Article:
Ieva, F, Gale, CP and Sharples, LD (2014) Contemporary roles of registries in clinical cardiology: When do we need randomized trials? Expert Review of Cardiovascular Therapy, 12 (12). 1383 - 1386. ISSN 1477-9072

https://doi.org/10.1586/14779072.2015.982096

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Journal:	*Expert Review of Cardiovascular Therapy*
Manuscript ID:	ERK-2014-0130.R1
Manuscript Type:	Editorials
Keywords:	Clinical Cardiology, Evidence Based Medicine, Clinical Registries, Routinely collected Data, Observational Data, Randomized Controlled Trials, Clinical Practice

TITLE

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ABSTRACT

Clinical registries are established as tools for auditing clinical standards and benchmarking quality improvement initiatives. They also have an emerging role (as electronic health records) in cardiovascular research and, in particular, the conduct of Randomized Controlled Clinical Trials (RCTs). Whilst the RCT is accepted as the most robust experimental design, observational data from clinical registries has become increasingly valuable for RCTs. Data from clinical registries may be used to augment results from RCTs, identify patients for recruitment and as an alternative when randomization is not practically possible or ethically desirable. Here we appraise the advantages and disadvantages of both methodologies, with the aim of clarifying when their joint use may be successful.

KEYWORDS

Clinical Cardiology, Evidence Based Medicine, Clinical Registries, Routinely collected Data, Observational Data, Randomized Controlled Trials, Clinical Practice

BODY

Introduction

Electronic health records have, in recent years, become increasingly important for the evaluating the quality of clinical care, the integration of clinical information and improvements in efficiency and cost effectiveness. In parallel with this, clinical registries have become established as tools for auditing clinical standards, and designing and benchmarking quality improvement initiatives. As a result, there has been a growth in the number, size and quality of clinical registries, particularly in the field of cardiology – many of which are now national in their coverage [1-4]. This development, coupled with an appreciation of the relevance of real "world data", has resulted in a greater use of clinical registries for observational research. Although theoretical and practical difficulties may arise, with careful design and data linkage these registries can also be used effectively, in a clinical trial format, to test hypotheses [5].

Limitations of RCTs

The Randomized Controlled Clinical Trial (RCT) is almost universally accepted as the most robust experimental design for estimating the effects of interventions and is promoted as the preferred approach to ensure study quality in a hierarchical 'pyramid of evidence' [6]. If properly designed and conducted, RCTs provide an unbiased assessment of treatment effects in the trial population, **enable a reliable estimate of small to moderate effects**, and form the basis for recommendations regarding prevention and treatment programmes. These explanatory trials have strong internal validity. However, they are often conducted in (sometimes highly) selected populations rather than in the population presenting in clinical practice, and so such trials may have limited external validity [7]. For example, compared with patients enrolled in the Acute Study of Nesiritide in Decompensated Heart Failure (ASCEND-HF) trial, patients in a simultaneous registry differed significantly on clinical characteristics, treatments, and inpatient outcomes [8]. When Stuart and colleagues [9] used propensity-score-based metrics to quantify the similarity of participants in an RCT with a target population, it was found that unmeasured characteristics differing between the sample and population impacted on the generalizability of the study. Moreover, RCTs do not necessarily answer questions of primary interest, such as, "will the programme be effective in a target population in

which it may be implemented?" [10]. That is, it is not always possible to be confident that results can be applied to routine clinical practice [11-12]. Yet, clinical practice may change considerably as a result of a 'positive' RCT outcome and the intervention subsequently applied to a much wider patient group who are less representative of the study population. **Last but not least, many RCTs are industry sponsored, which may incur bias such as more favorable results and conclusions compared with sponsorship by other sources. [13]**

Strengths of registries

The importance of the applicability of evidence to policy recommendations highlights the need to consider evidence from clinically relevant situations, not all of which have been assessed by RCTs. Data from clinical registries may be used to **formulate hypotheses for testing in RCTs** and, **with careful design and incorporation of modern causal inference analysis methods**, may be used as an alternative when randomization is not practically possible or ethically desirable. Although generally providing a lower evidence-level than RCTs, observational studies can make an important contribution to the evidence base when the study outcomes are clinically important, and the populations involved are representative.

Registries have value in clinical cardiology trials in a range of ways. They can inform trial design - providing information on recruitment, baseline characteristics, exclusions, attrition and outcomes. For some databases, in which reporting is complete due to regulatory body or other mandate, they can make trials more efficient by allowing enhanced recruitment and follow up [14-16], easing the linkage among different sources of data. Use of survival statistics linked to death registries at national level, in which information on the long term mortality due to any cause can be obtained, has long been established. Such data have been used both for trial design and alongside trial results. This serves to validate the results as well as put them in a wider, more generalizable, context [17-19]. Furthermore, data routinely collected in cardiovascular registries may be used for additional endpoints, and if necessary weighted by their importance to patients [20]. Clinical registries and administrative, routinely-collected data have great potential for clinical research, since they are population based and combine information from multiple centers. In so doing, if the design is consistent across districts (and possibly between countries) of interest, and properly managed at a central

level, they could capture complete health system use. Finally, they are usually inexpensive compared with RCTs [21].

