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Title:
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Date:
2018-12-01

Citation:
Foroughi, S., Wong, H. L., Gately, L., Lee, M., Simons, K., Tie, J., Burgess, A. W. & Gibbs, P. (2018). Re-inventing the randomized controlled trial in medical oncology: The registry-based trial. Asia Pacific Journal of Clinical Oncology, 14 (6), pp.365-373. https://doi.org/10.1111/ajco.12992.

Persistent Link:
https://hdl.handle.net/11343/284088

# Re-inventing the randomized controlled trial in medical oncology – The registry-based trial

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**Running title:** Registry-based trials

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**Acknowledgements**

**Word count (main text):** 3998

**Number of tables:** 5

This is the author manuscript accepted for publication and has undergone full peer review but has not been through the copyediting, typesetting, pagination and proofreading process, which may lead to differences between this version and the Version of Record. Please cite this article as doi: 10.1111/ajco.12992.

**Number of figures:** 1



**ABSTRACT**

Substantial progress has recently been made in optimizing the management of cancer patients, resulting in major gains in survival and quality of life. Much of this progress has resulted from the serial testing of promising treatment strategies, typically using prospective randomized controlled trials to compare outcomes achieved with the new approach versus the current standard(s) of care. However, there is an ever-expanding list of important questions that are difficult to investigate, particularly with respect to determining the optimal sequencing and combination of proven active agents. With the rapidly growing list of clinical, pathologic, and molecular characteristics that promise to predict treatment benefit and/or risk for defined patient subsets, many new questions regarding how best to personalize our approach to treatment selection are emerging. These questions can be investigated in the context of registry-based randomized clinical trials. Recently, the potential of registry-based randomized clinical trials was demonstrated in cardiology, highlighting the ability to rapidly recruit large numbers of patients to a trial addressing an important clinical question, with minimal cost and high external validity. In this review we discuss the challenges and limitations of conventional clinical trials in multidisciplinary cancer care, describe the potential advantages of registry-based randomized trials, and highlight several registry-based oncology studies that are already underway to demonstrate the feasibility of this approach.

**Word count (abstract):** 215

**Keywords:** Prospective Studies, Registries, Research Design, Registry-based Randomized Trial, Prospective Randomized Trial

MAIN TEXT

## Introduction

Randomized controlled trials (RCTs) serve as a tool for comparing existing treatments, as well as evaluating the efficacy of new therapies. These can be conducted in a broad patient population or in a specific subset of patients. Fundamental to the success of RCTs are the inclusion and exclusion criteria that impact patient enrolment, stratification according to known prognostic and predictive factors, and the use of randomization. Ultimately the aim is that any differences in outcome can be presumed to be due to the differential effects of the management strategies being compared. In an ideal world, each RCT would recruit a patient sample that is truly representative of the general population of cancer patients, thus maximizing the external validity of the results. However, the majority of conventional RCTs have highly selective inclusion and exclusion criteria, which can limit their true generalizability.

In this article, we aim to describe the challenges and limitations of RCTs in cancer medicine and the opportunity to bridge the gap between RCTs and real-world clinical practice using prospective, registry-based randomized clinical trials (RRCTs). We discuss how this approach can improve some of the prohibitive aspects of conducting an RCT and explore the drawbacks of using this study design. Finally, we introduce RRCTs that we are currently undertaking to demonstrate their feasibility and potential to accelerate progress in optimizing patient treatment and outcomes in medical oncology.

## Strengths and limitations of conventional randomized controlled trials

Randomized controlled trials (RCTs) form the evidentiary backbone of clinical practice guidelines and represent the gold standard in the clinical research paradigm.[1,2] RCTs are quantitative, comparative, controlled clinical experiments. The strength of the RCT rests on high internal validity, relying on the combination of stratification and randomization to ensure that the only systematic difference between two treatment arms is the patients' exposure to the intervention of interest.[3] Stratification can be applied to eliminate confounding by known strong predictive factors. When properly executed, stratification guarantees perfect balance between treatment groups on the characteristics included in the study, however, it is limited by sample size: it is impossible to have more strata than observations. As such, it is impossible to achieve perfect balance on all characteristics that are potentially relevant. Instead, randomization is used to minimize the imbalance on all remaining characteristics of patients, measured or unmeasured, casually related or unrelated to the outcome of interest.[4] Furthermore, RCTs are controlled, prospective trials and these properties help establish causality as opposed to mere correlation or reverse causality.

