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Title: The registry-based randomised clinical trial: efficient evaluation of generic pharmacotherapies in the contemporary era

Authors: Troels Yndigegn [1], Robin Hofmann[2], Tomas Jernberg[3], Chris P Gale[4]

Affiliations:

[1] Department of Cardiology, Clinical Sciences, Lund University, Sweden

[2] Karolinska Institutet, Department of Clinical Science and Education, Division of Cardiology, Södersjukhuset, Sweden

[3] Department of Clinical Sciences, Danderyd Hospital, Karolinska Institutet, Sweden

[4] Department of Clinical and Population Sciences, Leeds Institute of Cardiovascular and Metabolic Medicine, University of Leeds, Leeds, UK

Corresponding Author:

Dr Troels Yndigegn

Department of Cardiology, Clinical Sciences, Lund University

Skåne University Hospital

S-221 85 Lund

Sweden

Email: troels.yndigegn@med.lu.se

Telephone: +46-46173679

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Introduction

From small-scale investigations in the mid 20th century until the emergence of megatrials in the 1980s[1], the randomised clinical trial (RCT) has become the gold standard for clinical hypothesis testing and, therefore, the evaluation of the effectiveness of interventions. The key feature of the RCT is its ability, through random selection, to clarify proof of treatment effects by minimising selection bias and influence from known and unknown confounders.

Yet, the design and implementation of clinically relevant RCTs may be hindered by a number of factors. The primary concern is the increasing cost of clinical trials to bring new drugs to market [2]. Factors that influence these costs are, among others, the disease specifics, incidence of events to be prevented and the necessary trial infrastructure (multicentre studies being more expensive). Given the potential lack of return of investment, any evaluation of generic pharmacotherapies in a contemporary population is unlikely to be undertaken by industry. Additionally, excessive legislative and administrative elements present barriers to the conduct of RCTs[3]. In an attempt to overcome these barriers, new RCT designs have been proposed which utilise data from quality registries [4, 5, 6, 7]. The cohort multiple RCT and the cluster RCT are two such methodologies, but as yet have not been widely applied[4] [8]. The registry-based randomised clinical trial (RRCT) also leverages data from registries, and has been shown to rapidly recruit participants at a low overall study cost whilst maintaining high scientific quality.

In this review, we describe the RRCT concept, using the Swedish Web-system for Enhancement and Development of Evidence-based care in Heart disease Evaluated According to Recommended Therapies (SWEDEHEART) as an example of a national quality registry. We provide an example of how a RRCT may be designed to test the effectiveness of a generic pharmacotherapy: beta-adrenoreceptor blockers (beta blockers) after acute myocardial infarction (MI) among patients without heart failure or left ventricular systolic dysfunction. We also discuss how the uncritical use of register data in clinical trials may overlook

important observations , which may affect trial outcome. As such, the aim of this review is to enable readers to judge the quality of a registyr for use in an RRCT and thereby critically appraise trials based on this concept.

RRCT design applied in clinical trials to date

Whereas registries have been used in RCTs for some time, to our knowledge it was only in 2010 that the term 'registry-based randomised clinical trial' was first used[9]. Prior to this, registries were employed to track longer-term outcomes within a RCT framework, but did not have full integration of the trial within a registry[10].

Using a strategy containing either "registry-based" or "register based" and "randomized" or "randomised" trial (see appendix for details) we searched PubMed and Embase for manuscripts published concerning completed RRCTs or methodological descriptions of on-going RRCTs. In total, we found 161 publications, and after review of the abstracts identified 10 RRCTs that reported the collection of baseline and follow-up data from registries (see table 1). Of these, we found that the majority of completed RRCTs utilised the SWEDEHEART register for data collection. In general, the identified RRCTs tested interventions with a short duration of action in a parallel open-label design. The study populations were large and clinical endpoints were, foremost, all cause mortality and MI. A short intervention reduces the risk of crossover and enables a more reliable intention-to-treat analysis. Large sample sizes reduce the risk of an underpowered trial. Also the use of clinical endpoints facilitates the interpretation into routine care.

