Australian Clinical Trials Alliance

IMPLEMENTABILITY GUIDANCE DOCUMENT: AFTER THE TRIAL

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PURPOSE OF THIS DOCUMENT

This document will assist Clinical Trial Networks (CTNs) and individual trialists to identify whether clinical implementation of an intervention is appropriate based on the results of a particular trial. The document outlines practical considerations for trialists in evaluating whether the results of their trial warrant direct implementation into policy or practice. The document also provides practical suggestions and signposting of approaches to dissemination and implementation of trial results.

THE ROLE OF ACTA IN DEVELOPING THE GUIDANCE DOCUMENT ON IMPLEMENTABILITY: AFTER THE TRIAL

The Australian Clinical Trials Alliance (ACTA) is providing a framework for CTNs and individual trialists to assess clinical trials and identify whether clinical implementation is appropriate. The generic advice provided by ACTA should be considered and applied by each CTN, considering, the specific requirements of the CTN as well as State or Territory laws and regulations.

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USE OF THIS DOCUMENT

ACTA encourages the use of all materials listed on its website (www.clinicaltrialsalliance.org.au) in the pursuit of improving the clinical trials enterprise. ACTA requests that the following acknowledgment is included in any CTN authorship and publication guidelines that are developed and documented using knowledge gained from this document:

"[Name of CTN] acknowledges the contribution of ACTA in outlining practical considerations for trialists in evaluating whether the results of their trial warrant direct implementation into policy or practice. (Reference: *Implementability guidance document: After the trial)*".

DISCLAIMER

The information in this document is for general guidance only. ACTA does not make any representations or warranties (expressed or implied) as to the accuracy, currency or authenticity of the information provided.

IMPLEMENTABILITY GUIDANCE DOCUMENT: AFTER THE TRIAL

This guidance document is for trialists conducting late phase clinical trials (Phase IV) of interventions whose cost-effectiveness, safety, and efficacy have already been demonstrated (positive or negative).

It is recognised that there is a substantial gap between the health care that patients receive and the practice that is recommended (1, 2). Translation of evidence into practice frequently occurs slowly - it can take 17 years to implement 14% of the definitive clinical research results into clinical practice (3), or as long as 3 years with an implemented strategic strategy (4). It is therefore often difficult to sustain research advances over time (5, 6). This is critical for patients who fail to receive the best, evidence-based treatment and care currently available, and for health care organisations and community, who miss out on the potential financial value gains and returns on investment from research (7).

In the context of clinical practice guidelines, implementation is defined as below. This concept applies equally to clinical trials.

> *'Implementation' is 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.. 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 and execution that is not contingent on the results of a trial, whereas appropriate implementation is critically dependent on both the results and implementability (9)*

Although implementation takes place at the end of the trial, it must be planned for at the beginning (9). Considering implementation at the time of planning and designing the research intervention are essential, as an effective intervention that is not feasibly implementable will not be used, and therefore will not change patient outcomes. Early consideration of implementation will also save time and money.

The purpose of this document is to provide guidance only on the implementation activities **following the completion** of a clinical trial. It is appreciated that, in many cases, not all features outlined here are necessary for implementation. This is dependent on context and what is best achieved given the constraints of time

and budget. These can include updating of knowledge, policy change and/or practice/behaviour change.

To effectively implement clinical trial results into standard care requires a number of essential steps, including:

1. **Determining** there is sufficient evidence to support active implementation (i.e., introduction of an intervention into clinical practice) or de-implementation (removal of an intervention from clinical practice if it represents low-value care). This determination should be on the basis of current best evidence from the trial and other relevant research, in conjunction with clinical expertise and patient values.
2. **Disseminating and diffusing** the information to targeted audiences.
3. **Involving** of clinical leaders and champions.
4. **Translating** the knowledge through behaviour and policy change.

It is hoped that trialists find this a useful document to enhance the value of the trials they conduct.

