatic Explanatory Continuum Indicator Summary 2 tool
TIDieR	Template for Intervention Description and Replication checklist and guide
MCID	Minimum Clinically Important Difference
SPIRIT	Standard Protocol Items: Recommendations for Interventional Trials
EVPIM	Expected Value of Perfect Implementation
CONSORT	CONsolidated Standards Of Reporting Trials
IPDMA	Individual Patient Data MetaAnalysis
TGA	Therapeutic Goods Administration

GLOSSARY

Appropriate implementation: A decision about whether it is appropriate to implement a candidate intervention should be informed by a body of evidence of sufficient certainty, often a systematic review. This decision should consider the balance of likely benefits and harms, applicability of the evidence to the relevant context, acceptability of the intervention, resources available, feasibility of implementation, and other considerations such as equity. (Source: GRADE Evidence to Decision framework).

Early phase clinical trial: A clinical trial that aims to learn about the potential value of a candidate intervention, to determine whether further trials are warranted. Early phase trials are typically not designed to provide definitive evidence of the value of the intervention. Such trials typically evaluate surrogate clinical or biological outcomes, and are often underpowered to detect differences in clinically meaningful outcomes or end-points. Implementation is generally not appropriate for early phase clinical trials, although precision may be increased by inclusion in a synthesis. Early phase trials are considered out of scope for this work.

End-users: End-users of the results of late-phase clinical trials include health professionals, policy-makers and managers, consumers and the general public. In addition, other researchers may make use of the results in either conducting evidence synthesis or planning future trials (including to replicate the original trial or design a related trial). Researchers are the primary end-users of early-phase clinical trials.

Impact: The change in health outcomes or health system productivity or both that arises from the implementation of evidence, including clinical trials.

Implementability: Characteristics of the design, execution and reporting of a clinical trial, typically a late-phase trial, that determine the capacity for the evidence generated by that clinical trial to be used for implementation. Implementability is a feature of trial design and execution that is not contingent on the results of a trial, whereas appropriate implementation is critically dependent on both the results and implementability.

Implementation: The sustainable introduction to or removal of an intervention from clinical practice or policy. Implementation may or may not be appropriate following the completion of a clinical trial. Uptake into evidence synthesis is also an important step towards implementation into practice or policy.

Intervention: A drug, device, procedure, strategy or system delivered to patients or a population with the purpose of improving health outcomes or health system productivity or both.

Late-phase clinical trial: A clinical trial intended to estimate the effectiveness of a candidate intervention in comparison to alternative interventions or standard practice, and in large enough groups of people to provide precise and applicable estimates of the effects (both positive and negative) on health outcomes. Late-phase trials are intended to provide the information required to inform decisions about whether the candidate intervention should be adopted into practice or policy, should the results prove definitive. They may incorporate assessment of factors relevant to implementation such as health economic analysis, process outcomes, etc. For new drug and device interventions, late-phase trials may occur before or after the new drug or device is registered.

Pilot clinical trial: A trial that aims to determine the feasibility of conducting subsequent early and/or late-phase clinical trial(s). The outcomes of interest generally include aspects of feasibility such as recruitment, fidelity of delivery of the intervention, process separation between the intervention and comparator groups, and demonstration of capacity to measure the outcomes or end-points that would be used in subsequent trials. Pilot trials are considered beyond the scope of this guidance document.

Trial feasibility: The extent to which a clinical trial is practical and possible to conduct (e.g., given the constraints of the existing healthcare system or available resources).

EXECUTIVE SUMMARY

The Australian Clinical Trials Alliance (ACTA), with the expertise and knowledge of the Impact and Implementation Reference Group, has prepared this guidance document on optimising implementability of clinical trials. The objective of this document is to provide guidance on the planning, design and conduct and reporting of clinical trials, so that the results from late-phase clinical trials are optimised for implementability.

Implementability is a characteristic of the design, execution, and reporting of a clinical trial, typically a late-phase trial, that determines the capacity for the evidence generated by that clinical trial to be applied to improve practice or policy or both. Implementability is a feature of trial design and execution that is not contingent on the results of a trial, whereas appropriate implementation is critically dependent on both the results and implementability.

The information in this document is intended to be used by clinical trialists, but may also be useful to the end-users of clinical trials which can include clinicians, policy-makers, and consumers.

The trial planning phase should include consultation and co-design of the trial with end-users, understanding of the needs of end-users, and trial entry criteria that facilitate translation into practice and policy.

The clinical trial should build on current baseline clinical practices and policies, consider regulatory approvals and how they may enable implementability, whether there should be involvement of a clinical trial network, and whether the protocol considers issues relevant to implementation of the results.

During trial design and conduct, much of the focus lies with recruitment of the trial matching the population in which the intervention is intended to apply and ensuring that the intervention is delivered in a way that is similar to, or the same as, to how it would be used in the real world. Other aspects of trial design and conduct that are relevant include the choice of comparator, process evaluations and fidelity, and health economics.

Finally, trialists must commit to complete and timely reporting of the trial providing sufficient information to guide delivery of the intervention in clinical settings, share the data openly and make it accessible to end-users with any and all potential conflicts of interest being identified and managed appropriately.

It is hoped that the concept of implementability becomes more widely adopted and applied to late-phase clinical trials, and that trialists will find this document a useful framework that enhances the value of the trials that they conduct. This guidance is intended to be iterative, and feedback to enhance and improve the document are welcomed to facilitate production of updated versions.

OBJECTIVES

The objective of this document is to provide guidance on the planning, design and conduct, and reporting of clinical trials so that the results of late-phase trials are optimised for implementability (i.e., to optimise the characteristics of a clinical trial that determine the capacity for the evidence generated by that clinical trial to be implemented into practice and policy). It should be recognised that clinical trials are one of many steps necessary for better knowledge to lead to improved health outcomes – trials are necessary, but not sufficient. As outlined in the accompanying Figure 1, this process is a continuum that starts with a hypothesis that progresses through multiple steps leading to the final outcome of improved health outcomes.

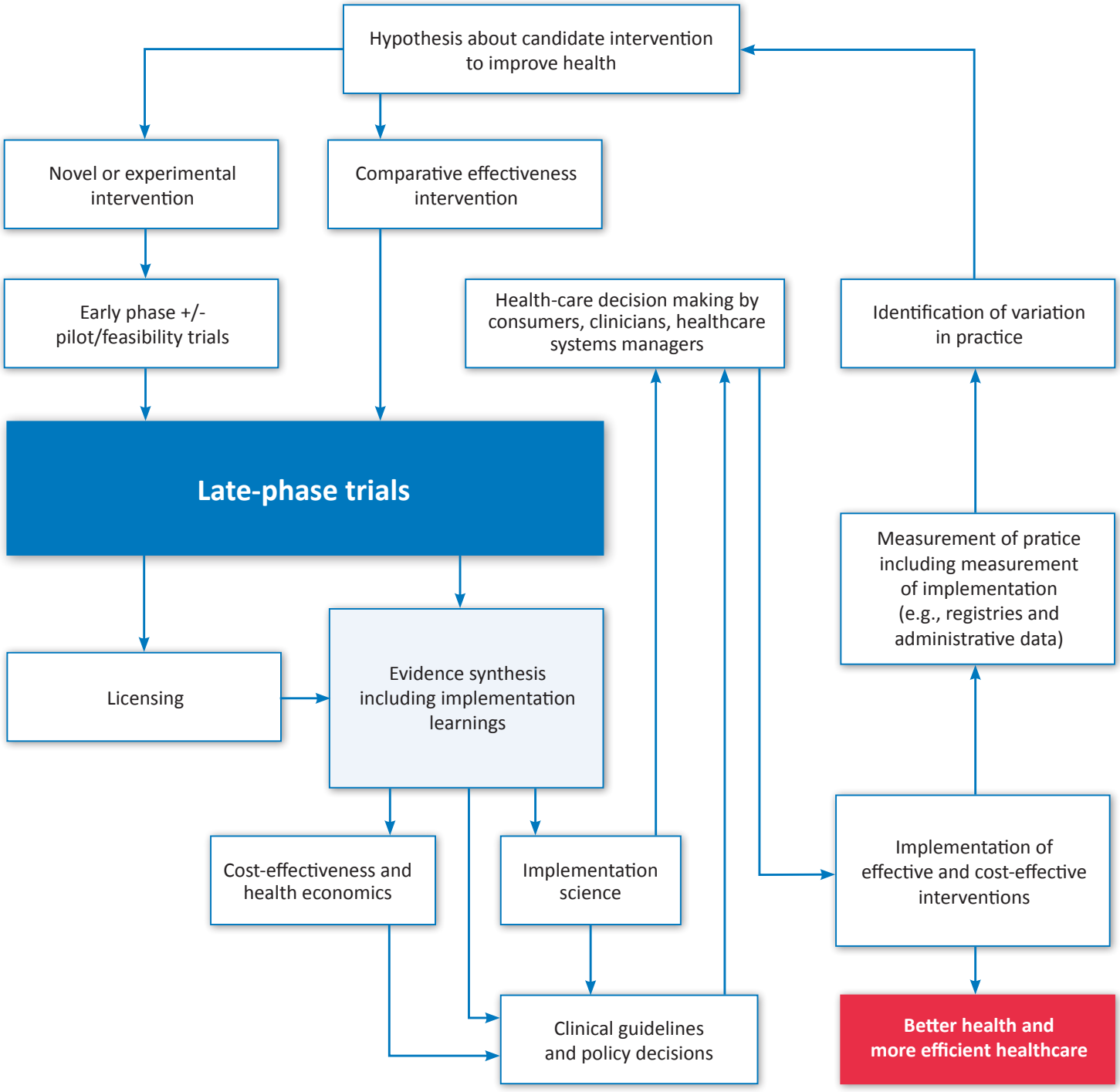

Figure 1: Steps in the process from developing a candidate intervention through to implementation in practice and policy leading to improved health outcomes.

ABOUT THIS GUIDANCE

It has been noted, that 'in order to be useful, clinical research should be true, but this is not sufficient' (Ioannidis, 2016). This document does not focus on those aspects of trial planning, design and conduct, and reporting that are necessary for the results of trials to be true (i.e., internal validity). It focuses on describing additional components that contribute to making the results of clinical trials as useful as possible. The document relates to the concept of implementability, which we define as the:

> *'... characteristics of the design, execution and reporting of a clinical trial, typically a late-phase trial, that determine the capacity for the evidence generated by that clinical trial to be used for implementation. Implementability is a feature of trial design, execution and reporting that is not contingent on the results of a trial, whereas appropriate implementation is critically dependent on both the results and implementability.'*

It is also acknowledged that all features contributing to implementability may not be necessary to optimise implementability and, in many circumstances, it is not possible to incorporate all components into the production of trials. It is also recognised that many aspects that contribute to implementability involve judgements and trade-offs. As such, differences of opinion among trialists regarding implementability are inevitable and appropriate. An intended application of this guidance is to assist trialists to identify and understand these trade-offs. All trials should also consider issues related to equity and issues that are vital when planning and conducting trials focused on improving health in groups that experience health inequities, particularly Indigenous people (see ACTA's forthcoming statement on equity).

While trialists should not generally carry responsibility for implementation, they do have a clear responsibility with late-phase trials to consider issues that would influence the capacity of the results to be implemented.

It is hoped that the concept of implementability becomes more widely adopted and applied to late-phase clinical trials, and that trialists find the document a useful framework to enhance the value of the trials that they conduct. This guidance is intended to be iterative and feedback to enhance and improve the document is welcomed to facilitate production of the updated versions.

BACKGROUND AND RATIONALE

THE PURPOSE OF LATE-PHASE TRIALS IS TO PROVIDE EVIDENCE TO END-USERS TO GUIDE DECISION MAKING

The purpose of **late-phase** clinical trials (see Box 1 related to clarification of trial phase terminology) is to answer clinical questions by generating evidence about the effect of interventions to improve health and/or health system productivity. Late-phase trials are intended to provide information to end-users to inform decisions about whether the candidate intervention should be adopted into (or removed from) practice or policy, should such action be appropriate based on the results of the trial either alone or, much more commonly, in combination with evidence synthesis of previous similar trials.

