Editorial

Register-based randomized trials: the new power-tool in orthopedic research?

Why register-based randomized trials?

Randomized controlled trials (RTCs) are often the key evidence for changing clinical practice. However, they are expensive and difficult to run, and often have low recruiting rates. External validity is low, thus such studies are sometimes not accepted as the bases for change of practice. This is inappropriate and imprudent as the results of such studies will never be implemented and will thus be a waste of research.

Another challenge to conducting RTCs is when complications are rare, as in some of the remaining challenges in the field of orthopedic surgery. Periprosthetic joint infection (PJI), dislocation or mortality are, luckily, relatively uncommon, necessitating disruptively large study populations within RCT settings. The classic RCT design is based on a few or perhaps a dozen participating centers, making such trials difficult or impossible to perform in a timely fashion. Moreover, the classic RCT design comes with other limitations: (i) it is too costly when based on numerous complex outcome measures that must be assessed by surgeons, study nurses, or physiotherapists in thousands of patients, and (ii) it is not feasible when inclusion and exclusion criteria become incompatible with the large real-life variation, and external validity is therefore often low. Thus, the idea of the register-based, pragmatic RCT has gained increasing interest in the orthopedic world.

The pragmatic, register-based RCT (r-RCT)

The term "register-based RCT" (r-RCT) was probably coined in the field of cardiology [1]. The nationwide interventional "Swedish Coronary Angiography and Angioplasty Registry" was used as a platform for an r-RCT investigating whether coronary thrombus aspiration during myocardial infarction reduced mortality, and this trial is often referred to as the first example of large-scale r-RCT. The term r-RCT is nowadays interpreted as a trial where register resources are used for all or selected steps pertinent to a classic RCT design [2]. All the steps mentioned are crucial and present with their own set of challenges.

Screening

By relying on the electronic platforms of nationwide registers, screening of eligible patients can be facilitated in that a physician who enters a specific diagnosis or planned intervention is alerted by the integrated study module that the current patient is a potential trial participant. Challenges to this procedure are that the screening sometimes is made an integral component of the ordinary workflow of already overworked physicians in an emergency room setting, thus hindering actual inclusions to be performed despite patients being clearly eligible.

Inclusion

The alerting system can be further refined in that the study module indicates eligibility only if the patient fulfills additional demographic criteria, such as a given age span, fracture type, or sex. The answer to no more than a handful of relevant screening questions then leads to the randomization tool, where, after confirmation of patient consent, the platform connects to a predetermined randomization sequence, resulting in inclusion and randomization to intervention or control treatment.

Some of the numerous advantages of this pragmatic register-based study design are that baseline characteristics of the study population are already automatically collected within the host register, thus, no pre-appointment or on-site baseline data collection at emergency departments needs to be performed by either study nurses or physicians. Disadvantages include the fact that all registers are hampered by incomplete or missing data, as opposed to the strict adherence to clinical report forms in a conventional RCT setting [3]. This also affects the next step of data collection within r-RTCs, outcome assessment.

Outcome

Strict r-RTCs also rely on regular register data when it comes to the assessment of outcomes such as revision, PROM, or mortality. This was relatively easy in the pioneering cardiologic r-RTCs, where mortality is a hard and unequivocal endpoint that makes adjudication almost unnecessary. In contrast, outcome assessment can become tricky when adjudication is an issue, for instance because the outcome is not easily defined within conventional register data: PJI or dislocation are outcomes that need to be based on sometimes-complex combinations of diagnostic and procedural codes that are not by default present in arthroplasty registers. Thus, secondary or even primary outcomes occasionally have to be collected outside the regular register variable set, but can still be based on other available registers that do collect the necessary diagnostic or procedural codes. In several ongoing studies in the Nordic countries, outcome variables that are not by default

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included in the arthroplasty register setup are therefore collected through access to national patient registers that prospectively include information on in- and outpatient visits together with all diagnostic and procedural codes associated with a specific hospital stay. A requirement of the primary and secondary outcomes is that they have to be validated in the included setting.

There are of course some additional disadvantages to the r-RCT setting. The absence of more complex biometric data in most quality registers such as the all-important radiographs is a limitation, not to speak of biomarkers or even genetic data that could be relevant to various research questions.

