Clinical Trials: A Resource for Australian Clinicians

A brief introduction to clinical trials in the Australian context, with practical information on how to help your patients on their clinical trial journey.

Research4Me®

Clinical Trials: A Resource for Australian Clinicians

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The Purpose of this Resource

Clinical trials are an integral part of the research and development of new treatments, interventions or tests, and the refinement of existing standards of care and clinical practices. As such they are vital to the future of healthcare. [1]

No-one should expect you to know all the clinical trials currently available. That is impossible. However, understanding the relationship between clinical trials and clinical practice, considering clinical trials a potential care option, and learning how to support patients who may wish to find, evaluate and participate in clinical trials can only add value to the care you provide patients and their families.

Clinical trials are an essential part of the development of new interventions and tests that will help your patients and may alleviate the symptoms of their disease or condition.[2] They are worth discussing with your patients.

The purpose of this guide is to give you a brief introduction to clinical trials, their context in Australia, and resources you can refer to in the event clinical trials are an option you and your patient might like to pursue. It's only a starting point, from which you can investigate further.

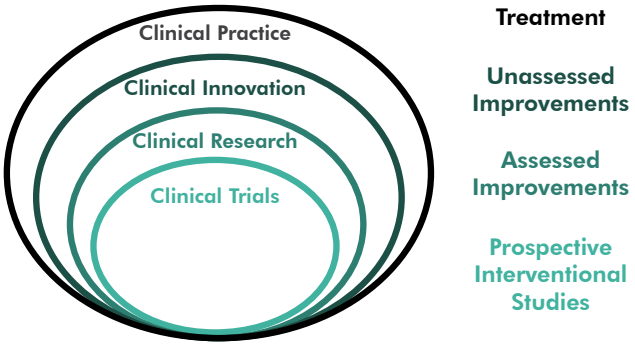
Clinical Trial Basics

What is Clinical Research, Clinical Trials?

Clinical research increasingly involves a range of different health professionals studying a wide range of matters, including disease prevention and causation, diagnostic methods, treatments, and effects of and response to illness. Such research can occur in a number of settings, including public and private hospitals and clinics, other institutions or organisations, community settings, and general or specialist medical practices.[2]

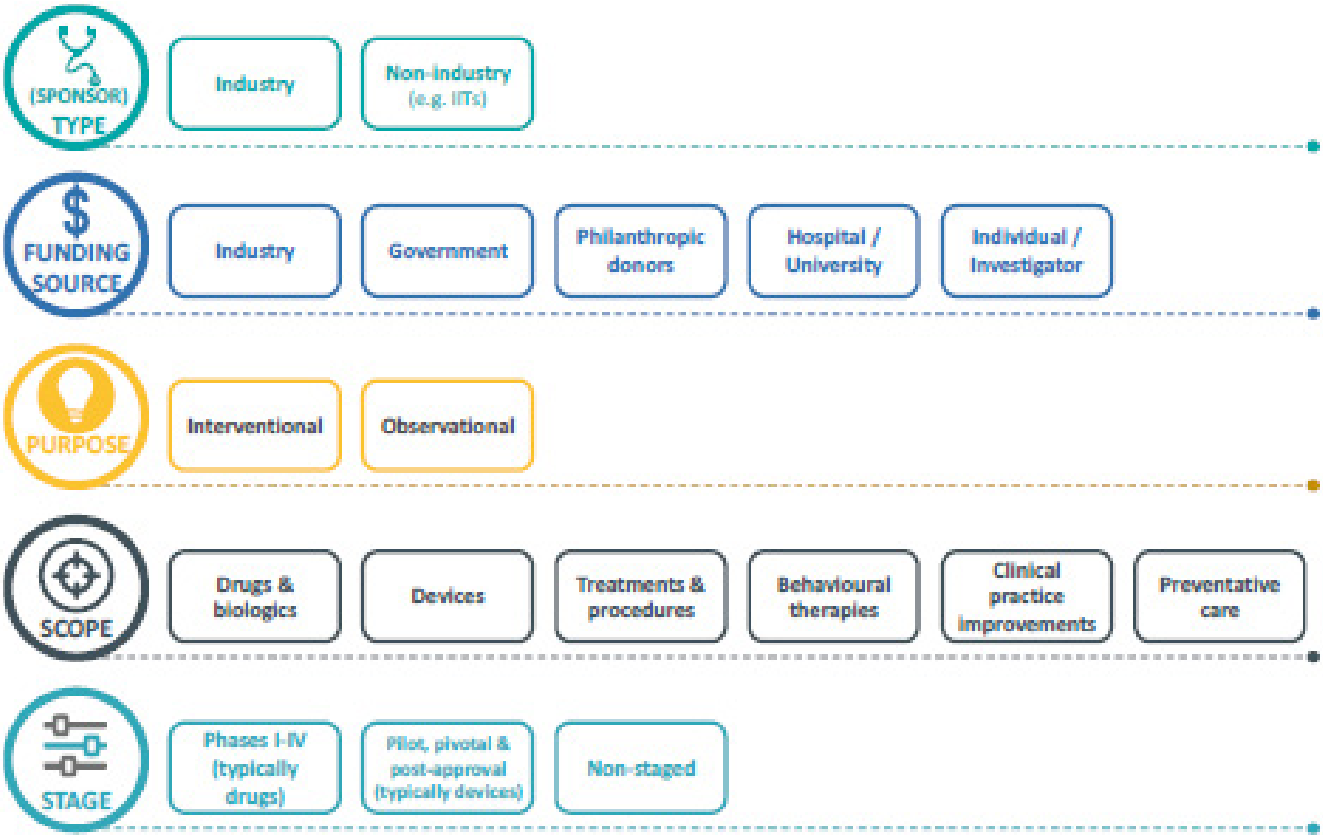
Clinical trials are just a subset of the type of activity that can lead to improvement in clinical practice, but are widely believed to provide a high level of evidence.