Late-phase trials are only one element along a chain of steps that lies between the possibility of benefit from a candidate intervention to successful and appropriate adoption in clinical practice and policy. The relationship between late-phase trials and other components in this chain has been outlined (see Figure 1).

When trials report findings, most commonly in combination with existing evidence, that should change clinical practice or policy, it is imperative that the results are implemented to improve patient outcomes or healthcare system productivity, or both. If the results of late-phase trials that should guide practice are not implemented, this completely undermines the rationale that led to the conduct of the trials. Trials intended to guide decision-making by end-users need to be designed to maximise their capacity to achieve change in practice or policy or both. The broad goal of this guidance is to encourage the conduct of trials that are as useful as possible to end-users.

Trials can be difficult to conduct and are often expensive (Eisenstein, et al., 2008). Given the 'sunk cost' associated with the conduct of trials it is important that all aspects of design, conduct, and reporting are optimised with respect to implementability. In this regard, it is recognised that trials often do not provide information that is useful to end-users (Ioannidis, 2016), and late-phase trials (Ford and Norrie, 2016) that do not provide usable information to end-users contribute to waste in biomedical research, noting that as much as 85% of resources used for biomedical research are wasted (Macleod, et al., 2014).

Terminology around the use of the term 'phase' can be challenging because trialists have different understandings and interpretation including differences between trials that test an Investigational Medical Product (IMP) and other types of candidate interventions (including licensed medical products, devices, surgical procedures, clinical and titration strategies, behaviour modification, and physical therapies). Pre-clinical studies involve in vitro or animal studies of biological activity and safety.

For an IMP, phase I refers to trials that are first-in-human or first-in-patient and tend to focus predominantly on safety and pharmacokinetics. Phase I trials may also evaluate some components of clinical or biological activity and often do not have control subjects. Phase II trials of IMPs are designed to evaluate whether the agent has biological activity. Some trialists will apply the term phase II to trials of interventions that are not IMPs but with the same aim, of establishing biological activity. The endpoints for phase II clinical trials often involve measurement of a biological or clinical endpoint that relates to a postulated mechanism of action and such endpoints are commonly surrogates for clinically relevant endpoints. The main purpose of phase I and phase II trials is to determine if further research is warranted and such trials are referred to as 'early phase trials' in this document.

Phase III trials are conducted to determine the impact of the intervention in clinical practice and, for IMPs, involve comparison with placebo (if there is no alternative treatment available using a superiority design) or against an already licensed comparator (if placebo is inappropriate and often using a non-inferiority design). Some trialists use the term phase III to test any intervention, including non-IMP interventions, when the purpose of the trial is to evaluate the role of the intervention in clinical practice. Most or all phase III trials meet the definition of late-phase trial used in this guidance.

Phase IV studies of IMPs usually involve post-marketing surveillance, particularly for reporting adverse events that may have occurred infrequently in registration trials. Such post-marketing studies are observational studies, not randomised controlled trials. The term phase IV is sometimes applied to confirmatory trials, where further 'phase III' trials of a licensed medicine are conducted or where an existing licensed drug is evaluated in a new indication. Some trialists also use the term phase IV for comparative effectiveness trials in which alternative licensed agents are compared to evaluate superiority. This guidance refers only to randomised trials, as phase IV observational studies are out-of-scope. Phase IV randomised trials would generally meet the definition of late-phase trials used in this document.

Pilot or feasibility trials are most commonly used for complex interventions (behavioural, clinical or titration strategies) to establish feasibility of conducting further trials that evaluate biological or clinical activity. Pilot and feasibility trials meet the definition of early phase trials used in this guidance. Similarly, mechanistic trials are not designed to evaluate a candidate intervention but, rather, uses a randomised trial design to evaluate some aspect of disease or biology.

The terms efficacy and effectiveness apply to where a trial lies on the explanatory to pragmatic spectrum. Efficacy trials test whether a candidate intervention has clinical and/or biological activity under ideal circumstances with tightly controlled entry criteria. Most efficacy trials are phase II and meet the definition of early-phase trial used in this document. Some phase III trials are positioned more at the efficacy end of this spectrum. Effectiveness trials seek to determine whether a candidate intervention can work to achieve clinically meaningful outcomes and under usual circumstances. Effectiveness trials would generally meet the definition of late-phase trial as used in this document.

Box 1: Terminology related to trial phases

DIFFERENT TYPES OF TRIALS HAVE DIFFERENT END-USERS

Although this guidance focuses on late-phase trials it should be recognised that there are many different types of trials (and approaches to their classification). One approach, which is used in this document, is to draw a distinction between late-phase trials, intended to provide useful information to guide practice and policy, and all other types of trials such as mechanistic, pilot, and early-phase trials (refer to definitions in the Breakout Box on the previous page).

The end-users for late-phase trials include consumers who make decisions about their healthcare, as well as policy-makers and healthcare system managers who make decisions regarding access, availability, and subsidisation of healthcare and preventative interventions. Issues related to trial design can impact on the equity of decisions that are made in association with access to interventions.

It is often the case that the main end-users of late-phase clinical trials are clinicians, who use evidence from clinical trials, in conjunction with an understanding of the goals and values of the patients they treat, to make shared decisions regarding choice of interventions during clinical interactions. As such, the requirements of clinicians, as end-users, can be critical to optimising the potential impact of clinical trials.

Some late-phase clinical trials, typically conducted by commercial entities that own the intellectual property associated with an intervention, are conducted for licensing or regulatory purposes and, in this situation, important end-users are the regulatory authorities that will make decisions regarding licensing and marketing. For investigator-initiated trials, it is less common that regulatory authorities are end-users, although it is still the case that regulatory approval is a necessary or desirable component contributing to implementation for some interventions evaluated by investigator-initiated trials. Where approval will be a necessary step, such trials must be designed with this goal in mind but should also seek to be as useful as possible to consumers and clinicians.

The end-users of mechanistic, pilot, and early-phase trials are typically other researchers who use the information to make decisions about further research, sometimes leading to the conduct of late-phase trials. In general, these types of trials should not be regarded as having clinicians, consumers, policy-makers and managers as end-users, and do not need to be designed to optimise implementability.

TARGET AUDIENCE AND SCOPE

The primary audience for this document is individuals who design and conduct late-phase clinical trials intended to generate evidence for end-users, who make decisions regarding clinical practice and policy, and who contribute to evidence synthesis. The document may also be useful to the full range of end-users, as well as others including those involved in translation of evidence into practice and policy, such as health economists, those involved in evidence synthesis and the writing of guidelines, and implementation scientists.

Those features of a trial design that contribute to internal validity, such as avoidance of bias and precision, are beyond the scope of this guidance. This guidance assumes that internal validity is necessary, but not sufficient, for implementability and focuses on elements of trial design, conduct and reporting that contribute to implementability.

IMPLEMENTABILITY AND ITS RELATIONSHIP TO PRAGMATIC AND EMBEDDED TRIALS

The concept of ‘implementability’ is central to this guidance document. Implementability is a feature of trial design and execution that is not contingent on the results of a trial, whereas appropriate implementation is critically dependent on both the results of the trial and its implementability. That late-phase clinical trials should be designed in ways that are useful to end-users is a widely recognised concept (Loudon, et al., 2015 [PRECIS-2]; Hoffman, et al., 2014 [TIDieR]; Pronk, 2003 [PIPE]; Glasgow, et al., 1999 [RE-AIM]). The importance of aspects of the reporting of trials that are necessary for end-users has been well described and this guidance draws heavily from this work (Loudon, et al., 2015; Hoffman, et al., 2014; Pronk, 2003; Glasgow, et al., 1999).

The characteristics that contribute to implementability overlap, in some respects, with two related concepts, which are trials that are embedded or pragmatic. This section will seek to identify similarities and differences between these two concepts and that of implementability.

This guidance draws substantially from the concepts of a pragmatic trial that are outlined using the PRECIS-2 tool (Loudon, et al. , 2015). This tool can be applied to determine where a trial lies on the spectrum between explanatory and pragmatic. Within the PRECIS-2 framework, pragmatic trials seek to answer the question 'does this intervention work under usual conditions?', whereas explanatory trials are focussed on the question 'does this intervention work under ideal conditions?' (PRECIS-2). The PRECIS-2 tool evaluates a trial design across nine domains to determine its location across the explanatory-pragmatic continuum and emphasises that trialists should tailor the design of their trial to meet the needs of the intended end-user (Appendix A).

The PRECIS-2 framework is highly useful and much that contributes to pragmatism also contributes to implementability. However, there are features additional to those outlined by PRECIS-2 that contribute to implementability, and it is possible for aspects of a trial design to be pragmatic but limited in its implementability.

Similarly, many aspects of trial design and conduct that contribute to embedding, will, simultaneously, also contribute to implementability. Embedding has been defined by the ACTA Embedding Reference Group as:

> *'The process of integrating research activities into routine patient care, to facilitate the appropriate, timely and efficient generation and implementation of the best available evidence.' (ACTA, 2018)*

However, the purpose of these design features, when utilised for embedding, is to promote efficiency of trial conduct, not necessarily to contribute to implementability of trial findings. It should also be noted that some features of trial planning and reporting do not contribute to embedding, but contribute substantially to implementability.

METHODS

This guidance was informed by a literature review that has been conducted previously. This review identified features of trial design, conduct, and reporting that contribute to implementability, and a survey of clinical trial networks regarding their approach to issues associated with the implementability of their trials has also been conducted by ACTA (ACTA, 2019). A one-day workshop was held to synthesise and interpret this information and, drawing on the expertise of the reference group, to develop this guidance. The reference group included individuals with experience in the planning, design, conduct and reporting of clinical trials; implementation science; and evidence synthesis (attendees are listed in Appendix B). This group developed a draft document that then underwent further iterative development among all members of the ACTA Impact and Implementation Reference Group.

The guidance is divided into three components relating to the trial planning phase, the design and conduct of the trial, and the reporting of the trial although, for some aspects of the guidance, there is overlap between components. The components are also presented as a checklist that can be referred to during trial planning, conduct, and reporting (Appendix C).

TRIAL PLANNING PHASE

INTRODUCTION

Trial planning takes months or years and represents an opportunity to acquire background information necessary to design the trial and plan its execution. It is assumed that this process includes an understanding of the context in which the trial is being planned, review of previous research including, where appropriate, a systematic review. The trial planning components that can contribute specifically to aspects of implementability comprise:

- consultation or co-design with end-users
- a well-developed understanding of current practice
- any necessary pre-trial establishment of feasibility of delivery of the intervention
- consideration of the appropriate trial design
- consideration of whether regulatory approval is a likely component of implementability
- consideration of conducting the trial within a network
- access to the skills necessary to consider issues of implementability, and
- consideration of including within the trial protocol a section that identifies and discusses issues related to the implementation of the results of the trial, contingent on the different results that might emerge from the trial.

CONSULTATION OR CO-DESIGN WITH END-USERS

1. Introduction

Clinical trialists and end-users should work in partnership with the end goal being appropriate implementation. End-users make decisions regarding practice and policy using evidence generated from clinical trials. As such, many components of trial activity contributing to implementability can be enhanced by involving end-users during the trial planning stage. Both consultation and co-design, where end-users are an integral part of the trial team, may offer advantages and are appropriate methods for involvement of end-users. Where implementation of the results of the trial may be different depending on cultural, language, or other social factors, understanding these factors, from the perspective of representative end-users is particularly important. For trials that aim to improve the health of Indigenous people, co-design or consultation are essential.

Elements of involvement of end-users should include explicit identification of the end-users, processes to understand the relevance of the proposed trial, involvement in specifying and identifying the trial population, and ensuring that endpoints chosen for the trial will have meaning and relevance for target end-users. This process serves to enhance the likelihood that the results of the trial will be 'believable' and, contingent on results, capable of influencing end-users.

It should be noted that involvement of end-users can improve other aspects of trial design and conduct, as well as determining priority among alternative research questions, contributing to trial efficiency and effectiveness, but are beyond the scope of this document.

