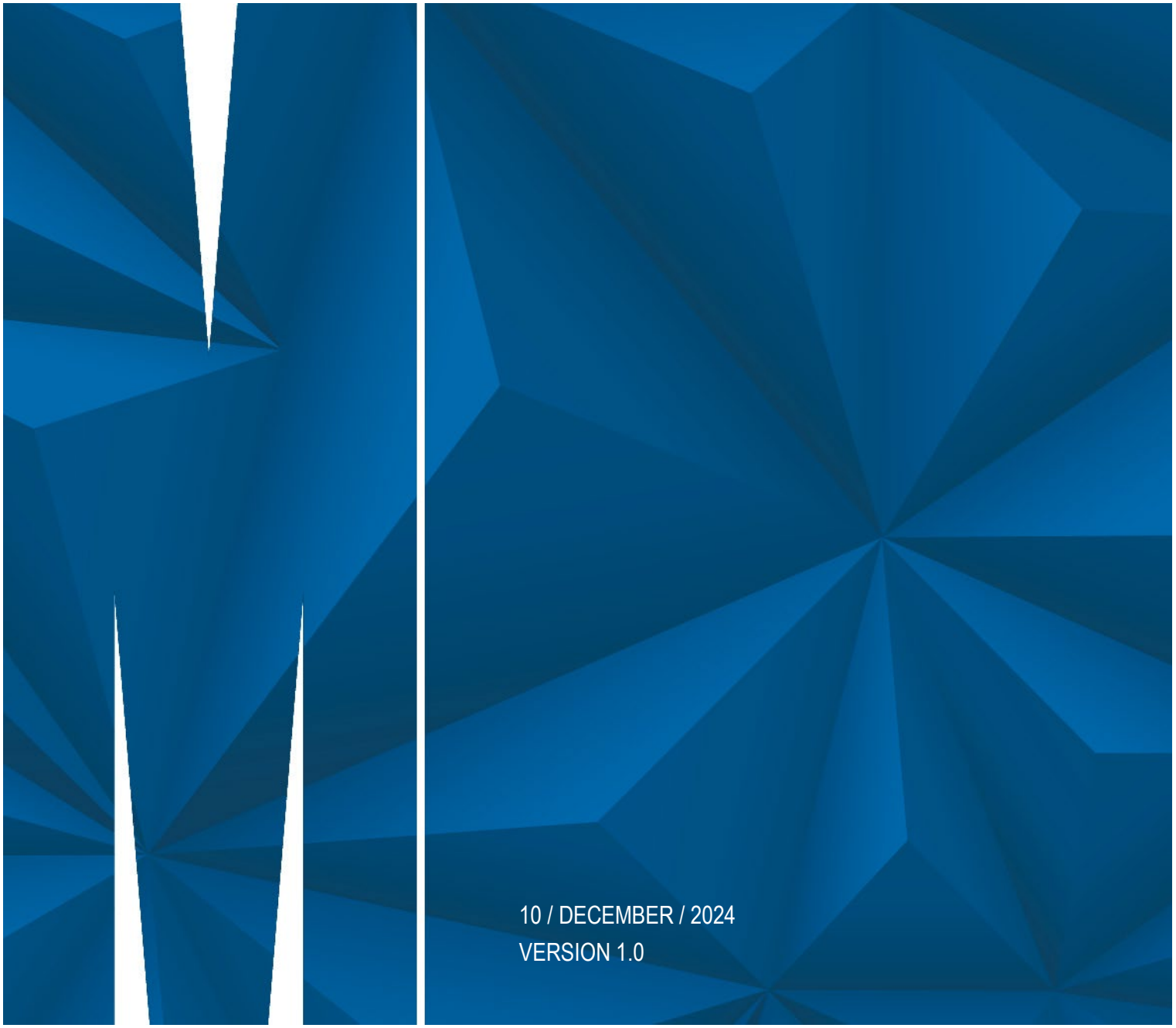
MONASH University

PUBLIC HEALTH AND PREVENTIVE MEDICINE

A GUIDE FOR REGISTRY-BASED TRIALS



10 / DECEMBER / 2024

VERSION 1.0

INTRODUCTION

This Guide for Registry-Based Trials provides guidance to researchers and clinical registry operators to support the design and conduct of registry-based trials in Australia. It may also be of interest to clinicians, consumers, health services, policy makers and other users and funders of health research as it provides context on registry-based trials in the wider research ecosystem. The Guide supports registry-based trials as a means of providing answers to important clinical research questions that will improve health outcomes for Australians through faster and more cost-effective methods and processes.

The modules that form the Guide are intended to support researchers aspiring to conduct registry-based trials by outlining aspects to consider and questions to ask. The Guide also provides some quotes as illustrative examples of issues and challenges and ways these have been addressed by other registry-based trials, as well as checklists and flowcharts to support implementation.

ABOUT THIS RESOURCE

This Guide has been developed by the School of Public Health and Preventive Medicine, Monash University, following an extensive scoping review of the literature, and consultation through a national stakeholder meeting and key informant interviews.

The authors (see Appendix) wish to thank all who provided their insights and experiences to support the development of this Guide.

This Guide was developed thanks to funding provided by the Australian Government Department of Health and Aged Care under the National Clinical Quality Registry Program.

PUBLIC CONSULTATION

Comments and feedback on this resource are welcome and can be sent to regtrialguide@monash.edu

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CONTENTS

PART 1 BACKGROUND

WHAT IS A REGISTRY-BASED TRIAL?

Registry-based (or registry-embedded) trials are prospective **interventional studies that use at least one clinical registry** to support the generation of evidence for effective clinical practice.

Such trials have gained prominence in the medical literature since 2010 when the study design and rationale of a randomised clinical trial that utilised the Swedish Angiography and Angioplasty Registry as a platform for the randomisation, case recording and follow-up of a comparative treatment trial, was published.[1] Since then, an increasing number of trials utilising clinical registries in some way for prospective intervention-based research (mostly out of Northern Europe and North America, and more recently from Australia) have been developed and reported.

As clinical registries are designed to both measure and change clinical practice and/or policy through the standardised collection, analysis and reporting of clinical (and other) data, the extension of this largely observational infrastructure to support clinical trials is feasible and a potentially efficient approach for some interventional studies.

Types of registry-based trials

Different types of registry-based trials have been described and are primarily defined by how the clinical registry is used to support the clinical trial. These include, but are not limited to:

- **Registry-based/registry-embedded/registry-nested trials** - trials that utilise the infrastructure and database of the registry for many or all elements of the trial.
- **Registry-linked trials** - trials that obtain a dataset from one or more registries (either planned as part of the design phase for the trial, or added post-trial to obtain longer-term follow-up data).
- **Registry-compared trials** - trials that compare their results/populations to a registry to determine compatibility/generalisability.
- **Registry-emulated trials** - trials that use data from a registry cohort to emulate or simulate a trial.

For the purposes of this Guide, we define a registry-based trial as a trial whereby:

- there is a priori involvement of a clinical registry as part of the trial planning;
- the trial is conceptualised to use a clinical registry as part of trial design;
- participants are prospectively assigned to one or more interventions;
- the intervention allocation is randomised.

A note about 'registries'

Variation in the use of the term 'registry/register' is common.

Administrative datasets (such as the National Death Index, Centrelink Electorate Data, Medicare Benefits Schedule data, Australian Immunisation Register, etc.) collate information primarily for administrative (not research) purposes. The Australian Institute of Health and Welfare has over 150 such datasets covering a range of fields.[2]

Clinical or patient registries are organised systems that use "*observational study methods to collect uniform data (clinical and other) to evaluate specified outcomes for a population defined by a particular disease, condition, or exposure, and that serves one or more stated scientific, clinical, or policy purposes*."[3 p.1] Many clinical registries become clinical quality registries as they mature.

Clinical quality registries are clinical registries that regularly provide feedback to participating sites and clinicians regarding performance against clinical quality indicators, with the aim of reducing variation and improving overall patient outcomes.[4]

A list of self-registered clinical and clinical quality registries can be found in the Australian Register of Clinical Registries maintained by the Australian Commission on Safety and Quality in Health Care.[5]

For this Guide, we are focussed upon trials that involve **clinical and/or clinical quality registries** (referred to in the Guide as 'clinical registries').

A note about other research uses of clinical registries

Clinical registries support a range of observational and interventional studies including, but not limited to:

- natural history studies;
- studies that measure clinical effectiveness and safety;
- studies of heterogeneous patient populations;
- surveillance for rare events/diseases;

- studies for treatments in which randomisation is unethical or not necessary;
- studies of health care access and barriers to care;
- evaluations of standard medical practice.[6]

Why the focus on registry-based trials?

The gold-standard approach to interventional research aimed at minimising bias and demonstrating cause and effect is a randomised controlled trial (RCT). However, reported limitations of traditional RCTs have included that they are not necessarily representative of real-world populations and circumstances, they can take too long to conduct, and that there are ever-increasing resourcing and funding needs.[7] As such, the sector is looking for more efficient methods given finite funding for trials.

Registry-based trials may offer opportunities and potential efficiencies over traditional RCTs such as:

- offering an alternative study type to answer research questions that may otherwise not be answered due to time / cost / rarity of events or conditions;
- matching of research with health care challenges affecting clinicians in their day-to-day practice;
- supporting access to trials for traditionally under-represented countries / ethnicities / diseases, etc.;
- supporting new uses of existing therapies;
- generating evidence of questions of treatment efficacy, noninferiority, and/or diagnostic accuracy;
- greater external validity (representativeness) of study populations to real-world populations;
- supporting (faster) adoption of evidence into practice.[8-13,27]

USES OF CLINICAL REGISTRIES FOR CLINICAL TRIALS

There are many ways that clinical registries can support interventional trials, including for:

- pre-trial testing of feasibility of the trial;
- participant/site identification;
- participant/site recruitment;
- participant screening;

and provision of:

- baseline data;
- intervention/exposure data;
- adverse event reporting;
- resource utilisation data;
- patient reported experience and outcome measurements (PROMs and PREMs);
- outcome data.

A registry-based trial utilises a number of these elements from the clinical registry to increase efficiencies in the conduct of a clinical trial. The more of these elements that may be used from the clinical registry, the greater the efficiencies that can be achieved.

The trial designs (e.g. 2-arm, 3+-arm, cluster, stepped-wedge, randomised, non-randomised, etc.) and the intervention types (e.g. procedural, surgical, drug, device, lifestyle, rehabilitation, screening, etc.) that can be evaluated using registry-based trials are diverse, but should first and foremost be appropriate for the research question.

The focus of this Guide will be on the elements of trial planning, design, conduct, analysis and reporting that are important when using a clinical registry for a trial; information related to trial design and methodology more generally is not included.

RESEARCH QUESTIONS FOR WHICH REGISTRY-BASED TRIALS ARE BEST SUITED

While registry-based trials have great potential, it should be noted that this trial type is not a one-size-fits-all response to the limitations of traditional RCTs or other interventional study types. Indeed, evidence generated by registry-based trials will need to sit alongside evidence generated by observational and other interventional study types to support the evidence-base for practice and/or policy.

Not all clinical registries will enable the embedding of trials, and not all interventions should be tested in this manner.[34] As such, the purpose of the clinical registry, the information available in it, the research question(s) to be answered, and the appropriateness of the study design to answer those

> *"[They] answer real world questions, … comparing one standard of care against another, … [so] you can determine if an expensive treatment is not as or more superior to a less expensive treatment."* Research Program Director

research questions are all important considerations as part of the planning of any trial.

Registry-based trials have been shown to be particularly suited for research questions:

- Evaluating comparative effectiveness of alternative **treatment strategies already used in clinical care** (e.g. when multiple standard-of-care options are available).
- Exploring **new signals and indications of approved interventions** i.e. therapies or devices (e.g. such as open-label assessment of commonly used therapeutic alternatives as part of post-marketing surveillance).
- **Testing non-pharmacological medical research interventions** (e.g. screening, organisation and coordination of care, etc.) where high-quality RCTs are usually not possible to perform.[9-12,14-17]

STRENGTHS OF REGISTRY-BASED TRIALS

Registry-based trials offer opportunities to researchers, registry custodians, consumers and clinicians to generate evidence in ways that maximise the strengths of traditional RCTs, while minimising the limitations.

