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Better health through best evidence

'Implementability': How to plan, design, conduct and report clinical trials optimised for value to end-users

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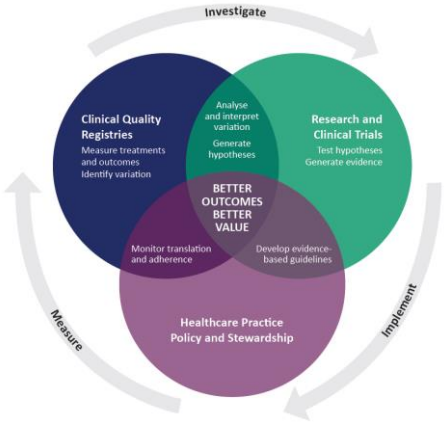
Board Sponsor, ACTA Impact and Implementation Reference Group

ACTA gratefully acknowledges operational funding from the Australian Government's Medical Research Future Fund

A Learning Healthcare System



Fundamental principles

1. High quality healthcare is critical to patients and saves money
2. High quality care (value-based healthcare) is evidence-based
3. Best evidence is derived from randomised clinical trials (RCTs)

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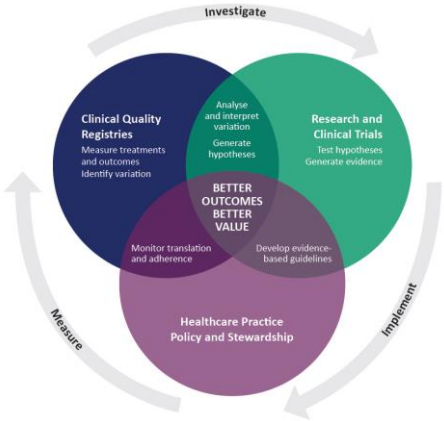

The role of RCTs is to test interventions to prove/disprove a hypothesis

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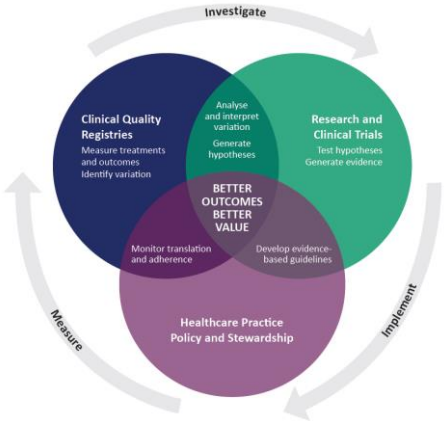

RCTs are critical to transitioning from opinion-based care to evidence-based care

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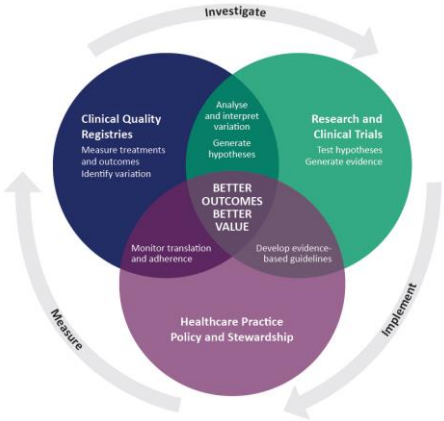

But, RCTs are necessary but not sufficient.

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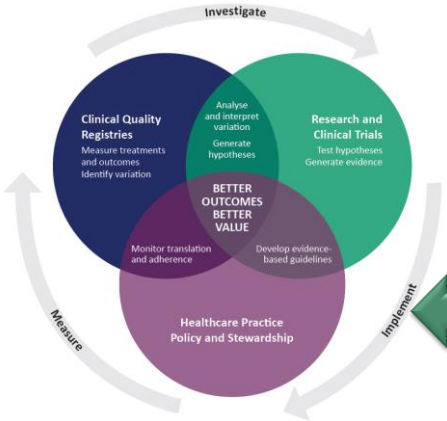

Evidence generated by trials needs to be implemented into practice and policy to have impact

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ACTA Impact and Implementation Reference Group

ACTA Guidelines for Designing Trials Optimised for Implementation

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Clinical Trial Phases

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 endpoints.

Implementation into practice and policy is generally not appropriate for early phase clinical trials.

