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Registry-Based Randomized Clinical Trials in Surgery: Working with ACS-NSQIP and the AHPBA to Conduct Pragmatic Trials

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Abstract

Randomized controlled trials (RCTs) represent the gold standard for evidence in clinical medicine because of their ability to account for the effects of unmeasured confounders and selection bias by indication. However, their complexity and immense costs limit their application, and thus the availability of high-quality data to guide clinical care. Registry-based RCTs are a type of pragmatic trial that leverage existing registries as a platform for data collection, providing a low-cost alternative for randomized studies. Herein, we describe the tenets of registry RCTs and the development of the first AHPBA/ACS-NSQIP-based registry trial.

Keywords

Pragmatic clinical trial; Randomized controlled trials; Surgical research methods; Registry-based trials; Surgical registry

Introduction:

The randomized clinical trial (RCT) is a powerful tool of clinical research, and considered the gold standard for evaluating the effectiveness of medical interventions. By evaluating a given therapy while accounting for the effects of unmeasured confounders and selection bias by indication, RCTs provide the highest quality data that can inform medical practice. Yet, RCTs comprise only 3 to 7% of all publications in surgical journals[1,2], questioning

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why this transformative research methodology is only used to answer a small fraction of clinical questions. Several characteristics of traditional RCTs, including excess complexity and expense, may underlie their infrequent utilization while selectiveness of trial participants limits the applicability of completed trials to real-world patients.

Observational registries are the substrate for the majority of surgical research. The American College of Surgeons-National Surgical Quality Improvement Project (ACS-NSQIP) is a nationally validated, outcomes-based, risk adjusted, peer-controlled program for the measurement and enhancement of the quality of surgical care[3,4]. ACS-NSQIP constitutes one of the largest prospective outcome registries in surgery worldwide, with over 700 participating centers[5]. Yet, despite the success of ACS-NSQIP as a quality improvement program, there are inherent limitations of research studies and quality improvement efforts based on its data registry. These include the risk of confounding when comparing groups of nonrandomized patients or a Hawthorne-like effect when hospital performance on selected outcomes is emphasized[6].

Registry RCTs (rRCTs) are one form of pragmatic RCTs that seeks to leverage existing data platforms for case records and data collection to reduce the administrative burden of trial implementation. In the era of big data and limited budgets, rRCTs have garnered enthusiasm as an ideal method to address comparative effectiveness research questions in real-world settings. Herein, we will review the history of rRCTs and their application in the field of surgery, as well as examine our personal experience in the development and enactment of the first ACS NSQIP-based randomized registry-based trial.

Description and History of rRCTs:

Traditional RCTs are an experimental framework where patients are randomly assigned to experimental and control arms to evaluate the effectiveness of a medical intervention while minimizing impact from both known and unrecognized sources of bias. Typically, successfully performing a RCT requires substantial financial resources and logistical coordination. There are attendant high costs to support dedicated study personnel who are critical to coordinate study enrollment, data collection, and required documentation. Moreover, study-specific labs, imaging, and visits that deviate from standard of care practice further increase cost as these are not typically billable events. Beyond financial concerns, RCTs commonly have restrictive inclusion criteria and poor representation of the population at large that can slow enrollment and limit the generalizability of the study results.

Registry RCTs also utilize randomization to address sources of bias, but leverage existing registries as platforms on which to conduct such trials. Data collection occurs within a previously-financed clinical registry by previously-trained data abstractors. Data is securely stored in established data management platforms. The registry has pre-defined outcome measurements, which are typically measured at standardized time points for clinical care. Together, such design elements allow for significant financial savings and greater efficiency by utilizing an existing research and data collection apparatus.

To further illustrate, consider the TASTE trial, a rRCT where patients diagnosed with acute myocardial infarction with planned percutaneous intervention (PCI) were randomly assigned to either receive thrombus aspiration or not prior to PCI[7]. As all relevant patient characteristics and clinical outcomes were already recorded in a national Swedish registry, no further deviation from usual practices was needed after randomization. In total, the TASTE trial enrolled 7,244 patients across 31 coronary centers. The authors of the study reported that the trial was able to be executed with an incremental cost of only $300,000, or about $50 per patient. This is substantially less than the tens of millions of dollars—or more—that a traditional clinical trial of this scale would require.