Limitations of registries

Despite the wide range of benefits brought by registries to clinical practice, their *caveats* must be borne in mind. The validity and practical utility of observational clinical research is dependent on a number of factors including, good study design, excellent data quality, consistent data definitions, reliable linkage, robust statistical methods and accurate interpretation especially if we are to infer causal relationships between clinical treatments and outcomes. Moreover, it is crucial to state clearly in which situations benefit from using clinical registries may arise, in order to encourage confidence in the validity of results among clinical peers. Situations in which clinical registries may be of use, among others, are those where,

- there is an easily measured, universally recorded, objective outcome in a stable identifiable population. For example, death within 30 days of primary percutaneous coronary intervention as recorded in a national database [22];
- chronic conditions, requiring long-term follow-up are the primary focus of the study; for example hospitalizations in patients with chronic heart failure;
- there is a limited funding, since answering the question under investigation is not profitable for industry or not relevant to research charities' agendas. For example, a comparative effectiveness analysis of New Oral Anticoagulant (NOAC) drugs [23];
- intervention vs. usual care evaluation is required. For example, the use of biomarkers to guide heart failure treatment [24];
- external validity with less selection bias is necessary; For example, the impact of specific antiplatelet therapies on major adverse cardiovascular and cerebrovascular events after acute coronary syndrome [25];
- there is an aim/need to inform healthcare decisions. For example, the use of a risk score for the evaluation of adherence to guideline recommended therapies in patients with acute coronary syndrome;

- cost-effectiveness analyses are needed, as for expensive highly desired treatment. For example, the use of transcatheter aortic valve implantation for aortic stenosis [26];
- other trials have failed to recruit. For example, TRIGGER-PCI which was stopped prematurely for futility because of a lower than expected incidence of the primary endpoint [27].

Combining RCT and registry data sources

With the availability of enhanced computational power, in recent years it has become easier to model the complexity and the constraints characterizing contemporary healthcare systems, so that synthesis of data from both RCTs and registries is possible. For instance, in the UK the appraisal of new treatments often involves the use of decision models which take account of evidence from RCTs (providing robust treatment effects) and registries (providing long-term survival estimates and baseline estimates of clinical risk) [16].

The desire for the joint use of RCTs and registries that, therefore, overcome the weaknesses of each type of study and take advantage of their benefits, has also led to innovative research designs such as the "Cohort Multiple Randomised Control Trials" [28]. In this design, the randomization is embedded in routinely presenting patient cohorts in order to eliminate selection bias, thus retaining the characteristics of normal clinical practice, but also maintaining the unbiased treatment allocation afforded by randomisation. The Thrombus Aspiration during ST-Segment Elevation Myocardial Infarction (TASTE) trial [29] enrolled participants from the national comprehensive Swedish Coronary Angiography and Angioplasty Registry (SCAAR), part of the wider SWEDEHEART registry [2]. This registry holds data on consecutive patients from all 29 Swedish and 1 Icelandic coronary intervention centers, is funded solely by national health authorities, and provides immediate and continuous feedback on processes and quality of care measures. All baseline and procedural data are entered online. The primary end point, 30-day all-cause mortality, was obtained from the national population registry. The secondary end points, for which data were obtained from the SWEDEHEART registry and the national discharge registry, included among others 30-day rates of myocardial infarction and stent thrombosis. After providing initial verbal consent, patients who fulfilled the study inclusion criteria were randomly assigned, in a 1:1 ratio, to thrombus aspiration followed by PCI or to

PCI only. This study achieved high recruitment rates at a much lower cost than a conventional RCT, and provided the clinical community with timely and generalizable results.

This is an example of how the joint use of clinical registries and RCTs may help mitigate some of the limitations characterizing the single methodologies. In the future, it is likely that much greater quantities of routine healthcare data will be collected and made available. If properly managed, these data may be used to enrich clinical information and possibly to monitor and evaluate results of classical trials in wider populations over time, increasing the applicability and effectiveness of research.

KEY ISSUES

Clinical Registries

Pros

- Provide evidence from clinically relevant situations, which may not have been assessed by RCTs.
- Can be used when randomization is not practically possible or ethically desirable.
- Inform trial design in clinical cardiology providing information on recruitment, baseline characteristics, exclusions, attrition and outcomes.
- **Generate hypotheses for testing in RCTs.**
- Make trials more efficient by allowing enhanced recruitment and follow up, easing the linkage among different sources of data.
- Provide strong external validity.
- Are population based and can capture complete health system use.
- Less expensive than RCTs.
- **Mitigate industry bias.**

Cons

- Validity and practical utility dependent on study design and data quality.

- Management and linkages still to be improved at national level.
- Not always suitable for inferring causal relationships between clinical treatments and outcomes.

RCTs

Pros

- Are the most robust experimental design for estimating the effects of interventions.
- Preferred approach to ensure study quality.
- Provide an unbiased assessment of treatment effects in the trial population.
- Strong internal validity.
- **Detect small to moderate effects reliably.**

Cons

- Often conducted in selected population - limited external validity.
- Are (sometimes prohibitively) expensive.
- **May incur industry bias.**

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