However, RCTs can be subject to extrapolation bias that limit their impact on the care of patients in routine clinical practice. Often the selective nature of inclusion criteria applied to clinical trials can restrict participation to a subset of patients,[5] typically those that are relatively young and fit and/or with minimal co-morbidities. In contrast, a large proportion of patients presenting for treatment advice in the real world are frail, of advanced age and/or have multiple co-morbidities. Determining the relevance and generalizability of the results achieved in RCTs conducted in patients with narrow selection criteria and strict protocols is a continuous challenge for clinicians.[6,7]

While generalization is non-trivial even in optimal circumstances, the reporting of selection criteria for RCTs is often incomplete and this further obstructs proper interpretation of the results.[8] A study examining the reporting

of selection criteria from 52 clinical trial protocols and the resulting publications found discrepancies in all trials assessed. Of the 1248 eligibility criteria pre-specified in the protocols, 479 were missing and 163 were modified in the final publication. Of concern, the vast majority of missing eligibility criteria (96%) and the majority of modified eligibility criteria (54%) suggested that broader populations than initially specified were included in the studies.[9] Modified, incomplete or inadequate reporting of eligibility criteria can drastically alter the context and applicability of trial results.

Another challenge associated with conventional clinical trials is the escalating cost of conducting RCTs, limiting the number of potential studies that can be undertaken in an increasingly resource-strained environment. Furthermore, the high cost of purchasing newer drugs prevent many of them from being tested in novel settings, such as a different patient group, a different disease or disease subset, or a different line of therapy. Exploring these new frontiers relies on substantial funding support being provided by the pharmaceutical industry in the form of free drug supply.

Increasingly, tumor types are being further sub-categorized according to clinical, pathologic, molecular, or prior treatment characteristics rather than simply the tumor site of origin. For example, studies of patients with metastatic colorectal cancer (mCRC) may focus on a clinical subset (e.g. resectable liver metastases),[10] a molecular subset (e.g. *KRAS* wild-type)[11] or mandate a prior number of therapy(ies).[12] Sub-classification can limit the number of available patients that can be recruited and by extension, the feasibility of individual sites to participate in new trials. Where the focus is on even more uncommon subsets, such as *BRAF*-mutated mCRC (8-12% of patients),[13,14] *HER2*-expressing mCRC (5%)[15] or mismatch repair deficient mCRC (5%)[14] very few sites can contribute significant numbers of patients. Given the time, effort and costs associated with opening a trial at each site, it may not be feasible for the investigator or the sponsor to open a study that is predicted to recruit only 1 or 2 patients over the projected study period.

By this mechanism, centers contributing patients to clinical trials are also increasingly selected, with the centers recruiting the majority of patients likely to have the largest patient volumes and an interest or expertise in the disease type being studied.[16] Treatment outcomes achieved at these major clinical centers may possibly be significantly different to those achieved with the same approach at a smaller, non-specialist center. Factors contributing to this potential discrepancy include the treatment being provided by highly expert subspecialist clinicians who are supported by expert trial nurses, pharmacists, and radiologists; and the patient population being fit and motivated to travel to the center to participate in a clinical trial that offers access to a promising new therapy.[17] Consequently, for many reasons the gains achieved in clinical trials do not necessarily translate to the broader clinical population across the spectrum of health care systems.[18] The outcomes of a drug given frequently at a major treatment center are conceivably quite different to the same drug being delivered infrequently at smaller centers.[19]

With a growing number of treatment options and potential biomarkers for cancer patients, there is a rapidly expanding number of unanswered questions related to the optimal combining or sequencing of treatment options and how best to tailor this for each individual patient and their circumstances. New approaches to advancing knowledge are needed, in particular approaches that deliver estimates that are unbiased and can readily be used to impact practice without the need to extrapolate to a significantly different patient population.