The purpose of this document is to help trialists to evaluate whether the results of their clinical trial should be implemented into policy or practice, and to provide an overview and resources for best practice in post-trial implementation. Information relating to the guidance of the planning, design and conduct of reporting of clinical trials from late-phase clinical trials, so that results are optimized for implementability has been outlined previously (9).

This guidance is intended to be iterative and feedback to enhance and improve this document is welcome to facilitate production of updated versions.

DISSEMINATION OF TRIAL RESULTS TO PARTICIPANTS, HEALTH PROFESSIONALS, THE PUBLIC AND OTHER RELEVANT GROUPS

Reporting trial results is an important part of clinical trials and is recommended in all toolkits, statements, funding and ethics requirements, and publication policies related to clinical trials. The dissemination of the key messages of the trial must be as far reaching as possible to provide the most impact in communities – be they research, health, or patient/consumer communities. The key messages for different target audiences must be identified and fashioned into language and active translation/implementation efforts in contrast to traditional and slow dissemination of publication knowledge. There are a large number of planned knowledge translation models, derived from different disciplinary, contextual, and target audience viewpoints (10). Most of these suggest that active knowledge translation for health care professionals and consumers is more likely to be successful if the choice of knowledge translation strategy is informed by an assessment of the likely barriers and enablers. Identification of these barriers and enablers will be discussed later in this document.

Identification of the stakeholders and end users involved in and impacted by your trial is an important first step. Different clinical trials have different end users, and they should be involved from the outset as an integral part of the trial team (9). This is described in ACTA's implementability guidance. In order to effectively disseminate trial results, it is essential to understand how best to approach your stakeholders and end users and to know what messages are appropriate and have impact. These end users may comprise a wide range of people including academics, researchers, clinicians (doctors, nurses and allied health practitioners), NGOs, and policymakers, or those that may benefit greatly from clinical trial interventions, such as patients, consumers, community members, and family members. It is important to identify these stakeholders and end-users early and involve them from the beginning of the trial. Consideration of a hybrid design blending clinical effectiveness and implementation evaluation may contribute to more effective implementation strategies and more rapid translational evidence gains in clinical intervention uptake (11). The dissemination and implementation strategy will therefore be determined by the targeted audience.

Dissemination to an academic and medical audience is primarily achieved through publication in peer-reviewed medical journals as well as through public reporting of results on clinical trial registries (12, 13). However, between 25 – 50% of clinical trials remain unpublished, sometimes years after study completion (14-16); and many clinical trials are not promptly reported in trial registries (17, 18). Further, there is ongoing publication bias toward studies with positive results. Trials with positive findings (defined as statistically significant, or perceived to be important

or striking, or indicating a positive direction of treatment effect) had nearly four times the odds of being published compared to findings that were not statistically significant, or perceived as unimportant, or showing a negative or null direction of treatment effect (19). Further, for the comprehensive reporting of clinical trials (20), use of the Consolidated Standards of Reporting Trials (CONSORT) guidelines are recommended (21).

Publish your trial as completely as possible within a reasonable time frame

Awareness of publication bias is important for both meta-analyses and the interpretation of statistical significance of positive trials. Therefore, it is essential that all clinical trial results (whether significant or not, positive or negative, or considered important or not) are reported and published as soon as possible.

Further dissemination of clinical trial results can be through conference proceedings, seminars, and invited speaker events. These events largely appeal to an academic audience but are sometimes open to other stakeholders such as patients, medical practitioners (nurses, doctors and allied health experts), health consumers and others. In such cases, it is imperative that the clinical trial findings are presented in a way that the information is accessible to all.

Public health messaging for patients, community members and consumers will necessitate another form of dissemination. The communication must be accessible, in plain language, consider the health literacy of the intended audience, and be delivered via other means besides journal publication. Consideration must be made if involving different subgroups of populations, such as culturally and linguistically diverse communities. In all cases, partnerships with the end users to coproduce resources is essential. The use of interpreters or the appropriate language to target specific culturally and linguistically groups may be necessary. Just as important may be the use of community leaders and/or champions who have influence within the community and can readily spread the public health messages.

