RCTs: Can the treatment work? Patient registries: Does the treatment work?

Patient registries and research databases as a source of medical information

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Abstract
The first part of this article compares the main features of studies based on patient registry data with those of randomised clinical trials, providing a basis for better understanding the differences between the two. The second part details how to report study-specific issues with patient registries, such as study objectives, patient populations, bias, confounders, missing data, study duration, and gives a few tips on how to improve the credibility of papers based on patient registry data.

Evidence-based medicine: patient registries and randomised clinical trials
Evidence-based medicine (EBM) strictly classifies different sources of medical information by the strength and reliability of the evidence they provide. In this EBM hierarchical model, meta-analyses and systematic reviews are on the top of the pyramid, and are closely followed by randomised clinical trials (RCTs), particularly blinded and controlled ones. Patient registries fall under observational studies and are classified as low-level evidence (Figure 1). RCTs are considered to be the golden standard of medical evidence primarily because of being a reliable...
unbiased source for inferring causality from observed associations. However, the reality is not always so clear and straightforward. The main concern related to RCTs as guidance in medical decision-making is their applicability to daily clinical practice and generalisability to a patient population at large.

RCTs are medical experiments with a predefined hypothesis – they are designed to confirm or deny the hypothesis; in other words, they should provide the clearest possible answers as to whether a given intervention works. To get such a clear and definite answer, the RCTs must be performed in a noise-free environment, almost as in a sterile laboratory where the only difference between the study and control arms is the intervention. Randomisation is one way to ensure this. Another is a list of subject selection criteria that are specific and often long. Both randomisation and specific inclusion and exclusion criteria ensure that the study population is homogenous and study arms similar (Figure 2). Obviously, designed in this way, RCTs are suitable for the purpose they serve i.e. to capture the efficacy of the studied intervention. However, what happens next, once the efficacy of an intervention has been proven and the new drug enters daily clinical practice? The results of RCTs are verified in patients who often do not resemble those from clinical study (Figure 3).

This problem is illustrated by Carter and colleagues, who analysed the inclusion and exclusion criteria from 17 RCTs on ulcer treatment (venous, diabetic foot, and pressure ulcers) and calculated the proportion of a typical wound-care patient population that would have been excluded from the studies. This proportion served as a surrogate for study applicability to daily clinical practice. The authors estimated that more than 50% of patients would have been ignored in 15 of 17 studies and, therefore, they concluded that these results are unlikely to effectively support management of a typical wound-care population.2

To better understand the role that a patient registry plays in medical decision-making and to capture the main differences between registries and RCTs, let’s start with the definition. According to the Agency for Healthcare Research and Quality, “A patient registry is an organised system that uses observational study methods to collect uniform data (clinical and other) to evaluate specified outcomes for a population defined by a particular disease, condition, or

Figure 1. Pyramid of medical evidence hierarchy according to evidence-based medicine.

Figure 2. Homogenous randomised clinical trial patient population, courtesy of Dr Henri Wallaschofsky, Germany

Figure 3. Heterogenous and diverse daily clinical practice patient population, courtesy of Dr Henri Wallaschofsky, Germany
purposes of registries: and Quality distinguishes among the following registries, the Agency for Healthcare Research collected data. In the same user guide for patient around, i.e. the goal of analysis is driven by the collection is purpose-driven, not the other way determined beforehand, implying that data lines that the purpose of a registry should be registry populations. Furthermore, it also under -

of pre-defined outcomes and identification of need for standardised data collection, evaluation applicability of observational study methods, the important aspects of patient registries, such as

characteristics Randomised clinical trial Patient registry

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Randomised clinical trial</th>
<th>Patient registry</th>
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<tbody>
<tr>
<td>Patient management</td>
<td>According to the protocol</td>
<td>According to clinical practice</td>
</tr>
<tr>
<td>Selection criteria</td>
<td>Very stringent</td>
<td>Much less stringent</td>
</tr>
<tr>
<td>Duration</td>
<td>Fixed</td>
<td>Often open-ended</td>
</tr>
<tr>
<td>Comparator</td>
<td>Often as part of the study</td>
<td>Various (e.g. part of the study or general population)</td>
</tr>
<tr>
<td>Bias</td>
<td>Low risk</td>
<td>High risk</td>
</tr>
<tr>
<td>Generalisability</td>
<td>Low</td>
<td>High</td>
</tr>
<tr>
<td>Applicability to target population</td>
<td>Various</td>
<td>High</td>
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Finally, each type of patient registry can be further characterised by the population enrolled, e.g. by a disease, phenotype, exposure to drug or medical intervention, region of origin, or pre-defined features. The principle distinction from RCTs is the fact that in registries patients are treated according to clinical practice, i.e. treatment and patient management are at the discretion of the treating physician, whereas in RCTs intervention is dictated by a protocol. Additionally, commonly, patient registries are run for a long time, collecting information on a large number of patients and cover many countries and regions whereas RCTs are of limited duration and enrol a strictly limited number of subjects, based on sample size calculations. The large number of enrolled patients replicates various types of patients managed in daily clinical practice and thus it allows for subgroup analyses (Figure 4). These properties are crucial particularly for registries focusing on rare disorders in which prevalence and incidence are per definition low, and therefore solely registries are capable of providing enough data to draw meaningful conclusions. The main differences between registries and RCTs are summarised in Table 1.