When done well, registry-based trials offer opportunities for:

Efficiency in trial conduct

Registry-based trials can facilitate the efficient conduct of trials through supporting:

- identification of sites/participants;
- rapid recruitment of sites/participants;
- screening of participants;
- harnessing data of routine care with minimal interference with usual care;
- reduced duplicative (non-critical) data collection;
- broader data linkage (to other clinical registries or administrative datasets);
- reduced study duration;
- reduced requirements for monitoring, audits and follow-up visits;
- greater length of follow-up for participants;
- collection of patient-reported experience and outcome data;
- availability of historical data (including controls for single-arm studies);
- comparisons with reference populations.[8,10-12,15-16,18-22,25-34,37-38]

"… one of the big advantages is the data burden to the clinical research coordinators is drastically reduced; because we look at what is already collected in the … registry and we don't double collect it again in our clinical trial." Trial Project Manager

Cost-effectiveness in trial conduct

Registry-based trials that use the existing networks, infrastructure and personnel of clinical registries may offer a cost-effective approach to prospective interventional research. It should be noted that costs to alter ethics applications, capture any additional required data, to adjudicate endpoints and to clean and access existing clinical registry data must be considered.[8,10-12,14-16,21-22,24-25,28-29,32-37] However, as noted by Krause et al (2023), the trial cost savings that may be achieved with a registry-based trial design result from a reduction in the costs related to initiating and setting-up of a new data framework to identify trial participants, and/or ascertain trial baseline data and/or the outcomes of interest.[36] Further, Li et al (2016) note that any 'cost-saving advantage' of registry-based trials relies on the use of the clinical registry to identify participants, collect baseline and outcome data of interest to minimise infrastructure and training site staff and research coordinator costs, so in effect, some of the costs of the trial are indirectly transferred to the registry.[11]

Generalisability (external validity) of trial results

"… by putting RCTs [randomised controlled trials] into a registry situation where you're measuring day-to-day practice from many hospitals over many sites, you get generalisability. It is the best of both worlds. Housing RCTs within a registry was the ideal way of doing RCTs for many questions." Clinician Researcher

A key concern of the traditional RCT is the highly selective population group studied, and the highly controlled circumstances of the trial (including monitoring, follow-up, compliance and adherence) which may not be reflective of real-world populations, or real-world circumstances.[7]

As registry-based trials offer the opportunity to a broader range of participants, with data collection occurring during usual care practice, the participants and outcomes of registry-based trials are potentially more reflective of real-world situations.[8-12,14-16,21-22,24,26,28,29,32,34-36]

They may also facilitate the recruitment of more patients from culturally and linguistically diverse backgrounds, older participants, participants with rare conditions/events and participants with co-morbidities (among other groups) that tend to be less well represented in standard RCTs.[19]

RCT-level rigour

As with any clinical trial, the validity, reliability and relevance of the outcomes of registry-based trials are impacted by the scientific rigour applied in the planning, conduct, analysis and reporting of the trial. The methodologically rigorous design elements espoused by traditional RCTs (such as randomisation, blinding, end-point adjudication, etc.) can be applied to registry-based trials.[10,27] In this way, detection and performance bias can be reduced, and cause and effect relationships established.

Clinical relevance

There is an increasing appetite for real-world data to be used as part of the collective knowledge for evidence-based healthcare practice. Registry-based trials support this and in doing so provide evidence to understand both the effectiveness of the intervention and to support the future implementation of trial results into practice or policy. As such, one major strength of registry-based trials is that they have the potential to produce clinically informative results that are generalisable to daily clinical practice, and in doing so, also enable the evaluation of eventual implementation of trial results in clinical practice.[24,28,32,34]

Benefits to the clinical registry

The impact of the involvement of clinical registries in trials is also reported to have potential benefits to the clinical registry, including:

- increased awareness of the clinical registry by consumers and healthcare professionals;
- increased involvement in the clinical registry of healthcare sites;
- opportunities to enhance data collection procedures;
- opportunities to review and change data items collected.[22,33]

> *"So, if what we want to do is enhance the value of what a clinical quality registry is and these really valuable datasets and cohorts of those within it, [then] the registry nested trial is adding value to that."* Registry Custodian

LIMITATIONS OF REGISTRY-BASED TRIALS

No study design is without weakness. Many of the limitations of the registry-based trial design result from the pragmatic nature of the design of these trials. In many cases, the research question, study design and study endpoints may be impacted by the clinical registry features.[8,11,32] A key question to be considered is: does the data collected by the clinical registry answer the research question, and if not, can the trial collect additional or complementary data to the clinical registry to do so?

In particular, the literature identifies the following limitations of registry-based trials:

Availability of (an) appropriate clinical registry/ies

> *"I think the challenge is … flexibility … because if you're using the registry, you don't have the same flexibility that you have if you are using your own data collection form, where you can just make changes if you need. … in the registry, you cannot do [that]."* Clinician Researcher

A number of characteristics of the clinical registry can impact upon the validity, reliability and relevance of the outcome of a registry-based trial, including:

- registry size (including capture of population/events);
- data available from the registry;
- degree of delay in data entry for the registry;
- potential selection bias of the registry;
- sustainability of the registry;
- adaptability/flexibility of the registry.[10-11,24,29-30,33,38]

Clinical registry data quality

The most commonly reported limitations of registry-based trials are the quality of the data available from the clinical registry; reported to impact internal validity, reliability and completeness. This includes a range of factors such as:

- insufficient or incomplete (missing) data;
- insufficient uniformity of outcome measurements, timing of, and approaches to data collection across sites;
- case ascertainment;
- limited monitoring of clinical registry data;
- limited or no endpoint adjudication of clinical registry data;
- limited or no adverse event reporting within registries;
- conflicting / overlapping information from multiple sources;
- low control of adherence / compliance with data collection.[8,10-12,14-16,18-19,21-25,27-30,32-38]

Access to clinical registry data

Limited access to clinical registry data because of ethics and governance requirements has been a commonly reported limitation for registry-based trials. In particular, issues associated with consent, privacy and confidentiality, data sharing, data use and jurisdictional issues have been reported.[10-12,14,19,21,25-27,30,32-33,36,38]

Additionally, the timeliness of registry-data may be a limitation; with variability in when data is collected, cleaned and analysed by the clinical registry impacting upon when data is available for the trial.[12,21,22,24-25,27,33,38]

Limitations otherwise associated with data linkage are also reported as potential limitations for registry-based trials.[20] Such limitations can be related to the cost to access registry data, time taken to access registry data, along with issues with the standardisation and harmonisation of data items.

Deviation from usual care

By design, registry-based trials are pragmatic in nature, aiming to be as close and therefore representative of usual practice (of both clinicians and consumers) as possible. The methods employed to improve scientific rigour of registry-based trials (such as consenting for a trial and blinding either clinicians or consumers to treatment), are alterations to usual care practices that may impact on the outcomes seen compared with usual practice.[27]

Overcoming the limitations

It is important to recognise that many of the challenges identified above are not only reflected in clinical registry data collection but also occur using other forms of data collection for trials. However, the impact of these can be minimised through other elements of the registry-trial design. For example, missing data may be handled during the analysis phase (e.g. through imputation), or funding from the trial could help to supplement the clinical registry data to minimise the amount of missing information. Also, while many clinical registries do not have endpoint adjudication and safety monitoring boards as part of their practice, these can be built into a registry-based trial to support those activities.

The following modules provide questions to consider when:

- deciding on a registry-based trial (Part 2);
- designing and conducting a registry-based trial (Part 3);
- analysing and reporting on a registry-based trial (Part 4);
- funding registries and registry-based trials (Part 5).

"… it's really an advantage because you already are collecting the data, so you're not doubling the work. … So, you save costs, you improve efficiency, you reduce the workload for the research coordinators and they can basically use this time to do other things like randomise patients, follow deviations, follow the protocol adherence. So, I really think there are a lot of advantages in using the registry, especially from a cost and operational perspective." Clinician Researcher

"So much of the infrastructure, data linkage, employing people, having coordinators, having an IT platform, it's already there. So for me to start a new clinical trial, I have to do all of those things myself. I have to build a platform by REDCap, I have to employ people, and I have to then try and arrange data linkage. I don't need to do any of that with a registry nested trial." Clinician Researcher

PART 2 DECIDING ON A REGISTY-BASED TRIAL

This section of the Guide focuses on providing guidance to support decision making about whether a registry-based trial is the right approach to answer a research question. It is split in two parts - guidance for researchers (trialists) and guidance for registry operators.

DECIDING ON A REGISTRY-BASED TRIAL - FOR RESEARCHERS (TRIALISTS)

Finding a suitable clinical registry

Clinical registries can vary with regards to their focus and the data they collect. The type of clinical registry that is right for a trial will ultimately depend on the research question and data requirements. The following are the types of clinical registries that may be encountered:

- **Disease-specific registries** which focus on patients diagnosed with a particular condition (such as cancer or diabetes).
- **Device registries** which track the effectiveness and safety of medical devices (such as breast implants).
- **Procedure registries** which collect data on outcomes related to specific medical or surgical procedures (such as joint replacement surgery).
- **Product registries** which focus on tracking the use and safety of pharmaceuticals, vaccines, or biologics over time.
- **Exposure registries** which monitor individuals exposed to specific environments or substances (such as chemicals or occupational hazards).

If these registries systematically monitor and provide feedback on the appropriateness and effectiveness of health care to drive ongoing improvements in safety and quality, they will also be referred to as *clinical quality registries*.[3]

There are many ways to identify clinical and/or clinical quality registries in Australia. The following is a list of suggestions and sites for identifying a registry that may be appropriate for a trial.

- **Australian Register of Clinical Registries**: The Australian Commission on Safety and Quality in Health Care has established the Australian Register of Clinical Registries to promote collaboration and increase awareness of registry activities among key stakeholders. The Register provides information about the purpose, structure and participating sites for registered clinical registries.
- **Australian Clinical Trials**: This government portal provides information on clinical trials being conducted in Australia, including details about trials and associated registries.
- **Professional Medical Associations**: Reach out to organisations related to specific medical fields, such as the Royal Australasian College of Surgeons (RACS) or other specialist societies (e.g., the Australian Diabetes Society), which may maintain or have access to relevant registries.
- **Patient Advocacy Groups/Not-for-Profit Organisations**: Patient organisations or advocacy groups for specific conditions often maintain or collaborate with clinical registries.
- **Universities and Research Institutes**: Many Australian universities and research institutes maintain their own disease-specific registries or are involved in national registry initiatives. Contact relevant departments or researchers directly.
- **Research Publications**: Reviewing research papers and publications can also provide leads on specific registries used in studies.
- **Google Scholar**: Use Google Scholar to search for academic papers and studies that mention specific registries in Australia. This can often lead you to the organisation or institution managing the registry.
- **PubMed**: Another useful resource for finding academic papers that reference clinical registries in Australia.
- **Health Departments**: If you are unable to find specific information online, consider directly contacting state or territory health departments or the federal Department of Health and Aged Care for guidance on locating specific registries.

Building a relationship between the clinical trial and registry teams

Key to successfully designing and conducting registry-based trials is ensuring a relationship between the clinical trial team and the registry team. Building a rapport, understanding the needs, requirements and limitations for both the registry and the trial is important for making sure the registry and the trial both benefit from the activity.

Early communication and planning are critical. Some registries may require submission of a detailed protocol along with details of the data required so they can assess whether the registry is able to support the trial.

> *"You need to engage with the registry early if you're going to want to use the registry to run a trial to work out what the logistics are."* Clinician Researcher

The extent to which registries can collaborate with researchers or their capacity and capability to support research can vary. Registries will generally require that the trial objectives/processes align or complement their goals and governance requirements, minimise burden to the registry and the registry participants, and do not impact upon the purpose and functions of the registry.

Determining if a registry-based trial is the appropriate design

A number of questions should be considered to determine if a registry-based trial is the appropriate study design and approach to answer a research question. In particular, consider:

- The **registry appropriateness** in the context of the trial (such as population coverage, maturity, resources, infrastructure, adaptability, method of consent, ethics processes, governance and potential sources of bias).
- The **data characteristics** (such as data items collected, capture rate, standardisation, harmonisation, validity, monitoring and completeness).
- The **methodological differences** between the trial aspirations and usual registry practice (such as eligibility criteria, recruitment processes, follow-up process, the capture and reporting of interventions, implementation and adverse events as well as outcome measure adjudication and blinding processes).[39]

> *"[Registry-based trials are] good for comparing standard of care treatments where there was a lack of evidence about what is the best treatment to use and so there was already substantial safety data. … It's really for a more pragmatic trial. ... we have got lots of safety data on them - we don't need more safety data. We want comparison efficacy data."* Clinician Researcher

As part of deciding whether a registry-based trial is the right approach, it is highly recommended that a research plan is drafted to support discussions with the registry team. It is recommended that this includes:

- The research question, hypothesis and rationale (including details of clinical and consumer involvement in determining this).
- The study team (including their skills and experience).
- Sources of funding (if already have).
- Details of the study sponsor (and their insurance arrangements for trials).
- A definition of the trial population, including inclusion and exclusion criteria, and required sample size.
- Baseline data to be collected (e.g. age, gender, comorbidity, disease severity).
- The study setting (e.g. international/national/state-based; rural/regional/metropolitan; individual/cluster).
- The intervention(s) you are testing, including how it will be administered and by whom and how often.
- What comparator is most appropriate (e.g. placebo or standard care).
- The primary and secondary outcomes measures, including how they are defined and measured for the trial.
- What intervals of follow-up are needed (e.g. 3/6/12 months, 5 years, etc.), and overall trial duration.
- Anticipated data items that would be required from the registry and when it is anticipated that these would be required (may not be able to finalise until after conversations with the registry team).
- Anticipated trial data items that would need to be collected outside of the registry (may not be able to finalise until after conversations with the registry team), along with potential access and use of that data following the trial by registry or other external parties.