Investigators should consider virtual platforms, including social media (twitter, Facebook, LinkedIn), interviews in news (e.g., The Conversation, news media), webinars (GoToMeeting, Zoom), videos (YouTube), and radio. Investigators may also provide information through newsletters, flyers and/or posters that are made available at libraries, general practices, resource centres, schools and other highly accessed centres by a variety of people (gender, ethnicity, age, disability, and so on) that would benefit from the intervention. Data sharing platforms and

repositories also provide new opportunities for studies and provide direct collaborations between the original data contributors and researchers (23).

WHEN TO IMPLEMENT YOUR TRIAL RESULTS

Sufficient evidence is defined according to the framework provided by the Grading of Recommendations Assessment, Development and Evaluation (GRADE) approach (23). GRADE provides a systematic approach for developing clinical practice guideline recommendations, rating the quality of evidence that is best applied to each outcome, as well as providing a guide for clinicians and clients/patients to using these recommendations in clinical practice, and policy makers for use in health policy (25).

Once published, an assessment of whether the trial results warrant implementation must be made. Individual trials, and systematic reviews of many trials must consider the generalisability of trial results to the specific setting. Individual clinical trials often focus on the internal validity at the expense of generalizability (22). The external validity (generalisability) of each study must be carefully assessed, and several techniques have been proposed including a priori and *posteriori* assessments (22). A priori assessments can be conducted by applying study eligibility criteria on a patient database to identify the study population and make comparisons between the demographics, clinical characteristics and outcomes between the study population and the target population (22). *Posteriori* assessments include comparisons between enrolled patients and the target population (22). The definition of the 'target population' will largely be influenced by the setting including the regulatory and reimbursement environment for drugs and devices, or the health care setting for systems-based interventions.

Proctor et al. (2009) suggest the following are considered (24, 26):

- how **feasibly** can an intervention be delivered in a particular health system?
- how much **fidelity** to the intervention is needed?
- how **acceptable** is it to the variety of stakeholders within the health system?
- what will the **uptake** be?
- what are the **costs** associated with having the intervention integrated into a system of care?
- how **sustainable** can it be?

The challenge of cost-effectiveness of individual trials versus considering the broader body of literature, and with more diverse populations, settings, and strength of evidence is important to consider before broad implementation.

There may be cases in which action is appropriate even in the context of insufficient evidence, such as rare conditions or conditions where the feasibility or ethical requirements make further or larger trials difficult; where a risk of a serious adverse effect has been identified; or where the purpose of the trial is to demonstrate the applicability of known effects in a specific population or context.

INCORPORATING YOUR TRIAL RESULTS INTO SYSTEMATIC REVIEWS, META-ANALYSES, AND EVIDENCE-BASED PRACTICE GUIDELINES

The results of all trials should contribute to relevant systematic reviews

Systematic reviews with meta-analysis of randomised clinical trials (RCTs) are the pinnacle of the hierarchy of evidence for intervention studies (28). The strongest inferences can be drawn if the Systematic Review is well conducted and includes methodologically sound RCTs with consistent results (28). Well-performed published trial results should be included in systematic reviews, meta-analyses and evidence-based practice guidelines. The key to their inclusion is ensuring that trials are conducted and reported in a rigorous manner.

Sufficient evidence for implementation will usually be attained by considering the trial results in the context of a completed systematic review. In some cases, single trial may produce evidence of sufficient precision and applicability to constitute certainty alone. These will usually be very large, multisite trials.

Systematic reviews make the available evidence more accessible to decision-makers, particularly given that most clinicians and public health professionals do not have the time to track down original articles (there are over 20,000 journals publishing millions of articles a year (29)), critically assess the information and obtain the evidence they need for their own clinical questions.

Despite the fact that the proportion of trials referring to systematic reviews has increased, many researchers do not seem to consider them when designing their trials (29). Meta-analyses integrate results from multiple studies and thereby can provide quantitative evidence over a whole body of related work (30).

The *Cochrane Handbook for Systematic Reviews of Interventions* provides excellent advice on the design, conduct and analysis of systematic reviews and meta-analyses (31). It includes interactive learning and training models on standard methods applicable to every review.