**Strengths and limitations of clinical registries to advance therapy knowledge**

A clinical registry is defined as an *organized* system that uses *observational* study methods to *systematically* collect *uniform* data to evaluate *specified outcomes* for a population defined by a particular *disease.* [20]

The Surveillance, Epidemiology, and End Results (SEER) Program (www.seer.cancer.gov) is one of the best-known efforts to collect a standard dataset on consecutive cancer patients.[21] Data collection for the SEER program began in 1973 and initially included data from 7 geographic areas in the United States.[22] Later this effort was expanded to include data collection across 20 geographic areas representing approximately 28% of the US population. SEER collects information on patient demographics, tumor characteristics, including primary tumor location and extent of disease, and the use of cancer-directed surgery, radiation therapy, systemic therapy, and patient survival.[21] The main limitation of SEER data is not its validity but rather the depth of clinical information;[23] in SEER, treatment data is only collected for the first course of treatment[24] which can limit analysis of treatment outcomes across different centers. Linkage of SEER data to Medicare claims for health care services allows a more comprehensive examination of treatment information, but SEER-Medicare only captures data on patients aged 65 years and older,[25] limiting its generalizability. Further, the SEER data on metastatic tumors is often inadequate (this data is only captured well if the tumour is metastatic at diagnosis); and SEER does not include detailed data on comorbidities, potentially important confounders of treatment responses and outcomes.[22,23]

The SEER program highlights some of the advantages and disadvantages associated with observational research based on analysis of clinical registry data. Broad inclusion criteria increase the probability that patient numbers are sufficiently large to explore outcomes in various subpopulations of interest, including those that are underrepresented in RCTs. Registries such as SEER can provide data on the benefit and safety of new therapies once they are adopted in the routine clinical setting.[26] However, in these analyses for efficacy and/or safety, therapy selection bias is always a confounding factor as almost inevitably it is the fitter patients with a better prognosis and potentially higher treatment tolerance that are more likely to receive the intervention,[27] and such patients have improved outcomes independent of treatment effect. While some of this can potentially be accounted for, e.g. in a stratified analysis, using propensity scores or adjustment in multiple regression, in the absence of randomization it is not possible to be confident that observed differences are truly the result of treatment impact. It is impossible to adjust for characteristics that were not measured. While all studies are limited to observed data, available registry data is limited by design choices that may not have been optimal for the research question. Lack of data availability is not limited to diagnostic or prognostic factors; efficacy analyses may also be influenced by non-standardized endpoints or endpoints that are difficult to evaluate retrospectively, although reliable outcome data can be achieved for hard endpoints such as overall survival. Finally, data quality is a common and legitimate concern for registry-based research, particularly where data are collected retrospectively or for data points that may be poorly documented in the clinical notes, such as performance status, co-morbidity, family history or patient preferences. Reporting specifications and standards may also be modified over time or differ between regions, which may lead to differences in quality and incompatible categorisations.

Despite statistical advances[28] comparative observational registry studies have generally not been accepted by the cancer research community as sufficient to change standards of care, mostly because they lack the credibility associated with pre-registration and randomization.[29] The "intellectual trap" described by Lauer and D'Agostino[30] between randomized trials that lack external validity (generalizability) and observational studies that lack internal validity, owing to unmeasured confounders, can be avoided using a randomized registry-based approach (Table 1).

These limitations of *post hoc* analyses of registry data can be overcome if comparisons are conducted prospectively by using high quality registries that mandate capture of critical data points, stratify patients according to important prognostic variables and (most importantly) incorporate randomization to effectively eliminate selection bias. The registry RCT thus presents an opportunity to harness the "untapped potential of observational research to inform clinical decision making".[31]

**Registry-based randomized clinical trials**

Registry-based randomized clinical trials (RRCTs) are a relatively new concept for clinical research in cardiology and other disease settings,[1] and are yet to be explored as an alternative to conventional randomized studies in oncology. By combining the major strengths of a conventional RCT, namely patient stratification and randomization, important questions could be reliably addressed using RRCTs with greater ease and at significantly lower cost. Rapid patient recruitment is typically achieved by consecutive enrolment using generous eligibility criteria, which also enhances the generalizability of results due to inclusion of a real-world population.[5,28]