Determining if the registry is right for the trial

> *"You really need to be quite careful with your existing registry and checking the data fields that they collect and checking how often it's updated, how the data is used, and also data ownership. Who owns the data? And how is it used? ... So that's the first thing I would say, really assess the registry."* Clinician Researcher

This planning phase may involve reviewing the clinical registry's data dictionary, annual reports and recent publications as well as discussions with the registry to obtain information related to the characteristics of the registry. Key questions to consider include:

- Who is the clinical registry data custodian, and do they have permission to share the data for research purposes?
- Is the registry set up to support the conduct of trials (i.e. are the governance processes in place)?
- What is the current financial position of the registry (i.e. who is funding the registry and for what duration)?

Relevance of the registry

An important consideration for a trial is to evaluate whether the registry's participant characteristics align with the trial's inclusion criteria - with regard to the population, condition, intervention and/or outcomes of interest. Additionally, it is important to consider whether the registry's size, geographic scope, and representativeness are sufficient for the trial. These factors will help determine whether the registry can serve as a primary data source or if additional data sources are required. Determining the alignment of the registry and the trial will take a number of conversations with the registry, and the parameters of sharing information about the proposed research plan, and the registry details will need to be agreed up front.

> *" … the coverage of the registry, in terms of its geographic location, number of sites, the type of condition and the clinical network, may lend itself better or worse to something. ... the scope and scale and focus of the registry, that's all very important."*
> Clinician Researcher

Key questions to consider include:

- Is data that is generated by the clinical registry able to address the question at hand (i.e. fit for purpose)?
- Is the data that is generated by the registry adequate for evaluating the clinical outcome(s) of interest?
- Is the data generalisable (i.e. does the registry reflect high site and patient participation rates compared with the total population)?
- Do linkages between the registry and other existing datasets to obtain additional data not captured directly in the registry need to be explored?
- Is the format of the registry data suitable for statistical analysis?
- Can the registry support regular data extraction/access for the researchers to the data for monitoring, checking quality, interim reporting, etc.?

Does the registry capture the required trial population?

When determining whether a clinical registry is suitable for capturing a trial target population, it is essential to consider the registry's scale, data capture methods, and geographic reach - which all relate to the likely case ascertainment of the population (the clinical registry may know the proportion of eligible patients that the registry captures). A registry's size and scope - whether local, state, national, international - will dictate its ability to include a sample that aligns with the trial target population, as well as the generalisability of the findings. If the registry does not fully capture the target population, consideration must be given to recruiting participants from outside the registry.

Key questions to consider include:

- Is the population captured in the registry with regards to diagnosis, disease severity, comorbidity, gender, age and geographical location, etc. relevant to the trial?
- How many participants meeting the trial inclusion criteria are enrolled in the clinical registry? Over what time period were they enrolled?
- Is there an adequate sample size within the registry to meet the needs of the trial?
- How representative is the sample in the registry? What proportion of the total eligible population does the registry cover and are there any segments (e.g. based on demographics, geography) that are notably underrepresented?

Does the registry capture the primary and/or secondary outcomes relevant for the trial?

Many registries have a core dataset that typically includes disease diagnosis, medical history, demographic data (e.g. age, gender, geographical location), comorbidities, disease severity and outcome data. To assess whether the registry will meet the data requirements of a trial, a clear understanding of the variables collected by the registry, how they are defined, and the timing of data collection is crucial.

Key questions to ask of the registry include:

- What data items are captured within the registry, or are able to be generated from the registry data? For example:
  - participant characteristics, demographic data, disease or treatment information;
  - exposure to other interventions;
  - adherence to trial intervention;
  - outcome data and adverse events.[36]
- What is the frequency of data capture for the registry (e.g. real time, monthly, quarterly, yearly)?
- How regularly is registry data cleaned and available to access?
- Is the registry data already linked to other datasets that may provide outcome measures (e.g. National Death Index, AIHW data, etc.)?
- Does the clinical registry collect follow-up measures, which may include Patient Reported Outcome/Experience Measures (PROMs/PREMs)?

Clinical registry data considerations

> *"And then the outcome measures ... not just [does the registry] have the correct outcome measures but ... are they collected in a valid and reliable manner? Who's collecting them? Does the person collecting them need training? Who's monitoring it? How accurate is it? Is somebody double-checking? Because it might be one thing for a registry just to put outcomes in, but for a trial, you need to be more rigorous about the accuracy of that data."* Clinician Researcher

Further to understanding what data the registry collects it is important to assess the quality of the data. In particular, data capture, validity, monitoring and completeness are important considerations, and where multiple data sources are being used - harmonisation and standardisation may also be important. Each clinical registry should have a standard operating procedure document that defines the processes and procedures for data collection and management, along with a data dictionary which describes the data items to support decision making. Important in this is ensuring alignment between the definition of variables in the clinical registry and the trial, and align the timing of the data collection for the clinical registry and the trial.

Key questions to ask include:

- Can the registry provide access to their data dictionary (or relevant parts of) and/or access to codes or algorithms used to define or derive outcomes?
- How often are changes to the data dictionary made and on what basis?
- Can documentation of changes made to the variables of interest over a certain period be provided?
- What are the standardised data collection and quality assurance protocols? For how long have these been in place?
- How is data accuracy assessed?
- How is data completeness monitored, and missing data handled?
- Is the data capture process in-built with data validation checks (e.g. data range and context sensitive validations)?
- What are the ongoing monitoring processes for the registry? Is it possible to add additional monitoring if required for the trial?
- Can sample data sets be provided to allow pilot testing of how data will be used?
- Can estimates of missing data be provided for variables of interest? What arrangements can be made for trial staff to contact sites to chase up missing data if required for the trial?
- Can any processes or data not provided by the registry be added or the registry reconfigured to accommodate these, and what would that require?

> *"The quality of data is really dependent on how good the data is going into it. So, a registry is only as good as the data you have available."* Clinician Researcher

If the trial is mis-aligned with the characteristics of the clinical registry, alternative trial designs may need to be considered including not using the registry, or may require supporting improvements in the registry data collection to minimise bias while using the registry.

How can the registry be used for the trial?

Clinical registries can be also used to support the trials in ways that are beyond baseline and outcome data collection.

Key questions to ask (as relevant to the trial) may include:

- What information is available from the registry to support pre-trial feasibility assessments?
- Is the registry able to provide data to support participant and/or site identification for the trial?
- Is the registry able to support participant recruitment (for example through providing contact information to the research team, or through contacting the registry participants on behalf of the trial, or through a dual consenting process)?
- Does the registry support access to its network of clinicians for trials recruiting study sites?
- Is the registry data able to support screening of participants for the trial? If so, how would this occur?
- Does the technology platform used by the registry enable the addition of other modules to support the trial?
- Could adverse events be reported separately to the registry if required for immediate action?

Tools available to support implementation

- A decision tree for clinical registry suitability assessment.
- A spreadsheet-based checklist for in-depth assessment of the clinical registry for the trial.

DECIDING ON A REGISTRY-BASED TRIAL - FOR REGISTRY OPERATORS

Setting up for success

Each clinical registry has been created (or for those in development, will be created) for a specific purpose and will have governance arrangements which will impact upon whether it is able to be used, or appropriate to use, for clinical trial activity. Many of the key functions of a clinical (quality) registry (see Figure 1) have the potential to be set-up and utilised in ways that do enable registry-based trials, with particular consideration to governance structures, data custodianship, data collection, data quality and management, and data analysis and outcome reporting. Harnessing registries for clinical trials, when done well and in partnership, has the potential to benefit both the trial and the registry.

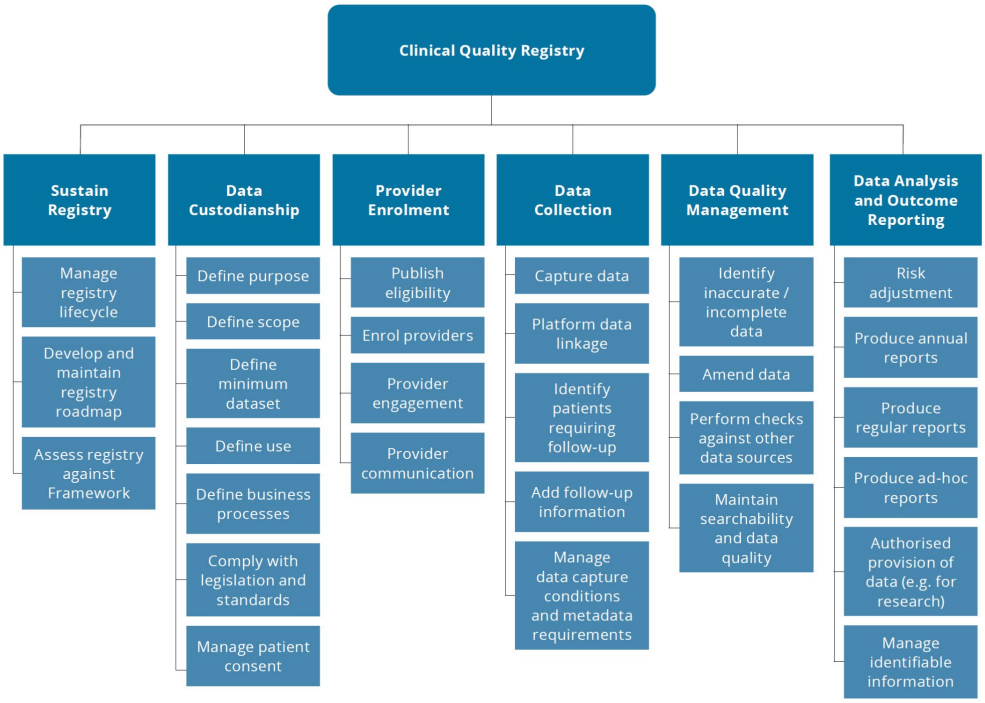

Figure 1 Functional overview of Australian National Clinical Quality Registries

Source: Australian Framework for National Clinical Quality Registries 2024[4]

What capabilities does the registry have to support trials?

Registry governing bodies (either for existing registries or those under development) need to decide if being part of clinical trials fits with the intended purpose of the registry, and if so, what capabilities and governance processes the registry has (or needs to develop) to support registry-based trials.

"From a registry management point of view, you have to cost the ability to do this properly. So researchers have to understand that if they're doing a registry-based trial, there's advantages to them by having this captive population, whether it's hospitals or patients, but there's still a cost to the registry to organise that information for them. So [the trial] needs to have a good system of getting a quote and putting money aside for some of those things … there needs to be some cost recovery for the registry. And … it's extra work for the registry. So, they need to consider funding for that." Registry Custodian

"… we are always trying to refine the registry to ensure we're not collecting more data than we need to, and if we [know we have a trial using the registry] we won't touch those variables that we've committed to the trial to collect. So that's quite important as well. … it's a reminder that we're not going to alter those variables in any way because we have a commitment to x, y and z trials to collect those for the next five years." Registry Project Officer

As the registry's governing body sets the strategic direction and defines the purpose and intended outcomes of a registry, either that body or a delegated authority of it (such as an associated Advisory Group), should be responsible for reviewing requests to access or use registry data or infrastructure for clinical trials. Ideally, members of this Group would include registry staff and/or clinicians who have some knowledge and understanding of clinical trials and/or good research practices, and be supported in their review by clear, structured processes on how to review and assess requests. Depending on the registry governance structure, it may be appropriate for that Group to be the decision-

making authority following review, or for them to make recommendations to the governing body about the registry's involvement in proposed trials.

Key questions to ask may include:

- Is the registry governance structure set up to support the review of requests to use the registry for registry-based trials?
- Does the registry's ethics and governance approvals support involvement in registry-based trials?
- Have criteria and processes for assessment of registry-based trial requests been established?
- Are there mechanisms in place to enable a productive working relationship between the clinical registry and the research team?
- Does the registry platform enable interoperability or adaptability to support registry-based trials? What restrictions or requirements can enable this?
- Is there an approach to determining required resourcing for clinical trial activity and for providing potential registry-based trials with pricing and cost recovery mechanisms?
- Are any changes to the registry reporting and feedback processes (e.g. benchmarking) required to account for clinical trial activity?