The quality registry

The basis of the quality registry is the disease specific collection of individualised patient data about medical interventions and outcomes. This information can be utilised to evaluate and compare the quality of care provided by participating

units and assess implementation of guideline-based therapy. Typically, healthcare professionals have established the quality registries[11], as seen in Sweden and the UK. SWEDEHEART is one of over 100 national clinical quality registries in Sweden. It is a publicly funded and collects information regarding clinically important variables concerning the whole chain of care in patients with MI.[12]

Data collection and data quality in the RRCT

In SWEDEHEART, at each of 77 reporting centres, a dedicated nurse and doctor report data on patient characteristics and medication at time of admission to hospital and in-hospital treatments. Data is manually entered in an online case report form, whereupon they are anonymised. Up to 150 variables are collected in patients undergoing coronary angiography/angioplasty. Internal monitoring by the registry holder shows a consistency of registry data with source data in the electronic health record of 96%[12]. Recently, automatic data transfer from the electronic patient record has been introduced in two centres, limiting the resources needed for data collection. Beyond the patient record, linkage to the National Cause of Death Register, the National Patient Register and the National Register on Drug Prescriptions [12], enable access to data for adherence to drug interventions, re-admission to hospital (future events) and vital status(see Figure1).

Strengths of the RRCT

The RRCT has several strengths when compared with the RCT (see box 1). Patient screening in traditional RCTs is often manual and therefore recruitment can be low. In RRCTs, online registration identifies patients eligible for inclusion and in the case of the TASTE trial more than 50% of all STEMI patients referred for primary PCI were included.[7] Randomisation of interventions is undertaken via an online module embedded into the registry. The setup is integrated in routine clinical care (as opposed to contracted core facilities) and therefore the informed consent process is incorporated into the clinical care setting. Although

ethically distinct from the medical advice offered to patients it is important to recognize that the treating physician is also an investigator. This integration into clinical routine is not unique in RRCTs and has been utilised in pragmatic RCTs in the past.[13] The study population in SWEDEHEART at present consists of more than 90% of all patients with MI in Sweden. In this way, by selecting patients from a national disease or treatment register that covers nearly all patients, RRCTs have good external validity for the patient population [14]. Additionally, if a hard clinical outcome (as opposed to a complex and/or surrogate endpoint) is chosen for a RRCT there is limited need for endpoint adjudication[15, 16] [17] (also see Table 1, Outcome column). Mortality is perhaps the only undisputed hard clinical endpoint – the disadvantage being its infrequent occurrence in many clinical settings, which entails a large sample size to avoid type II error. In RRCTs such as TASTE [15] and DETO2X-trial,[16] the primary endpoint was mortality without adjudication. On the contrary, the Validate-trial had the composite endpoint of re-infarction and bleeding which necessitated adjudication. Rigorous internal monitoring ensures that data captured in the patient record is also reflected in the SWEDEHEART registry [12]. Finally, the RRCT has been suggested to reduce costs by as much as 90% (in addition to the cost of the existing registry) of a traditional RCT design,[7] making it an attractive methodology for sponsors to choose, if access to a register exists. Hence, through this integrated randomisation process of patients that are already part of an all-comer registry, the RRCT may collect vast quantities of baseline data and follow-up events at a low expense and with a high degree of generalisable results (see Figure 2).

Ethical and legal aspects of the RRCT

Both ethical and legal aspects separate the quality registry from the RRCT and the RCT (see table 2) and one must be aware of local and national guidelines and laws[18]. In Sweden, the patient data law and personal data act (based on Directive 95/46/EC) governs the handling of personal data. Patients provide informed consent such that anonymised data may form part of the quality

registries. The patient data law allows patients the right to withdraw consent from the registry at any time and if so requires that all corresponding individual data be removed. In a clinical trial setting, this challenges Good Clinical Practice[19] given that trial data must be saved for future analysis and external audit trail by the sponsor or regulatory authorities. In practice, this has not been a major weakness. In the DETO2X-trial none of the 6629 patients enrolled chose to withdraw consent for their anonymised data to enter the SWEDEHEART registry and thus part of the database for the trial. Of the 18.000 registered patients yearly in SWEDEHEART, only 2 to 3 patients per year withdraw consent. This, however, might be unique to the SWEDEHEART registry and stakeholders should be mindful of, and ascertain, the extent of missing cases.

Re-testing generic drugs

In recent years, the approach to cardiovascular care has seen that new health technologies and pharmacotherapies are often added to existing treatments. This approach raises concerns about escalating treatment costs and decreasing drug adherence[20]. Indeed, a concept of drug redundancy is emerging whereby the effectiveness of a historical pharmacotherapy is possibly weakened by the advent of newer agents added to a patient's treatment regimen.