Essentially replacing the case report form (CRF) used for a conventional RCT is the registry database, which captures the key data relevant to the patient group, the treatment administered and the outcome of interest. Typically, the registry database will have far less data for each patient than is captured for a conventional RCT, but where the treatments are with standard agents or common treatment combinations with well described adverse events, the focus of the RRCT can be upon a hard clinical endpoint such as overall survival. An exhaustive effort to collect all clinical and adverse event data is not made, but most cancer registries can capture key adverse event data, including serious adverse events. In addition, linkage to population-based registry data (e.g. the National Death Index) and administrative data (e.g. pharmacy databases) can complement RRCTs and improve data accuracy.[23]

Although lacking the credibility of a conventional RCT, registry-based RCTs can still retain key aspects of study conduct such as sample size calculations, interim analyses for futility and data audits. The economic advantage of RRCT's is largely due to the externalization of costs usually associated with conventional RCT's (Table 2). Typically, these costs lie in establishing infrastructure for study databases, personnel costs associated with data capture and monitoring, as well as to conduct protocol specific procedures outside standard of care. By leveraging resources from an existing registry, these costs are indirectly transferred and result in a significant reduction in administrative and training costs. However, data quality may be affected as toxicity and dosing data are not always captured and radiological assessments are often not standardized, impacting measurement of response rate and progression-free survival. In addition, other valuable endpoints such as quality of life are not usually captured as these are not typically included in standard registries. Thus, registry-based trials are most useful in pragmatic study designs that measure hard endpoints and compare treatments where toxicity profiles are already well known.

The Thrombus Aspiration in ST-Elevation Myocardial Infarction in Scandinavia (TASTE) trial was a landmark proof-of-concept RRCT designed to determine if routine intracoronary thrombus aspiration before percutaneous coronary intervention (PCI) reduced mortality in patients with ST-segment elevation myocardial infarctions (STEMI).[32] The study protocol was developed based on the Swedish Coronary Angiography and Angioplasty Registry (SCAAR) which formed the platform for randomization.[33] SCAAR is one of four registries that form

part of Sweden's national online cardiac registry: the Swedish Web-system for Enhancement and Development of Evidence-based care in Heart disease Evaluated According to Recommended Therapies (SWEDEHEART).[34,35] Using an established online registry as the basis for randomization, case record form data collection and follow-up made the trial economically and administratively feasible.[36] A total of 7,244 patients, representing 60% of all STEMI patients referred for PCI in Sweden and Iceland during the study period, were randomized to receive PCI with or without thrombus aspiration. The study found no statistically significant difference in mortality at 30 days between the two groups. The study was completed in less than three years at an estimated cost of US$50 per randomized patient, a >90% cost saving compared to a similar conventional RCT.[1,37]

Despite the benefits we have highlighted and the suitability of registry-based randomized clinical trials to answer questions about effectiveness of treatments in real-world practice, challenges exist and care needs to be taken when determining if a registry-based approach is suitable (Table 1). A search of the clinicaltrial.gov website[38] identified at least 9 ongoing RCTs implementing a registry-based approach (Table 3); notably none of these trials are enrolling patients with cancer.

**The potential of registry-based RCTs in medical oncology**

In oncology practice, it is common to have multiple treatment options to select from, often with no clearly superior approach. Frequently this is because head-to-head RCTs have not been conducted successfully or that completed RCTs have not identified benefits in a specific patient subset, the RCT being essential to capturing the relative treatment effects of the available interventions.[39] As debates about comparative-cost effectiveness of clinical research intensify, it is becoming clear that many proposed clinical trials are too complex, difficult and expensive. The low cost of utilizing large-scale cancer registries as the platform for RCTs provides an opportunity to develop a new, and complementary, approach to clinical trial research (Figure 1). Logically, this requires the existence of suitable established clinical registries.

