Realising the potential: leveraging clinical quality registries for real world clinical research

Broader use of clinical quality registry infrastructure will enhance research-driven improvements in health care

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".[1] Clinical quality registries (CQRs) in Australia refer specifically to 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.[2] They are recognised as important quality improvement initiatives by the Australian Commission on Safety and Quality in Health Care, which released a framework for clinical registries in 2014.[2] The Commission has over 90 clinical registries listed in Australia, across diverse clinical areas, surgeries, procedures and devices on its Australian Register of Clinical Registries.[3] Nationally, the importance of maximising the impact of CQRs in achieving better health outcomes was recently recognised by the release of the National Clinical Quality Registry and Virtual Registry Strategy.[4] However, while CQRs produce technical reports and their data are used for secondary research purposes, their role as an effective research tool in their own right in Australia has received limited specific attention, resulting in a significant unrealised potential in Australian clinical research infrastructure.

Developing and maintaining CQRs allows for the systematic collection of outcome data, and embedding research into CQRs creates efficiencies in the collection and use of outcome data for multiple purposes. There is a clear overlap between measuring quality in health care through CQRs and using their infrastructure for health care improvement. Utilising the existing large-scale data collection that is the core business of CQRs, and asking more specific questions about existing and emerging health care practices in terms of their safety, efficacy, comparative outcomes and use in different populations, provides a cost-effective and efficient mechanism for improving health care. However, as long as CQRs are inconsistently funded by both health care and research funders, this potential remains largely unrealised.

Registry-based clinical trials: advantages and limitations

During the past decade, the need for a research approach that combines scientific rigour yet is inclusive of real world patients and clinical practice has become increasingly clear. The necessity to minimise the time and costs associated with interventional trials while still maintaining scientific standards has led to interest in leveraging existing forms of high quality data collection to support research in broader, more representative population groups and through usual care processes. A method to achieve this is through a registry-based trial. Registry-based trials may utilise a CQR for the recruitment of participants into a trial, and/or for access to baseline and/or outcome data. As CQRs systematically collect prospective data regarding a significant number of people, conditions, devices and treatments of interest, they are a potentially rich clinical infrastructure which can be leveraged to support a range of research methodologies. This includes cohort sub-studies, post-marketing surveillance activities, and clinical trials.

The potential advantages of registry-based clinical trials to evaluate interventions compared with standard randomised controlled trials (RCTs) have been well documented.[5-9] A major benefit is that registry-based trials can represent broader population groups. Additionally, design elements aimed at improving the scientific rigour of RCTs can be applied to registry-based trials — including the ability to randomise participants to different trial arms, single or double blinding, per-protocol statistical analysis, and adjudication of outcome measures — depending on the registry infrastructure and the research question requirements. CQRs may also link to other registries (including death and cancer registries) and biobanks, collect longer term follow-up than traditional RCTs, and have enhanced data integrity through longer term data storage and management. As a result, registry-based trials can appropriately sit alongside evidence generated by the existing observational and interventional study types, as well as evidence generated from other newer trial types such as pragmatic trials and platform trials to support regulatory, clinical and policy decision making.

Where registry-based trials are particularly suited is in comparative studies of real world outcomes of different existing clinical care practices.[5] A 2020 scoping review noted, based on a strict definition of a registry-based RCT, that there were 17 outcome trials in the literature published between 1996 and 2017, predominantly from European countries or the United States, and one from Australia.[5] This highlights the extent of the missed opportunity of registry-based trials, from both a lack of explicit support from research funding bodies until very recently, and challenges with implementation. Establishing the number of registry-based trials being conducted in Australia (or elsewhere) is not easily determined. Not all trials listed in the Australian New Zealand Clinical

Susannah Ahern[1]
Belinda J Gabbe[1]
Sally Green[1]
Carol L Hodgson[1,2]
Erica M Wood[1,3]
John R Zalcberg OAM[1,2]
Tsharni Zazryn[1]