> *"It's not a small job incorporating these clinical trials into the registries. And so, if there's not a clear protocol that lays out all the processes that need to be taken, if there's not ethical approval yet, if they haven't engaged with the sites and engaged interest, then we're a little bit hesitant on talking to them about incorporating it into the registry, because while these sites are participating in the registry, it doesn't necessarily mean that they've got the capacity to participate in a clinical trial."* Registry Project Manager

It is recommended that clinical registries prepare information to provide upon request by research teams and, where possible, document on a publicly available website the following:

- If supporting registry-based trials (either through data requests, linkage or embedding) is a function of the registry.
- The purpose of the registry, the inclusion and exclusion criteria for sites and participants, the data dictionary (with timelines and frequency of data collection), and quality management and data management processes.
- The policies and processes for collaborations with external organisations including what is within scope, decision-making processes, data sharing, data analysis and publication policies, and any restrictions on who the registry may collaborate with.
- A template for registry-based trial requests.
- A template for a collaborative research agreement or similar for the conduct of registry-based trials.

Determining if the trial is right for the registry

To determine this, consider the value of the trial/research question and how that aligns with the purpose of the registry, along with specific information about who is responsible for the trial, what impact the trial might have on the registry, the burden of trial involvement for the registry or registry participants, etc.

Key questions to determine if the trial is right for the registry include:

- Does this trial align with the goals and purpose of the registry?
- Could involvement in the trial negatively impact the registry (e.g. might there be differential follow-up/data completeness for trial patients compared to other registry patients, or could patients be preferentially identified and registered for the trial over the registry)?
- Would the results of this trial be valuable to consumers/clinicians/health services that are part of the registry?
- What might be the benefits of participation in the trial for the registry?
- Who is the trial sponsor?
- Does the sponsor have the requisite trial insurance cover?
- Is the trial investigator/clinician-initiated or industry initiated? Are there potential conflicts of interest as a result of this?
- What other studies and trials is the registry currently or future committed to? Are there competing trials using the registry and how will the registry manage approaches from different investigators with competing studies?
- Is there an existing relationship with this research team? Has that been positive?
- What does the trial require from the registry, when and how often?
- How much involvement of registry staff would be required to support/facilitate the trial?
- What is the cost to the registry for involvement in the trial, and has this been/will it be appropriately budgeted for in the trial budget?
- What risk management processes might the registry and/or the trial team need to employ with regard to adverse events as a result of the intervention?

> *"... when we talk about introducing new data points we're acutely aware of how difficult some of this data is to find at the site level. … If the trial says this needs to be collected, and it's in a separate form, then that's fine, because [sites] know that it's concerned with the trial itself; it's not the main registry."* Registry Project Manager

To support this process, a draft template which can be adapted as appropriate to support the collection of information from the research team about the proposed registry-based trial is provided. This will then support the clinical registry in deciding if the trial is right for the registry.

Tools available to support implementation

- A word template for registries to obtain required information about a trial.
- A spreadsheet-based checklist for assessment of the trial through registry-governance processes.

APPLICATION PROCEDURE AND GOVERNANCE

The process by which clinical registries approve a research project may involve several steps to ensure the intended research is compliant with the registry's governance standards as well as any nationally accepted regulatory and ethical frameworks. Some examples of request requirements and procedures include:

- https://www.anzdata.org.au/anzdata/data-requests/request-guidelines/
- https://auscr.com.au/research/research-proposal-procedures/
- https://www.anzics.org/information-requests/

Typically, submissions to partner with clinical registries will require:

Requirement	Inclusive of	Responsibility
A formal application process to the registry	• Detailed synopsis of the research objectives, methodology and data requirements • Evidence that the trial has been submitted/approved by a Human Research Ethics Committee or details of the plans to do so	Trial staff
Scientific and technical review of the trial	• Review of formal application by the registry's governing committee to assess the scientific rigour and feasibility of the research (and the capabilities of the registry), alignment with the purpose of the registry and impact of the proposed research • Review of the trial compliance with the registry's regulations, guidelines, and codes of practice • The time frame for approval can vary depending on the request/submission; this should be considered as part of trial timeline planning	Registry staff
Budgeting discussions	• Discussion and quote provision from the registry for the trial for the services they will be providing - may be inclusive of costs for time spent on processing an application, facilitation and delivery of data, recruitment of study participants/sites, etc. • Inclusion of registry-related costs in trial budgets submitted as part of a grant proposal	Trial and registry staff
Formal agreements	• A formal agreement between the trial team organisation/institution and the registry to address any legal matters, including contracts, indemnity, or insurance requirements; and to outline reporting requirements, publication approvals, any agreements on how the data can be used (either by the registry or the trial), and an undertaking that the source of the data will be acknowledged	Trial and registry staff

Table 1 Documentation to support registry-based trial design and conduct.

PART 3 DESIGNING AND CONDUCTING A REGISTRY-BASED TRIAL

This section will provide details to support the design and conduct of registry-based trials as determined through the national meeting and key informant interviews. It covers key considerations related to a) ethics, governance and legislation, b) methodology and approach, c) technology, and d) funding. Where appropriate, considerations for trialists, considerations for existing clinical registries, and considerations for clinical registries in development (new), are provided separately.

ETHICS, GOVERNANCE AND LEGISLATIVE CONSIDERATIONS WHEN DESIGNING A REGISTRY-BASED TRIAL

While designing a registry-based trial, it is important that trialists and clinical registry personnel work together to understand the current ethical, governance and legislative requirements and potential implications of these for the clinical registry and the trial.

Of particular importance are issues of:

- consent;
- data governance (access/use);
- site governance;
- withdrawal of participation;
- conflicts of interest.

Consent

As part of designing a registry-based trial, it is important to understand the way in which individuals become participants of the clinical registry and what the ethics approval and governance processes for the clinical registry allow in terms of contact with clinical registry participants and access to their registry data. As clinical registries can use opt-in, opt-out or waivers of consent, there are different considerations for the planned trial depending on which method is used by the registry.

It is also important to remember that all registry-based trials require their own additional opt-in informed consent process for trial participants, regardless of the original clinical registry consent process.

The timing of recruitment is also an important consideration:

- In some cases, the process for consent for both the clinical registry and the trial can happen at the same time, although consent for each must be obtained separately.
- If recruitment into the clinical registry is occurring first - it needs to be clear to registry participants what they are consenting to (or what there is a waiver of consent for) and whether this allows data to be used for future research or contact of registry participants.
- If recruitment into the trial is occurring first - it needs to be clear to participants that they will be included in a clinical registry and they will need to consent to being on the registry (or notified they are on a registry if it has a waiver of consent).

> *"I think a lot of people thought, wow, we would accrue patients a lot quicker [through a registry]. But there's still the study investigator that has to consent patients for clinical trials. ... A lot of people hear the word clinical trial and think, you know, lab rat, and I don't want to do that. So that is still is a barrier in itself to accrue patients to clinical trials, that patient factor, which we cannot take away [with] a registry[-based] trial."* Clinician Researcher

Considerations for trialists

- Participants who consent to their involvement in a registry-based trial must also provide consent to the access and collection of their data from the clinical registry for the clinical trial. As such, it must be clear in the explanatory statement (participant information and consent form) that some (or all) of their data will be obtained from the clinical registry and how and when this will occur.
- Where possible, it is recommended that consent for inclusion in the clinical registry be incorporated into the clinical trial consent process or vice versa. A streamlined consent process reduces the burden on participants and/or their families as well as the burden on research staff.
- Informed consent from the participant of a registry-based trial is required in all cases, regardless of the clinical registry consent and ethics approvals.

Consent-related questions to ask the clinical registry

- What are the current methods for consent to the clinical registry? Please note often different methods of consent are used for different sites/jurisdictions for the one clinical registry.
- If opt-in/opt-out consent:
  - When and how is this done?
  - What are individuals specifically consenting to (e.g. clinical registry enrolment, follow-up at particular time-points, medical record access, future research, etc.)?
- For waiver of consent within a registry:
  - Are there additional processes that will need to be completed when doing the consent for the trial (e.g. provide details about the clinical registry and associated waiver of consent)?
  - Does the clinical registry ethics approval allow for participants of a research activity (such as a trial) to be included in the registry (i.e. can they opt-in to the registry via a research project)?

Considerations for existing clinical registries

- It is important to review the existing ethics approval to determine what is and is not approved in terms of access to clinical registry participant data (including contact details).
- Where current ethics approvals do not support the use of clinical registry data for other purposes, consider amendments to the approvals (such as allowing consent for future contact and/or use of data for research purposes and/or consent to provide contact details to a third party for research purposes) to enable this.
- When making an amendment to the ethics approval, consider if it is only for future (prospective) clinical registry participants, or is there an opportunity to get approval for this to be retrospectively applied to existing registry participants.
- Consider the burden (e.g. staff time, costs) of enabling trial involvement for the clinical registry for activities such as changes to ethics applications, changes to standard operating procedures, training, and any required database and/or technology platform changes.

Considerations for new clinical registries

- When applying for ethics approval, those establishing a new clinical registry may wish to consider seeking approval for the possibility of future contact for the purposes of research or the secondary use of registry data for research purposes.

Data governance (use and access)

The governance structures of clinical registries are set up to ensure appropriate data governance for the collection, management and analysis of patient (individual)-level data. In doing so, they must ensure that they meet the relevant privacy principles and legislation set at jurisdictional/national levels. As part of designing a registry-based trial, it is important to understand:

- the clinical registry's primary purpose and their data use and sharing policies and legislative restrictions;
- who owns the data that is obtained from a registry and are there limitations on how and when that data from the registry can be used or reported publicly;
- if identifiable, re-identifiable, or completely de-identified data is required for the trial as registries will have policies and set procedures as to what can be shared.

Considerations for trialists

- Some clinical registries may have incorporated the use of registry data for research purposes in their ethics submission and waiver of consent/consent processes while others may not be able to share data at all. Researchers should check that their planned use of the registry data complies with the existing approval and/or consent requirements for the clinical registry.
- If access to the registry data for trial purposes is not already covered by the clinical registry ethics approvals or registry data sharing policies, an amendment will be required to gain the necessary approval and/or consent. The following are potential pathways (in some cases a combination may be required):
  - Utilising the clinical registry's existing data sharing process.
  - Requesting ethics approval to access the data via an amendment to the registry's ethics.
  - Requesting ethics approval to access the data via the registry-based trial ethics application.
  - Requesting consent from trial participants to access their registry data via the registry-based trial consent process.

- Clinical registries may have data governance procedures that restrict the sharing of registry data (either identifiable or coded or from certain sites or jurisdictions), so early conversations with the clinical registry team are important to establish what is and is not possible in terms of the availability of identifiable, re-identifiable or de-identified registry data.
- During the design phase of a registry-based trial, consider whether identifiable (or potentially re-identifiable/coded) data is required to conduct the trial. If identifiable or re-identifiable data is required by a trial, researchers should seek specific consent to access the identifiable (or coded) registry data.
- If contact with existing clinical registry participants is required for the trial (for screening, eligibility review, trial consent purposes, etc), this may be an activity the registry staff need to undertake (as opposed to providing the contact details to the trial staff).

Data governance-related questions to ask the clinical registry

- Does the existing ethics approval and registry governance processes have restrictions on who can access the registry data and/or specific items of registry data?
- Does the existing registry ethics approval and registry governance process allow third party access to the registry data (either individual/site level or aggregate)?
- Does the existing ethics approval for the registry allow individuals to be contacted for purposes other than the clinical registry (e.g. for other research purposes)?
- Does the existing ethics approval allow access to identifiable (or potentially re-identifiable) data from the registry?
- If none of the above are allowable, would the clinical registry consider modifying/amending ethics to allow for any of these?
- If direct contact with registry participants is not allowable, would the registry be willing to contact registry participants on behalf of the trial?
- What mechanisms does the clinical registry use to share data (for example, does the registry have data sharing agreements, data request procedures, or a secure portal where they upload the data and if so, can other trial data be uploaded onto the secure site to link the datasets)?
- What security protocols does the registry require in terms of how data is managed by the trial?
- Does the clinical registry have requirements in terms of reporting back to them following use of the data registry (e.g. prior to publication, including a registry team member as an author, approval from the registry team for the project, etc.)

Considerations for existing clinical registries

- Before embarking on registry-based trial activity, it is important to understand the existing policy around data sharing and how data is shared for research purposes (i.e., de-identifiable/re-identified/identifiable) and consider if this needs to be reviewed.
- Consideration should be given to understanding if the trial's access/use of data from the registry could potentially impede the registry's primary purpose (for example, releasing trial results which influence the collection of data at certain sites).
- If not already approved, custodians of existing clinical registries that are still recruiting participants may wish to consider an amendment that incorporates the possibility of contacting new (and possibly existing) registry participants for research purposes.
- It is important to consider how data will be shared to maintain the privacy and confidentiality of registry participants.
- It is important to consider if data needs to be made available to registry participants (consumers), and how this would be done.

Considerations for new clinical registries

When developing a new clinical registry, the governing body should consider the creation of data access sharing and use policies and ethics approvals that support the use of registry data for trial purposes. Some key questions to consider include:

- What are the consumers (registry participants) perspectives on data sharing and use policies for the registry?
- Will the registry data be available for other research purposes?
- How will registry participants be made aware of (and consent to) their data being used for secondary purposes?
- How will registry participants' data be shared with others for research purposes?