2. Define end-users

As part of the trial planning process, late-phase clinical trials should explicitly identify all intended groups of end-users and consider the relative importance of each end-user group from the perspective of implementation of the results of the trial. This process should acknowledge and incorporate that different end-users have different perspectives, values, and interests. The process of identifying all relevant end-users is critical to understanding their needs and requirements, which can contribute to appropriate implementation of the results of the trials. Involvement of end-users in the design and conduct of trials can be useful in understanding and overcoming the risk that the trial intervention will not be implemented (or de-implemented) as appropriate. Understanding and anticipating these risks, particularly in conjunction with experts in implementation science, can be useful in planning aspects of the trial.

3. Understand evidence needs and requirements of end-users

Pre-trial work can be used to establish relevance and priority of the research question with end-users. Formal processes, such as those utilised by the James Lind Alliance (http://www.jla.nihr.ac.uk), are particularly useful, but more informal processes, such as Delphi and nominal group techniques can still be very valuable. Consumers can provide valuable insights regarding the acceptability of candidate interventions, as well as issues related to equity of access to the intervention if the intervention were to be applied in practice. Clinical trial networks that include active clinicians are also highly useful at ensuring trial questions and process have face-validity for clinicians who will interpret and apply evidence generated by the trial.

The relevance or interest in the intervention(s), the appropriateness of comparators, choice of trial endpoints including, but not limited to, Patient Reported Outcome Measures, the minimum clinically important difference, duration of follow-up, methods for delivery of the intervention, and characterisation of the trial population can all be established by involvement of end-users in setting and prioritising research questions.

When the purpose of a clinical trial is to generate evidence that can guide or change practice or policy, a critical element is the choice of endpoints for the trial and, in particular, whether it is known that the endpoints can be assumed to be sufficient to result in a change in behaviour by end-users. In late-phase clinical trials, there should be a reasonable likelihood that the hypothesised difference in the primary endpoint will be sufficient for end-users to believe that a change in practice or policy is appropriate. An understanding of how secondary endpoints, particularly serious adverse events, may also influence implementation is important, and the trial planning phase should identify appropriate and relevant secondary endpoints. Where economic considerations may be critical to implementation, agreement on methods of analysis and a threshold willingness to pay can be established. In some situations, pre-trial work may be necessary to establish whether end-users regard an endpoint as sufficient to effect change. Such work can include surveys and focus groups, targeting appropriate and representative end-users.

Two aspects of involvement with end-users that relate to endpoints deserve particular emphasis. First, the use of core outcome sets, where available, is strongly encouraged as the use of such sets encourages standardisation among both trialists and end-users (Tong, et al., 2015). The second, more important, component is involvement of consumers in the development and selection of endpoints that are important to those with a lived-experience of the disease. Across several disease areas it has been acknowledged that endpoints for trials chosen by researchers and clinicians were not those that had most relevance to patients with the disease (Hsiao and Fraenkel, 2017). Trialists within a shared discipline, are encouraged strongly to establish links with patient organisations and undertake work to ensure that the endpoints used for trials capture outcomes that are important to patients (King, et al., 2018).

An additional consideration, with respect to the choice of end-points relates to whether end-points are patient-centred or surrogates. Patient-centred endpoints, which are those that relate to one or more aspects of how a patient feels, functions, or survives, should always have traction with end-users and so have value for implementability (Prentice, 1989). Many trials utilise surrogate or composite endpoints that include components of the composite that are not patient-centred endpoints. If a discipline has a history of these endpoints being regarded as clinically significant and have been demonstrated to be sufficient to influence practice and policy, the ongoing use of these endpoints is quite appropriate. Issues relevant to implementability of composite endpoints can include situations in which end-users would regard different components of the composite having major differences in clinical significance or situations in which components of the composite move in opposite directions. Endpoints that are not patient-centred, and for which there is no history of the endpoint being sufficient for end-users, would be considered to have major limitations with respect to implementability.

It is sometimes observed that trials using endpoints that are unvalidated surrogates (Prentice, 1989) result in changes in practice and policy. In this situation, trialists and those with a role in implementation should provide advice to clinicians and policy-makers to encourage them to change practice and policy only in response to trials that utilise clinically meaningful endpoints.

4. Evidence of minimum clinically important difference

During the planning stage of a trial it is necessary, by making estimates of the risk of type II error, to determine the power of the trial to detect a treatment effect of a pre-specified size. Many factors contribute to determining the size of the treatment effect that a trial should be capable of detecting. The estimate of the size of treatment effect that can be detected is particularly important for ensuring that trials have sufficient power to detect a difference that end-users would consider to be meaningful. This is particularly important for trials where a result that shows no difference or non-inferiority is intended to guide practice. Two related concepts may be useful at the planning stage in determining the size of treatment effect that is relevant for implementation: ‘minimum clinically important difference’ and ‘minimum public health significant difference’.

First, the term, ‘minimum clinically important difference’ (MCID) describes ‘the smallest difference in score in the domain of interest which patients perceive as beneficial and would mandate, in the absence of troublesome side effects and excessive cost, a change in the patient’s management’ (Jaeschke, et al., 1989). Several different methods have been established to estimate MCID (Redelmeier, et al., 1996; Wells, et al., 2001) and trialists should consider establishing the MCID in diseases of interest.

A second, and related, concept might be referred to as the ‘minimum public health significant difference’, which defines the relationship between a meaningful effect size and the size of the public health burden of the disease. Public health burden can be regarded as the incidence (or prevalence) of a disease multiplied by its impact in terms of death, disability, and symptom burden. Some, but not all, elements of public health burden can be captured through the Disability Adjusted Life Years associated with a disease. In determining the minimum size of treatment effect that the trial is powered to detect, it may be appropriate to do so taking into account the public health burden (i.e., for a disease of high burden it may be appropriate to power a study to detect small differences in treatment effect, because such differences would still be meaningful and warrant implementation). Although important as a concept, how this translates into actual effect sizes has not been well characterised but can be considered based on a combination of the potential impact on burden of disease, the known incidence of the disease, and the distribution of disease, particularly as it relates to inequity.

5. Trial entry criteria can be understood and interpreted by end-users

Trial entry criteria, including, where appropriate, criteria used for stratification, are crucial to implementability, as they define the population that would need to be identified in practice or within a policy for implementation of the results of the trial. As such, trial entry criteria that are complex, require access to information, a test result, or biomarker that is not available routinely, are burdensome or take excessive time to acquire, can represent substantial barriers to implementation into clinical practice or policy. Pre-trial work can focus on ensuring that end-users find trial entry criteria easy to use and interpret, and testing of candidate criteria with end-users.

DEFINE CONTEXT FOR A TRIAL – WHAT IS CURRENT BASELINE PRACTICE AND POLICY?

Implementation of the results of a trial will always occur in the context of current practice and policy. As a consequence, understanding current practice can be critical to aspects of implementability. In many circumstances, surveys of current practice (asking clinicians what they think they do) or observational studies of current practice (measuring what clinicians actually do) provides an important context for trial planning that can be highly relevant to implementability. Such work should define whether the proposed trial intervention is part of the spectrum of standard care and, if so, how frequently the intervention is utilised. Some candidate interventions, often in the context of comparative effectiveness, are a member of a set of interventions with a common mode of purpose for which the different alternatives comprise mutually exclusive options (for example, antibiotics that are used to treat a particular infection). The frequency with which alternative options are utilised may be important to ensuring that the trial has a comparator that will meet the requirements of end-users for implementation. A comparator that is not part of the spectrum of standard care, or only used infrequently, will likely face challenges with respect to implementability.

A systematic review of existing evidence (and a review of trials already recruiting) regarding the intervention should always be conducted. If there is already sufficient evidence to justify implementation of the intervention, another trial is unlikely to be warranted. Rather, where there is sufficient evidence, and implementation has not occurred, this should be regarded as an issue related to implementation, needing involvement of experts in implementation science. Trials of how to implement may be quite appropriate, but not trials to generate evidence of effectiveness.

An intervention that is already implemented should generally only be evaluated in a trial, compared with placebo or a 'no treatment option' if there is a relevant clinical question about de-implementation (i.e., for potentially ineffective or harmful interventions). This generally applies only when there are reasonable grounds to suspect net harm or absence of effectiveness for an intervention that is expensive or burdensome (3.3.10, National Statement). It is important to note that, in this situation, implementation has already occurred, and evidence to promote implementation is not needed. Where neither harm is suspected nor burden present, a trial that removes an element of standard care to establish the effectiveness of an already implemented intervention answers an academic question, but does not promote better health outcomes or health system productivity.

The context for a trial is important to other aspects of design, such as equipoise, willingness of clinicians to randomise, and willingness of patients to be randomised, and the options available if a patient chooses not to be in a trial. These contextual issues are all important to design of the trial but have limited relevance to implementability and so are not considered further in this guidance.

CONSIDERATIONS WHEN REGULATORY APPROVAL CONTRIBUTES TO IMPLEMENTABILITY

For some interventions, particularly those related to a medicine, extension of an indication for a medicine already approved in Australia, or a medical device obtaining regulatory approval may be necessary for implementation or may facilitate substantially achieving implementation. Obtaining such approval will involve a regulatory submission to the Therapeutic Goods Administration. Benefits of obtaining regulatory approval can include improved access to therapeutic options, facilitating access to subsidisation, and effective safety monitoring for treatment-related adverse events.

Features that should be considered at the design phase pre-empt the information necessary to be submitted in support of registration. This includes a clear rationale for the study, particularly with respect to clinical (unmet) need, justification of the population selected for the trial and the dosage chosen for the trial, detailed plan and explanation of the rationale for the selected statistical approach, justification of the efficacy and clinical relevance of the selected efficacy end-points, sufficient information to describe and understand safety-related events, and an overview of how the results of the trial, related to trial quality, efficacy, and safety, all support the regulatory submission.

The specific requirements will depend on the nature of the application and details are available at https://www.tga.gov.au/collection/argpm and disease and therapeutic area-specific TGA adopted guidelines are also available at https://www.tga.gov.au/ws-sg-index

It should be noted that any information in this guidance is advisory and is neither binding on nor represent the views of the Therapeutic Goods Administration.

POPULATION-LEVEL AT WHICH INTERVENTION IS INTENDED TO BE APPLIED

Some candidate interventions are designed to apply to populations, rather than individuals (i.e., policies). In considering implementability for interventions that are intended to apply to populations types of trial design such as cluster, cluster cross-over and stepped-wedge designs, may be necessary. An advantage of applying these types of designs, to population-level interventions is that the trial also allows evaluation of how the intervention can be applied in practice.

PRIOR DEMONSTRATION OF FEASIBILITY OF DELIVERY OF INTERVENTION

Pre-trial activities that include a pilot trial that demonstrates capacity to deliver that planned intervention with fidelity and separation from the comparator, are often recommended, particularly for complex interventions (Delaney, et al., 2008; Craig, et al., 2008). Such pilot trials do not contribute directly to implementability, except where the conclusion of the pilot is that delivery of the intervention is not feasible. This has clear implications for implementability, as if an intervention is not feasible in a trial it will not be capable of subsequent implementation into practice. It is essential that trials that demonstrate lack of feasibility are reported and published, as this communicates the absence of implementability of the intervention in the way applied in that pilot or feasibility trial. Such work is also valuable for identifying barriers and enablers that may inform further attempts to establish feasibility.

TRIAL TEAM

The impact of the composition of the trial team on implementability should be considered during the planning stage. As outlined with respect to end-users, involvement of consumers, clinicians, and policy-makers, as appropriate, as members of the trial team is likely to enhance implementability. Particularly for complex interventions (Delaney, et al., 2008; Craig, et al., 2008), consideration should be given to involvement of clinicians who will be involved in delivery of the intervention.

Where health economic considerations are likely to be relevant to implementation, involvement of a health economist should be regarded as mandatory as elements of an appropriate health economic analysis may not be possible unless incorporated into planning and designing the trial. Where implementation, or particularly de-implementation, is likely to be challenging, strong consideration should be given to including implementation scientists in the trial team so that insights regarding implementation challenges and opportunities can be incorporated within the planning and design of the trial.