**Oncology clinical registries in Australia: ready for primetime**

Multiple cancer registries have been established in Australia. To support a registry-based RCT critical data items need to be captured, including known prognostic and predictive factors, and the data need to be captured in close to real-time as clearly patients cannot be randomized retrospectively after therapy has been initiated. The Treatment of Recurrent and Advanced Colorectal Cancer (TRACC) registry (Melbourne Health ethics number: 2009.113)[40], is an Australian mCRC registry established in 2009 and expanded internationally to Hong Kong in 2016.[41] This multi-site prospective clinical registry captures baseline data, multidisciplinary treatment data across all lines of therapy, and outcome data on consecutive patients with mCRC managed at the participating centers. All information relevant to prognosis and treatment selection is recorded routinely, often at point of care, and typically at multiple important landmarks that occur well after the diagnosis. For example, the sites of metastatic disease and the Eastern Cooperative Oncology Group (ECOG) scale of performance status (PS) are recorded at the beginning of each new line of therapy. Details of the primary tumor and any adjuvant therapy are also available in the database. A general description of data items collected in the TRACC registry is provided in Table 4.

The TRACC registry provides a secure, 128-bit SSL encrypted, web-based platform allowing data to be entered directly by clinicians or data officers into an electronic database. The electronic platform is designed to minimize data errors through features such as mandatory fields, logic rules and built-in data dictionaries. As of the third quarter of 2017, patient enrolment is ongoing at 32 sites across Australia and Hong Kong and 2870 participants have been recruited. De-identified data from TRACC is accessible to researchers by application to

BioGrid Australia (https://www.biogrid.org.au), a process which includes ethics and scientific review as well as custodian approval.[42] TRACC has been used to examine the impact and safety of bevacizumab in routine care,[43] and to explore whether the results are relevant in other populations of interest such as patients with *RAS* mutations, the elderly or those with peritoneal disease.[44]

Similar registries have been established for prostate cancer (trial ID: ACTRN12616000585426), pancreatic cancer (trial ID: ACTRN12617001474347), HER2+ breast cancer (neoadjuvant and metastatic) (trial ID: ACTRN12615000232538), and more recently efforts are underway in brain tumors, bladder cancer, testicular cancer, and gastro-esophageal cancer. Each of these new registries will involve sites across Australia, including both public and private settings, as well as metropolitan and regional centers. There is also increasing international engagement, now including multiple participating centers in the Asia Pacific region (New Zealand, Singapore, and Hong Kong) in many of the registries.

**Recently initiated and proposed registry-based RCTs in Australia**

With funding support from the Victorian Comprehensive Cancer Centre (VCCC), our group is initiating randomized registry-based trials in three different tumor types: mCRC (ALT-TRACC), glioblastoma (EX-TEM) and pancreatic cancer (PAN-PAL), the first two now having ethics approval and opening at multiple sites. In each instance, all the required treatment and outcome data is being captured in existing registries coordinated by the Walter and Eliza Hall Institute of Medical Research (WEHI) (Table 5), with the only intervention being the need to randomize patients to receive treatments that are either current or emerging standard of care therapies. The disease types and trial designs are described below.

*Metastatic colorectal cancer (mCRC). The ALT-TRACC trial*

ALT-TRACC is an RRCT randomizing patients with treatment-naïve mCRC to alternating 2 cycles of oxaliplatin and irinotecan doublet chemotherapy versus standard continuous doublet chemotherapy. The hypothesis is that using alternating schedules of oxaliplatin and irinotecan doublets might increase efficacy by delaying the emergence of cell resistance and will also mean exposure to all active chemotherapy agents in the first-line setting, an alternative to giving all three drugs at once (FOLFOXIRI) where toxicity concerns have limited clinical uptake. Further justification for ALT-TRACC comes from recent phase II data from the Sequential and Concurrent FOLFOXIRI/Bevacizumab Regimens Versus FOLFOX/Bevacizumab in First-Line Metastatic Colorectal Cancer (STEAM) study, presented at the 2016 American Society of Clinical Oncology Gastrointestinal Cancers Symposium.[45] Two hundred and eighty patients were randomized in a 1:1:1 ratio to FOLFOXIRI plus bevacizumab versus alternating FOLFOX and FOLFIRI plus bevacizumab (as per the ALT-TRACC protocol) versus FOLFOX plus bevacizumab. The alternating FOLFOX-FOLFIRI regimen appeared to have comparable efficacy to FOLFOXIRI without the additional toxicity associated with the triplet regimen. Compared to standard FOLFOX-bevacizumab, the alternating regimen resulted in an improved response rate and progression-free survival (PFS), with no evident increase in toxicity. To validate this approach a randomized phase III study powered to show an overall survival difference is required, hence the ALT-TRACC study.