Site Governance

Registry-based trials may be implemented at sites already involved in a clinical registry (some or all of those sites) or may involve a mixture of registry sites and sites that are not involved in the registry. Reasons for this may include the timeliness of data collection, the registry not being approved at certain sites, the population available at different sites, etc.

Regardless of whether a site is involved in the clinical registry, each site will need to approve the registry-based trial through their research governance office (RGO); this is in addition to the ethics approval.

> *"I guess the first thing is ... to work out your expression of interest to see which of the registry sites ... may be interested in joining the trial. And then also looking at a registry-based trial and thinking [about] smaller regional sites or smaller private sites, that haven't had a lot of experience in a clinical trials unit and they're looking for a registry-based trial to start their Clinical Trials Unit as their first trial or their first few trials. So targeting those sites and talking to them …. [We also went to sites outside of the registry and] a lot of sites came back and said, look, we're happy to join your trial, but we don't want to join your registry. As in we've got enough personnel to put on, say, five patients for the trial and update those five patients, but if you're telling me I need to enter 50 cancer patients a year onto your registry, we don't have the staff to update 50 patients. And then working out - if we were happy for it, and we said, yes, we were happy for that. Since then, interestingly, all those sites have joined up to our registry because they've enjoyed the experience so much. So it's actually had a positive effect, but back the other way. Which is good. We're very happy about that."* Clinician Researcher

Considerations for trialists

- An understanding of the sites involved in the clinical registry (including the number of participants enrolled in the registry with selection criteria that match the clinical trial) is needed to assist with trial recruitment.
- As per usual trial design processes, choosing which sites will conduct the trial and undertaking relevant site assessments and obtaining site approvals through the relevant RGO is required for registry-based trials. It may be that the trial only opens at sites involved in the clinical registry, or at only some of those registry sites, and at some sites that are not involved in the clinical registry. Discussions with the clinical registry may support the process of onboarding sites that are involved in the registry by building upon the relationships, infrastructure and experience already developed through the registry. Additionally, if sites are recruited for the trial that are not part of the clinical registry, discussions with the clinical registry and site about the inclusion of that site in the clinical registry should be encouraged.
- If sites are required to collect additional data than what is collected for the clinical registry, consider usual trial processes and costs such as recruitment and training of site staff, consent processes, costs per participant payments, etc.
- Whether trial data is exclusively coming from the clinical registry and/or via other mechanisms at each site, consider what monitoring and auditing processes are required for the trial at each site and how this will be conducted.

> *"Sometimes you can have a bit of missing data that is more frequent with the registry than with a standalone trial, and this is something that maybe we need just to emphasise to the site, say, look, we are using the registry, if you can please just keep in close contact with your data collector, just [to ensure they know that] we need this information. This can happen."* Clinician Researcher

Considerations for existing and new clinical registries

- It is important to be clear on how the registry can facilitate access to its sites for trials. This may include providing contact details for sites and site contacts or could extend as far as supporting RGO approval for the trial and enabling registry site data collectors to also collect data for the trial.
- If trials intend to use registry sites (and possibly registry site staff), consider any implications for the clinical registry in terms of potential conflicts of interest, who and when trials can contact the sites, any potential issues in terms of preferencing the trial data collection over the registry data collection, any other costs for the registry, and implications or approaches needed if outcome measures of the trial are meant to be blinded.

Withdrawal

Participants involved in clinical trials have the right to withdraw their consent at any time (either with or without the exclusion of already collected data). Further, participants in a clinical registry may be able to withdraw from or opt-out of the registry (either with or without the exclusion of already collected data). As such, it is important to consider the impact that withdrawal from either the registry or the trial may have on the registry-based trial and how this will be handled during the trial period.

Considerations for trialists

- A protocol for these scenarios (i.e. withdrawal from the registry-based trial and withdrawal from the registry) should be developed during the design phase and clearly explained in the relevant trial documentation (e.g. explanatory statements and consent forms, statistical analysis plan and trial protocol).
- An agreement on notification processes should be made with the registry for either withdrawals from the trial or from the registry.
- A process should be developed to notify sites of withdrawals and how to proceed with data already collected.

Withdrawal-related questions to ask the clinical registry

- What withdrawal or opt-out procedures does the clinical registry have?
- What is the approved use of previously collected registry data if a participant withdraws from the clinical registry?
- Historically, what is the rate of withdrawal from the clinical registry?
- How would the clinical registry like to be notified if a trial participant withdraws from the trial?

Considerations for existing clinical registries

- Clinical registries should have a protocol for the withdrawal of participants from the registry, including identifying whether participants are withdrawing due to trial involvement or not, as well as well documented processes for how the data is handled in such situations.
- To support registry-based trials, where possible, registries should have a process for notifying trial staff of withdrawals of individuals from clinical registries who may be involved in a trial. This should include notification of date of withdrawal, reason for withdrawal and whether data already collected is able to still be accessed or retained by the trial.

Considerations for new clinical registries

- When developing a new clinical registry that is intended to support registry-based trials, the registry should develop protocols and processes to support the documentation, notification and data use associated with those that withdraw from the registry if they are part of a registry-based trial.

Conflicts of Interest

An explicit conflict of interest (COI) management procedure should be developed, implemented and continually updated for a registry-based trial. Such procedures should have the wellbeing and rights of the participants at the core of any decision.

Considerations for trialists and existing and new clinical registries

Key COI issues to be addressed include:

- How will any competing interests between the clinical registry and the trial (such as when there is an overlap of staff, infrastructure, reporting requirements, timelines, etc.), be managed?
- For additional data collected for a clinical trial (that was not previously included in the clinical registry), who is the custodian of that data?
- How will any competing interests between funders of the clinical registry and funders of the trial be managed?

Additional considerations for existing and new clinical registries

- If there are multiple trials using the clinical registry, how will the clinical registry manage approaches from different investigators with competing studies?
- How will funding for clinical registry activity, and trial activity being undertaken by the clinical registry, be separately accounted for?

METHODOLOGY CONSIDERATIONS WHEN DESIGNING A REGISTRY-BASED TRIAL

Methodological considerations when designing and conducting a registry-based trial include consideration of how the registry will be used to support the trial, the trial design elements to minimise bias, and ways to manage data quality. This section covers:

- embedding or linkage for registry-based trials;
- building scientific rigour into registry-based trials;
- planning for data quality;
- planning for adverse event reporting;
- considerations of timing for registry-based trials.

Embedding (utilising registry infrastructure) or linkage (with registry data)

One of the first considerations when designing a registry-based trial is whether the trial is to be embedded within the clinical registry (that is, will the trial utilise the infrastructure and database of the registry for many or all elements of the trial), or will the trial use linked registry data (that is, will it obtain a dataset from one or more clinical registries which will be linked to a trial-specific dataset or used to create a trial-specific dataset), or a combination of these two approaches.

"There are some trials where the trial gets embedded completely in the registry. So, that means that the registry would ... create extra data points in the registry, so that [they can see] - yes, this patient's enrolled in this trial, then maybe a couple of extra points would open in the registry for people to fill in [trial specific data] and then you'd get all of the data from the registry." Clinician Researcher

"... we collect the registry ID of the patient in the registry form. So in principle, you can go back and link with the patient. But in practice [for our trial] ... it's easy just to have all the fields required for the trial separate in the trial platform so that you can do all your auditing and … everything that you need to do, and that's all in one spot." Registry Data Manager

"If you've built the database specifically for the trial and the data is entered straight into it, and you've been cleaning it as you go ... you're in charge of the data. When you embed it in a registry, you're no longer in charge of the data, you're relying [on a] second party to be responsible for giving you the data; making sure it's clean; making sure you can link it; ... just the linking of the data can be really complex." Clinician Researcher

There are strengths and limitations to each approach which are briefly outlined below:

Embedded registry-based trials (using registry infrastructure)

Strengths

- May minimise participant burden (contacted by only one group for data collection, may be consented to both at the same time, etc.)
- May simplify data collection at the site level (e.g. single person collects data for site for both the registry and the trial)
- Can enable screening, recruitment, randomisation, baseline data collection (including additional items), and follow-up (including additional items) all within the one infrastructure; potentially the most efficient & cost-effective approach
- Minimises additional trial requirements for site governance, training, etc.
- All trial data housed together

Limitations

- Limited control over data quality
- May limit safety and adverse event reporting
- Data items and timeliness of data collection determined by clinical registry processes
- Ability to collect additional trial-specific data may be dependent on technology platform & flexibility of other infrastructure of the clinical registry

Linked registry-based trials (using linked registry data)

Strengths

- Enables greater control over
  - trial-specific data collection
  - data quality for trial-specific data items
  - safety and adverse event reporting
  - timeliness of data collection
  - site training, monitoring and auditing processes

Limitations

- May increase participant burden - contacted for data collection for clinical registry and data collection for trial
- Can cause confusion for participants and sites in terms of what is for the trial versus what is for the registry (e.g. may increase the complexity at a site level for data collection for the registry versus data collection for the trial), so protocols at site level should be detailed and updated through the project
- All the general issues associated with linkage apply (e.g. lack of common identifiers, ethics/privacy concerns, technical issues, inconsistent or incomplete datasets, delays in approvals, etc.)

Considerations for trialists

There are several factors that may impact whether a trial can or should be embedded within a clinical registry, or whether a linkage approach would be more appropriate. These include:

- the alignment of the clinical registry (including sites, data, data collection processes) for the trial;
- the extent/amount of data for the trial that is already available in the clinical registry versus other sources;
- the flexibility of the clinical registry to collect additional trial data items if required and/or add trial-specific modules to existing data platforms (for example, for randomisation, etc.);
- preference/ability of the clinical registry to enable embedding and/or how the registry can provide data access;
- any other relevant needs of the trial and how these align with the characteristics of the clinical registry.

Considerations for existing & new clinical registries

- The ability to embed registry-based trials within a clinical registry infrastructure is dependent upon several factors including the privacy and data access requirements of the registry, and the flexibility of the technology platform that houses the registry data. It is important for both existing clinical registries and those being developed to consider if embedding trials within the registry is appropriate and possible, or if data extraction and linkage to a trial database would be a preferred option.

Trial type

Registry-based trials have been used for multiple trial types including single and multiple arm studies, studies where the units of randomisation are individuals or clusters (e.g. sites), and for cross-over and stepped-wedge designs, among others. The decision of what trial type is appropriate should be driven by the methods most appropriate to answer the research question, and is less impacted by the involvement of a clinical registry.

Scientific rigour considerations

While registry-based trials are often conducted to answer questions about effectiveness of treatments or interventions in real-world situations and using pragmatic strategies for data collection, they should where appropriate be conducted using the scientifically rigorous methods synonymous with traditional RCTs - such as randomisation and allocation concealment, blinding and/or central adjudication of outcome measures.[9]

Randomisation and allocation concealment

The methods chosen for randomisation and allocation concealment for a registry-based trial will need to be appropriate for the trial design.

Considerations for trialists

It is recommended that the trial team:

- Consult with a statistician/methodologist when designing the registry-based trial to consider the best allocation approaches.
- Discuss with the clinical registry if there are ways that activities such as randomisation including allocation concealment may be built into the registry platform.
- Consider if funding for third party services for randomisation and/or concealment is required.
- Explicitly state the methods for randomisation and allocation concealment in the study protocol and publications.

Blinding

Given the pragmatic nature of registry-based trials, blinding clinicians and participants to an intervention may not be feasible, however the blinding of data collectors, and/or DSMB members, and/or data analysts, and/or Endpoint Adjudication Committee members, and/or investigators interpreting the data may be possible. To minimise bias, blinding should be instituted into the registry-based trial processes if possible.

Where blinding is used, it is important to have open and ongoing communication between the registry team and the trialists during the study period to minimise the risk that registry reporting (such as to sites) may unblind trial sites/results/investigators or unduly influence the conduct of the trial.

Outcome adjudication

An important limitation of clinical registry data for trials is the lack of central outcome adjudication, and in particular - blinded central outcome adjudication. As outcomes are not usually adjudicated for a clinical registry, data on outcome events used for a registry-based trials may be subject to uncertainty. Therefore, when designing a registry-based trial, it is important to consider if the absence of (blinded) outcome adjudication in the clinical registry is likely to lead to inaccuracies in measurement and reporting of the trial primary or secondary outcomes.

A common approach to minimising the impact of this on registry-based trials is the use of hard clinical endpoints (such as mortality or hospitalisation) from clinical registries (or other administrative datasets) as they are less susceptible to ascertainment bias or definitional differences. In registry-based trials where no central adjudication of study endpoints is to be conducted, this hard end point approach is preferred.