INVOLVEMENT OF A CLINICAL TRIAL NETWORK

Many, but far from all, clinical trials are undertaken by a network. The majority of the members of most networks are individuals who have dual roles as researchers and clinicians. Many networks also have consumers as members. An important feature that contributes to the impact of trials conducted by networks, is that these end-users contribute, via formal or informal processes, to the planning, conduct and reporting of trials. The involvement of these end-users within the network is also believed to contribute to appropriate implementation of the results of trials conducted by the network.

Other aspects of conducting a trial within a network that can contribute include access to accumulated experience with all aspects of planning, design, conduct and reporting that facilitate implementability. Networks can also provide access to trial sites that are representative of the clinical sites and population in which the results would be applied. Lastly, some networks, either by themselves or in conjunction with an associated registry, are well positioned to monitor actual implementation.

PROTOCOL CONSIDERS ISSUES RELEVANT TO IMPLEMENTATION OF RESULTS

The SPIRIT check-list for elements to be included in a trial protocol does not have a section related to issues of implementation (https://www.spirit-statement.org). Implementability may be enhanced by clinical trialists choosing to include a section within the trial protocol that considers issues relevant to potential implementation of the results.

This could include identification of the trial as being late-phase, coupled with explicit definition of the intended end-users. There can also be specification of the population to which implementation might apply with an estimate of the size of that population and the associated burden of disease. The protocol could also consider a range of possible results of the trial- benefit, harm, and no difference (in a classic superiority design). For each possible result, the protocol could specify what would be regarded as appropriate implementation of the results, including how issues of implementation should be influenced by incorporation of the results of the current trial within an evidence synthesis. This pre-specification of potential for implementation is important for results that show no difference, particularly where the effect size for which the trial is powered may be above the minimum clinically or public health significant difference.

The implementation section could also consider the impact on inequities, barriers and enablers to potential implementation, and justify how the trial has been designed in light of such factors. Where implementation, or de-implementation, are likely to be challenging, the section also provides an opportunity to demonstrate engagement with implementation scientists to ensure that elements that may facilitate their work have been incorporated into the design. This section of the protocol can also include a discussion of the extent to which other aspects of trial planning, including those outlined above, have been undertaken and incorporated into the decision-making for the trial.

While trialists do not generally carry responsibility for implementation, they do have a clear responsibility with late-phase trials to consider issues that would influence the capacity of the results to be implemented. The protocol should include a clear commitment to publish the results of the trial (including the reasons if the trial does not progress sufficiently to have analysable results such as insufficient recruitment or inability to deliver the intervention with separation), and to indicate the planned pathways for dissemination and interaction with those who do take responsibility for evidence synthesis and implementation. This may include observational work, that runs in parallel to the trial, that measures uptake of the intervention before, during and after the results of the trial have been disseminated, as well as parallel work to evaluate and optimise implementation.

TRIAL DESIGN AND CONDUCT PHASE

1. INTRODUCTION

During the design and conduct phase of the trial, many decisions are made that can have implications for implementability. These include the nature of the sites or locations in which recruitment and trial activities occur, the population that will be enrolled in the trial, the way the intervention is delivered and adjusted, the choice of comparator, monitoring of compliance and adherence, operating characteristics of endpoints, options for concomitant care, and incorporation of process evaluation and health economic analysis. The contribution of each of these to implementability will be considered.

2. POPULATION TO WHICH RESULTS OF TRIAL APPLY

a. Trial site characteristics

To optimise implementability, trial sites should be as representative as possible of the sites in which the intervention, if supported by evidence from the trial, would be implemented. If implementation would only occur in tertiary or quaternary hospitals, then it is appropriate that these are targeted as sites for the trial. If an intervention would be applied in all types of hospitals, including in rural and remote locations, then the trial sites should reflect this distribution, as much as possible. For interventions that would be applied in the community, recruitment and delivery within the community or via primary care should occur. Where an intervention is primarily targeted at individuals who suffer social disadvantage or other deprivation, the trial should be conducted at sites where the target population can be recruited. The effectiveness of an intervention may be influenced by the context in which it is provided, so implementability of the results is enhanced by reproducing this context in the trial.

b. Relationship of trial entry criteria to target population

In general, late-phase trials should target the broadest possible population for which it is intended that the results of the trial would apply in practice. Trialists are sometimes tempted to choose narrow trial entry criteria, in the hope of identifying a population with the greatest likelihood of the intervention showing benefit.

Many trials in cardiovascular medicine exclude patients with chronic kidney disease even though one-third of patients with cardiovascular disease have chronic kidney disease. The results from patients without kidney disease may not be generalisable to this population and implementability for patients with chronic kidney disease may be limited.

While sometimes appropriate, narrow populations may limit the capacity for implementability as the results of a trial cannot necessarily be extrapolated to patients who would not have been eligible for the trial. As such, trial entry criteria that result in the exclusion of patients with co-existing illnesses (Stuart, et al., 2017), specified age ranges, language-restrictions, or a specified gender from late-phase trials should be avoided so as to enhance the generalisability of results to the relevant target population. Differences in distribution of disease that occurs among disadvantaged groups can result in inappropriate exclusion from clinical trials. For example, among Indigenous people, the age of onset of many diseases is much younger than occurs in other members of the community and age-based trial entry criteria can result in such patients not being eligible for trials, affecting both equity of access and implementability.

Where there is a reasonable pre-trial likelihood of differential treatment effect in defined sub-groups, stratification of randomisation by these sub-groups may offer a better solution than exclusion. This may be important where there is a likelihood of heterogeneity of treatment effect, as implementation is enhanced by understanding the 'break point' at which fixed adverse effects of an intervention balance a reduced beneficial effect where benefit is proportional to severity of the disease (Iwashyna, et al., 2015). Wherever possible the distribution of factors that could influence heterogeneity of treatment effect should be similar to the expected distribution in the target population. Clearly, to be implementable, the variable used for stratification must be known and available at the time of randomisation, as it would be to clinicians at the time of implementation during a clinical encounter. Where narrow entry criteria are appropriate, trialists should avoid encouraging excessive extrapolation to wider groups of patients and acknowledge that additional trials, that enrol the wider population, are necessary for implementation.

c. Implementability of trial entry criteria

As outlined in the trial planning section, the ease of use of trial entry criteria can influence implementability. In general, entry criteria should be easily interpretable and accessible by clinicians who would be utilising the criteria to identify patients for the intervention in practice. This is achieved by entry criteria that are as limited in number as possible, do not require calculation of scores, and utilise only information that is easily accessible to clinicians.

Trials in critically ill patients often want to enrich for patients with more severe illness. One approach, used by some trials, applies the APACHE II scoring system (Ranieri, et al., 2012, (PROWESS-SHOCK)). This involved enrolling only patients above a threshold score, with the score being calculated by identifying the most abnormal values for 12 physiological variables collected during the first 24 hours of admission to an intensive care unit. An alternative method is to use an entry criterion that specifies that the treating clinician believes the patient will still require admission to intensive care unit the day after tomorrow (Finfer, et al., 2009, [NICE-SUGAR]). This method was highly effective at identifying a population with high severity of illness and is much easier to apply in practice than calculating a score.

Where entry criteria are to be selective, trialists should also consider such criteria, as it will often enhance recruitment as well as implementability.

Trials should avoid, as much as possible, entry criteria that cannot be evaluated in routine practice. For example, trials that utilise entry criteria based on a research-only biomarker, or other research-only tests, are not capable of implementation unless there is a clear pathway for the test to also be available in routine practice. Two examples are included in Box 2, overleaf.

1. The use of urinary tissue inhibitor of metalloproteinases-2 (TIMP-2) and insulin-like growth factor binding protein-7 (IGFBP-7) has been suggested as a biomarker for the early detection of acute kidney injury in various clinical settings. However, the early detection of patients at risk is hindered by the low sensitivity of the established tests in clinical routine practice (Adler, et al, 2018). Only patients at high risk of acute kidney injury could be identified after a certain amount of time following a clinical procedure.

2. Interferon-γ Enzyme-Linked Immune SPOT assay (IFN-γ ELISPOT), as a biomarker, has been suggested to differentiate and predict risk of kidney injury and acute rejection in kidney transplant recipients (Crespo, et al., 2017; Montero, et al., 2019). Yet, the evidence for the use of INF-γ ELISPOT as a biomarker remains inconsistent. Montero and colleagues found from a diagnostic test accuracy meta-analysis of 12 studies, that pretransplant IFN-γ ELISPOT was significantly associated with increased risk of acute rejection but provided suboptimal predictive ability at the individual level. However, in a multicentre clinical trial in organ transplantation (Hricik, et al., 2015), within the subset of 176 patients with available INF-γ ELISPOT results, pretransplant INF-γ ELISPOT positivity did not correlate with either the incidence of acute rejection or estimated glomerular filtration rate at 6 or 12 months.

d. Screening and recruitment

Where possible, screening and recruitment should occur in the same types of location and using the same staff as would be involved in implementation in practice. Pragmatic and embedded trials seek to screen and recruit patients in routine care often using clinical staff and processes (PRECIS-2). Screening and recruiting trial participants in this manner also enhances implementability as the processes utilised to identify patients for the trial are the same or similar to those that would need to be utilised in practice to identify patients for implementation.

3. CHARACTERISTICS OF INTERVENTIONS

a. Delivery of interventions

Implementability is optimised if interventions in a trial are delivered in exactly the same way as would occur if adopted into clinical practice or as already occurs in clinical practice.

The principles of the PRECIS-2 checklist for pragmatic clinical trials are important for distinguishing between trials that ask the question 'Can an intervention work under ideal circumstances?' and those that ask the question 'Does the intervention work under usual circumstances?' As such, several of the PRECIS-2 criteria relate to the way in which candidate interventions are delivered in the trial and have informed this section of the guidance (Loudon, et al., 2015).

Delivery of an intervention, as it is intended to be used in practice, ensures that if an intervention is effective in the trial it is reasonable to presume that it will also be effective when implemented into actual practice. Interventions that are novel and not available in routine care, can still be delivered in the same way and by the same staff who would be responsible for delivery, if adopted into practice. If the intervention requires training of routine staff, then the trial should train routine staff, and expected that similar training will be feasible for routine staff if implementation is to subsequently occur. Delivery of interventions to Indigenous participants should be done by Indigenous staff or by non-Indigenous staff with a demonstrated track record of working safely and appropriately with Indigenous peoples.

Interventions that are delivered by research staff who are supernumerary or would not be available in routine practice may have uncertain implementability (Kress, et al., 2000). In open-label studies, which are often necessary in trials of complex interventions, the involvement of research staff in delivery of the intervention also creates the possibility that additional attention may lead to changes in co-interventions, which may be responsible for any observed treatment effect.

Some trials specify rigorous measures of adherence or compliance with the intervention. In many circumstances this is quite appropriate but unless similar approaches are feasible and intended as part of implementation it cannot be assumed that the intervention will be effective in the real world. Some trials also have a run-in phase, prior to randomisation, in which adherence or compliance of potential enrolees are evaluated, and only those patients who have proven to be able to adhere to the intervention are randomised (Larsen, et al., 2019).

What is a run-in period?

A run-in period is a time period after inclusion, but before randomisation, used to exclude certain patients. Other pre-randomisation periods exist, for example, extended screening periods and washout periods. These different pre-randomisation periods may overlap in purpose, design and terminology.

What types of run-in periods exist, and which patients are excluded?

During the run-in period, all patients receive the same intervention, such as active treatment, placebo treatment or no intervention. Examples include lead into diet (Angelin, et al., 2014), assessing symptom stability (Bleeker, et al., 2014), washout of previous medication (Maneechotesuwan et al., 2014), assessing medication compliance (Martinez, et al., 2014) or placebo effects (Diamond, et al., 2014). Patients are excluded due to noncompliance to treatment or data collection, non-response to treatment or response to placebo.

What are the reasons for using a run-in period?