Safety is another important field where a patient registry is a valuable tool to collect rare adverse events or atypical treatment reactions, which are unlikely to be captured in RCTs due to their limited size and duration (Figure 5). Furthermore, a patient registry may provide clinical context for adverse events reported spontaneously. Patient registries are often used to fulfil health authority requirements, for example running post-marketing authorisation surveil - lance studies.

Finally, it should be highlighted that frequently it is impossible or unethical to perform an RCT and medical-decision making has to be based on evidence derived from observations. Smith and Pell in a humoristic way presented the results of systematic review of RCTs on the use of a parachute during free fall. Obviously, they could find no RCTs so they concluded: “As with many interventions intended to prevent ill health, the effectiveness of parachutes has not been subjected to rigorous evaluation by using randomised controlled trials.”

As a result, many taskforces and working groups involved in Grading of Recommenda - tions, Assessment, Development and Evaluations (GRADE) suggest that observational studies may provide stronger and more relevant evidence as long as they are of high quality and the data are reported in a balanced and comprehensive way.

**Publishing patient registry data: how to maintain high quality?**

Overall, publishing patient registry data follows the same rules as publishing any other scientific data with clarity, conciseness, accuracy and precision being the milestones of high quality. Moreover, the completeness of published information related to the study design and methodology allows readers to properly evaluate the value and reliability of presented results.

As already said, a patient registry uses observational methodology and, therefore, reports of their data should be in line with the STrengthening the Reporting of OBServational studies in Epidemiology (STROBE) guidelines. These help researchers to share their work in a transparent way, and to select enough information for critical assessment of the study design, conduct and analysis – in other words sufficient information to evaluate the credibility of their work.
Despite the fact that these general rules and recommendations apply to publications on patient registry data, a few specific issues are worth discussing in detail.

**Objective and methods:**
As for any other publication, the objectives of the study or analysis must be specified, and the methods section needs to effectively describe the way the study was performed, particularly how it addressed the objectives. At the same time, this section aims at convincing readers that the way the data were collected and analysed guarantees high quality, reliable, robust results. However, it seems that for patient registry papers this section is even more important than for papers reporting RCT results; there is no strict protocol behind a patient registry, so at least in theory there could be more room for data manipulation.

**A few tips:**

1. **Study objectives** – always separately describe the general purpose of a patient registry and the specific aims of the presented study using a subset of patient registry data. If you analyse all data, also clearly state that the purpose of the study was the same as for the general purpose of the patient registry. For example, Odeyemi et al used the data from the General Practice Research Database (GPRD) in the UK to study overactive bladder (OAB) symptoms. They first described GPRD as a longitudinal general practice database collecting data from a representative sample of general practices in the UK, and then specified the purpose of their study: to estimate the incidence and prevalence of OAB symptoms; to analyse the use of anticholinergic/antispasmodic drugs and healthcare resources.8

2. **Description of patient population including selection criteria** – as with the objectives, the selection criteria for a registry and for the specific study should be discussed in detail. This is very important not only to understand whether the analysed population reflected that of the registry but also whether it was representative of the target patient population. It can happen that a registry population constituted a good representation of the patient population but the analysed cohort did not. On the other hand, sometimes the analytical dataset aims to include all patients in the registry, and only excludes patients with incomplete data for pre-defined variables. An example is the analysis of fracture risk in adult patients with growth hormone deficiency (AGHD), bothuntreated and treated with growth hormone.9 The authors first referred to the already published Hypopituitary Control and Complications Study (HypoCCS) and then described its specific inclusion and exclusion criteria. Secondly, they selected the following variables as inclusion criteria for their study: age, sex, disease onset (adult onset or childhood onset), at least one follow-up visit after study entry, treatment with growth hormone. Only patients with no missing information for all of these pre-defined variables were included in the study.