However, depending on the research question and outcome measures, a hard clinical endpoint may not be appropriate. In those circumstances, it is recommended that the trial team implement other practices to determine the accuracy of outcome data. This may include:

- implementing usual-trial practices (outside of the registry data collection) to collect the relevant data from the original sources (e.g. hospital records, etc) and centrally (and ideally blindly) adjudicate outcome events (such as having an **Endpoint Adjudication Committee**);
- performing **audits** of outcome measures reported in the registry by checking a random selection of original source documentation (from hospital sites, etc);
- use supplementary datasets (such as other registries or administrative datasets) to **triangulate the data** to better understand the data validity and integrity.

Having a limited number and relatively non-complex primary and secondary endpoints can minimise the data collection and reporting requirements and burden to investigators and the Endpoint Adjudication Committee and help keep costs down whilst still maintaining scientific integrity in the registry-based trial.

Data availability

A clinical registry may not collect all the required data items for a trial. In such circumstances other mechanisms to collect required trial data will need to be employed. There are three common approaches to achieving this within registry-based trials, including:

- adopting surrogate outcomes using the registry data;
- adding new measures to the registry dataset (which requires working with the registry to add this into their data collection);
- collecting the required data items separate to the registry (for example, collecting data or linking using measures from multiple registries and/or administrative datasets).

"… you need to align your outcomes and the variables that you collect to what is already established in the registry. And the limitation with that will be that it may not necessarily match what would be the best possible outcome for you to consider." Statistician

Considerations for trialists

Where additional data items are to be added to the registry dataset for the trial, considerations include:

- Who owns and can access that data (e.g. if the trial pays for the collection of these items, is the registry able to report these data items in their benchmarking/annual reports? After the trial, are other researchers able to access those data items?)
- What is the cost for the trial period of adding these data items to the registry?
- Where multiple registries or datasets are to be used to collate trial data, or some data items will be collected separate to a registry, considerations include:
    - How will these datasets be linked (based on what parameters) and what is the accuracy of this method?
    - What is the cost to access and link to each of the external datasets?
    - How often can the external datasets be accessed and linked?
    - What is the timeliness of the linked data?

Considerations for existing and new registries

Where additional data items are to be added to the registry dataset for the trial, considerations include:

- Are these data items to be collected only for trial participants in the registry and only for the trial period or will this be collected for all registry-participants and in an ongoing manner?
- Who owns and can access that data (e.g. if the trial pays for the collection of these items, is the registry able to report these data items in their benchmarking/annual reports? After the trial, are other researchers able to access those data items?)
- What is the cost for the trial period (and potentially beyond) of adding these data items to the registry?

These issues need to be agreed before commencement of the additional data collection.

Data quality management

Regardless of whether data for a registry-based trial is already collected as part of the clinical registry or is collected as part of trial-specific data collection processes, the quality of the data is paramount.[40] The specific methods employed to verify data (including the clinical registry data), including possible auditing and monitoring of data collection processes, and processes for querying provided data, should be outlined in a trial-specific data management plan, which should be developed during the design phase of the trial and discussed and agreed upon by the trialists and clinical registry governing body as appropriate; and then implemented and adjusted as required during trial conduct (with all changes documented). As the original source data for clinical registries and trials are often the same (e.g. medical records and reports and other clinical databases), issues with data quality are often related to a lack of understanding of definitions, requirements, measurements or where or how to input data, or transcription or data entry errors.

"[The registry] monitor[s] what ... is important to the registry at all of the sites to ensure data quality, but that might differ from what the randomised control trial thinks is most important. They might be monitoring their primary outcome which isn't necessarily the primary outcome of the registry." Registry Project Manager

"If you have more than one registry, then it's really complex because you need to harmonise the data from different registries ... there is no standardisation. There is no one format that is used across different registers. Everything is different. The name of the variable, the point of collection, the units that we use, everything is different." Clinician Researcher

Considerations for trialists

The methods for data quality management will be specific to each trial and the types and methods of data collection, however the trial team should ensure:

- **Ongoing review and discussion with the clinical registry** including their data dictionaries and data collection processes to support early identification of any changes in definitions or measurements, or to rectify data issues.
- **Data cleaning, extraction and transformation** processes (these may be done as part of usual clinical registry processes, expand upon usual registry processes and/or happen outside of clinical registry processes).

"There are some things for your quality assurance and your oversight of a clinical trial you really want it to be very robust." Clinician Researcher

- Quality checks of key data through **monitoring processes** (e.g. validation rules) to alert to erroneous and missing data, any out-of-range values, logical inconsistencies, etc., along with triggers for corrective action if necessary.
- **Auditing** of a random selection or all key data (e.g. reviewing essential documents; interviews with the site staff; direct observation of study processes and procedures; verification of data accuracy by comparing source documents (e.g., medical records).

Mathes et al (2018) suggest that a pilot test to determine if the data quality is appropriate for a trial during the planning stage may be useful. This could be achieved by testing validation through an audit process on a subset of the registry clinical data.

Adverse event reporting

While some clinical registries may collect data related to adverse events, it is highly recommended that for registry-based trials where the safety of the intervention is largely unknown, that a separate trial-specific adverse event reporting and review process is implemented. For example, serious adverse events for a clinical trial may need to be reported to the ethics committee within 24 hours.

Considerations for trialists

As per normal clinical trial processes it is important that adequate measures are put in place to detect and promptly report including to a Data Safety and Monitoring Board (DSMB), possible, probable or causal safety concerns in a timely manner and in accordance with the study protocol and interim and final analysis plans.

"[The trial separately collects data related to] serious adverse events and protocol deviation so that they are notified as soon as possible and goes directly to the [trial] Project Manager." Registry Project Officer

Timeliness of data collection

One of the strengths of clinical trials is real time data collection and the ability to analyse data on an interim basis to determine next steps. One potential advantage of collecting data for a trial through a clinical registry is the existing network of sites and data collectors. However, clinical registries don't always collect data in real time. Data may be collected at specific time points (e.g. annually, quarterly etc.), and registries that do collect data on a more regular basis often don't do so real-time or close to real-time. Therefore, the timeliness of the registry data collection will need to be considered when planning and conducting a registry-based trial.

"[A] disadvantage of registry data is [that] some registries only update their data periodically. So if you're doing a study [and] they're recruiting at quite a rapid rate [and] you want to go back to the registry database to get the data - the data is outdated. [This is a problem as] then you run the risk of having another 1000-2000 [participants recruited] into the study and should there be an issue with the study [or] there's some evidence of harm, it turns out you might have been recruiting patients for a few months while there has been harm. So that is a potential problem." Statistician

Some things to consider include:

- **Recruitment of newly diagnosed patients** – determine the timeliness of case ascertainment. In many cases by the time newly diagnosed patients appear in the registry they are already receiving treatment. This can be problematic for registry-based trials seeking newly diagnosed, treatment naive patients.
- **Data collection** – real time data is important for surveillance of safety within clinical trials involving experimental interventions or investigations of existing therapies for new indications. Real time data is less important when the registry-based trial is investigating one or more standard care treatments. Timeliness is also less important for data not related to safety (for example quality of life questionnaires, participant reported outcome questionnaires). Where timeliness is very important for the trial because of risks of adverse events, the trial should pay for site data collection to ensure that it is sufficiently timely for the needs of the trial.
- **Clinical registry commitments** – clinical registries will have their own objectives, key performance indicators and reporting responsibilities. Trial staff will need to be mindful of times when registry staff may be focused on the needs of the registry and trial activities such as data queries may not be their priority. The registry should be funded by the trial to regularly review and manage the data relevant to the trial, and to share this regularly with the trialists so that they are reassured with the quality and timeliness of the data collection.

TECHNOLOGY CONSIDERATIONS WHEN DESIGNING A REGISTRY-BASED TRIAL

> *"... we had to make sure that [the IT platform] was flexible so that it was able to be used not just for the specific trial that we were happy to run, but for future trials. So we basically wanted to build a flexible … platform on which other trials could be done."* Clinician Researcher

The technology platform that houses the clinical registry data and, in many cases, supports the input of data into the dataset plays an important role in registry-based trials.

To best support registry-based trials the clinical registry technology platform should:

- be flexible (able to change/edit things within the system);
- be interoperable and integrate with other platforms/systems;
- be built on a robust framework;
- be modular (for example, to enable randomisation modules or trial-specific data collection to be added);
- enable scale up (for example, to enable multiple trials at the one time, or site access for non-clinical-registry sites etc.);
- enable (easy and quick) identification of trial participants and/or data items to support participant matching for linkage purposes (or availability of a linkage key);
- enable data from the clinical registry relevant for the trial to be extracted in a systematic (and potentially periodic) manner;
- enable extracted data to be housed in a secure data environment (which could be combined with other non-registry data) for analysis.

It should be noted that this is not a list of technology platform prerequisites to successfully complete a registry-based trial - having only one of these may be enough to support a registry-based trial.

Considerations for trialists

It is important for trial planning and conduct that there is an understanding of what is and is not possible for the clinical registry technology platform in terms of:

- Structural changes (such as the addition or 'turning on' of modules for screening, randomisation, additional data collection, etc.).
- Access requirements (for instance if there are sites involved in the trial who are not part of the registry, but the data collection is occurring within the registry, can those sites have access to the platform).
- Security requirements in terms of how access will be given access to the clinical registry data.
- How regularly the registry staff can export / provide access / run queries on the data for the trial.
- How trial participants can be identified and/or what data items could be used for linkage (e.g. unique patient identifier, date of birth, etc.).
- What contingencies are in place for the trial data if something goes wrong with the technology platform.

Involving a statistician in the conversations with the registry about how the data will be extracted and provided for the trial and if there are limitations on the environment for sharing data will help set up a registry-based trial for success.

Considerations for existing and new clinical registries

Based on the technology considerations documented above, the registry will need to consider:

- What changes (if any) the registry is willing and able to make to the platform to increase the capability to support registry-based trials, along with what would be required to do that (resources including people and time).
- What costs would the registry need to recover to build add-ons to the platform, enable data access and house data in secure environments to support clinical trials.

> *" … the registry wasn't set up with running trials in mind. It was set up years ago, and [registry-based trials] has come along more recently. So I … would imagine a world where you could design it, so that it is more flexible, and it would be easy to add these things on as you go; and that would … make things potentially easier."* Registry Data Manager

FUNDING OF REGISTRY-BASED TRIALS

> *" ... I think one big point to make is that it's important to have a separation for funding purposes. ... so that it's very clear that this is a registry responsibility, and this is trial responsibility."* Registry Project Officer

Although conducting a registry-based trial is an avenue for potentially reducing the cost of a clinical trial, as with any research activity, funding still needs to be available to support the research activity. When considering funding for a registry-based trial, researchers are encouraged to be mindful that a well-designed registry-based trial has the potential to not only streamline the conduct of the trial but also to support and enhance the infrastructure of the registry for further trials.

When drafting a budget and seeking funding, in addition to the usual activities required when establishing a clinical trial, the following considerations may be of assistance:

- **How is the existing clinical registry being funded?** A clinical registry that has core funding for the period of the trial will provide assurance to the researchers, and trial funders, that the registry will be in existence for the minimum required period of time.
- **What is the cost to the registry to collect, collate, clean and export the data for the registry-based trial?** While a clinical registry may already be collecting all (or most of) the data required for the registry-based trial, there is still a cost to the clinical registry to clean, collate and export that data. Therefore, trialists should liaise with clinical registries to determine the cost of that activity to the clinical registry, so that those costs can be included in any funding applications.
- **What trial-required activities are outside usual practice for the clinical registry?** While many of the clinical registry activities required by the registry-based trial may already be taking place, if the registry-based trial requires the clinical registry to undertake additional work (for example: collect additional data, contact participants more frequently etc.), then additional funding will be required to support these activities. Researchers are advised to request a costing from clinical registry staff as early as possible to include in their funding submissions.
- **What is the most efficient way to complete the activity?** Researchers should consider the most efficient way of achieving the required outcome and whether financially supporting the registry may be more cost effective than doing stand-alone data collection, monitoring, cleaning, etc.

> *"… we used the money from [a successful MRFF registry-based trial] grant to build a bespoke system … we built our own IT system within our registry … [that is] an adaptable platform. So we can set whatever time periods we want for follow up, we can change the survey questions, the outcome tools you know, whatever it is we're getting the patients to answer. And we can add fields, subtract fields, add time points, subtract time points and basically rejig the system for specific trials."* Clinician Researcher

WRITING THE PROTOCOL AND STATISTICAL ANALYSIS PLAN

Once the needs and requirements of the registry and the trial are understood, as per usual good clinical research practice approaches, the protocol and (where possible) the statistical analysis plan for the registry-based trial should be drafted; and published as appropriate. These documents should include all usual good clinical trial practice components as per the CONSORT 2010 Statement or SPIRIT 2013 Statement as well as specific details related to the use of the clinical registry for the trial.