1 Monash University, Melbourne, VIC.
2 Alfred Hospital, Melbourne, VIC.
3 Monash Health, Melbourne, VIC.

susannah.ahern@monash.edu

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1 Currently listed Australian New Zealand Clinical Trials Registry trials using a registry listed on the Australian Register of Clinical Registries

Trial acronym	Trial ID (ACTRN/NCT)	Registry*	Patient population	Comparison	Current status
BEST-Fluids	ACTRN12617000358347	Australia and New Zealand Dialysis and Transplant Registry	End-stage kidney disease receiving a deceased donor kidney transplant	Two standard care approaches	Active, not recruiting
BLENDER	NCT03841084	Australian and New Zealand extracorporeal membrane oxygenation registry	Severe acute respiratory and/ or cardiac failure or following refractory cardiac arrest	An alternate therapy *v* standard care	Recruiting
CRISTAL	ACTRN12618001879257	Australian Orthopaedic Association National Joint Replacement Registry	Total hip arthroplasty and total knee arthroplasty	An alternate therapy *v* standard care	Stopped early
DETECT	ACTRN12611000538943	Australia and New Zealand Dialysis and Transplant Registry	Colorectal cancer in people with chronic kidney disease	Testing a screening test kit	Completed
DIAAMOND: Ava FIRST; Ava NEXT	ACTRN12619001042134; ACTRN12619001043123	Aplastic Anaemia and Other Bone Marrow Failure Syndromes Registry	Treatment-naive and relapse/ refractory severe aplastic anaemia	Addition of a therapy in combination with standard care	Recruiting
DISTINCT	ACTRN12621000069853	Australian Orthopaedic Association National Joint Replacement Registry	Femoral neck fractures	An alternative therapy *v* standard care	Recruiting
ECMO-Rehab	NCT05003609	Australian and New Zealand extracorporeal membrane oxygenation registry	Patients in ICU receiving extracorporeal membrane oxygenation for between 24 and 72 hours	Early rehabilitation *v* standard care	Not yet recruiting
FAN Trial	ACTRN12618001124224	Australian and New Zealand Fontan Registry	Fontan-associated nephropathy	An alternative therapy *v* standard care	Not yet recruiting
FRAIL-M	ACTRN12619001199101	Myeloma and Related Diseases Registry	Multiple myeloma	Alternative therapies	Recruiting
MINOCA-BAT	ACTRN12618001858280	Coronary Angiogram Database of South Australia	Myocardial infarction with non-obstructed coronary arteries	Alternative therapies	Recruiting
My-PROMPT	ACTRN12618001878268	Myeloma and Related Diseases Registry	Newly diagnosed multiple myeloma	An alternative feedback approach *v* standard feedback approach	Active, not recruiting
PEPTIC	ACTRN12616000481471	Australian and New Zealand Intensive Care Society registries	Patients who are mechanically ventilated with 24 hours of intensive care unit admission	Two standard care approaches	Completed

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Trial acronym	Trial ID (ACTRN/NCT)	Registry*	Patient population	Comparison	Current status
PROpatient	ACTRN12619001126101	Upper Gastrointestinal Cancer Registry	Upper gastrointestinal cancer	A symptom monitoring and care coordination intervention *v* standard care	Recruiting
P2S	ACTRN12617001205325	Australian Stroke Clinical Registry	First episode of acute stroke or other indexed stroke event	An alternative therapy *v* standard care	Completed
RASKAL	ACTRN12621000205831	Australian Orthopaedic Association National Joint Replacement Registry	Total knee arthroplasty	Alternative surgery techniques	Recruiting
STELAR	ACTRN12619001072101	Australian Stroke Clinical Registry	Hospitals that have provided data to the Australian Stroke Clinical Registry for at least 6 months	An alternative feedback approach *v* usual feedback approach	Completed
SWIFT	ACTRN12620001061921; ACTRN12618001976279	Australia and New Zealand Dialysis and Transplant Registry	Kidney failure managed with chronic haemodialysis	Addition of a therapy in combination with standard care *v* standard care	Not yet recruiting
SABRE	ACTRN12620000321943	Australia and New Zealand Dialysis and Transplant Registry	Patients receiving satellite haemodialysis	Addition of a therapy *v* standard care	Not yet recruiting
No acronym	ACTRN12615001369516	Prostate Cancer Outcomes Registry – Victoria	Prostate cancer	Alternative feedback approaches *v* standard feedback approach	Completed
No acronym	ACTRN12610000337077	Australian Stroke Clinical Registry	Registered case on the stroke registry	An alternative feedback approach *v* standard feedback approach	Completed