By excluding certain patients, for example, noncompliers or placebo responders, the run-in period may increase a study's power, that is, chance of detecting a potential treatment effect, but in a population that is not necessarily representative of the population to which the results are intended to apply.

What potential problem does a run-in period cause?

The use of a run-in period may affect implementability. By exclusion of patients from the clinical study population, as clinicians who would apply the therapy in practice do not know at time of the decision whether a patient will comply (Larsen, et al., 2019).

While useful in establishing the activity of an intervention, such measures may have an adverse impact on implementability, as the results apply to patients who will be more likely to adhere with an intervention, and such patients may not be capable of being identified prospectively in practice.

Some interventions require adjustment, fine-tuning or titration against clinical endpoints, either to achieve efficacy or to avoid potential adverse events. The implementability of a trial is enhanced if these aspects of adjustment of the intervention correspond to those that would occur when applied in practice.

The RALES trial (Pitt, et al., 1999) demonstrated that adding spironolactone to standard therapy reduced morbidity and mortality amongst patients with severe heart failure. Spironolactone is known to increase the serum concentration of potassium, which can result in life-threatening complications. In the trial, patients had monitoring of serum potassium every four weeks for the first 12 weeks, then every three months for up to one year and every six months thereafter until the end of the study.

The results of RALES appear to have resulted in implementation of the intervention into clinical practice. A population-based study in Ontario (Juurlink, et al., 2004) reported that among patients treated with ACE inhibitors who had recently been hospitalized for heart failure, the spironolactone-prescription rate was 34 per 1,000 patients in 1994, and it increased immediately after the publication of RALES, to 149 per 1,000 patients by late 2001 ($P<0.001$). The rate of hospitalisation for hyperkalemia rose from 2.4 per 1,000 patients in 1994 to 11.0 per 1,000 patients in 2001 ($P<0.001$), and the associated mortality rose from 0.3 per 1,000 to 2.0 per 1,000 patients ($P<0.001$).

As compared with expected numbers of events, there were 560 (95 percent confidence interval, 285 to 754) additional hyperkalemia-related hospitalizations and 73 (95 percent confidence interval, 27 to 120) additional hospital deaths during 2001 among older patients with heart failure who were treated with ACE inhibitors in Ontario. Publication of RALES was not associated with significant decreases in the rates of readmission for heart failure or death from all causes. The Ontario study raises the possibility that implementation of the treatment evaluated in the RALES study, which, in the real-world, occurred without the intensive monitoring provided in the trial context, did not result in improved outcomes for patients.

Similarly, to optimise implementability, the criteria and process for discontinuation of an intervention in a trial should reflect that which would occur in clinical practice. Modified safety requirements may be quite inappropriate in trials of Investigational Medical Products, where prior knowledge of the safety and effectiveness of the intervention is limited, but quite appropriate in comparative effectiveness trials where the interventions are widely available, in routine use, and the counterfactual is that the participant would have been receiving one of the treatment options as part of routine care.

The issues of implementability related to the delivery of the intervention are of major importance in complex interventions (Delaney, et al., 2008). The delivery of complex interventions within a trial often involves training of staff and the development and application of study tools and guides to facilitate delivery. If the methods used to train staff for the trial cannot be applied or expanded for the training of routine staff, this may have implications for implementation.

b. Choice of comparator

As outlined in the trial planning section surveys and, preferably, observational studies of actual practice are vital in ensuring that the choice of comparator is optimised to facilitate implementability.

Where there is substantial variation in actual practice, making a choice about the comparator that enhances implementability can be challenging. Some trials compare new or existing treatment options where all options are within a set of interventions that have a common mode of purpose and for which the different alternatives comprise mutually exclusive options (e.g., antibiotics for infection, antihypertensives for elevated blood pressure). If the comparator is not commonly used, clinicians will not know how to interpret the result in the context of their own practice because they do not use the comparator. In this situation, the most commonly used alternative or guideline recommendation should generally be regarded as providing the best option to enhance implementability.

Some trials evaluate complex interventions such as a treatment algorithm or titration of a treatment to a physiological or biochemical target. The choice of comparator (or comparators) in such trials can be challenging, particularly around how the results of the trial might be implemented into practice. The research question is, typically, 'Is a new strategy better than the current strategy?', but this is complex when there are many variants of the current strategy.

There are two broad options; one option is to compare the new strategy against a single variant of current standard care which could be referred to as protocolised control (i.e., the trial compares two protocolised strategies, one which is new and one which serves as control). However, this approach may limit capacity for implementation, particularly if the protocolised control group is not actually practised by the majority of practitioners. The capacity for implementation may be limited, especially when the trial does not provide a meaningful comparison of a new option, compared with what each practitioner usually does.

The second option is to not protocolise the control group, but rather to allow all clinicians participating in the trial to treat control patients as they would normally do so. This might be referred to as non-protocolised (or wild-type) control (Delaney, et al., 2008). This approach provides a valid comparison between the new strategy (which is delivered according to a protocol) and the 'average' treatment effect of different alternative strategies that are part of current standard care. If a non-protocolised control is chosen, it is important that the clinicians and sites chosen to participate are as representative as possible. A disadvantage of the non-protocolised control group is that it only answers the research question against the current 'average' strategy, and it does not preclude that there may be variants of the current strategy that are better or worse than other variants, including the new strategy.

These two options are not mutually exclusive. Some trials have tested the new strategy, against a protocol that is believed to best reflect the current standard care, as well as having a third arm for non-protocolised care (Angus, et al., 2014, [ProCESS]). However, additional arms in trials will have an adverse effect on power or the required sample size, and consequently the burden on participant recruitment and cost.

ARISE, ProMISe, and ProCESS were three coordinated trials that compared a complex treatment algorithm for the resuscitation of patients with septic shock. Components of the treatment strategy included targets for the amount of resuscitation fluid, the administration of vasopressors to achieve a target blood pressure, and transfusion of red cells and administration of dobutamine to achieve a target mixed venous oxygen saturation level.

ARISE and ProMISe both utilised a 'wild-type' control in which patients randomised to the control group received whatever resuscitation strategy the treating clinician would have otherwise used. ProCESS utilised a three-arm design, comprising the intervention strategy against a protocolised control group (designed, as much as possible, to reproduce 'average' standard care and a wild-type control (Peake, et al., 2009, [ARISE]; Mouncey, et al., 2015, [ProMISe]; Angus, et al., 2014, [ProCESS]).

Another issue exists for trials that titrate the dose of a treatment to achieve a physiological or biochemical target (Wollert, et al., 2004, [BOOST], Finfer, et al., 2009, [NICE-SUGAR]; Young, et al., 2019, [ICU-ROX]). It is often the case that trials choose two targets, towards either end of the spectrum of current standard care, which is necessary to achieve separation between groups. The issue for implementability of these trial designs is that many clinicians might usually have chosen a target that lies between the two extremes or choose different targets for different categories of patient, (i.e., personalise the target). Trials that compare two separated targets can answer important questions but may still have limitations with respect to how clinicians interpret the results in the context of their own practice. One option for such trials is the addition of a third arm, which allows the clinician to choose the target that they would have otherwise used for that patient (i.e., non-protocolised control). From a trial ethical perspective, as well as an implementation perspective, the addition of a non-protocolised control arm allows for the possibility that current standard care, including personalisation, is superior to protocolised targeting at either end of a spectrum of options.

Designing and conducting trials of complex interventions provides multiple challenges many of which involve trade-offs. In such trials, the choice of comparator(s) can have a major impact on implementability.

ROLE OF BLINDING AND USE OF PLACEBO

The vast majority of late-phase trials should use blinding and placebo, wherever practicable and feasible. However, where the efficacy of an intervention has already been established conclusively, there can be situations in which further placebo-controlled and double-blind studies do not contribute further to implementability.

With respect to de-implementation trials, particularly those of surgical procedures, the use of blinding and placebo (sham-surgery) can contribute substantially to subsequent implementability (Buchbinder, et al., 2009).

ALIC^{4}E is a trial of oseltamivir in patients presenting in primary care with influenza like illness (ILI) (Butler, et al., 2020). Previous double-blind and placebo-controlled trials of patients with ILI and in the subgroups with proven influenza had shown a modest reduction in duration of symptoms. The relatively modest effect had resulted in controversy in the value of oseltamivir. The designers of ALIC^{4}E faced two major issues. Firstly, in general practice influenza testing is often either not done or the results are not available for several days. The question for implementability of this intervention is 'What is the effect of the treatment in patients?' The primary care physician might think about treating, based mainly on clinical suspicion. The second issue was whether to use a placebo. The researchers noted that, in usual practice, they would be making a choice between treating purely symptomatically with say paracetamol and self-care advice, and prescribing oseltamivir in addition to this: they wouldn't be making a choice between prescribing placebo or oseltamivir. Once efficacy has been proven, as it has been for oseltamivir by many systematic reviews of placebo-controlled trials, issues of cost effectiveness in routine care become critically important. The study question was not, 'Does oseltamivir work?', but rather, 'What is the clinical and cost effectiveness of adding oseltamivir to existing care?' Estimating cost effectiveness (rather than efficacy) has to take future consulting and subsequent medication and resource-use into account. This is influenced by patients' knowledge of what they have been prescribed and are taking. As such, the researchers chose to conduct an open-label study to answer the question of whether prescribing oseltamivir in addition to usual care improved outcomes. This answers a pragmatic question, 'Does it work for patients?' but doing so was contingent on prior trials that had already demonstrated that oseltamivir had clinical and biological activity, in comparison to placebo.

1. Concomitant Care

Some trials provide detailed protocols with regard to concomitant care. The principle that is being applied is to control the amount of background variation so that the major source of difference between patients arises from their exposure to intervention or control. This may enhance the likelihood of showing difference (although randomisation, with sufficient sample size should also balance variation between groups). However, tight control over background care can have an adverse impact on implementability. This arises because the trial evaluates the intervention in the context of background care that may not reflect or be achievable in the real world. With this type of design there is legitimate uncertainty for end-users if they are not confident that the same background care can be provided. Implementability is generally enhanced by placing few or no restrictions on concomitant care.

2. Intention-to-treat and sub-group analyses

Implementability is generally enhanced by restricting analysis to the intention-to-treat population as value in clinical practice or policy applies to this population, not to groups that receive or can tolerate an intervention. As such, per protocol analyses may have limitations with respect to implementability, with the exception of non-inferiority trials where per protocol analysis is the recommended approach (Scott, 2009). Implementability may apply to pre-specified sub-groups, so long as rules for multiplicity of testing are followed. Implementability should be regarded as low for any sub-group that was not specified a priori (i.e., these should always be regarded as hypothesis generating). Sub-group analyses that rely on a variable that is not available at the time a clinician would make a treatment decision are very limited with respect to implementability.

3. Population context information

Where possible, embedding a trial within a registry or use of existing registry data can be useful to report information on characteristics and outcomes for patients who would have met the entry criteria for the trial but were not trial participants. This information helps provide context of trial results and enhances capacity for implementation when patients randomised in the trial have similar characteristics to those patients who are eligible but were not participants in the trial (Lasch, et al., 2019).

4. Process evaluation and fidelity

Process evaluations should be strongly considered for any late-phase trial of a complex intervention. Measurement of fidelity of the delivery of the intervention and separation from control are important components of validity as well as contributing to implementability. Parallel process evaluations involve a mixed-methods approach to provide a more detailed understanding of the factors affecting the fidelity of delivery of the intervention that can be used to inform subsequent implementation into practice. Components of process evaluation include the framework of implementation used in the actual trial including structures, resources and processes through which delivery is achieved, the quantity and quality of what is delivered, understanding the mechanism of impact (how intervention activities, and participants' interactions with them, trigger delivery), and context (how external factors influence the delivery and functioning of interventions). (Please see http://decipher.uk.net/process-evaluation-guidance/ or refer to Minary, et al., 2019 for a systematic review.)