The re-testing of generic drugs for redundancy and / or re-purposing using a traditional RCT approach is likely to be costly and logistically difficult. Moreover, it is unlikely that industry (who often re-test phase II and III drugs that fail to show benefit for their originally assigned indication [21]) , would re-test generic drugs because the return on financial investment is potentially very low. Thus, the strengths of the RRCT design could be ideal to this area of research. Examples of RRCTs exploring this concept include the recently started SPIRRIT-HFpEF RRCT where investigators evaluate the efficacy of a generic aldosterone-antagonist in patients with heart failure and preserved ejection fraction [22]. The recently completed Validate-SWEDEHEART RRCT showed equal efficacy of

generic Heparin when compared to Bivalirudin in patients with acute AMI undergoing coronary intervention, which has the potential to reduce annual healthcare costs in Sweden by about £5 million[23].

Should the effectiveness of beta blockers in MI without heart failure be re-tested?

Assuming therapeutic equipoise as the basis for re-evaluation of established therapies [24], there is growing uncertainty as to the effectiveness of beta-blockers for the management of MI without heart failure [25] [26]. In the early 1980s, after a series of landmark trials, which showed improved outcomes and reduced mortality, beta blockers were approved for the treatment of MI [27, 28, 29]. However, these trials preceded the reperfusion era and enrolled mainly patients with large infarcts and/or heart failure. A systematic review of studies from the post-reperfusion era found no net mortality benefit of long-term beta blockers therapy following MI[30]. This evidence is strengthened by contemporary register data from the UK which points to a non-beneficial survival effect of beta blockers in patients that survive MI and who have normal left ventricular function and no heart failure [31].

Can the RRCT platform be used to test the effectiveness of beta blockers post MI without heart failure?

To establish whether an RRCT design can be applied, several questions should be asked (see table 3 for summary). The first question is whether there is an existing registry with sufficient quality that it can be used for a clinical trial. Probing a quality registry with multiple questions regarding disease ascertainment (coverage), quality of data and losses to follow-up, may uncover limitationss that could endanger data quality in a clinical trial by introducing bias. A nationwide register of MI could be considered an ideal platform for the

conduction of a pragmatic register-based study on generic therapeutic interventions as described above with/without BB post MI. Of importance is patient safety in a clinical trial of long-term secondary prevention, especially in RRCTs with no additional structured follow-up of serious adverse events other than routine clinical visits. In the study of generic therapies, however, with more than 50 years' of clinical routine with beta blockers, it is not unreasonable to believe that no new information will arise concerning serious adverse events in such a trial. Due to the large sample size needed in such a trial, the RRCT design might currently be the only available trial platform to address this clinically relevant question.

If there is no access to a registry, the questions listed in Table 3 could serve as the basis for professional societies to engage with health legislators in an effort to establish registries for the purpose of assessing the healthcare quality and undertaking research obligations with potential great clinical impact.

Limitations of the RRCT design

A precondition to perform a RRCT is the existence of a quality registry covering the population to be studied [6]. Whereas there is a tradition for these registries across Nordic countries, many others do not have this opportunity. The quality of data in a RRCT is bound by the quality of the data in the register. In the Nordic countries and the UK, the validity of national registry data is generally considered to be high. Even so, an internal systematic review from a Norwegian endovascular register showed that early deaths were underreported by as much as 28%.[32] Indeed, concern over the quality of register data is perhaps the main reluctance towards the RRCT framework for a clinical trial[33]. This highlights the need for regular audit of quality registry and the continued transparent reporting so that data in the RRCTs is complete and valid. Furthermore stakeholders in primarily pre-market drug efficacy testing have raised concern about safety issues concerning lack of structured follow-up and allowing for crossover between arms equalising the treatment effect[34]. Here, the balance between cost and trial design should be carefully weighed in any decision to use

RRCTs which may rely on interventions being tested in low-cost hospital units rather than contracted core-facilities. The contrast between these choices can be highlighted with the example of drug adherence and possible crossover. In traditional RCTs, regular visits to the core facility, follow-up telephone calls and rigorous pill-counting measures are instituted to ensure high levels of adherence to determine the explanatory drug efficacy. In the pragmatic RRCT, where an effectiveness measure is sought, adherence is encouraged through routine doctor-patient encounters in-hospital and during follow-up, and no additional visits other than routine care are scheduled. In the SPIRRIT-trial, a definition suitable for this type of pragmatic clinical trial has been adopted,[22] whereby data from the prescription registry is evaluated to determine whether 'written' (electronic) prescriptions were continuously renewed and collected by the patient indicating drug adherence. Another important challenge for the RRCT is the capture of clinical endpoints. If endpoints are chosen that are not readily sampled by the register, this could lead to risk of type II error, that is an abnormal low event rate and no detection of a true effect. In the case of a'negative' RRCT, weight should be given to analysis of the capture of events and the estimated event rate. Beforehand, consideration should be made with regard to sample size and follow-up time to account for potential underreporting of events. Event-driven trials could help mitigate this weakness.