Ongoing r-RTCs

Despite the obvious drawbacks, the charms and advantages of performing trials based on well-functioning national registers with excellent coverage and completeness are irresistible, and numerous r-RTCs are now ongoing in the Nordic countries. 3 r-RTCs on hip fracture patients are currently running in Sweden. The first to go live was the "Hipsther" study, which is nested within the Swedish Fracture Register (SFR) [4]. It investigates whether arthroplasty is superior to internal fixation in non-displaced femoral neck fractures [5]. Nearly 1,000 of the scheduled 1,440 patients have been included so far. "Duality," the second SFR-nested study, examines the proposed superiority of dual-mobility cups over standard cups in patients with displaced femoral neck fractures [6]. About 1,200 of the planned 1,600 patients have been included so far, with recent support from a separate UK study arm. The third Swedish hip fracture study uses a cluster-randomized design to investigate whether double antibiotic-loaded cement can reduce the risk of surgical site infections in patients treated with hemiarthroplasty [7], an area in which observational findings are contradicted by a recent r-RCT [8,9]. A fourth r-RCT nested within the SFR compares surgery with nonoperative treatment of thoracolumbar burst fractures [10].

The only large RCT investigating the effect of antibiotic-loaded cement after knee arthroplasty, with nearly 3,000 knees included, showed no difference in PJI when comparing antibiotic and non-antibiotic loaded cement; however, the antibiotics used were colistin and erythromycin [11]. In Norway and the rest of Europe, the use of gentamycin-loaded cement dominates, thus necessitating the Norwegian ALBA study [12]. The Norwegian Arthroplasty Register has therefore initiated a large r-RCT comparing the effect of the presence of antibiotics in bone cement, with revision surgery due to PJI as the primary outcome [13]. Power calculations showed the need to include over 9,000 patients, and the web-based platform introduced in 2021 for surgeon reports to the Norwegian Arthroplasty Register is used for the study. The Norwegian ALBA study has so far included approximately over 2,000 knees; however, inclusion speed is slower than the anticipated 200 knees a month. The Norwegian Knee Ligament Register has also started an r-RCT using the same web-based platform, investigating ACL reconstructions with minimum 6 months' active rehabilitation compared with early surgery within 3 months (Improve-ACL).

In Denmark, the national Pro-Hip-Quality trial was initiated 1 year ago [14]. The objective is to compare the effect of a single versus multiple doses of prophylactic antibiotics administered within 24 hours in the presence of PJI following primary total hip arthroplasty (THA). The study is embedded in several national databases. 2 of the key databases are the Danish Hip Arthroplasty Register (DHR) and the Hospital Acquired Infections Database (HAIBA) from which baseline data, outcome regarding revision, and microbiology are reported and collected. The study is designed as a crossover, cluster-randomized, non-inferiority trial. All clinical centers use both antibiotic practices (1 year of each intervention). All Danish orthopedic surgery departments are recruiting, and 2-year cohorts of approximately 20,000 primary THAs conducted at 39 public and private hospitals will be included. The primary outcome is PJI within 90 days after primary THA, and this and all secondary outcome measures will be extracted from national databases. The primary outcome has been validated in earlier studies [15,16].

In Australia, there is an ongoing multicenter, blinded, randomized, 2×2 factorial r-RCT including 300 TKA patients [17]. The study investigates robotic-assisted vs. computer-assisted surgery and kinematic vs. mechanical alignment, with a PROM as its primary outcome. It is nested within the Australian Orthopaedic Association National Joint Replacement Registry (AOANJRR) and uses the RAPID (Real time Automated Platform for Integrated Data) platform to detect implant survivorship. Another Australian r-RCT enrolled almost 10,000 patients and compared the effect of aspirin with enoxaparin in preventing symptomatic venous thromboembolism (VTE) following THA. The cluster-randomized CRISTAL trial was also nested within the AOANJRR, and each hospital was allocated to consecutive periods of either enoxaparin or aspirin treatment [18].

In the UK, the World Hip Trauma Evaluation (WhiTE) is a multicenter framework that is nested within the National Hip Fracture Database (NHFD) [19], and the WhiTE platform has been used to conduct several large-scale RCTs. Fernandez et al. [20] conducted the WHiTE 5 trial to compare health-related quality of life in adults 60 years of age or older with a displaced intracapsular hip fracture who were randomly assigned to undergo either cemented hemiarthroplasty or modern uncemented hemiarthroplasty. The pivotal White 8-trial investigating the effect of double-antibiotic-loaded cement on the incidence of surgical site infections after hemiarthroplasty of the hip has been mentioned earlier [9].

Future perspectives

There is clearly a need for solid substitutes for the classic RCT as it is too expensive, the recruiting time is too long, and the external validity is often low. The r-RCT is a viable option

and should be designed to enhance participation across countries to achieve the best national coverage, thereby increasing acceptance and the likelihood of implementation of new guidelines. The design may be suitable for future studies in need of thousands of patients, such as for infection prevention. Such studies can also be multinational, and the NARA framework may prove ideal for this type of study. Future r-RTCs should aim to address the big remaining problems in hip and knee arthroplasty: dislocation, infection and periprosthetic fractures in hips, and instability and stiffness in knees.

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