The concept of rRCTs has received increasing attention in the medical literature as a form of pragmatic trial design[8–10]. However, it is hardly a new concept; the first reported rRCT was conducted in Sweden in 1976[11], followed by rRCTs in Canada, Denmark and the United States in the 1980s and 1990s. Registry-based RCTs are an increasingly utilized methodology due to contemporary computing technologies, along with improvements in registry design and reach. Still, their application to surgical trials is rare. To date, there have been three registry-based trials in cardiovascular surgery[12–14]and at least 4 trials completed by the Cleveland clinic Hernia center[15]. As over 20% of surgical RCTs are discontinued early, and one third of completed surgical RCTs go unpublished[16], the broader application of this methodology in the field of surgery holds promise to rapidly improve the quality of available evidence that guides clinical practice.

Use of ACS-NSQIP as a rRCT platform:

The ACS-NSQIP alone cannot be immediately re-purposed as a platform for registry-based trials. While trained surgical clinical reviewers (SCRs) collect extensive and well-defined data elements, an algorithm is used to select a representative sample of cases (approximately 10%). However, ACS NSQIP has been expanded to include procedure-targeted modules, which collect additional variables relevant to specific procedure types[17]. Starting in 2011, a pancreatectomy-targeted module was launched including pancreaticoduodenectomy (PD), distal pancreatectomy, total pancreatectomy, and pancreatic enucleation procedures. Although not mandatory, most sites which participate in the pancreatectomy-targeted module abstract 100% of these cases. Hence, this pancreatectomy-targeted module was amenable as a rRCT platform.

The ACS-NSQIP rRCT emerged from the Americas Hepato-Pancreato-Biliary Association (AHPBA) clinical trials committee, which was specifically created to perform RCTs among hepatectomy and pancreatectomy patients. Coordination and collaboration between the AHPBA and ACS-NSQIP ultimately produced the mechanism of registry RCTs for these patients. Registry RCTs are best suited for testing hypotheses involving any intervention already available in the real-world clinical setting but where there is variable implementation or multiple standard-of-care options available. In the case of PD, there was a clinical question regarding the optimal antibiotic regimen for surgical prophylaxis to prevent surgical site infections (SSIs). Surgical Care Improvement Project (SCIP) guidelines currently recommend use of a second-generation cephalosporin (or first-generation cephalosporin with metronidazole) as prophylaxis for gastrointestinal operations[18]. However, multiple

studies have shown high rates of antimicrobial resistance among bacterial isolates from intraoperative biliary and would cultures. Cortes et al. evaluated bacterial resistance patterns of intraoperative bile cultures during PD and noted that only 17% of isolates were susceptible to cefoxitin, compared to 66% which were susceptible to piperacillin-tazobactam[19]. Similarly, all *Enterococcus* isolates from intraoperative bile cultures taken during PD were resistant to cefazolin[20] and cefoxitin[21]. Moreover, in a single institution observational study where preoperative prophylaxis were changed from SCIP-recommended antibiotics to piperacillin/tazobactam prior to PD, there was a large observed reduced rate of SSI (6.6% vs. 32.4%)[22]. Based on this limited, non-randomized data, there was rationale to explore whether more broad-spectrum antibacterial prophylaxis would reduce the occurrence of SSI after PD.

In this case, it was important that the research question involved two FDA-approved, insurance-reimbursable interventions, where either could be considered appropriate clinical care. Moreover, the outcome (SSI) could be answered by the existing registry. It is worth drawing the explicit distinction between a typical RCT, where the trial is designed to answer a specific clinical question, and a registry RCT, where the question must also fit the registry. In the ACS-NSQIP, patients are followed for 30-days postoperatively and a wide range of outcomes are captured, including mortality and wound and infectious complications. These variables are rigorously defined and graded, and standardized across all participating hospitals. Thus, the ACS-NSQIP registry was well suited to ask research questions where the outcome occurred in the perioperative period.