The World Health Organization (WHO) definition for a clinical trial is 'any research study that prospectively assigns human participants or groups of humans to one or more health-related interventions to evaluate the effects on health outcomes'.[4]



Clinical trial interventions[4] include but are not restricted to:	
experimental drugs	surgical procedures
cells and other biological products	psychotherapeutic and behavioural therapies
vaccines	health service changes
medical devices	preventive care strategies
medical treatments and procedures	educational interventions

There are also many different ways to segment clinical trials:[1]



Phases of Clinical Trials

Clinical trials of medicines and biologicals typically proceed through 'phases' of development whereas clinical trials of medical devices are more appropriately represented by 'stages' (see Appendices).[3] For other types of clinical trials not involving medicines and devices, the phase/stage terminology is generally not used.

It should be noted that clinical development pathways are becoming less rigid with respect to phase and that seamless adaptive trial designs and other cross-phase studies exist (for example, Phase Ib-II and Phase IIb-III).[3]

Benefits & Risks of Clinical Trials

Clinical trials generate a range of flow-on benefits including early access to improved treatment in Australia, for trial participation, and increase in the number of quality-adjusted life years across subsets of the population that participate in trials.[1]

Depending on the trial, participant benefits may include:

- access to leading clinician researchers;
- extra care and attention monitoring their health and progress;
- trial appointments, extra tests and researched treatments that are usually free;
- reimbursement of travel costs to attend the trial site;
- potential access to treatments not yet available or covered by Medicare;
- more active awareness of their own health, which can reap its own benefits.

More broadly, there is some evidence patients attending hospitals which are more research-active may demonstrate superior health outcome. These observations can be traced back to the training of staff and incorporation of new evidence into wider clinical practice.[1]

As a doctor, the benefit to you of clinical trials is that they provide additional options you might be able to offer to your patients. They also provide the evidence for you to be confident about the care you are providing to your patients.

Clinical trials may potentially carry risks that you should work through with your patients. These should be outlined in the participant information sheet trial staff will provide.

Two of the risks many patients fear is getting placebo, or not the 'new' treatment. If a placebo is involved, it usually means no additional care above what is standard treatment. A placebo arm will usually only be approved if there is no agreed proven treatment that works for that condition, as it is unethical to withhold treatment otherwise. Not getting the new treatment is also OK, because, clinical trials are only done if there is clinical equipoise – i.e. there really is a question about which treatment is better. It is unethical to run a trial if it is already proven that one treatment is better than the other. While there might be hope the new treatment is better, about 50% of the time it is not. Not getting the 'new treatment' isn't necessarily a disadvantage.