Systematic reviews and meta-analyses contribute significantly to bridging the evidence-practice gap (32), but this benefit is limited due to the lack of uptake and time taken to incorporate new evidence. The time from the date of the last search to systematic review publication is at least a year (33), with the average time taken for primary study results to be incorporated into a published SR ranging from 2.5 to 6.5 years (34), and only a minority of published systematic reviews are updated within 2 years of publication (35). This inability to maintain the up-to-date information can result in significant inaccuracies in practice, as new evidence can substantively change conclusions about the effectiveness or harms of treatments (36).

Make your results available in a usable format for systematic review authors

Accelerated systematic reviews have been implemented to target this gap. Accelerated systematic reviews includes the development of Systematic Review Automation tools to expedite the process of conducting a systematic review. These reviews have limitations, however, and policymakers should rely on full systematic reviews unless there is an immediate requirement for evidence (37, 38).

Recommendations and clinical practice guidelines

As with systematic reviews and meta-analyses, well conducted trials will be eligible for inclusion in guideline development. Clinical practice guidelines and recommendations are often the result of professional medical group expert panels and conferences that attempt to synthesise practical guidance on the best standard of care based on evidence derived from research, namely RCTs. The National Health and Medical Research Council (NHMRC) has specific requirements for development of guidelines, including assessing the body of evidence using GRADE criteria (8, 39-56).

The National Health and Medical Research Council has published the *Guidelines for Guidelines Handbook* which contains comprehensive information on the development and review of clinical guidelines (8)

As yet, the NHMRC guidance does not include information on updating guidelines (8). Regular review and updates are critical to ensure new evidence is incorporated into guidelines to ensure they are kept up-to-date and relevant. Guidelines should be updated where there are (56):

1. Changes in evidence on the existing benefits and harms of interventions
2. Changes in outcomes considered important
3. Changes in available interventions
4. Changes in evidence that current practice is optimal
5. Changes in values placed on outcomes
6. Changes in resources available for health care

Routine surveillance can be used to ensure guidelines remain current. NICE conducts standard checks every five years, although this frequency may need to be increased where changes are rapid. The NHMRC also regularly reviews and updates guidelines. Rescinded guidelines are archived on the Australian Government web archive. Triallists can also assist in ensuring guidelines are kept up to date through engagement with policymakers.

Consider proactively contacting authors of systematic reviews and guidelines in the field to alert them about completion of your trial

One approach to keep guidelines up-to-date, is to use a 'living guidelines approach', which involves a systematic and continuous approach prioritisation and update (58).

Given differences in health care systems, regulatory and reimbursement environments between jurisdictions, it is important that Australian guidelines are developed and maintained. Standardisation of guideline development should be a priority so that recommendations can be made on the basis of the strength of evidence (or in some cases, the lack of such evidence). Tensions will also exist between the different groups using the guidelines or benefiting from them: surgeons may require something different to specialists and practitioners, who may again require guidelines different to those of the patients, consumers, and other end users. Further, rigorous guidelines, such as those produced by the NHMRC must be used to ensure transparency in reporting and evaluation against standard quality criteria. Ideally guidelines should be endorsed by independent agencies such as the NHMRC. This should address anu concerns around the involvement of industry (59, 60), generalisability, and lack of transparency (61-65), which have been issues in the past.

It might be that the approach to evidence synthesis and moving health research towards practice and policy changes may require some revaluation. This requires the development of multidisciplinary and multiple stakeholder communities,

such as researchers, health professionals, guideline developers, policymakers, and patients, and the encouragement of them all to commit to working together to effect practice and policy change from evidence-based medicine. Importantly, guideline development must be based on robust methods, with all key stakeholders being present and engaged in the approach. This will also require making living evidence synthesis the norm so that clinical decision-making is based on current evidence (66-68).

UNDERSTANDING CURRENT PRACTICE

Trialists may not be in a position to conduct implementation activities directly but should identify and engage with others who may be in a position to do so.