Implementation of the ACS-NSQIP rRCT:

In order to establish feasibility, the AHPBA clinical trials committee polled participating centers to ensure that (1) each center could provide full coverage of their PD cases into the ACS-NSQIP pancreatectomy-targeted module, (2) there was equipoise between the two antibiotic choices and (3) there was interest and ability to participate in the trial. A total of 26 centers organized to participate in our trial (NCT03269994)[23]. The cost to each participating institution was limited to the administrative fees of regulatory review, and approximately one-quarter of a FTE of a research coordinator – which was often already salaried by each department. At our institution, which was the primary study site, the trial was coordinated within the existing research infrastructure of our hepatopancreatobiliary division and partially subsidized by the AHPBA Foundation. Here, the study was reliant on a half an FTE and 10% of an FTE-biostatistician.

A REDCap system[24,25] was used to alert and remind the surgical teams of the outcome of the central randomization and thus minimize protocol violations. Central randomization occurred via a computer program at the primary site. As a pragmatic trial, the treatment assignments were not blinded to participants, healthcare providers, or data abstractors. The rationale to use an open label study was based on the knowledge that the primary outcome —SSI—has relatively little susceptibility to performance or observation bias. Additionally, with both study drugs being readily available, omitting the processes necessary to mask the identity of the study drugs from the surgical and anesthesia teams dramatically reduced the study costs.

Data collection occurred within the standard abstraction process of the ACS-NSQIP pancreatectomy-targeted module. Trial patient abstraction did not change the ACS-NSQIP data collection workflow, except for three additional datapoints specific to trial patients: assigned treatment arm, protocol violations, and antibiotic-related adverse effects. These were added to the data abstraction portal for participating trial sites and were coded by the already assigned SCRs. This allowed all trial data to be contained in a single dataset with a negligible increase in abstraction burden. Lastly, because ACS-NSQIP data abstraction occurs up to 90 days following surgery, there are limitations in the ability to capture time-sensitive outcomes (e.g., severe adverse events (SAEs)). To ensure that such events were addressed in a timely fashion, trial patients were monitored for SAEs by SCRs and the coordinating institution for 30 days after surgery. For this trial, SAEs were limited to postoperative deaths and adverse reactions to the assigned antibiotic and were reported by research personnel to their institutional research board (IRB) in accordance with local IRB policy. This ensured patient safety while maintaining efficient and cost-effective data collection. To date, this trial has accrued 782 patients over 3.4 years and is currently being evaluated in a planned interim analysis. Although final results remain to be analyzed and reported the mechanism worked favorable with easy and rapid accrual with few protocol violations.

Conclusion:

The ACS-NSQIP is a high-quality surgical registry that collects standardized patient data in a real-world clinical setting. However, despite statistical advances, comparative observational studies utilizing ACS-NSQIP data are limited by the lack the rigor of randomization. Herein, we highlighted a novel approach to using a surgical specialty society (AHPBA) and a procedure-specific module of the ACS-NSQIP as the platform for a registry RCT. This trial demonstrates the tremendous potential for prospective trials utilizing the ACS-NSQIP infrastructure, with a low cost design and the potential for high quality, practice-changing results. With the large number of procedure-targeted modules currently available, any study evaluating the effect of a preoperative or intra-operative intervention on 30-day postoperative outcomes for a targeted procedure would be a candidate for an ACS-NSQIP-based rRCT. Future trials are currently under development and will continue to refine this research platform.

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Data Availability:

Data sharing is not applicable to this article as no new data were created or analyzed in this study.

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Synopsis:

Registry-based randomized controlled trials (RCTs) are a type of pragmatic trial design that leverages an existing registry as a platform for data collection, providing a low-cost alternative for randomized studies. We describe the tenets of registry RCTs and the development of the first AHPBA/ACS-NSQIP-based registry trial.