Fast Facts about Clinical Trials in Australia

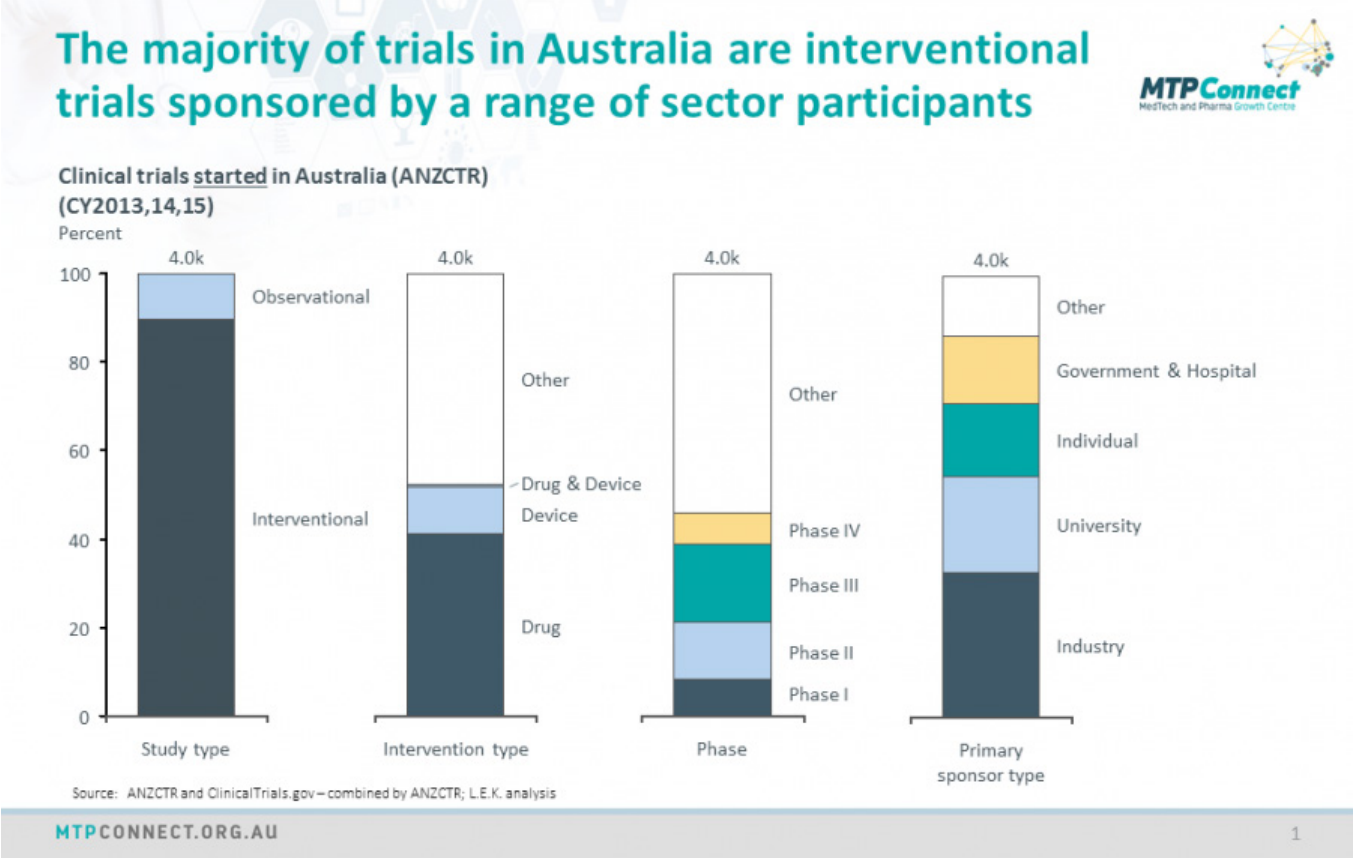
In 2015, 1360 clinical trials started in Australia. Between 2012 and 2015, the number of clinical trials grew by 2% pa, with trials involving a device growing 10% year on year. [1]