Clinical Trial Phases

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 information to **end-users** to inform decisions about whether the candidate intervention should be adopted into practice or policy, should the results prove definitive.

For interventions that are a drug or device, late phase trials may occur before or after the new drug or device is registered.

Implementation

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.

Appropriate Implementation

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.

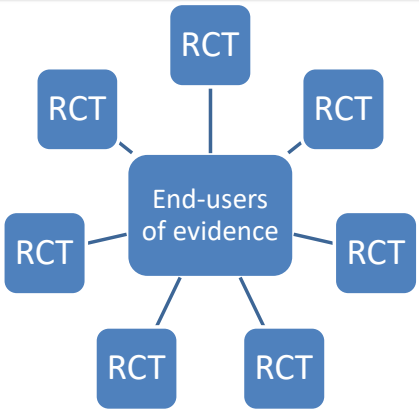
This decision should consider the balance of likely benefits and harms, applicability of the evidence to the relevant context, acceptability of the intervention, resources available, feasibility of implementation, and other considerations such as equity.

Implementability

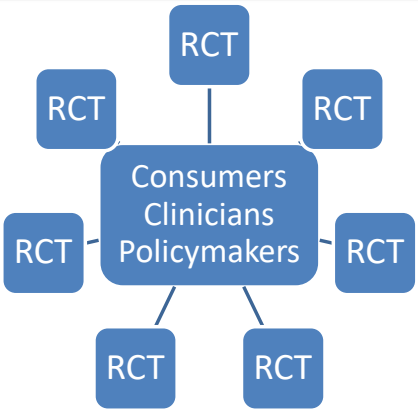
Implementability: Characteristics of the design, execution and reporting of a clinical trial, typically a late phase trial, that determine the capacity for the evidence generated by that clinical trial to be used for implementation.

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.

End-users



End-users



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ACTA Guide to Optimisation of Implementability

Objective is to provide guidance on the planning, design and conduct, and reporting of clinical trials so that the results of 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).

Intended to apply to late-phase clinical trials.

A guidance document, with selected examples, and a check list.

Make trials that are useful to consumers, clinicians, and policymakers

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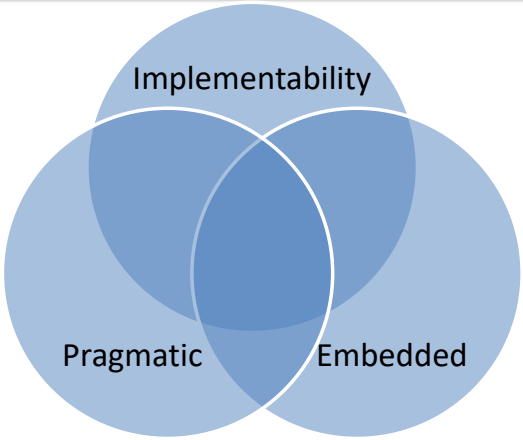
Implementability, Pragmatic Designs, Embedded Designs



Optimising Implementability

Planning Phase

Design and Conduct Phase

Reporting Phase

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Optimising Implementability

Planning Phase

Consultation or co-design with end-users

Define context for the trial

Composition of the trial team

Demonstration of feasibility of delivery of the intervention

Protocol section related to implementability

Consultation or co-design with end-users

1. Define the end-users

   Which end-users are critical to implementation?

   Different end-users have different preferences, perspectives, and values

2. Understand the evidence needs and requirements of end-users

   Relevance of question to practice and policy

   Choice of comparator

   Methods for delivery of intervention

   Choice of end-points

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Consultation or co-design with end-users

3. Minimum clinically significant difference

   Particularly where a conclusion of 'no difference' is intended to influence practice or policy / non-inferiority designs

4. Trial entry criteria can be applied by end-users

   Ensure easy identification of the target population in practice

Context- what is current baseline practice or policy

- Implementation always occurs in the context of current practice
- Is trial intervention part of current standard care? If so, in what proportion of patients?
- What are the alternatives? Is the proposed comparator valid?
- A de-implementation trial of a widely implemented, but unproven, intervention should only occur if there is suspected harm or known burden
- Surveys, focus groups, observational studies

Can complex interventions be delivered in a trial?