5. Health economics

A prospective well-designed health economic analysis may be critical to implementability. The need for an economic analysis may not be known until the results of the trial are available. For example, where an expensive and an inexpensive option are equivalent, or the inexpensive option is superior, little or no economic analysis may be required. However, valid economic analysis requires planning and incorporation within the trial design, with collection of necessary data during trial conduct. Facilitation of implementability will almost always require a pre-planned economic analysis. Once the economic evaluation results are known for a trial, these need to be adjusted for the Australian context. Often this requires a new economic evaluation to account for any difference in clinical pathways in Australia, Australian values for health-related quality of life, health care resource use, and Australian costs. Following this, a value of implementation analysis (known as the Expected Value of Perfect Implementation – EVPIM) can be undertaken to determine the associated costs and benefits from implementation and the costs and benefits of not implementing the intervention. EVPIM includes factors such as prevalence, likely uptake of the intervention, and cost of rolling out the new intervention. These factors are typically not reported in clinical trials (Tuffaha, et al., 2015; Tuffaha, et al., 2016; Mewes, et al., 2017).

TRIAL REPORTING PHASE

INTRODUCTION

The reporting phase is critical to implementability. A trial that is never reported or is very poorly reported cannot have its results implemented into practice and policy. Furthermore, there are additional aspects of reporting that can have a major bearing on implementability including following international guidelines produced by the International Committee of Medical Journal Editors that allow evaluation of aspects of the trial that influence internal validity and external validity, as well as contribute to implementability. The aspects of reporting that contribute to implementability are well described in the literature and are summarised here.

COMMITMENT TO REPORT AND REPORTING THAT IS COMPLETE AND TIMELY

All trials should be reported. This is particularly important if the trial has insufficient recruitment or because it is unable to deliver the intervention. This information assists future trialists to avoid repeating the same trial and interventions that cannot be delivered within a trial are unlikely to be capable of implementation into practice.

Implementability is enhanced by a clear commitment to report the results of the trial as soon as possible and to follow the reporting requirements (i.e., CONSORT or equivalent for different trial types, http://www.consort-statement.org). Selective reporting must be avoided. The best method for achieving this is publication of a Statistical Analysis Plan (Gamble, et al., 2017) prior to locking the database of the trial and ensuring that the trial manuscript adheres to the Statistical Analysis Plan. Where a trial does deviate from the Statistical Analysis Plan, the rationale or requirement to do so should be provided.

SUFFICIENT INFORMATION TO GUIDE DELIVERY OF INTERVENTION

Particularly for complex interventions, reporting of trials has often been insufficient to describe the intervention and how it is delivered. Clearly, an intervention that is incompletely described in a trial manuscript cannot be implemented into practice. Interventions should be comprehensively described by, for example, using the TIDieR checklist (Hoffmann, et al., 2014). The TIDieR checklist is reproduced in Appendix D. Study tools and education material used to implement the intervention in the trial should be made publicly available, for example on a study website, so that the methods used in the trial are available to practitioners. If the comparator group followed a protocol, all methods used to deliver the comparator intervention should also be made available (Aziz, et al., 2015).

DATA SHARING

All late-phase trials should have a data ownership and sharing plan (Chapter 4.2, Research Data; NHMRC Open Access Policy, 2018), although such plans must incorporate issues regarding data sovereignty, particularly if the trial has focussed on Indigenous participants. This can include agreements about access to and sharing of raw data and code used in analysis. Capacity for implementation is enhanced by transparency of data and how it was analysed and cooperation with evidence synthesis, for example being responsive to requests for unpublished data or clarification of results, as well as willingness to share data to undertake Individual Patient Data Meta-analysis (IPDMA).

ACCESSIBLE FOR END-USERS

Implementation is impaired if end-users cannot access trial results. Publication in an open-access journal or in a journal that provides open-access as an option is not always possible but should be considered wherever possible. Other strategies that promote access include presentations at key conferences, lay summaries for patients, policy briefs, and both traditional and social media.

DECLARATION OF INTERESTS

Investigators should maintain and declare a registry of real or perceived conflicts of interest. Ideally, studies designed to guide implementation should be conducted transparently and with conflicts of interest identified. Some trials, particularly those that evaluate questions of comparative effectiveness, are managed and conducted by investigators who are truly agnostic to the interventions being evaluated and this can serve to manage conflicts of interest associated with the intervention.

REFERENCES

ACTA Embedding Clinical Trials in Healthcare Reference Group. (2018). *International best practice towards a learning healthcare system. A scoping activity to map international approaches to embed clinical trials into the healthcare system*. [cited December 2019] Available from: https://clinicaltrialsalliance.org.au/resource/international-best-practice-towards-a-learning-healthcare-system

ACTA Impact and Implementation of Clinical Trials Reference Group. (2019). *Approaches to Implementability, Implementation and Impact of Clinical Trials: A survey of Australian clinical trials networks and coordinating centres*. [cited December 2019] Available from: https://clinicaltrialsalliance.org.au/resource/approaches-to-implementability-implementation-and-impact-of-clinical-trials-a-survey-of-australian-clinical-trials-networks-and-coordinating-centres

Alonso-Coello, P., Schunemann, H. J., Moberg, J., Brignardello-Petersen, R., et al. (2016). GRADE Evidence to Decision (EtD) frameworks: A systematic and transparent approach to making well-informed healthcare choices. *BMJ*, 359.

Angus, D. C., Barnato, A. E., Eaton, T. L., et al. (2014). A randomized trial of protocol-based care for early septic shock. *NEJM, 370*, 1683–93. doi: 10.1056/NEJMoa1401602.

Aziz, Z., Absetz, P., Oldroyd, J., Pronk, N. P., Oldenburg, B. (2015). A systematic review of real-world diabetes prevention programs: learnings from the last 15 years. *Implementation Science, 10*, 172. doi: 10.1186/s13012-015-0354-6.

Bernard, G. R., Vincent, J-L., Laterre, P-F., et al. (2001). Efficacy and safety of recombinant human activated Protein C for severe sepsis. *NEJM, 344*(10), 699–709.

Buchbinder, R., Osborne, R. H., Ebeling, P. R., Wark, J. D., et al. (2009). A randomized trial of vertebroplasty for painful osteoporotic vertebral fractures. *NEJM, 361*(6), 557–68.

Butler, C. C., van der Velden., Bongard, E., et al. (2020). Oseltamivir plus usual care versus usual care for influenza-like illness in primary care: an open-label, pragmatic, randomised controlled trial. *The Lancet, 395*(10217), 42–52.

Craig, P., Dieppe, P., Macintyre, S., Michie, S., Nazareth, I., Petticrew, M. (2008). Developing and evaluating complex interventions: the new Medical Research Council guidance. *BMJ, 337*, a1655. doi: 10.1136/bmj.a1655.

Crespo, E., Cravedi, P., Martorell, J., et al. (2017). Post-transplant peripheral blood donor-specific interferon-γ enzyme-linked immune spot assay differentiates risk of subclinical rejection and de novo donor-specific alloantibodies in kidney transplant recipients. *Kidney Int, 92*(1), 201–13.

Delaney, A., Angus, D. C., Bellomo, R., Cameron, P., Cooper, D. J., Finfer, S., Harrison, D. A., Huang, D. T., Myburgh, J. A., Peake, S. L., Reade, M. C., Webb, S. A., Yealy, D. M. Resuscitation in Sepsis Evaluation (ARISE); Protocolized Care for Early Septic Shock (ProCESS) Investigators; Protocolised Management In Sepsis (ProMISe) Investigators. (2008). Bench-to-bedside review: the evaluation of complex interventions in critical care. *Crit Care, 12*(2), 210. doi: 10.1186/cc6849.

Eisenstein, E., et al. (2008). Sensible approaches for reducing clinical trial costs. *Clin Trials, 5*(1), 75–84.

Finfer, S., Chittock, D. R., Su, S. Y., Blair, D., Foster, D., Dhingra, V., Bellomo, R., Cook, D., Dodek, P., Henderson, W. R., Hébert, P. C., Heritier, S., Heyland, D. K., McArthur, C., McDonald, E., Mitchell, I., Myburgh, J. A., Norton, R., Potter, J., Robinson, B. G., Ronco, J. J., NICE-SUGAR Study Investigators. (2009). Intensive versus conventional glucose control in critically ill patients. *N Engl J Med, 360*(13), 1283–97. doi: 10.1056/NEJMoa0810625. Ford, I., and Norrie, J. (2016). Pragmatic trials. *NEJM, 375*, 454-463. doi: 10.1056/NEJMra1510059.

Gamble, C., Krishan, A., Stocken, D., et al. (2017). Guidelines for the content of statistical analysis plans in clinical trials. *JAMA, 318*(23), 2337–43. doi: 10.1001/jama.2017.18556

Glasgow, R. E., Vogt, T. M., Boles, S. M. (1999). Evaluating the public health impact of health promotion interventions: The RE-AIM framework. *Am J Pub Health, 89*, 1322–27.

Heeger, P. S., Greenspan, N. S., Kuhlenschmidt, S., Dejelo, C., Hricik, D. E., Schulak, J. A., Tary-Lehmann, M. (1999). Pre-transplant frequency of donor-specific, IFN-gamma-producing lymphocytes is a manifestation of immunologic memory and correlates with the risk of posttransplant rejection episodes. *J Immunol, 163*(4), 2267–75.

Hoffmann, T., Glasziou, P., Boutron, I., Milne, R., Perera, R., Moher, D., Altman, D., Barbour, V., Macdonald, H., Johnston, M., Lamb, S., Dixon-Woods, M., McCulloch, P., Wyatt, J., Chan, A., Michie, S. (2014). Better reporting of interventions: template for intervention description and replication (TIDieR) checklist and guide. *BMJ, 348*, g1687. doi: 10.1136/bmj.g1687. https://www.equator-network.org/reporting-guidelines/tidier

Hricik, D. E., Augustine, J., Nickerson, P., Formica, R. N., Poggio, E. D., Rush, D., Newell, K. A., Goebel, J., Gibson, I. W., Fairchild, R. L., Spain, K., Iklé, D., Bridges, N. D., Heeger, P. S., for the CTOT-01 consortium. (2015). Interferon Gamma ELISPOT Testing as a Risk-stratifying Biomarker for Kidney Transplant Injury: Results from the CTOT-01 Multicenter Study. *Am J Transplant, 15*(12), 3166–3173. Published online 30 July 2015. doi: 10.1111/ajt.13401.

Hsiao, B., Fraenkel, L. (2017). Incorporating the patient's perspective in outcomes research. *Curr Opin Rheumatol, 29*(2), 144–149. doi: 10.1097/BOR.0000000000000372.

Ioannidis, J. (2016). Why most clinical research is not useful. *PLoS Med, 13*(6), e1002049.

Iwashyna, T., et al. (2015). Implications of heterogeneity of treatment effect for reporting and analysis of randomized trials in critical care. *Am J Respir Crit Care Med, 192*(9), 1045–51.

Jaeschke, R., Singer, J., and Guyatt, G. (1989). Measurement of health status. Ascertaining the minimal clinically important difference. *Control Clin Trials, 10*(4), 407–15.

Juurlink, D. N., Mamdani, M. M., Lee, D. S., Kopp, A., Austin, P. C., Laupacis, A., Redelmeier, D. A. (2004). Rates of hyperkalemia after publication of the Randomized Aldactone Evaluation Study. *N Engl J Med, 351*(6), 543–51.

King, M. T., Stockler, M. R., O'Connell, R. L., Buizen, L., Joly, F., Lanceley, A., Hilpert, F., Okamoto, A., Aotani, E., Bryce, J., Donnellan, P., Oza, A., Avall-Lundqvist, E., Berek, J. S., Sehouli, J., Feeney, A., Berton-Rigaud, D., Costa, D. S. J., Friedlander, M. L., GCIG Symptom Benefit group. (2018). Measuring what matters MOST: validation of the Measure of Ovarian Symptoms and Treatment, a patient-reported outcome measure of symptom burden and impact of chemotherapy in recurrent ovarian cancer. *Qual Life Res, 27*(1), 59–74. doi: 10.1007/s11136-017-1729-8. PMID: 29248998.