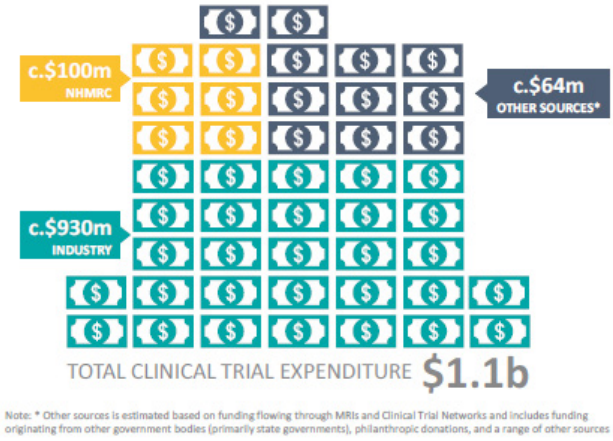
Australia also plays a role in international clinical trials. 31% of the trials being run in Australia are also being conducted outside of Australia.[1]

The conduct of clinical trials in Australia involves a number of key sector participants with different roles. These include MedTech and Pharmaceutical (MTP) companies, services providers such as Contract Research Organisations (CROs), and clinical research affiliated organisations such as Medical Research Institutes (MRIs), public and private hospitals, universities, private clinical trial sites, clinical trials networks and GP networks.[1]

While there is a common belief that most clinical trials are run to benefit the pharmaceutical and medical technology/device sectors, actually only around a third of the clinical trials in Australia are sponsored by industry. [1]

Only about half the clinical trials run in Australia involve drugs and/or devices.[1]





According to a 2011 report, the annual spend on clinical trials at that time was $1.1billion, with the majority of that expenditure coming from industry. [1]

Australia is regarded as world leader in the design and conduct of high impact investigator-initiated (non-commercial) 'public good' clinical trials. There are some 37+ clinical trial networks in Australia covering a range of clinical disciplines and disease groups incorporating upwards of 10,000 clinical researchers. [5]

A recent evaluation found considerable economic value if the results of a number of trials conducted by trial networks were implemented in 65% of the eligible patient population (see Appendix). [6]

What You & Your Patient Can Expect On the Clinical Trial Journey

There are a number of steps involved in starting and completing a clinical trial.

1. Finding the trial

Patients may hear about trials from many places including their doctor, family and friends, internet searches, advertising, patient support groups or search on clinical trial registers. A patient does not generally require referral into a clinical trial, though referrals from doctors are most welcome. Despite not needing a referral, patients are encouraged to involve and inform their doctors if they are interested in a clinical trial. This is so the trial doctors can (with the patient's permission) contact you if needing to check a patient's medical history, medications, etc., and keep you updated and informed about the patient's progress.

By being proactive and supportive of your patient's interest in a clinical trial, you can actually help them evaluate the suitability of a trial for their circumstances, and be a partner in keeping them safe during the trial.

2. Getting into the trial

Once a person has contacted the doctor or clinic running the clinical trial (called the trial investigator/ clinical trial site), some initial questions will be asked to see if they could be suitable for the trial. If it looks promising, the trial site will provide them with detailed information which outlines the reason for the research, what is involved, the risks/benefits/alternatives to participation, how their data and privacy will be protected and other administrative information. Increasingly, written information may be supplemented or replaced by electronic participant information and consent portals. In some cases, language support may be available in the form of translated materials or an interpreter. If your patient likely needs this, they should ask whether this support is available for this trial.

If you are helping your patients review the participant information sheet, check that the contact details for the investigator and human research ethics committee (HREC) that has approved the conduct of the study are indicated. Contact either party should you have any questions about the study. HREC approval is mandatory for every clinical trial in Australia, and the absence of information about the HREC might indicate the study has inappropriate oversight and approval. Another red flag to look for is if the patient is being asked to pay for the treatment being researched. This would be very rare, and should be checked with the HREC. The NHMRC provides a list of registered and accredited HRECs should you have any concerns about the authenticity of an HREC.