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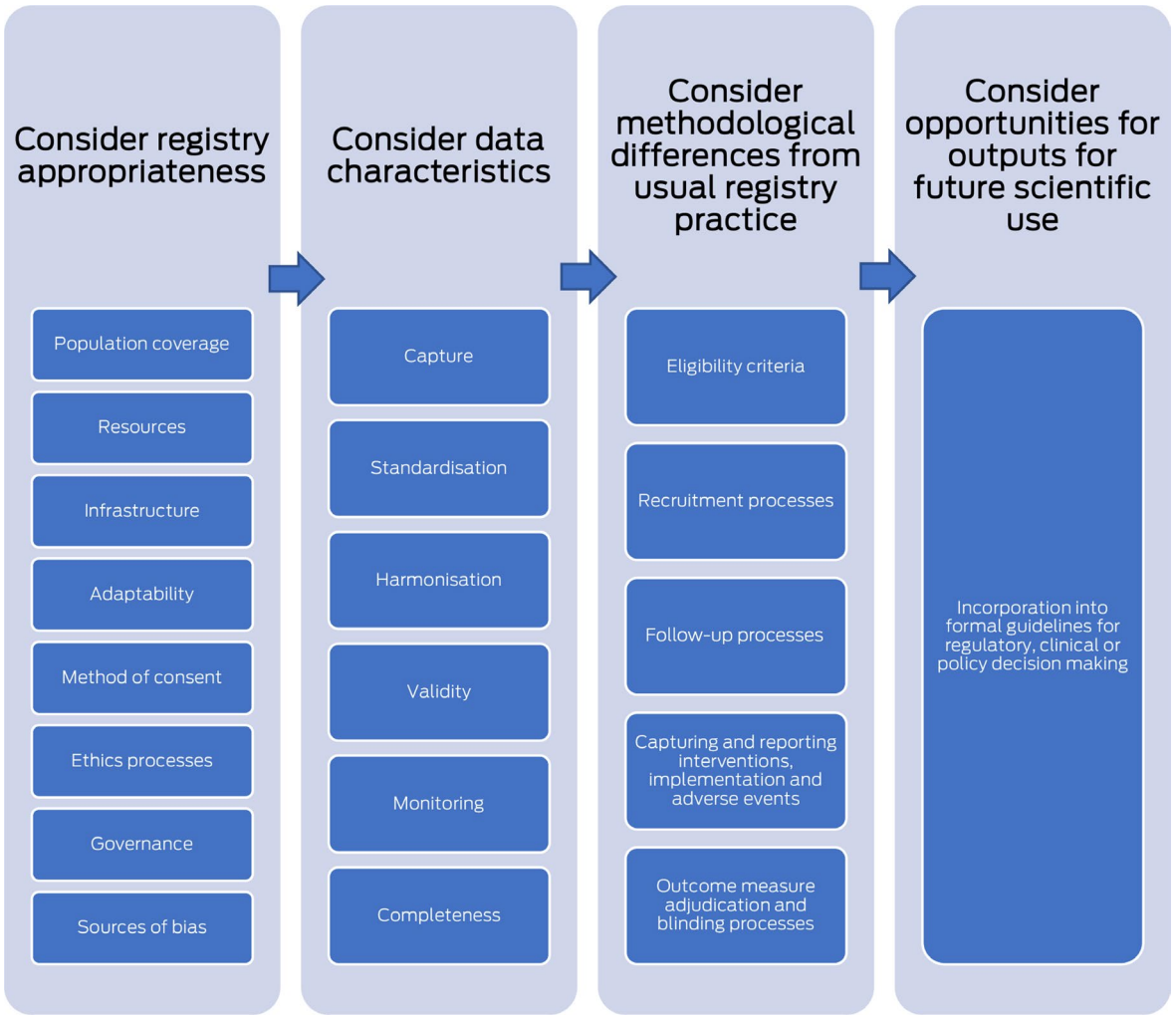
Trials Registry note whether a registry is being used as part of the research, and some Australian trials are listed on international trial registries (such as ClinicalTrials.gov) instead. Based on available data, at least 20 registry-based trials (using clinical registries or CQRs) are currently being conducted in Australia. Box 1 provides a list of these trials identified in the Australian New Zealand Clinical Trials Registry (using the search term "registry" and study type "interventional") that have documented that they are using a CQR listed on the Australian Register of Clinical Registries for their recruitment and/or baseline and/or outcome data.