*Glioblastoma: EX-TEM*

EX-TEM is an RRCT where recently diagnosed glioblastoma patients will be randomized to receive the standard 6 months of temozolomide following initial combination radiation therapy and temozolomide (as per

the STUPP protocol[46]) or to an additional 6 months of temozolomide. Notably, there has been little improvement in the survival outcomes of patients with newly diagnosed glioblastoma since the introduction of chemotherapy following the seminal trial results in 2005.[46] The justification for a definitive randomized study is that several small retrospective studies and limited randomized phase 2 studies have suggested that extending post-radiation chemotherapy up to 12 cycles can improve survival, without an increase in toxicity.[47–49] The small numbers of patients included in the randomized studies, as well as the multiple confounders in any unselected clinical series create concern regarding the significance of the reported findings. Nevertheless, many oncologists in the United States and Canada have now adopted 12 cycles as their routine standard of care. To our knowledge EX-TEM will be the first randomized phase 3 clinical trial to examine the relative effectiveness of 6 versus 12 months of post-radiation chemotherapy in this patient population. Recently this study has been endorsed by the Cooperative Trials Group for Neuro-Oncology (COGNO), with a commitment to support this study at a large number of centers across Australia.

*Pancreatic Cancer: PAN-PAL*

PAN-PAL will randomize patients with recently diagnosed metastatic pancreatic cancer to early palliative care integrated with standard oncologic care or standard oncologic care alone, with palliative care referral in the standard arm at clinician discretion. Previous studies have indicated that late referrals to palliative care compromise the meaningful effect that these services can provide to quality of life and end-of-life care for patients with metastatic disease.[50] Along with this however is the seminal RCT in metastatic non-small cell lung cancer that demonstrated that early integration of palliative care resulted in clinically meaningful and statistically significant gains in overall survival.[51] In the absence of an explanation for this survival gain, the clinical community remains uncertain about the survival impact of early palliative care referral, however it is clearly a study that is worth repeating, albeit in a different poor prognosis tumour type. A further RCT in pancreatic cancer demonstrated that early palliative care improved quality of life and had a significant positive impact on indicators of end-of-life treatment aggressiveness, however no difference in survival outcomes was found.[52] This study was arguably limited by treating oncologists in the control arm being trained in palliative care delivery, thereby reducing the impact of the interventional arm. Furthermore, the palliative care intervention involved a single physician expert only. PAN-PAL will evaluate this intervention in a multi-centre fashion, utilizing a RRCT platform.

Each of these registry RCTs will be powered to show a difference in the same hard endpoint, i.e. overall survival, and linkage with the cancer registry and national death index will be undertaken to ensure accurate survival data is obtained.

**Conclusions**

Registry-based RCTs can provide a timely and cost-effective solution to answering clinical questions, which could be practice changing while bridging the gap between RCTs and observational studies, including phase IV clinical trials. Registry-based randomized trials can reduce costs and simplify trial conduct while achieving both high internal and external validity. However, they rely on the availability of extensive, accessible, high-quality registries and appropriate methods for the randomization for each trial question. We have identified several registries which provide a platform for oncology data collection, randomization, and follow-up. These registries and the proposed registry RCTs provide a unique and significant opportunity for a new approach to clinical research in oncology.

ACKNOWLEDGMENTS

SF is supported by an Australian Government Research Training Program Scholarship.

HLW, LG, ML, KS and AWB have no conflicts to declare.

JT has received honoraria from Roche, Amgen and Merck.

PG has received honoraria from MSD, Amgen, Merck and Roche. His institution has received research funding from Amgen, Merck and Roche.