If the person consents to a trial, they will most likely undergo some screening tests to confirm their eligibility before starting the trial. This is both to make sure the trial has a population with similar characteristics, and that the trial will be safe for the person to participate in. All clinical trials have a set of inclusion and exclusion criteria that must be checked for all trial participants.

Once a person is found to be eligible, their participation in the trial will start. The patient information sheet will outline what will be required from the person participating in terms of visits, procedures, what they need to do between visits, etc. As a doctor, you can help your patient to remain compliant with the trial's requirements, both for their own safety, as well as for the integrity of the research.

3. Completing a trial

At the end of the trial, patients will usually end the intervention being tested and may undergo some final safety checks. If it is a trial of a new medicine not yet approved, depending on the phase of the trial, your patient may be offered access to the new medicine post-trial if it looked like it was beneficial to the participant. The participant information sheet should outline what the options are once the trial has ended.

At some point after the end of the trial, the participant may be provided with information on the intervention they were receiving (if a blinded trial), and a summary of the trial results. Given results can take a while to analyse and report (a year or more after all the participant in the trial have finished is not uncommon), sometimes sites may forget to contact the former participants or lose their contact details. If your patient hasn't heard anything after about a year post finishing the trial, they should be encouraged to follow up with the trial investigator for this information. It is also important for you to find out from your patient the treatment they received in a trial. For example, if the trial was for a new drug that later goes on to be approved, knowing whether or not your patient received and responded to it during the trial will inform your decision to prescribe it to the patient post its approval.

Additional Resources

Useful websites

The following sites can support you with additional information and resources relating to clinical trials that may help you, and your patients.

AustralianClinicalTrials.gov.au

This website is the Australian government's centralised portal of information for consumers, industry, researchers, and healthcare providers on clinical trials. Specific areas of the website you might find helpful include:

- Searching for a clinical trial – This is where you and your patients can go to look for clinical trials. This pulls data from the ANZ Clinical Trials Register (ANZCTR). The ANZCTR presents trial submitted directly to ANZCTR, and trials pulled from the US clinical trials register indicating an Australian site. ANZCTR estimates it holds information on 75-80% of clinical trials in Australia. It does not have 100% coverage because trial registration is not mandatory in Australia, though usually required by many journal editors and funders, and human research ethics committees. As a tip, anyone can set up alerts to be notified when new trials of all or specific conditions are registered.

- For Consumers – The basics about clinical trials in lay language

- For healthcare professionals – This section includes information on:
    - Why talk to your patients about clinical trials?
    - How to talk to your patients about clinical trials
    - How to refer your patient for a clinical trial
    - Useful links to government agencies, useful clinical trial resources and guidances, human research resources and ethics guidelines

- The NHMRC has produced some e-learning models that cover the clinical trials environment in Australia, ethics isues, and governance issues related to clinical trials.

- Real Stories: patients, participants, researchers, industry personnel and more share their stories

- Further Resources – include links to trial registries, patient support groups, a toolkit for those running trials and more.

The Consumers Health Forum of Australia (CHF)

CHF is the national peak body representing the interests of Australian healthcare consumers. Useful information on their website includes:

- CHF Clinical Trials FactSheet: CHF released a factsheet for consumers providing information on clinical trials.

- Blog post: Clinical trials: myth and reality

The TGA

The TGA is Australia's regulatory authority for therapeutic goods.

Among other things, the TGA regulate the use of therapeutic goods in Australia (see: https://www.tga.gov.au/how-therapeutic-goods-are-regulated-australia), which includes those supplied in clinical trials (see: https://www.tga.gov.au/clinical-trials).

The Australian clinical trial handbook provides guidance on the legislative, regulatory and good clinical practice (GCP) requirements when conducting clinical trials in Australia using 'unapproved' therapeutic goods.

The Clinical Trial Notification (CTN) and Clinical Trial Exemption (CTX) schemes provide for the importation into and/or supply in Australia of 'unapproved' therapeutic goods for use in a clinical trial. Clinical trials that do not involve 'unapproved' therapeutic goods are not subject to requirements of these schemes. It is the responsibility of the Australian clinical trial sponsor to determine whether a product is considered an 'unapproved' therapeutic good.