Pilot studies of feasibility

If a complex intervention can't be delivered in a trial, probably can't be delivered in practice

Composition of trial team

Consumer membership

Clinician and policymaker membership

Health economics

Implementation science

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Consideration of implementation in trial protocol

Designation as a late phase trial, intended to have capacity to influence practice or policy

Explicit identification of the end-users, results from consultation or co-design

Intended population to which results are applicable (and burden of disease)

Pre-specification of how different results should influence implementation

Enablers and barriers to implementation (or de-implementation)

Plans for contribution to evidence synthesis and measurement of implementation

Optimising Implementability

Design and Conduct Phase

Population to which trial results apply

Characteristics of implementability of the intervention being tested

Concomitant care

Outcome measures

Population context information

Process evaluation and fidelity

Health economics

Population to which trial results apply

1. Trial site characteristics and generalisability
2. Relationship of trial entry criteria and target population

   Narrow populations may enhance likelihood of 'positive trial' but limit implementability

   If suspected differential treatment effect, consider stratification
3. Screening and recruitment

   Pragmatic and / or embedded enhances implementability

Delivery of trial intervention

1. Want to know if intervention works under 'real-world' conditions
2. Interventions should be delivered in the same way in trial as intended to occur in practice

   Train clinical staff, avoid research staff delivering the intervention

   Processes to enhance adherence or compliance should be those that occur in practice

   Adjustment or titration of intervention should be those that are feasible in practice

Choice of comparator

1. Comparator should be clinically meaningful
2. What if there is marked variation within current standard care

   Choose most common variant as compactor

   Allow clinician to do what they would normally do
3. Blinding and placebo

   Can be critical for implementation (especially de-implementation)

   But not always necessary and placebo is not a treatment option in actual practice

Health Economics

Often critical to decision-making regarding implementability

Requires planning and incorporation of appropriate data collection at design phase

Needs a health economist

Further design and conduct features

Population context information

Where possible, a trial should report information on eligible but non-randomised patients, i.e. nesting within registry

Process and fidelity evaluation

For complex interventions, process evaluation using mixed methods to understand factors associated with fidelity of delivery

Optimising Implementability

Trial Reporting Phase

Commitment to complete and timely reporting

Sufficient information to guide delivery of the intervention

Data sharing

Accessibility of trial results

Declaration of interests

Commitment to timely and compete reporting

A trial that is not reported has no capacity to influence implementation

Particularly important for trials that failed to recruit or deliver an intervention

Report as per CONSORT or its variants

Published SAP prior to database lock

Sufficient information to deliver intervention in practice

Particularly for complex intervention, if intervention not described can't be implemented

TIDIER checklist

Availability of study tools and training material

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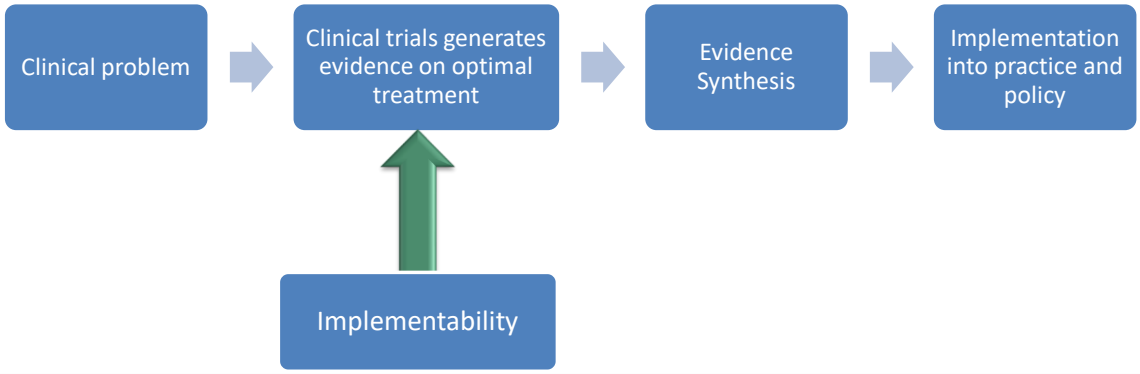
Other aspects of reporting

Data sharing

- Respond to requests to assist evidence synthesis
- IPDMA

Accessibility of results to end-users

Declaration of interests



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Impact

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

Impact maximised by optimising implementability

"in order to be useful, clinical research should be true, but this is not sufficient"
Michael Ioannidis