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TABLES

**Table 1.** Comparison of conventional and registry-based randomized clinical trials

| | Conventional, randomized clinical trials | Registry-based randomized clinical trials |
|---|---|---|
| **Key features** | • NHMRC Level I and II data<br>• Randomization<br>• Blinding<br>• Typically investigates new treatments<br>• Highly controlled and monitored | • Identification and recruitment of eligible patients defined via a registry database search<br>• In-built, or easily accessible, randomization module with less selected and consecutive patient enrolment<br>• Standard agents in their usual setting, with standard of care investigations<br>• Generous inclusion criteria and contributions from centers that would otherwise not participate |
| **Strengths** | • Quantitative, comparative, and controlled experiments with adequate power (gold-standard clinical design)<br>• Removes confounding factors<br>• High internal validity (robust comparison between intervention and control) | • High external validity through inclusion of real-world patients and smaller centers<br>• Answer simple, pragmatic questions that are otherwise unlikely to be explored<br>• Rapid patient recruitment due to broad eligibility criteria<br>• Data collection can be part of routine care<br>• Substantially lower cost than conventional RCT |
| **Limitations** | • Low external validity (highly selected populations due to strict inclusion and exclusion criteria)<br>• Very complex<br>• High cost | • Requires existing high-quality registry<br>• Research question and study design limited by registry features; cannot address all clinical questions due to reliance on hard endpoints such as overall survival<br>• Uncertainty about data quality due to:<br>  ○ Limited monitoring<br>  ○ Incomplete or missing data<br>  ○ Definition and accuracy of dataset |

**Table 2.** Costs associated with the conduct of conventional versus registry-based randomized clinical trials.

| Costs | Conventional RCT | Registry-based RCT |
|---|---|---|
| Study setup | | |
| Protocol development | ✓ | ✓ |
| Ethics and governance submissions | ✓ | ✓ |
| Case report form and database development | ✓ | × |
| Study conduct | | |
| Investigational agent | ✓ | × |
| Study specific investigations | ✓ | × |
| Radiology disease assessments | ✓ | × |
| Additional pathology costs (e.g. sample retrieval) | ✓ | × |
| Personnel | | |
| Research nurse | ✓ | × |
| Data manager | ✓ | ✓* |
| Study monitor | ✓ | × |
| Project manager | ✓ | ✓ |
| Statistician | ✓ | ✓ |

* Existing registry resource

**Table 3.** Active registry-based randomized clinical trials

| Trial | Status | Condition | Country of Origin | Clinicaltrials.gov identifier | Study start date |
|---|---|---|---|---|---|
| A Registry-Based Randomized-Controlled, Double-Blinded Clinical Trial of Pimozide in Patients with Neuromuscular Junction Transmission Dysfunction Due to Amyotrophic Lateral Sclerosis | Active, but not recruiting participants | Amyotrophic Lateral Sclerosis (ALS) | Canada | NCT02463825 | April, 2015 |
| Bypass Equipoise Sleeve Trial, Gastric Bypass or Sleeve Gastrectomy: A Randomized Controlled National Multicenter Study (BEST) | Recruiting | Severe Obesity | Sweden | NCT02767505 | September, 2015 |
| Ffr-gUidance for compLete Non-cuLprit REVASCularization - a Registry-based Randomized Clinical Trial | Recruiting | Coronary Artery Disease, ST-elevation Myocardial Infarction | Sweden | NCT02862119 | August, 2016 |
| Timing of Oral Anticoagulant Therapy in Acute Ischemic Stroke with Atrial Fibrillation: a Prospective Multicenter Registry-based Non-inferiority Randomized Controlled Clinical Trial | Recruiting | Ischemic Stroke, Atrial Fibrillation | Sweden | NCT02961348 | February, 2017 |
| Randomized Evaluation of Decreased Usage of betablocCkErs After Myocardial Infarction in the SWEDEHEART Registry - A Registry-based, Randomized, Parallel, Open-label, Multicenter Trial (REDUCE-SWEDEHEART) | Recruiting | Acute Myocardial Infarction,<br><br>Non-ST Elevation Myocardial Infarction,<br><br>ST Elevation Myocardial Infarction | Sweden | NCT03278509 | September, 2017 |
| Registry-Based, Prospective, Single-Blind, Randomized Controlled Trial: Robotic vs. Laparoscopic Ventral Hernia Repair with Intraperitoneal Onlay Mesh (IPOM) | Enrolling by invitation | Ventral Hernia | United States of America | NCT03283982 | September, 2017 |