The following guidelines are relevant to clinical trials conducted under the CTN and CTX schemes:

- ICH Guideline for Good Clinical Practice with TGA annotations
- The National Statement on Ethical Conduct in Human Research
- Note for guidance on clinical safety data management: definitions and standards for expedited reporting
- The NHMRC Guidance: Safety monitoring and reporting in clinical trials involving therapeutic goods

National Health and Medical Research Council (NHMRC)

The NHMRC is Australia's leading expert body promoting the development and maintenance of public and individual health standards. NHMRC brings together within a single national organisation the functions of research funding and development of advice.

NHMRC issues advice and guidelines on ethics and related issues in the fields of health, human research and animal research in Australia. The Primary guidance of relevance here is:

- The National Statement on Ethical Conduct in Human Research consists of a series of guidelines made in accordance with the National Health and Medical Research Council Act 1992.

This guidance is applicable to ALL health and medical research involving humans in Australia, not just clinical trials being conducted under the CTN/CTX scheme.

The NHMRC has played a role in efforts designed to improve clinical trials in Australia, as outlined here: https://www.nhmrc.gov.au/research-policy/clinical-trial-reform

Research4Me is a social enterprise looking to support the needs of the public for information and connection around clinical trials, and to make it easier for triallists to engage with the public to improve their trials.

Our Knowledge Centre provides answers to a lot of common questions about trials and our Publications page has a number of useful downloads, including a clinical trials jargon buster, acronyms guide, and questions to ask researchers before participating in a clinical trial. Our online and Facebook communities facilitate questions and discussion about research, and our Newsletter provides monthly updates on the trials starting in ANZ and more. Visit our Website for more information on how we support you and your patients around research. You might even like to join our referral program.

Clinic Posters

Sometimes patients need a hint that you are open for questions. The last appendix provides a choice of mini-posters you can freely print for your office in the event you would like to have a visual cue to patients that it is OK for them to ask you about clinical trials, and to remind you to consider whether clinical trials could be an option you might like to look into for your patients.

Clinical trials are not just for patients with serious or life-threatening conditions. By considering if there may be available clinical trials every time you go to recommend a course of care, or write a prescription, you can help advance the practice of medicine more quickly and potentially benefit the health of your patient.

References

The following references were last accessed 19 Sep 2019.

1. MTPConnect LEK Report Jun 2017: ' Clinical Trials in Australia: the economic profile and competitive position of the sector' - the first comprehensive overview of the entire clinical trials landscape in Australia.

2. The National Statement on Ethical Conduct in Human Research

3. Australian clinical trial handbook

4. https://www.australianclinicaltrials.gov.au/what-clinical-trial

5. Report on the Activities and Achievements of Clinical Trials Networks in Australia 2004-2014

6. Economic evaluation of investigator-initiated clinical trials conducted by networks

Acknowledgements

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- Behnaz Carney – Eli Lilly Australia
- Maria Mury – Member of the public
- Vicky Jones – Member of the public

In September 2019 hyperlinks that had changed were updated, along with the information available through Research4Me.

Contact

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Appendices

1. Summary of clinical trial phases for medicines and biologicals

Phase	Indicative number of participants	Objectives
Phase 0: Human pharmacology (micro-dosing)	10-15 Involves dosing a limited number of humans with a limited range of doses for a limited period of time	**Assess pharmacokinetics** Gather preliminary data on pharmacokinetics and bioavailability to determine if the drug behaves as expected from preclinical studies 'Micro-dosing' studies
Phase I: Human pharmacology	10-100 May involve the first administration to humans, usually to small numbers of healthy volunteers or to patients	**Safety and tolerance** Define or describe pharmacokinetics and pharmacodynamics Determine dosing Explore drug metabolism and drug interactions Identify preferred routes of administration Phase Ia: Single ascending dose Phase Ib: Multiple ascending dose
Phase II: Therapeutic exploratory	100-300 May be undertaken in a larger group of human patients (several hundred)	**Efficacy and safety** Phase IIa: Demonstrate clinical efficacy or biological activity through pilot studies Explore therapeutic dose range Phase IIb: Determine optimum therapeutic dose and regimen (with efficacy as primary endpoint) Resolve uncertainties regarding the design and conduct of subsequent trials
Phase III: Therapeutic confirmatory	300-3000 Usually involve a large group of patients (from several hundred to several thousand)	**Safety, efficacy or effectiveness** Phase IIIa: Determine the therapeutic effect in patient populations for which the drug is eventually intended Provide a definitive assessment of risk-benefit balance (to support drug registration or change in clinical practice) Phase IIIb: Increase patient exposure and support marketing claims or publication
Phase IV: Therapeutic use	1000's	**Post marketing surveillance or resolution of treatment uncertainties** Monitor safety in real world populations To refine knowledge of the risk-benefit balance, detect rare or long-term adverse effects, drug interactions Pharmacoeconomics to gather data in support of the use Comparative effectiveness and community based research (sometimes described as Phase V trials) Trial combinations with existing products