What are the barriers and enablers to changing practice?

Dissemination: Understanding who your stakeholders and end-users are

Identification of the stakeholders and end-users involved in or impacted by your trial, is an important first step. As mentioned earlier in this guidance document, clinical trials have different end users who are an integral part of the trial team (9). Consultation with all stakeholders, including the clinicians, researchers, policymakers and patients, throughout the clinical trial phases enables researchers and triallists to develop a better understanding of what is important to the stakeholders, which if adhered to, ensures their engagement and continued support and assistance with trial success.

The divide between clinical research and clinical practice

There are a number of factors noted that contribute to the divide between clinical research and clinical practice including:

a. Community practitioners not being actively engaged in clinical research resulting contributes to a lack of knowledge of drug development and use in various conditions, reduction in physician referrals of patients to clinical studies as well as the number of investigators available to conduct research.
b. Conduct of clinical research in academic medical centres means that implementation to community centres can require added resources due to absence of trained staff and lack of embedding of trial outcomes and processes to standard care. Furthermore, physicians are less engaged if not actively participating in clinical research. In order to create a health care system capable of improvement and self-evaluation, systems of clinical research and practice must come together (69).
c. In trials, the characteristics of the study participants, their comorbidities and therapeutic regimens, and the setting and conditions in which the trial is conducted, often bear little resemblance to typical community practice and their patient population.
d. This often means that the outcomes in community practice are very different to what are seen in the clinical trial.

Barriers to implementation

There are many barriers to implementation, not the least the distinction between clinical research and community practice. However, a number of other barriers have been identified including barriers within the health system, lack of clarity, lack of credibility in the evidence, difficulties finding and assessing, interpreting and applying current best evidence (70, 71). These barriers can largely be overcome by seeking the advice of implementation specialists.

Enablers of implementation

To derive maximum benefit from research, it is critical to bring together evidence from stakeholders, research, practice, data and evidence from implementation.

A **Learning Health System** framework can be useful for implementation of research into practice (72, 73). Learning Health Systems are defined as systems where 'science, informatics, incentives, and culture are aligned for continuous improvement and innovation, with best practices seamlessly embedded in the delivery process and new knowledge captured as an integral by-product of the delivery experience' (74). Such systems embed data driven research into health care systems (75). Learning Health Systems are based around four pillars (75):

1. People
2. Culture
3. Standards
4. Resources and infrastructure

These four pillars are underpinned by evidence from stakeholders, research, data and implementation. As the Monash report states, '*each is essential to capture, identify and address health service and community priorities and emergent challenges and need to be integrated to create the systems level intervention needed for a Learning Health System to deliver health impact' (75).*

Research evidence underpins Learning Health Systems

Learning Health Systems are capable of self-evaluation and improvement and accelerate both the development of interventions and the translation of research into practice that will improve patient outcomes and patient care.

Further information on Learning Health Systems can be found in the Monash University Report, *A Learning Health System: Learning together for better health* (75)

ACTIVE IMPLEMENTATION

The implementation drivers are the building blocks of infrastructure needed to support practice and can include effective staffing with required skills, training, coaching, facilitative administration, and organisational systems. Implementation teams facilitate implementation by providing internal support structure through the various implementation stages. These teams help by increasing 'buy-in' and readiness, installing and sustaining the implementation infrastructure, assessing fidelity and outcomes, building linkages with external systems and problem-solving. Finally, connecting practice to policy is the ultimate, key aspect to successful implementation.

A number of frameworks used in implementation research have been proposed and are summarised in the table below.