It is important to acknowledge that reclassification of only a small number of events may change the result of a trial and the lack of adjudication in RRCTs should merit consideration. This is important if events are classified by use of ICD codes or cause of death through public registries. External validation has shown that consistency is at most moderate for some events, such as death due to stroke [35], while at the same time high for diagnoses such as admission due to heart failure.[36] It should be emphasized that the reporting of MI in the SWEDEHEART register is not based on ICD codes, but reported by dedicated doctors with reference to the register manual. Should there be need to examine endpoints that are less likely to appear in public registries (such as minor bleeding events), a hybridisation model maybe chosen to ensure adequate capture and validation of endpoints.[17] That said, such addition of structured

follow-up and adjudication committee to the RRCT, will of course increase the trial costs.

Going forward with RRCTs

For the RRCT concept to expand to drug development trials, stakeholders from the pharmaceutical industry[37] have highlighted the need for greater stringency and clarification. Yet a balance must be acknowledged between rigorous and expensive RCTs and informative, but less stringent RRCTs. At present, there is no clear definition of the RRCT and it is difficult to identify if trials are based on the RRCT methodology of quality registries or simply incorporate public register data for event capture. A revision of the CONSORT guidelines to include information about the conduct and reporting of RRCTs may facilitate the design and implementation of clinical trials based on this concept that, due to the high costs of RCTs, would otherwise not be conducted.[38] [33] Going forward, the combination of the RRCT with the adaptive trial[39] to make the 'adaptive RRCT' offers the promise of combining efficiency at scale with the modification of trial parameters in accord with real-time observations.

Conclusion

In the contemporary era, bringing forward new drugs is constrained by cumbersome administrative procedures and escalating costs. Beyond safety and efficacy testing, a demand for value (against existing drugs) generates non-inferiority testing that necessitates huge sample sizes with increase in trial complexity and additional resources. Drug efficacy testing RCTs are hampered by their lack of generalisability and, in the search for 'positive' results, the use of composite endpoints and prolonged follow-up may hinder readily uptake of new drugs into clinical routine. Nowadays, there is compelling societal need for a change in trial design which relates to enabling lower overall national healthcare costs. When introduced to market, drugs are often used off-label in a broad heterogeneous patient population for which the drug might be useful, due to a

lack of post market effectiveness testing. This may lead to drug redundancy and patient adherence trade-off to multiple therapies. Therefore, re-testing generic drugs in a pragmatic effectiveness setting could prove valuable in reducing health care cost and improving population health. Beta blockers in MI with normal ejection fraction is an area with an urgent need for clarification. Building on assets of public nationwide quality registries, the RRCT fuses random sampling and pragmatic trial design in a new robust framework for inexpensive, clinically relevant trials. While the use of national registries in clinical trials should not be undertaken without careful consideration, to date the RRCT framework has delivered an able proof of concept.[40]

Box 1. Aspects of a clinical trial that may be covered by the quality register in the RRCT

- Screening/patient identification
- Informed consent
- Randomised treatment assignment
- Collecting baseline characteristics
- Follow-up (with/without adjudication) of outcome events
- Cost

Table 1. Literature search results for registry-based randomised controlled trials. Entries in this table were derived from the search Registry-based Randomised Clinical Trial in PubMed and Embase (search strategy, see appendix), performed 24th October 2017. STEMI ST-elevation myocardial infarction;NSTEMI Non-ST-elevation myocardial infarction; SAP Stable angina pectoris; ACS Acute coronary syndrome; AMI Acute myocardial infarction; HFpEF Heart Failure with preserved ejection fraction; PCI Percutaneous coronary intervention; iFR instantaneous wave-free ratio; MI Myocardial infarction; TLR Target lesion revascularisation