As with all research, appropriate ethical considerations (including consent) are required, and the study design chosen to answer the research questions must be fit for purpose. Registry-based trials have several different characteristics, some of which may pose methodological and other challenges or uncertainty compared with traditional trial methods. Additionally, within this relatively new area of research methodology, no agreed approaches, or standardised methods to undertake registry-based trials yet exist, and their processes, data and reporting are neither uniform nor standardised.[5,7] This is currently limiting the potential use and uptake of registry-based trials as a scientifically validated approach to answering research questions. Some of the specific methodological and other considerations for registry-based trials are highlighted in Box 2.

The way forward for registry-based trials in Australia

Research needs for data quality and integrity, and the broad range of research questions that potentially could be answered with the use of CQRs, should drive further investment into such infrastructure in Australia.

2 Methodological and other considerations related to registry-based trials



The opportunities afforded by using CQRs for timely and cheaper trials (as some or all of the required infrastructure is or may be separately funded) — and importantly, reduced duplication of effort — has the potential to significantly expand Australia's clinical research capability. CQRs can investigate variations in health care processes and can provide insights into whether evidence (from research) is being implemented in practice. They can also support implementation planning and monitoring for drugs and devices. The post-marketing role of CQRs for drugs and devices has been acknowledged in Australia by the Pharmaceutical Benefits Advisory Committee (eg, with the Australian Cystic Fibrosis Data Registry) and by the Therapeutic Goods Administration (eg, with the Australian Orthopaedic Association National Joint Replacement Registry), as described in the Therapeutic Goods Administration's 2021 clinical evidence guidelines.[10-12] Registry-based longitudinal collection of patient-reported experience and outcome measures can enhance current standards of care as well as provide patient-derived information that is often required in a traditional RCT, increasing the knowledge available for future clinical decision making. Where these data are already collected as part of the CQR, this can be an efficiency gain for the trial, although it may require additional costs if such measures are not already routinely collected by the CQR.

The important role of CQRs in regulatory decision making has been recognised by the major regulators in Europe and the US for over a decade. The European Medicines Agency recently released guidelines on registry-based studies for drug marketing authorisation applicants planning such studies, and the US Food and Drug Administration has developed policies regarding the use of real world data and evidence to support efficacy claims.[13-14] A recent US publication calls for a better alignment of the regulatory policies underpinning the use of registries for post-marketing surveillance with the methodology and approaches to such surveillance (particularly with regard to device-to-device comparisons), to better facilitate research into comparative effectiveness.[15] To further Australia's contribution to international action in this area, a similar approach would be beneficial. In particular, the following questions need to be answered:

- What key features must exist in a registry to make it appropriate for registry-based trials?
- What types of interventions are appropriate to be evaluated in registry-based trials?
- What does good clinical research practice look like in a registry-based trial?
- How are registry-based trials viewed by regulators, funders and clinicians in terms of excellence, validity, scientific value, cost-effectiveness, policy, and guideline development?
- What is the importance of secondary use of registry data for clinical trials from a consumer perspective?

Addressing these methodological and broader considerations will allow existing and new CQR infrastructure to more extensively support and enhance research-driven improvements in health care for the Australian community. Realising the research potential of CQRs within Australia will be an important objective in sustaining a flourishing clinical research sector, in what will be a fiscally constrained post-pandemic clinical research landscape.

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