Templates for these documents are available from:

- Protocol - https://spirit-statement.org/
- Statistical analysis plan - https://clinicaltrialsalliance.org.au/resource/statistical-analysis-plan/

For registry-based trials, specific information related to the clinical registry infrastructure and population should be in these documents as detailed below.

Protocol

- Name and type of clinical registry.
- Eligibility criteria (population inclusion and exclusion criteria) for registry and for trial.
- Population coverage (and if relevant, how the registry participants are selected) / case ascertainment, and what proportion of these sites will be involved in the trial.
- Methods of consent for participation in the registry (and any implications of this for the trial).
- Registry maturity/participant size at the time of trial activity.
- Purpose of the clinical registry.
- Sources of funding of the clinical registry (and until what date).
- How the clinical registry is to be used for the trial (e.g. participant identification/screening, baseline data, outcome data, etc).
- Whether the trial is embedded or will use linked data from the clinical registry.
- What data items are to be derived from the clinical registry (including definitions and measurement parameters and details of how that registry data is collected, including how often).
- How registry data is managed regarding timeliness, completeness, accuracy, etc.

Statistical analysis plan

Should detail how the clinical registry data will be:

- Extracted and provided to the trial team (including how regularly).
- Cleaned and transformed.
- Linked with other data (if relevant).
- Handled in terms of missing data (e.g. imputation), or inaccurate data (e.g. ask the registry to provide the correct data, or trial staff auditing to update the data).
- Analysed (in terms of intention-to-treat effects versus per-protocol effects, and when this analysis needs to occur - for example is an interim analysis required and if so, after how many events or a certain follow up period, etc.).

These documents will then form the basis for the conduct of a registry-based trial and should be amended as appropriate throughout the trial.

It is important for the registry and trial teams to continue discussions during the conduct of the trial, to ensure any changes that may be made by the registry during the trial period do not or minimally impact the trial or can be accounted for during the analysis and interpretation of the trial data.

PART 4 ANALYSING AND REPORTING A REGISTRY-BASED TRIAL

ANALYSING A REGISTRY-BASED TRIAL

Like traditional clinical trials, analysis of a registry-based trial is dependent upon decisions made during the design phase of the trial and articulated in the approved trial protocol and statistical analysis plan and should adhere to ethics requirements to protect participant safety and confidentiality.

> *"It's unlikely that you would change the analysis [because it is a registry-based trial]. I mean at the end of the day you're analysing data … it doesn't matter so much where the data comes from. ... the only thing that would impact might be your interpretation of the data at the end. Your level of confidence might be greater, or it might be less depending on the quality of the data that you're getting."* Statistician

Considerations for trialists

As with all RCTs, registry-based trials need to be rigorously reviewed for sources of bias.

Using the Cochrane risk-of-bias tool for randomised trials (RoB 2),[41] specific considerations for registry-based trials include:

> *"The only time you're going to have a problem from an analysis perspective is if there's systematic bias. For [example, if for] some reason the registry is better at collecting data on patients that were in one arm than they were in the other, which is highly unlikely."* Statistician

Effect of interest ('intention-to-treat' effects versus 'per protocol' effects)

An intention-to-treat analysis (ITT; where trial participants are analysed based on the treatment group they were originally randomly allocated to, regardless of what treatment (if any) they actually received)[42] for registry-based trials is preferred, and ideally there is no missing (primary) outcome data. This may be problematic where the clinical registry has been the source for the outcome data, and measures to minimise missing data have not been employed or effective.

An important consideration for ITT analysis is to consider if deviations from the intended intervention arise because of the experimental context of the trial (i.e. did not reflect usual practice), and, if so, was this unbalanced between the control and intervention groups. Given registry-based trials are often more reflective of usual practice approaches it may be that this is less likely to be an issue for registry-based trials than traditional RCTs.

An important consideration for per-protocol analysis (where trial participants are analysed based on the treatment administered, i.e. per the protocol)[42] is whether non-protocol interventions are balanced across the control and intervention groups. Valid estimation of per-protocol effects requires more data, so if per-protocol effects are to be estimated for a registry-based trial, availability of baseline data on factors related to adherence is important. This is especially important if the clinical registry has been used for screening, recruitment and/or baseline data.

Missing (primary) outcome data

To be confident that the main results of the trial are not biased by missing outcome data, it is important that primary outcome data is available for all, or nearly, all participants that are randomised within a registry-based trial. Identifying the proportion of missing data, reasons for missing outcome data, and possibly relationship with unobserved true value, between intervention groups for a registry-based trial is thus important.

Bias arising from the randomisation process and deviation from intended interventions

Assuming the allocation sequence was random, and adequately concealed, the bias associated with the randomisation process in registry-based versus traditional RCTs is likely similar. Bias due to deviation from intended interventions may be different in that blinding may not be possible, so participants, clinicians and carers are aware of the assigned intervention.

Bias in measurement of the (primary) outcome

Like traditional RCTs, if the method of measurement of the outcome was inappropriate, or the measurement of ascertainment of the outcome could have differed between intervention groups (for example for cluster (site) based registry-based trials), then bias in the measurement of the outcome may be apparent. Additionally, if outcome assessors were aware of the intervention received by registry-based trial participants and the assessment of outcome was likely to have been influenced by knowledge of the intervention, this may have introduced bias. Opportunities when designing the trial for outcome adjudication and blinding can help minimise this risk.

Bias in selection of the reported result

To minimise bias in the selection of the reported result, registry-based trials should be analysed in accordance with the statistical analysis plan written during the design phase.

Timeliness of data

When planning the analysis of registry-based trials, any delays in registry data being availability must be considered. Determine early if a registry and/or sites may be receptive to prioritising trial participant data entry to assist the trial in achieving reporting or publication timelines.

Access to data

When planning the analysis of registry-based trials, researchers should be aware of the way registry data will be accessed (i.e. whether they will be receiving a copy of relevant registry data or if they are being granted access to the data e.g. in a secure environment but won't be able to retain a copy of the data). This should be determined during the design phase of the registry-based trial to avoid issues during analysis.

Cleaning of the trial database and a database lock should occur before any analysis commences; with analysis conducted in accordance with the CONsolidated Standards Of Reporting Trials (CONSORT) statement.[43]

REPORTING A REGISTRY-BASED TRIAL

Many registries have authorship and publication policies that researchers will need to comply with when reporting on a registry-based trial. This may include specific acknowledgement or referencing of the registry and its governing body; including the registry committee or committee members as an author of papers; providing a statement regarding ethics approval and/or clinical trial registration; and/or a declaration of any conflicts of interest. Some clinical registries also require that manuscripts be submitted for review and approval by the registry team before submission to a journal.

> *" ... [the registry has] got some publication rules around people using our data. About how they have to acknowledge the registry ... the really important thing is ….. there should be clear reporting guidelines for registry-based trials, ... to include information about both the registry and the clinical trial."* Clinician Researcher

To ensure quality and transparency in reporting and publishing of registry-based trials researchers should follow the CONSORT statement, with the addition of specific details regarding the registry and any associated methods and/or processes. To support this, an extension of CONSORT was published in 2021 - the CONSORT-ROUTINE tool[44] - which provides additional details on the reporting of trials that use routinely collected data such as registry data.

> *"... describing how the registry was used in the trial actually helps the reader understand about the trial."* Clinician Researcher

Based on CONSORT-ROUTINE, the following are registry specific items that at a minimum should be included in protocol and results publications (and/or supplementary materials) for registry-based trials. Examples from the published literature are provided.

Title of publication (CONSORT 1a)

State that the trial is a registry-based trial or protocol for a registry-based trial, and if possible, the name of the registry.

> "Dual mobility versus conventional total hip arthroplasty in femoral neck fractures (DISTINCT): protocol for a registry-nested, open-label, cluster randomised crossover trial."[45 p.1]

Abstract (CONSORT 1b)

Include the registry name and a brief indication of how it was used to conduct the trial.

> "We are conducting an Australia and New Zealand Dialysis and Transplant (ANZDATA) registry-based cluster randomised controlled trial to determine ... SWIFT is the first registry-based trial in the Australian haemodialysis population to investigate whether ..."[46 p.1]
>
> "This is a cluster-randomised, crossover, open-label trial nested within the Australian Orthopaedic Association National Joint Replacement Registry (AOANJRR)."[45, p.1]

Methods - Trial design (CONSORT 3a)

Describe the trial design (e.g. parallel design, cluster randomised) and how the registry was used for the trial (e.g. identification and enrolment of patients/sites, randomisation, collection of baseline data, collection of outcomes, sample size calculations, data linkage, etc).

"DISTINCT (Dual mobIlity verSus conventional Total hip arthroplasty In femoral Neck fractures, a registry-nested, open-label, Cluster-randomised crossover Trial) is a pragmatic, superiority, open-label, cluster-randomised crossover trial nested within the Australian Orthopaedic Association National Joint Replacement Registry (AOANJRR). The setting is eligible Australian hospitals (public and private) performing THA [total hip arthroplasty] for femoral neck fractures. ... As both treatment arms are considered standard, common and accepted treatment for management of femoral neck fracture in Australia without specific consent, we elected for a cluster-randomised design. A cluster design simplifies trial administration at sites by allowing for an opt-out consent process. This is the same opt-out consent process that governs the collection of patient operative data collected by the hospital and provided to the AOANJRR."[45 p.2-3]

"This 2-arm registry-based single-blinded randomized clinical trial was conducted at 6 academic and community hospitals in the US from March 2019 to March 2021 with a 30-day follow-up period following surgery."[47 p.667]

Methods - Registry (new section subheading for CONSORT-ROUTINE)

Describe the registry and provide a rationale for why it was used for the trial.

Cite any relevant references which describe the registry's methods. This should include a reference to the registry website (if available).

Specific sections should include:

- **CONSORT-ROUTINE-1.** Name and describe the clinical registry. Provide information on the setting and location in which the registry collects data (e.g., hospital emergency departments nationally; rural, metro, national, state or specific location if applicable), and dates for recruitment, follow-up and/or data collection as appropriate.
- **CONSORT-ROUTINE-2.** Describe the registry's patient population (e.g. any inclusion/exclusion criteria or information regarding conditions, medical procedure where relevant), population size of the registry and percentage of total population captured by the registry.
- **CONSORT-ROUTINE-3.** State if the trial included person or institutional level data from the registry, and if data linkage was used to combine two or more datasets, and if so, the linkage techniques used/to be used.

"To be eligible, participating centers must perform a minimum of 100 bariatric procedures annually and report to the national register in Sweden/Norway for bariatric surgery (Scandinavian Obesity Surgery Register, SOReg) [9].[48 p.2] ... Baseline data regarding demographics and health parameters will be collected by the participating centers using standardized questionnaires and measurements. The registration of the collected data is facilitated by the central computerized system of the Scandinavian Obesity Surgery Registry (SOReg), which also constitutes the case report form (CRF) for BEST. SOReg contains data from all operating centers for bariatric surgery in Sweden since 2013 and from all but two centers in Norway since 2017. The Swedish audits show an accuracy of data of > 98% [9]."[48 p.3]

Methods - Trial participants (CONSORT 4a)

Include details about the trial participant/site inclusion and exclusion criteria and recruitment strategy and period of recruitment, especially if these are linked with the clinical registry.

Where trials have used the registry to recruit sites, reporting should include the number of trial sites and key characteristics of these such as type of site and location.

Trials recruiting participants directly through the registry should provide the criteria used for selection.

Specific sections should include:

- **CONSORT-ROUTINE-4.** Describe the consent process for both the registry and the trial (if separate) including what participants/sites were consenting to. Provide a statement regarding ethics approval for both the registry and trial (if separate) and details of the approving ethics committee (and approval number if required).

"Patients will be eligible for participation in the trial if they meet the Australian and New Zealand Hip Fracture Registry (ANZHFR) criteria for treatment of a displaced femoral neck fracture with THA [total hip arthroplasty]."[45 p.3]

Methods - Outcome data and data linkage (CONSORT 6a)

Define all primary and secondary outcome measures for the trial and the follow-up period.

Specific sections should include:

- **CONSORT-ROUTINE-5.** Identify and define which trial variables were collected using the clinical registry as well as any that were collected externally or via other sources. If relevant, include any changes in outcome variable coding (in the registry) that may have occurred during the data collection phase and how this was managed by the trial.
- **CONSORT-ROUTINE-5.** Provide details on the accuracy and validity of the registry data, referencing any validation studies or any methods used to assess the validity of registry data.
- **CONSORT-ROUTINE-5.** Describe the data quality of the registry including completeness, issues of misclassification and any methods used to minimise this.
- **CONSORT-ROUTINE-5.** Detail whether there was any adjudication of outcomes and what methods were used.

If linking data across registries, provide information on the registries that were used, what data were collected from which registry and describe the linkage methods used (e.g. deterministic or probabilistic and what identifiers were used for linking data).

Methods used to quantify, interpret, and account for errors in the linkage should also be described. Details on how frequently the data was collected during the trial period should also be described.