Study	Acrynym	Status	Target population	No. patients	Intervention	Outcome
Erlinge D[17]	VALIDATE-SWEDEHEART	Completed	STEMI, NSTEMI	6006	Heparin vs Angiox	Composite of death from any cause, myocardial infarction, or major bleeding,180 days
Götberg M[41]	iFR-SWEDEHEART	Completed	SAP, ACS	2037	iFR-guided PCI	Composite of death from any cause, nonfatal myocardial infarction, or unplanned revascularization, 1 year
Rao SV[42]	SAFE-PCI	Completed	Women undergoing PCI	1787	Radial vs. femoral access	Bleeding or vascular complications
Zwisler AD[43]	DANREHAB	Completed	High-risk	770	Cardiac rehabilitation	Composite of total mortality, myocardial infarction, or acute first-time readmission due to heart disease
Fröbert O[15]	TASTE	Completed	STEMI	7244	Thrombus aspiration	All-cause mortality, 30 days
Hofmann R[44]	DETO2X-AMI	Completed	Suspected AMI	6629	Supplemental oxygen	Death from any cause, 1 year
Lindholt J[45]	DANCAVAS	On-going, not recruiting	Men Age 65-74	45000	Cardiovascular screening	Death from any cause
Jensen LO[46]	SORT OUT VII	On-going, not	SAP, ACS	2314	Siolimus vs. biolimus stent	Composite of cardiac death, MI or TLR at 1 year

		recruiting				
Fröbert O[47]	IAMI	Recruiting	STEMI, NSTEMI	4400	Influenza vaccination	Composite of time to all-cause death, a new AMI, or stent thrombosis at 1 year
Lund LH[22]	SPIRRIT	Recruiting	HFpEF	3500	Spironolactone initiation	All cause mortality, event driven (5 years)

Table 2. Contrasting ethical and legal aspects of the quality register and the randomised clinical trial

Quality register	Randomised clinical trial
Data in the register must be deleted at the person's request.	Data in the study, collected until the person chooses to leave the study, can be retained.
Data in the register may be deleted after a number of years, unless permission has been obtained for its retention.	Study data should be archived.
Aggregated data in the register may be used for clinical audit and quality assurance. If approved by ethics committee, identifiable data may be used.	A study may only use the data approved by the ethical review board. Additional data outputs may be possible but require an amendment to the ethics approval.
Data in the register can be modified, should there be corrupt or inaccurate data.	Data in the study data base ought not to be changed after the clean file has been removed.
Changes to register data are not required to be logged.	Changes to study data must be logged until the point at which the clean file is removed (audit trail).

Modified with permission from the Uppsala Clinical Research Center.

Table 3 Questions to ask when considering if a registry-based randomised clinical trial design is an appropriate design, along with example answers from the beta-blocker in myocardial infarction with normal heart function trial.
The questions may be used in conjunction with existing tools for pragmatic trial design, such as the PRECIS-2 tool[48].

Questions	Answers
Is there a pre-existing quality registry collecting data?	Yes, SWEDEHEART
Can patients be identified/screened by their attributes (inclusion and exclusion) when entering the registry?	Patients with acute myocardial infarction and normal left ventricular function are identified as part of routine clinical care
Can the informed consent process be integrated in routine clinical care?	Informed consent has previously been obtained as part of routine clinical care in this patient group and setting
Is there full case ascertainment of the disease of interest (all-comer inclusion of patients)?	Coverage in SWEDEHEART is almost 95%
Is there sufficient uncertainty in clinical practice?	Meta analyses, observational studies and guidelines do not give sufficient evidence for effectiveness in this patient group
Is the intended intervention at phase IV or generic therapy?	Yes, generic therapy
Do the intervention and the comparator constitute part of routine clinical care?	At present, patients with acute myocardial infarction and normal left ventricular function may be treated with either beta-blockers and usual care or only usual care
Is routine clinical care delivered according to its evidence-base?	Yes
Is it possible to setup a randomisation procedure as part of the quality registry?	Yes, the randomisation module will be online and available at all hospital participating in the SWEDEHEART network
Do less controlled conditions create a safety issue?	No, beta-blocker therapy has well known contraindications and its safety profile is well c - with more than 50 years' clinical experience
Is there a network of hospitals which	In total, 76 centres report to

can facilitate a high rate of participant inclusion?	SWEDEHEART. A high proportion of these centres have previously participated in a SWEDEHEART RRCT.
Is the outcome of interest frequent and readily identified in clinical patient registries (and therefore clinically relevant)?	Swedish public registries and SWEDEHEART cover almost 100% mortality or subsequent myocardial infarction during follow-up
Can minimal lost to follow-up be secured (through continuous follow-up in the clinical patient registries)?	Yes
Is there an interference with real world practice during follow-up?	No, patients are otherwise treated according to guidelines - only the prescription of beta-blockers and subsequent titration occurs
Is trial arm crossover and the potential for equivalence acceptable?	Per protocol analysis can be added to the intention to treat analysis
Public funding for implementation of study findings?	Yes, this is an important clinical question that can potentially generate public funding for its implementation

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