Kress, J. P., Pohlman, A. S., O'Connor, M. F., Hall, J. P. (2000). Daily interruption of sedative infusions in critically ill patients undergoing mechanical ventilation. *NEJM, 342*, 1471–77. doi: intervention in complex10.1056/NEJM200005183422002.

Larsen, D. R. T., Paludin-Müller, A. S., Hróbjartsson A. (2019) Randomized clinical trials with run-in periods: frequency, characteristics and reporting. *Clinical Epidemiology, 11*, 169–184.

Lasch, F., Weber, K., Koch, A. (2019). Commentary: On the levels of patient selection in registry-based randomized controlled trials. *Trials*, *20,* (article number 100). doi:10.1186/s13063-019-3214-x.

Lichtman, S. M., Harvey, R. D., Smit, M. D., et al. (2017). Modernizing Clinical Trial Eligibility Criteria: Recommendations of the American Society of Clinical Oncology–Friends of Cancer Research Organ Dysfunction, Prior or Concurrent Malignancy, and Comorbidities Working Group. *J Clin Oncol, 35*(33), 3753–3759. doi: 10.1200/JCO.2017.74.4102.

Loudon, K., Zwarenstein, M., Sullivan, F., Donnan, P., Treweek, S. (2013). Making clinical trials more relevant: improving and validating the PRECIS tool for matching trial design decisions to trial purpose. *Trials, 14*, 115. doi: 10.1186/1745-6215-14-115. https://www.precis-2.org

Macleod, M., et al. (2014). Biomedical research: increasing value, reducing waste. *The Lancet, 383*(9912), 101–4.

Mewes, J. C., Steuten, L. M. G., IJsbrandy, C., IJzerman, M. J., van Harten, W. H. (2017). Value of implementation of strategies to increase the adherence of health professionals and cancer survivors to guideline-based physical exercise. *Value Health, 20*(10), 1336–44.

Minary, L., Trompette, J., Kivits, J., et al. (2019). Which design to evaluate complex interventions? Toward a methodological framework through a systematic review. *BMC Med Res Methodol, 19*, 92. doi: 10.1186/s12874-019-0736-6.

Montero, N., Farouk, S., Gandolfini, I., et al. (2019). Pretransplant donor-specific IFNγ ELISPOT as a predictor of graft rejection: A diagnostic test accuracy meta-analysis. *Transplant Direct, 5*(5), e451.

Mouncey, P. R., Osborn, T. M., Power, G. S., et al (2015). Protocolised Management In Sepsis (ProMISe): a multicentre randomised controlled trial of the clinical effectiveness and cost-effectiveness of early, goal-directed, protocolised resuscitation for emerging septic shock. *Health Technol Assess, 19*(97), i-xxv, 1–150. doi: 10.3310/hta 19970.

National Health and Medical Research Council. Open Access Policy. (November 2018). Available from: https://www.nhmrc.gov.au/about-us/resources/open-access-policy [cited December 2019].

National Health and Medical Research Council. The National Statement on Ethical Conduct in Human Research. (2007, updated 2018). Available from: https://www.nhmrc.gov.au/about-us/publications/national-statement-ethical-conduct-human-research-2007-updated-2018 [cited December 2019].

Nickel, P., Presber, F., Bold, G., Biti, D., Schönemann, C., Tullius, S. G., Volk, H-D., Reinke, P. (2004). Enzyme-Linked Immunosorbent Spot Assay for Donor-Reactive Interferon-Gamma-Producing Cells Identifies T-Cell Presensitization and Correlates with Graft Function at 6 and 12 Months in Renal-Transplant Recipients. *Transplantation, 78*(11), 1640–1646.

Peake, S., Bailey, M., Bellomo, R., Cameron, P., Cross, A., Delaney, A., Finfer, S., Higgins, A., Jones, D., Myburgh, J., Syres, G., Webb, S., Williams, P., the ARISE Investigators for the ANZICS-CTG. (2009). Australasian Resuscitation of Sepsis Evaluation (ARISE): A multi-centre prospective, inception cohort study. *Resuscitation, 80*, 811–18. IF 2.51.

Pitt, B., Zannad, F., Remme, W. J., Cody, R., Castaigne, A., Perez, A., et al. (1999). The effect of spironolactone on morbidity and mortality in patients with severe heart failure. *N Engl J Med, 341*, 709–717.

Prentice, R. (1989). Surrogate endpoints in clinical trials: definition and operational criteria. *Stat Med, 8*(4), 431–40.

Pronk, N. P. (2003). Designing and evaluating health promotion programs: Simple rules for a complex issue. *Dis Manage Health Outcomes, 11*(3), 149–157.

Ranieri, V. M., Thompson, B. T., Barie, P. S., et al. (2012). Drotrecogin Alfa (activated) in adults with septic shock. *NEJM, 366*, 2055–64.

Redelmeier, D., Guyatt, G., Goldstein, R. (1996). Assessing the minimal important difference in symptoms: a comparison of two techniques. *J Clin Epidemiol, 49*(11), 1215–9.

Scott, I. A. (2009). Non-inferiority trials: Determining whether alternative treatments are good enough. *MJA, 190*(6), 326–30.

Stuart, B. L., Grebel, L. E., Butler, C. C., Hood, K., Verheij, T. J. M., Little, P. (2017). Comparison between treatment effects in a randomised controlled trial and an observational study using propensity scores in primary care. *Br J Gen Pract, 67*(662), e643-e649. doi: 10.3399/bjgp17X692153.

Tong, A., Manns, B., Hemmelgarn, B., Wheeler, D. C., Tugwell, P., Winkelmayer, W. C., van Biesen, W., Crowe, S., Kerr, P. G., Polkinghorne, K. R., Howard, K., Pollock, C., Hawley, C. M., Johnson, D. W., McDonald, S. P., Gallagher, M. P., Urquhart-Secord, R., Craig, J. C., SONG-HD Collaboration. (2015). Standardised outcomes in nephrology – Haemodialysis (SONG-HD): study protocol for establishing a core outcome set in haemodialysis. *Trials, 16*, 364. doi: 10.1186/s13063-015-0895-7.

Tuffaha, H. W., Gordon, L. G., Scuffham, P. A. (2016). Value of information analysis informing adoption and research decisions in a portfolio of health care interventions. *MDM Policy Pract 1*(1), 2381468316642238.

Tuffaha, H. W., Roberts, S., Chabover, W., Gordon, L. G., Scuffham, P. A. (2015). Cost-effectiveness and value of information analysis of nutritional support for preventing pressure ulcers in high-risk patients: implement now, research later. *Appl Health Econ Health Policy, 13*(2), 167–79.

Wells, G., et al. (2001). Minimal clinically important differences: Review of methods. *J Rheumatol, 28*(2), 406–12.

Wollert, K. C., Meyer, G. P., Lotz, J., Ringes-Lichtenberg, S., Lippolt, P., Breidenbach, C., Fichtner, S., Korte, T., Hornig, B., Messinger, D., Arseniev, L., Hertenstein, B., Ganser, A., Drexler, H. (2004). Intracoronary autologous bone-marrow cell transfer after myocardial infarction: the BOOST randomised controlled clinical trial. *The Lancet, 16*;364(9429), 141–8.

Young, P., Mackle, D., Bellomo, R., Bailey, M., Beasley, R., Deane, A., Eastwood, G., Finfer, S., Freebairn, R., King, V., Linke, N., Litton, E., McArthur, C., McGuinness, S., Panwar, R., ICU-ROX Investigators the Australian New Zealand Intensive Care Society Clinical Trials Group. (2019). Conservative oxygen therapy for mechanically ventilated adults with sepsis: a post hoc analysis of data from the intensive care unit randomized trial comparing two approaches to oxygen therapy (ICU-ROX). *Intensive Care Med, 46*(1), 17–26. doi: 10.1007/s00134-019-05857-x.

APPENDIX A: PRECIS-2 TOOL

Extracted from PRECIS-2 toolkit, available at: https://www.precis-2.org

HOW TO USE PRECIS-2 – DESIGNING TRIALS THAT ARE FIT FOR PURPOSE

We think there are four steps to using PRECIS-2, which may be iterative depending on what you discover after going through the steps.

Step 1: Why are you doing your trial?

Your first step is to be clear about why you are doing your trial. Are you:

1. Aiming to take an explanatory approach to answer the question 'Can this intervention work under ideal conditions?'
2. Aiming to take a pragmatic approach and answer the question 'Does this intervention work under usual conditions?'

Both approaches to trial design have their place but trialists should be clear which path they are on. As Schwartz and Lellouch pointed out, triallist have often taken the first approach by default rather than as a considered judgement.

Step 2: Consider your trial design choices for each of the nine PRECIS-2 domains

This step is explained in more detail for each domain later on.

Step 3: Score 1 to 5 for these choices made in Step 2 and/or mark on the PRECIS-2 wheel

Having considered your design choices in Step 2, the PRECIS-2 wheel is used to record how pragmatic or explanatory these choices are for each domain. Each domain is a 5-point Likert scale:

1. Very explanatory
2. Rather explanatory
3. Equally pragmatic/explanatory
4. Rather pragmatic
5. Very pragmatic

A table can be used in conjunction with the PRECIS-2 "wheel" or instead of the wheel to give rationale to scores. You can use this to assist discussion with trial collaborators.

Step 4: Review your PRECIS-2 wheel

Review your design choices (Step 2) on the PRECIS-2 wheel to see whether they will produce a trial that will support the aim identified in Step 1. Go back to Step 2 and modify your design choices if required.

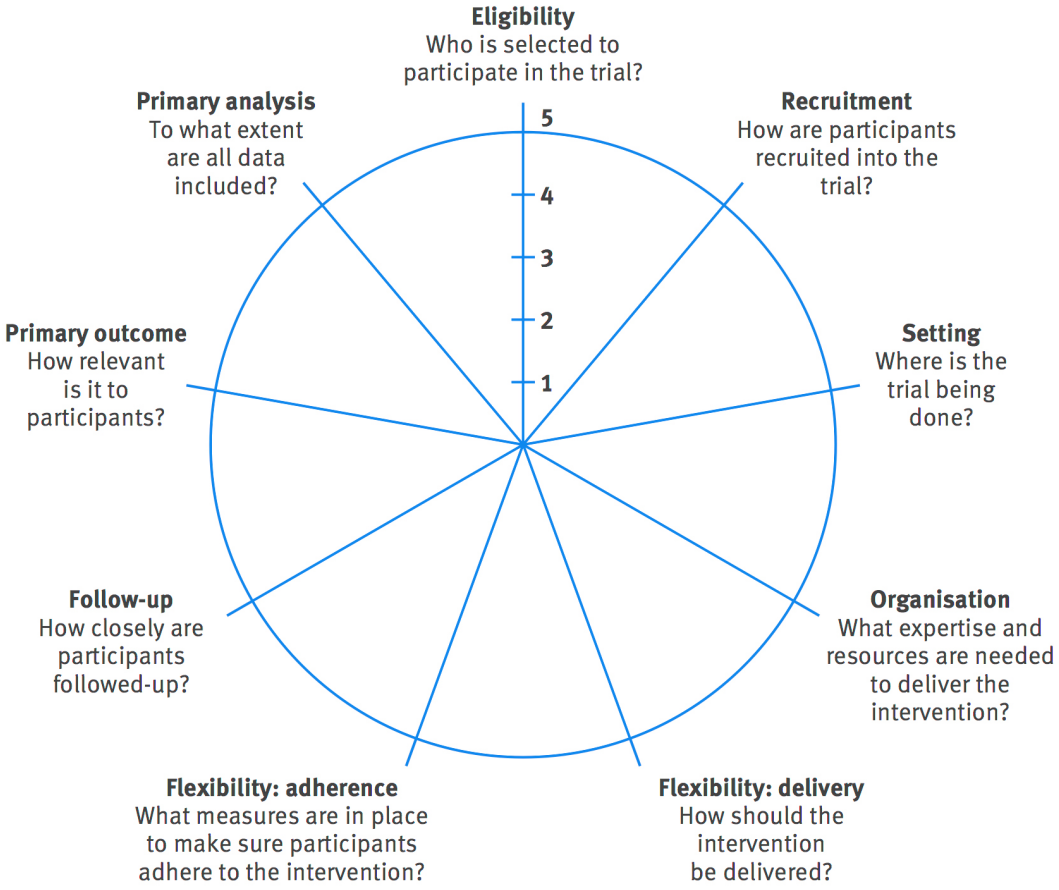

Figure A1: PRECIS-2 wheel (source: https://www.precis-2.org)