Framework	Description
Promoting Action on Research Implementation in Health Services (PARiHS) (76)	The PARiHS framework provides an interpretive viewpoint on theory development and application, comprised of a three-dimensional framework that measures elements of successful implementation on a continuum of 'high' to 'low' context and evidence.
Quality Implementation Framework (77)	The QIF outlines the implementation process, including 14 steps that are spread across four different phases. The framework raises questions and actions that should be considered at each step to ensure quality implementation and can be applied across various disciplines.
Consolidated Framework for Implementation Research (CFIR) (78)	CFIR is an integration of theories and frameworks, important and effective in implementation research and implementation and translation. Domains include effective interventions from trials, the processes required to adapt them for implementation in a given setting and population, the outer context or policies / drivers, inner context within an organisational.
Equity-based framework for Implementation Research (EquIR) (79)	Equity-centred implementation outcomes, intended to measure outcome differential between advantaged and disadvantaged communities. Factors, including appropriateness, acceptability, feasibility or coverage, could be different for disadvantaged individuals in comparison with advantaged individuals. The role of EquIR serves to minimise current health inequalities, rather than enlarging current ones, or at the very least, reducing any adverse impacts of health inequalities with the implementation of new interventions.

Framework	Description
Active Implementation Frameworks (AIFs) (80)	Are a set of evidence-based frameworks developed following a systematic review and synthesis of the implementation evaluation literature (80). The AIFs outline suggested mechanisms and strategies to use when attempting to put into practice any intervention and consider the "formula for success." The "formula for success" proposes that desired health outcomes are a result of multiplying an effective innovation (what needs to be done), effective implementation (how it will be done and by whom) and enabling contexts (where it will thrive).

ECONOMIC EVALUATION

Health economics must be considered for the implementation of all trials

Finally, health economics must be considered for the implementation of all trials. Economic evaluation can inform whether strategies designed to improve the quality of health care delivery and the uptake of evidence-based practices represent a cost-effective use of limited resources. Economic evaluations are often carried out 'ex-post' or 'after the fact', using empirical methods applied to cost and outcome data extracted from trials or other research designs used to evaluate initiatives being tested in specific populations and settings. Economic evaluations can also be applied 'ex-ante'—to inform option appraisal and pre-implementation decision-making using available evidence and modelling to simulate the expected costs and outcomes of the intervention and its alternatives, for example, in relation to population scale up or geographical spread of strategies and methods for improvement and evidence uptake (84). Bringing evidence into routine practice is a fundamental aim of implementation science, and numerous programmes and strategies have evolved to affect the uptake of health care delivery, including education, financial incentives, feedback and regulation (85).

Uptake of implementation changes has been associated with significant reductions in patient readmission rates (86), increased survival (87), increased patient quality of life (88), and in reducing risk factors (89). Implementation-related change was also linked with improvements in understanding, skills and knowledge to embed a desire for change at a group level (90). Effectively implemented changes are associated with increased cost-effectiveness and improved staff and patient outcomes, although even with a sound theoretical framework, few interventions are successfully implemented (91), and even fewer are sustainable long-term (92). Ramifications of failed implementation of effective interventions can often be costly and significant, as staff can be burdened by additional workload required by the intervention, leading to potential disruption of workflow, inefficient use of resources and a reduction in the quality of patient outcomes (93). Greater understanding of the barriers involved with implementation is important in contributing to a change-process that is sustainable, smooth and cost-effective.

Types of Economic Evaluation:

Type	Definition
Cost-minimisation analysis	Costs of two or more interventions are measured where the outcome is identical. This method can only be used when all intervention outcomes are the same.
Cost-effectiveness analysis	This method is used to measure cost against the effectiveness of the intervention.
Cost-utility analysis	The cost of the intervention is compared against the "utility" related to health. Outcome measures of this method are Quality Adjusted Life Years (QALYs) or Disability Adjusted Life Years (DALYs).
Cost-benefit analysis	A comparison is made between the cost of the intervention and the benefit incurred. Costs and benefit are measured in monetary terms.

Further explanations of the types of economic evaluations

1. **NICE (94)**
2. **Sanders et al. 2016 (95)**
3. **Hoomans & Severens (2014) (96)**

CONCLUSION

Following completion of a clinical trial, trialists undergo a range of activities to work towards translating their evidence into practice. The information reiterated in this document provides information on supporting trialists in contributing to systematic reviews and guidelines, and outlines the practical considerations necessary for trialists when evaluating whether their trial results can be successfully implemented into policy or practice.

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