3. **Duration** – Here it is very important to precisely report the timeframe when the data were collected, preferably in calendar dates, or at least years, and also the follow-up time. Usually, registries continuously enrol patients, so at the time of analysis (database cut-off point) patients have been followed for various durations, i.e. some of them may have been enrolled for many years before the database cut-off point, and some for just a short time, very close to the time of analysis. Therefore, it is recommended to report median and percentiles (or range) of follow-up, not the mean, which can be misleading. Using the KIMS database (the registry of AGHD), Tritos et al compared AGHD caused by different underlying aetiologies; they reported that the median follow-up was 6.7 years for one aetiology group and 5.8 years for another with a range of 0-18 years.10 No doubt, the medians provide much more precise information. Furthermore, studies with long-term follow-up should report the number of patients per year of follow-up.11

4. **Endpoints or outcomes** – As with RCTs, it is critical to clearly define the study endpoints or outcomes to be evaluated in the analyses. These should be defined before retrieval of the patient data begins and before the analyses are performed. Sometimes, researchers decide to check the availability of the data before they decide which outcomes should be included; this is done by simple frequency tables including the number of patients with missing and non-missing data for given variables. The HypoCCS paper on fracture risk clearly defines all outcomes included in the analyses, and especially clearly the fractures: how the data were collected; how they were defined and categorised.9

5. **Ethical aspects** – Often these aspects are discussed and the need for patient informed consent and ethics committee approval is questioned. In the majority of countries both are needed, and at least obtaining ethics committee opinion should be a standard.

6. **Statistical methods** – Applying proper statistical methodology is absolutely crucial for the credibility of results; therefore, this section must not be neglected. In simple descriptive studies, simple descriptive statistics are enough,
but whenever researchers deal with more sophisticated questions such as comparisons between treatment groups, prediction of treatment outcomes, or mortality analysis, more advanced techniques must be used. Basically, in registries, treatments are not randomised, so patients belonging to one group may be systematically different from another group (e.g. treatment group vs. non-treated group). The analysis must consider such selection bias, and that is where advanced statistical methods come into place and must be precisely described in the paper. Similarly, the statistical analysis should account for all known or potential confounders. A paper based on the data from the KIGS registry (children with short stature treated with growth hormone) analysed changes in body mass index (BMI) during long-term growth hormone treatment. The change in BMI was compared in various primary aetiology groups; since there were differences between patient groups before growth hormone treatment started, the authors had to use advanced statistical methods, and these are well described in the paper.12

Results and discussion:

1. Results – General rules relating to the presentation of results also apply to papers based on a patient registry, namely that the way the results are presented needs to be factual, structured according to the study objectives, providing exact data and avoiding interpretation. The STROBE guidelines provide a very comprehensive guide for how to present results.13

2. Completeness of data – The level and type of missing data should be predicted at the time of study design and further assessed when data are being cleaned and analysed. Depending on the extent and type of data missing (missing completely at random, missing at random, missing not at random), different statistical approaches can be employed.3 This approach needs to be precisely described in the statistical method section. Nevertheless, good practice recommends reporting the number of observations on which given results are based. This is clearly seen in the table of baseline characteristics for the 2,589 patients with AGHD in whom cardiovascular risk factors were analysed in the KIMS study. The column number of non-missing shows that almost complete data were available for lipids and blood pressure but information on body composition was available only in a proportion of patients.14

3. Study limitations – This section is particularly important in papers reporting patient registry data. It should cover not only aspects relating to certain analyses but also general issues inherent to this type of research. The importance of identification and discussion of study limitations (bias, confounding, imprecision) is highlighted in the STROBE guidelines. The guidelines also recommend referring discussed limitations to other studies in terms of validity, generalisability and precision.13 The already cited analysis on fracture risk addresses a number of limitations, and whenever possible explains the attempts to minimize their impact on the credibility of the results. As an example, the authors recognised that patients on growth hormone treatment differed from untreated patients, so the statistical analyses accounted for identified confounders; however, residual confounding could exist which is acknowledged in the discussion.9

4. Conclusion – The general rule is that studies performed with registry data do not prove causality and can solely indicate associations between observations. Indeed, this rule should be followed and conclusions must be drawn with caution, taking into consideration the nature of the study, potential sources of bias, confounding, including residual and unknown confounding and imprecision.13 The results of sensitivity analyses and subgroup analyses may help formulate balanced and reliable conclusions.11

To summarise, both types of studies, RCTs and those based on patient registry data, provide useful medical information: RCTs answer the question, “Can it work?” Patient registry data – studies answer the questions, “Does it work? How does it work in real life?”

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References

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Maria Kołtowska-Häggström, MD, PhD, has extensive experience in reporting data from patient registries. She has been a leading member of numerous research groups investigating quality of life and patient-reported outcomes. Currently, she has medical responsibility for projects at Proper Medical Writing, the first medical writing agency in Poland.