Table A1: PRECIS-2 scores for trial domains (source: https://www.precis-2.org)

	Domain	Score	Rationale
1	Eligibility criteria		
2	Recruitment path		
3	Setting		
4	Organisational intervention		
5	Flex of experimental intervention – delivery		
6	Flex of experimental intervention – adherence		
7	Follow-up		
8	Outcome		
9	Analysis		

THE PRECIS-2 DOMAINS

The nine PRECIS-2 domains are:

- **Eligibility** – to what extent are the participants in the trial similar to those who would receive this intervention if it was part of usual care? For example, score 5 for very pragmatic criteria essentially identical to those in usual care; score 1 for a very explanatory approach with lots of exclusions (e.g., those who don't comply, respond to treatment, or are not at high risk for primary outcome, are children or elderly), or uses many selection tests not used in usual care.
- **Recruitment** – how much extra effort is made to recruit participants over and above what that would be used in the usual care setting to engage with patients? For example, score 5 for very pragmatic recruitment through usual appointments or clinic; score 1 for a very explanatory approach with targeted invitation letters, advertising in newspapers, radio plus incentives and other routes that would not be used in usual care.
- **Setting** – how different is the setting of the trial and the usual care setting? For example, score 5 for a very pragmatic choice using identical settings to usual care; score 1, for a very explanatory approach with only a single centre, or only specialised trial or academic centres.
- **Organisation** – how different are the resources, provider expertise and the organisation of care delivery in the intervention arm of the trial and those available in usual care? For example, score 5 for a very pragmatic choice that uses identical organisation to usual care; score 1 for a very explanatory approach if the trial increases staff levels, gives additional training, require more than usual experience or certification and increase resources.
- **Flexibility (delivery)** – how different is the flexibility in how the intervention is delivered and the flexibility likely in usual care? For example, score 5 for a very pragmatic choice with identical flexibility to usual care; score 1 for a very explanatory approach if there is a strict protocol, monitoring and measures to improve compliance, with specific advice on allowed cointerventions and complications.
- **Flexibility (adherence)** – how different is the flexibility in how participants must adhere to the intervention and the flexibility likely in usual care? For example, score 5 for a very pragmatic choice involving no more than usual encouragement to adhere to the intervention; score 1 for a very explanatory approach that involves exclusion based on adherence, and measures to improve adherence if found wanting. In some trials (e.g. surgical trials where patients are being operated on or Intensive Care Unit trials where patients are being given IV drug therapy), this domain is not applicable as there is no compliance issue after consent has been given, so this score should be left blank.
- **Follow-up** – how different is the intensity of measurement and follow-up of participants in the trial and the likely follow-up in usual care? For example, score 5 for a very pragmatic approach with no more than usual follow up; score 1 for a very explanatory approach with more frequent, longer visits, unscheduled visits triggered by primary outcome event or intervening event, and more extensive data collection.
- **Primary outcome** – to what extent is the trial's primary outcome relevant to participants? For example, score 5 for a very pragmatic choice where the outcome is of obvious importance to participants; score 1 for a very explanatory approach using a surrogate, physiological outcome, central adjudication or use assessment expertise that is not available in usual care, or the outcome is measured at an earlier time than in usual care.
- **Primary analysis** – to what extent are all data included in the analysis of the primary outcome? For example, score 5 for a very pragmatic approach using intention to treat with all available data; score 1 for a very explanatory analysis that excludes ineligible post-randomisation participants, includes only completers or those following the treatment protocol.

NOTES

"Participants" include patients or other individual recipients of an intervention, and/or providers of the intervention. This may include individual participants and/or one or more levels of clusters. For example, in a trial of a continuing education intervention, participants may be health professionals and trained instructors and the trial may be randomised into clusters at the level of the instructor.

During the design process, if there is uncertainty over how explanatory or pragmatic a domain is, then we suggest the score for this domain should be left blank. This will then highlight uncertainty and encourage discussion. If PRECIS-2 is used to look at how pragmatic included trials are in systematic reviews, then a score of 3 may be chosen if there is inadequate information. This is different to the "3 = equally pragmatic/explanatory".

APPENDIX B: LIST OF ATTENDEES

The attendees at a workshop held in Melbourne on 21 May 2019 to discuss the guidance regarding implementability were:

Chair: Sally Green

Participants: Paul Cohen, Davina Ghersi, Stephen Jan, Samantha Keogh, Philippa Middleton, Angela Scheppokat, Greg Sharplin, Val Theisz, Sophia Zoungas and Steve Webb.

APPENDIX C: IMPLEMENTABILITY CHECKLIST

PLANNING PHASE

1. Has trial planning involved end-users?

a. Who are the intended end-users of the results of this trial?
b. Which end-users could have a role in implementation?
c. Can end-users help define how the range of possible results of this trial would be applied to the range of possible changes in practice or policy and map these to potential impact on patient outcomes or healthcare system productivity or both?
d. Does the research question have relevance to end-users?
e. Are the trial end-points patient-centred outcomes and, if not, are the outcomes accepted as clinically meaningful in the discipline?
f. Are the trial end-points that are under consideration known to be sufficient to influence end-users to change practice or policy?
g. Is the trial powered to detect the minimum clinically significant difference that would be important to end-users?
h. Does the choice of comparator reflect current and likely ongoing practice and so provide a meaningful comparison for end-users? If trade-offs are required have all alternatives or multiple comparator groups been considered?
i. Does the population recruited to the trial reflect the population in which the interventions would be implemented?
j. Can the trial entry criteria be interpreted easily and quickly by clinicians who would need to identify similar patients to change practice or policy?

2. Has the clinical context of the trial been defined sufficiently?

a. Has a systematic review been conducted and demonstrated that there is unmet need for evidence regarding effectiveness of the candidate intervention?
b. Is current standard care, including variation in standard care, described?
c. If the intervention is already in clinical practice, is there evidence of harm or burden sufficient to justify a trial of withdrawal of a component of standard care?

3. Is regulatory approval likely to be needed to contribute to implementation?

4. Have trial designs that randomise populations, rather than individuals, been considered?

5. For complex interventions has feasibility of delivery of the intervention in a trial been established?

6. Does the trial team have sufficient expertise to ensure that issues related to implementability have been considered during trial planning?

7. Is the trial best conducted within a trial network?

8. Has there been consideration of including a section within the trial protocol that discusses potential issues that relate to implementation

a. Pre-specification of the implication of different trial results to implementation
b. Consideration of barriers and enablers to potential implementation
c. Consideration of trial design issues that contribute to implementability
d. Planned pathways for dissemination and evidence synthesis
e. Whether parallel observational work is planned to measure implementation

DESIGN AND CONDUCT PHASE

1. Population to which trial results apply

a. Are trial sites representative of sites that would undertake implementation?
b. Is the target population as generalisable as possible?
c. If there are concerns about differential treatment effect within the target population can this be better managed with stratification?
d. Can trial entry criteria be applied easily and quickly in clinical practice or into policy?

2. Delivery of intervention is optimised for implementation

a. Is the intervention being delivered in the same way and by the same type of staff who would implement into practice?
b. Are trial activities related to adherence, compliance, and monitoring similar to clinical practice?
c. For complex interventions, are the methods used to train staff during the trial suitable for training routine clinical staff?

3. Choice of comparator and background care

a. Does the choice of comparator allow meaningful comparison that will facilitate implementation?
b. Are any restrictions regarding concomitant care capable of being implemented into practice or policy?

4. Plan of analysis and sub-group analyses

a. Is the trial planned to be analysed on an intention-to-treat basis?
b. Are planned sub-group analyses based on variables known at the time a decision to implement would be made during a clinical encounter?

5. Nesting the trial within a registry

a. Is it possible for the registry to provide information about characteristics and outcomes of patients who would have been eligible for the trial but were not enrolled?

6. Process evaluation and fidelity

a. For complex interventions, is a process evaluation being incorporated into the trial so that this information can guide potential implementation

7. Health economics

a. Where there is differential cost of interventions has a health economic analysis been planned and incorporated into the study design?

REPORTING PHASE

1. Is there a commitment that the results of the trial will be reported, irrespective of results or completion of the trial?

2. Is there a commitment to report using CONSORT or the appropriate modification of CONSORT for alternative trial designs?

3. Does the trial report sufficient information to allow implementation of the intervention into practice or policy? For example, does reporting meet the requirements of the TiDIER check-list?

4. What is the trial's data sharing policy?

5. Has accessibility of trial results been considered?

6. Have all conflicts or duality of interest been identified and reported?

APPENDIX D: TIDieR CHECKLIST

The TIDieR (Template for Intervention Description and Replication) Checklist*:
Information to include when describing an intervention and the location of the information

Item number	Item	Where located ** Primary paper (page or appendix number)	Where located ** Other† (details)
	BRIEF NAME		
1.	Provide the name or a phrase that describes the intervention.		
	WHY		
2.	Describe any rationale, theory, or goal of the elements essential to the intervention.		
	WHAT		
3.	Materials: Describe any physical or informational materials used in the intervention, including those provided to participants or used in intervention delivery or in training of intervention providers. Provide information on where the materials can be accessed (e.g., online appendix, URL).		
4.	Procedures: Describe each of the procedures, activities, and/or processes used in the intervention, including any enabling or support activities.		
	WHO PROVIDED		
5.	For each category of intervention provider (e.g., psychologist, nursing assistant), describe their expertise, background and any specific training given.		
	HOW		
6.	Describe the modes of delivery (e.g., face-to-face or by some other mechanism, such as internet or telephone) of the intervention and whether it was provided individually or in a group.		
	WHERE		
7.	Describe the type(s) of location(s) where the intervention occurred, including any necessary infrastructure or relevant features.		
	WHEN and HOW MUCH		
8.	Describe the number of times the intervention was delivered and over what period of time including the number of sessions, their schedule, and their duration, intensity or dose.		
	TAILORING		
9.	If the intervention was planned to be personalised, titrated or adapted, then describe what, why, when, and how.		
	MODIFICATIONS		
10.‡	If the intervention was modified during the course of the study, describe the changes (what, why, when, and how).		
	HOW WELL		
11.	Planned: If intervention adherence or fidelity was assessed, describe how and by whom, and if any strategies were used to maintain or improve fidelity, describe them.		
12.‡	Actual: If intervention adherence or fidelity was assessed, describe the extent to which the intervention was delivered as planned.		

** **Authors** – use N/A if an item is not applicable for the intervention being described. **Reviewers** – use '?' if information about the element is not reported/not sufficiently reported.

† If the information is not provided in the primary paper, give details of where this information is available. This may include locations such as a published protocol or other published papers (provide citation details) or a website (provide the URL).

‡ If completing the TIDieR checklist for a protocol, these items are not relevant to the protocol and cannot be described until the study is complete.

* We strongly recommend using this checklist in conjunction with the TIDieR guide (see BMJ 2014;348:g1687) which contains an explanation and elaboration for each item.

* The focus of TIDieR is on reporting details of the intervention elements (and where relevant, comparison elements) of a study. Other elements and methodological features of studies are covered by other reporting statements and checklists and have not been duplicated as part of the TIDieR checklist. When a **randomised trial** is being reported, the TIDieR checklist should be used in conjunction with the CONSORT statement (see www.consort-statement.org) as an extension of **Item 5 of the CONSORT 2010 Statement**. When a **clinical trial protocol** is being reported, the TIDieR checklist should be used in conjunction with the SPIRIT statement as an extension of **Item 11 of the SPIRIT 2013 Statement** (see www.spirit-statement.org). For alternate study designs, TIDieR can be used in conjunction with the appropriate checklist for that study design (see www.equator-network.org).

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