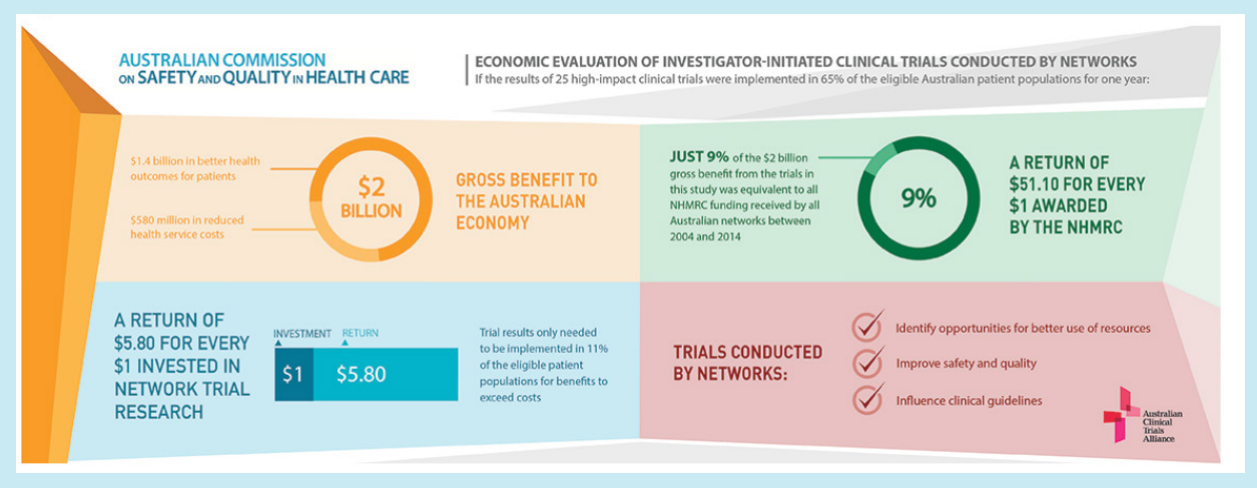
Source: Australian clinical trials

2. Summary of clinical trial stages for medical devices

Stage	Indicative number of participants	Objectives
Pre-market pilot	10-30 Usually involves a small group of human patients	Exploratory investigations to determine preliminary safety and performance information to plan design modifications or provide support for a future pivotal study. (Includes first in human and feasibility studies or proof of concept)
Pre-market pivotal	100's	Confirmatory investigations to evaluate performance and safety for a specified intended use to satisfy pre-market regulatory requirements
Post-market	1000's	Confirmatory investigations to establish performance and safety, for example, in broader populations OR Observational investigations or surveillance to gain better understanding of device safety, long-term outcomes, health economics

Source: Australian clinical trials handbook

3. Economic Impact of Trials Conducted by Networks



Source: Australian Clinical Trials Alliance

4. Clinic Posters

Feel free to print any of the following mini-posters for your office to remind yourself and your patients to consider clinical trials a possible care option.


I’m a doctor and a partner in your health.
Let’s have a conversation about clinical trials.
Research4Me


I’m a doctor and a partner
in your health.
Let’s have a conversation
about clinical trials.
Research4Me


I’m a doctor and a partner
in your health.
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