| | | | | | |
|---|---|---|---|---|---|
| A Multi-centre, Open-label, Nationwide Registry-based, Randomized, Pragmatic Trial Comparing 2 Post-PCI Management Strategies in High-risk PCI Patients with Complex Clinical and Lesion Characteristics | Not yet recruiting | Coronary Artery Disease with Myocardial Infarction | Republic of Korea | NCT03217877 | August, 2017 |
| Spironolactone Initiation Registry Randomized Interventional Trial in Heart Failure with Preserved Ejection Fraction, SPIRRIT-HFPEF | Not yet recruiting | Heart Failure with Preserved Ejection Fraction | Sweden | NCT02901184 | December, 2017 |
| The Effect of Higher Protein Dosing in Critically Ill Patients: A Multicenter Registry-based Randomized Trial | Not yet recruiting | Critical Illness,<br><br>Malnutrition | Canada | NCT03160547 | January, 2018 |

**Table 4.** Variables recorded in the TRACC registry

| |
|---|
| **Data items related to patient prognostic factors** |
| Gender |
| Age |
| Patient medical history including comorbidities |
| Performance status |
| **Data items related to disease factors** |
| Primary tumor location |
| Metastatic disease sites |
| Tumor staging |
| Biomarker status (CEA, extended ***RAS, PIK3CA, BRAF***, MMR) |
| **Data items related to clinical decision-making** |
| Treatment location and type |
| Treatment intent |
| **Data items related to local and systemic therapy (captured across all lines of therapy)** |
| Chemotherapy regimen |
| Biologic therapies |
| Treatment start and stop dates |
| Adverse events and serious adverse events |
| Best response to treatment |
| Date of progressive disease |
| **Data items related to surgical interventions and outcomes** |
| Resection of primary tumor |
| Resection of metastatic disease |
| **Data related to supportive care** |
| Referral to palliative care |
| **Data related to survival outcomes** |
| Date of death |
| Date of last follow-up |

**Table 5.** Key features of ALT-TRACC, EX-TEM, and PAN PAL.

| Trial name | Registry | Patient population | Treatment arms | Number of patients | Number of study centers | Endpoint |
|---|---|---|---|---|---|---|
| **ALT-TRACC** | Treatment of Recurrent and Advanced Colorectal Cancer (TRACC) | Metastatic colorectal cancer | Continuous versus alternating oxaliplatin and irinotecan doublet chemotherapy | Initially 140, to be expanded to 1000 | 6 initially | Primary:<br>Feasibility<br>Secondary:<br>OS, PFS, RR |
| **PAN-PAL** | Pancreatic cancer: Understanding Routine Practice and Lifting End results (PURPLE). | Pancreatic cancer | Early palliative care integrated with standard oncologic care, versus standard oncologic care alone | 300 | 6 initially | Primary:<br>Feasibility<br>Secondary:<br>OS, QOL indices including chemotherapy utilization |
| **EX-TEM** | The Brain Registry Australia: Innovation and traNslation (BRAIN) | Newly diagnosed glioblastoma | 6 versus 12 months of post radiation chemotherapy | 320 | 6 initially. Study is COGNO endorsed and new sites will be opened. | Primary:<br>OS<br>Secondary:<br>PFS, SAEs |

ALT-TRACC: Alternating oxaliplatin and irinotecan doublet schedules versus continuous doublet chemotherapy in previously untreated metastatic colorectal cancer: A Treatment of Recurrent and Advanced Colorectal Cancer registry-based prospective randomised trial; PAN-PAL: A randomised study of early referral of pancreatic cancer patients to palliative care; EX-TEM: Phase III Trial of Extended Temozolomide in Newly Diagnosed Glioblastoma; OS: overall survival; PFS: progression free survival; RR: response rate; SAE: serious adverse events

FIGURES

**Figure 1.** Registry RCTs complement conventional RCTs.