"For evaluation of superiority, SC's [substantial complications] will be identified from the national registries during 5 years of follow-up. ... A Data and Safety Monitoring Committee (DSMC) is responsible for monitoring adverse events and complications during the trial follow-up...[p.5] In the evaluation of the incidence of SC's, we expect close to 100% retention rate because data will be collected through the national register linkage.[48 p.4] … The DSMC will review data for the primary endpoints and safety at 30 days and after 1, 2, 3, and 4 years of follow-up. These data will be presented to the DSMC by the trial monitor and independent statisticians. … Presentations will be blinded so that treatment groups cannot be identified."[48 p.5]

"Adherence to the study protocol will be determined using standard AOANJRR data forms, completed by the surgical team at the time of surgery. The AOANJRR has completeness for more than 98% of arthroplasty procedures performed in Australia via standard forms submitted for both primary and revision procedures,30 and this process will remain unchanged. Bimonthly meetings of site principal investigators will occur to discuss study recruitment and identify barriers to study adherence. Sites will be provided written monthly updates on recruitment numbers, as well as protocol violations. Where protocol violations occur, site principal investigators will be required to provide a reason for the violation."[45 p.4]

"The Abdominal Core Health Quality Collaborative, a hernia-specific nationwide registry, served as the primary platform for data collection. Details regarding the Abdominal Core Health Quality Collaborative and registry structure, governance, and data assurance process have been previously reported.[7] Supplemental data not captured by the Abdominal Core Health Quality Collaborative were prospectively recorded in a Research Electronic Data Capture database."[47 p.668]

Methods - Sample size (CONSORT 7a)

Where trials have used the clinical registry to determine sample size and power calculations, details on what data was used, and how, should be reported.

"The sample size calculation is based on evaluation of the primary objectives. Based on retrospective analyses of data from SOReg [Scandinavian Obesity Surgery Register], it is assumed that 13% of patients who undergo LGBP [laparoscopic gastric bypass] will have SC's [substantial complications] (as defined in the trial outcomes) over 5 years."[48 p.4]

Methods - Allocation concealment mechanism (CONSORT 9)

Where the registry was used for randomisation, include details of how the random sequence allocation was implemented (e.g. registry randomisation module) and describe what steps were taken to conceal allocation.

> "The investigators enrolled the patients, who were randomly allocated to treatment groups after diagnostic coronary angiography and before percutaneous coronary intervention (PCI). Block randomization by center (permuted blocks of random sizes [2/4/6]) was used to assign patients in a 1:1 ratio to receive the DTS [dual-therapy sirolimus-eluting and CD34+ antibody–coated Combo stent] or the SES [sirolimus-eluting Orsiro stent]. The allocation sequence stratified by sex and presence of diabetes was computer-generated by an independent organization. Patients were assigned to treatment through a web-based randomization system. All individuals who were involved in the clinical event detection were blinded, whereas operators were not blinded to treatment assignment."[49 p.2156]

Results - Participant Flow (CONSORT 13a)

A diagram which clearly outlines: the number of participants recruited from the registry and other sources; numbers screened for eligibility; number randomised, number receiving the intervention, number lost to follow-up and number of analysed for primary outcome should be included.

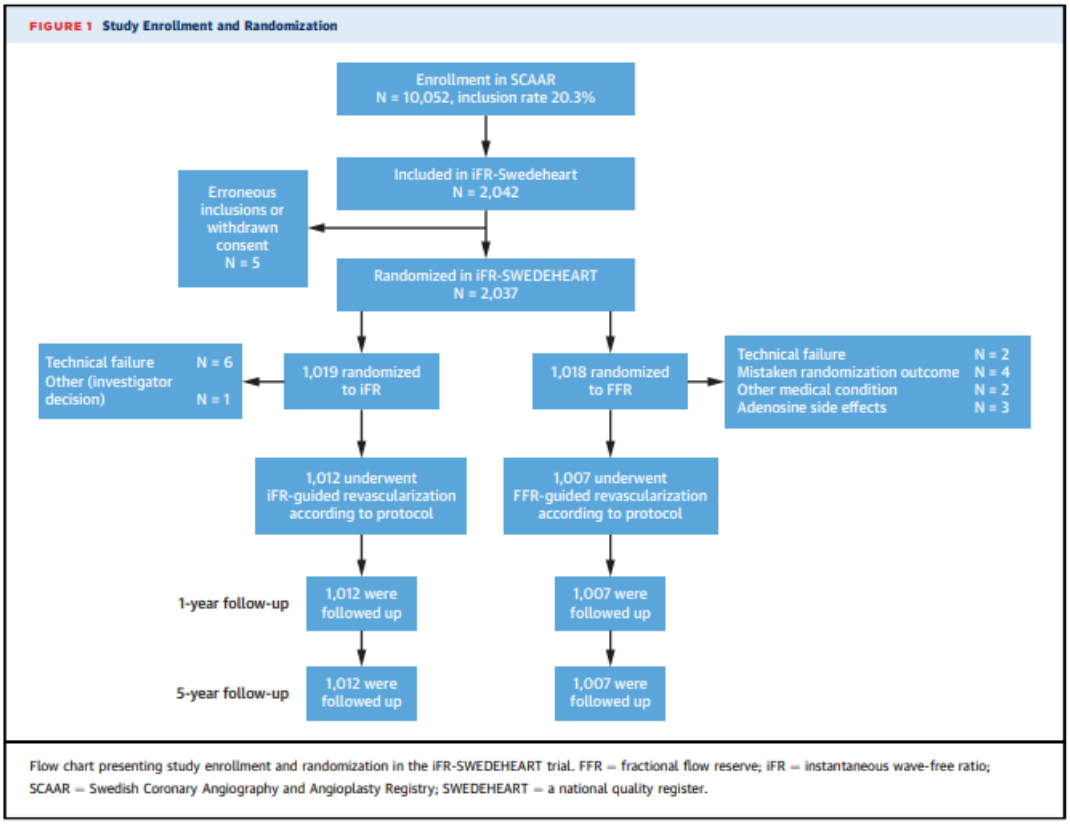

Figure 2 Example of a participant flow diagram

Source: Götberg et al 2022[50]

Discussion – Interpretation (CONSORT 22)

Should detail any benefits and/or limitations associated with using the registry for the trial.

Example limitations may include:

- Selection bias and generalisability of the registry population and how it relates to the broader population and/or the generalisability of the trial population and how it compares with the remaining registry population or those who have declined to participate in the trial
- Any issues relating to changes in coding of outcome variables during the trial or variables that may have impacted patient selection should be discussed

- Potential effects of linkage error on the results and how this has been mitigated
- Any limitations regarding the accuracy and validity of the outcome measures.

> "BEST is a register-based RCT, which provides several advantages. First, data on all patients undergoing bariatric surgery during the inclusion period in Sweden and Norway will be captured in the registry, regardless of whether or not they are included in the trial. We will therefore have the possibility of comparing included versus non-included patients during the same time period. Moreover, use of the registry as the CRF [case report form] simplifies and secures the collection and storage of data. Finally, there is an established routine for audit in place, which should maintain a high level of accuracy of the data.
>
> Another advantage is the possibility to cross-match the BEST/SOReg registry data to other national health care registries, which is enabled by the use of personal identification numbers given to all individuals in Sweden and Norway. For example, this means that we can cross-match data from the National Diabetes Registry and the Prescribed Drug Registry with BEST data, and thereby receive information on whether patients receive any pharmacological treatment for diabetes and their HbA1c levels, even if they decline to attend their follow-up visits after bariatric surgery."[48 p.6]

Other information – Funding (CONSORT 25)

Funding sources for both the trial and the clinical registry should be declared, along with the role of the funders in the trial.

> "Funding for this work is supported by the National Cancer Institute of the National Institutes of Health [R01CA211625 to A.Y.K.], the Rutgers Cancer Institute of New Jersey Comprehensive Cancer Center core grant from the National Cancer Institute [NIH/NCI, 3P30CA072720] including the use of the Biostatistics Shared Resource and the University of New Mexico Comprehensive Cancer Center core grant from the National Cancer Institute [NIH/NCI P30CA118100] including use of the services provided by the Behavioral Measurement and Population Sciences (BMPS) and Biostatistics Shared Resources. Support is also provided by the New Jersey State Cancer Registry, Cancer Epidemiology Services, New Jersey Department of Health, funded by the National Cancer Institute's Surveillance, Epidemiology and End Results (SEER) Program (#75N91021D00009), Centers for Disease Control and Prevention's National Program of Cancer Registries (#5NU58DP006279) with additional support from the State of New Jersey and the Rutgers Cancer Institute of New Jersey; New Mexico Tumor Registry, contract number HHSN261201800014I, Task Order HHSN26100001 from the National Cancer Institute; and the Colorado Cancer Registry, cooperative agreement NU58DP006347-02 from the CDC, with data collected and provided, in part, by the Colorado Central Cancer Registry (CCCR), a participating registry in the National Program of Cancer Registries (NPCR), CDC, cooperative agreement number 5 NU58DP006347."[51 p.975]

ASSESSING THE IMPACT OF A REGISTRY-BASED TRIAL

There is an ever increasing requirement to demonstrate the health and economic impact of clinical trials. Evaluating the impact of a registry-based trial is no different to how one might approach the evaluation of a traditional RCT. The Australian Clinical Trials Alliance released a scoping review of the literature in 2021 that identified existing research impact frameworks, measures, approaches and tools to support this sort of assessment.

For more information, please see: https://clinicaltrialsalliance.org.au/resource/assessing-the-impact-of-clinical-trials-a-scoping-literature-review/

PART 5 REGISTRY-BASED TRIAL CONSIDERATIONS FOR FUNDERS

CONSIDERATIONS FOR FUNDERS OF REGISTRIES

- Registry-based trials can only be conducted within clinical registries that have confirmed funding for at least the minimum time expected for trial recruitment, conduct and follow-up. As such, clinical registries with single year funding are unlikely to be able to support registry-based trials.
- Supporting registry-based trials is not a cost-free activity for clinical registries. At a minimum, registries require funding support for their staff to clean and extract data for registry-based trials (as these activities are undertaken for specific trial data and participants which is different from usual registry practice).
- Depending on the clinical registry, additional funding may be required to support the amendments to ethics and site governance approvals to support registry-based trials.
- Depending on the clinical registry, additional funding may be required to upgrade existing technology infrastructure to support registry-based trials.
- When funding new clinical registries, it may be prudent to fund these registries to design and develop infrastructure with the intention to support registry-based trials if that is an intended or expected use of the registry.

CONSIDERATIONS FOR FUNDERS OF REGISTRY-BASED TRIALS

- The sustainability of the clinical registry is an important consideration when deciding to fund registry-based trials. The clinical registry needs to have confirmed funding for at least the minimum time expected for trial recruitment, conduct and follow-up.
- While registry-based trials may be a cost-effective approach to trials, they are not cost-free for either the clinical registry or the trial. It should be expected that costs associated with using the registry infrastructure or obtaining data from the registry are in registry-based trial budgets. This may include funding to support registry staff (project management and data management), data cleaning and extraction, data hosting in secure environments, data collection, technology platform changes, etc.

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GLOSSARY

Terminology	Definition
Administrative data[52]	Information collected routinely from the patient's medical record, primarily for administrative (not research) purposes. This type of data is collected by hospitals, government departments and other organisations for the purposes of registration, transaction and record keeping, usually during the delivery of a service.
Benchmark[52]	A measurement taken at the outset of a series of measurements of the same variable, sometimes meaning the best or most desirable value of the variable. A standard or point of reference.
Clinical quality outcomes datasets[52]	Datasets that include a combination of clinical and patient-derived data for a particular clinical domain. This universal term is inclusive of Clinical Quality Registries and other mechanisms like virtual registries (i.e. those that draw data from existing platforms).
Clinical quality registry/ies (CQR)[52]	Clinical registries that regularly provide feedback to participating sites and clinicians regarding performance against clinical quality indicators, with the aim of reducing variation and improving overall patient outcomes.
Clinical or patient register/ies[3]	Organised systems that use "observational study methods to collect uniform data (clinical and other) to evaluate specified outcomes for a population defined by a particular disease, condition, or exposure, and that serves one or more stated scientific, clinical, or policy purposes."
Clinical trial[52]	Any research project that prospectively assigns human participants or groups ... to one or more health-related interventions to evaluate the effects on health outcomes.
Data linkage[53]	Method of bringing together information derived from different sources, but relating to the same individual or event in a single file.
Interoperability[52]	The ability of computer systems or software to exchange and make use of information.
Registry-based trial	Is a prospective interventional study that uses at least one clinical registry, whereby: • there must be a priori involvement of a clinical registry as part of the trial planning; • the trial is conceptualised to use a clinical registry as part of trial design; • participants are prospectively assigned to one or more interventions; • the intervention allocation is randomised.

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