

Reflections on the Challenges of Infertility-Based Randomized Controlled Trials

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Abstract

Successful randomized clinical trials (RCTs) are considered the gold standard in clinical research, but require sufficient recruitment, adequate sample size, appropriate participant selection, pre-defined outcomes, and transparent reporting of outcomes. Infertility-related RCTs harbor a unique set of logistical and ethical challenges, as highlighted by our multicenter RCT evaluating clinical differences in low-dose versus high-dose gonadotropin in poor responders undergoing assisted reproductive technology. This is a descriptive review and reflections of frequent difficulties faced by researchers while conducting RCTs and their implications, as well as potential solutions when conducting this type of research. While our RCT in poor responders undergoing *in vitro* fertilization (IVF) failed to demonstrate superior clinical outcomes with high-dose versus low-dose gonadotropins, the study was significantly underpowered. Despite this, our results help underscore universal difficulties in the recruitment, conduct, and publication of RCTs. We review our challenges and suggest available tools to aid in recruitment and enhance trial completion. Recruitment, conducting, and publishing an RCT have numerous challenges, particularly in an infertile population, which are not unique to our study.

Addressing these barriers, despite the shortcomings, provides significant value to the scientific community.

Keywords: Gonadotropin; IVF; Infertility; Randomized controlled trial; Enrollment

Introduction

Advancements in healthcare depend on a diversity of research that provides the basis for patient care. Randomized clinical trials (RCTs) represent the most evidence-based research and are considered the gold standard for elucidating significant associations in clinical research due to their unbiased nature, randomization, and control of confounding factors [1, 2]. However, conducting an RCT has become increasingly complex, costly and often fails to meet expected recruitment. Furthermore, infertility-related RCTs harbor a unique set of logistical and ethical challenges specific to this population. Finally, although we recently published data from our RCT, the manuscript was submitted to several peer-reviewed journals with underlying criticisms from each reviewer that included: “underpowered,” “asked the same question as prior studies,” and “an exploratory study.”

Although frustrating, the peer-review process must be endorsed as a learning process. After undergoing multiple edits, the manuscript gained publication [3]. Subsequently, we were encouraged by editors to detail and discuss the challenges in completing our RCT, including when to decide to terminate the trial, and what to do with our findings despite a possible beta (type II) error. Thus, we present the logistic travails of running an RCT, especially an investigator-initiated infertility RCT, and we discuss why it is imperative to publish even negative findings in the case of an underpowered RCT for the purpose of serving future systematic reviews and meta-analyses.

Our RCT

“Increased gonadotropin dosing (375 vs. 225 IU/day) does not improve clinical outcomes in poor prognosis patients undergoing IVF: results of a multicenter randomized controlled trial.”

The results of our multicenter RCT aimed to determine whether the use of higher gonadotropin dosing was associ-

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ated with improved cumulative clinical pregnancy rate (cCPR) in expected poor responders undergoing *in vitro* fertilization (IVF) [3].

While multiple trials related to this topic have been reported, including several RCTs, various methodological issues have precluded a conclusive approach to these patients [4-8]. According to the latest guidelines, the use of increased gonadotropin dosing is not recommended during IVF; however, often in daily practice, 450 - 600 IU gonadotropins per day are prescribed [9]. In planning this trial, we attempted to design a clinical trial to address issues from the previous trials to better answer the question “is higher dosing better than lower dosing?” This included identification of poor responders based on POSEIDON criteria [10], use of the same stimulation protocols in all arms, the exclusion of the use of oral agents where international unit conversion is not possible, prohibiting dose escalation during treatment cycles, and using internationally agreed clinically relevant endpoints. Furthermore, the trial was designed as a multicenter prospective RCT from six Hungarian IVF centers to enhance external validity.

In determining the necessary sample size, 350 patients in both the lower-dose and higher-dose arms were needed to show the superiority of higher gonadotropin dosing. The trial was initially planned for 1 year based on expected patient enrollment by the co-investigators, with an interim analysis after enrollment of the first 350 patients to assess for the benefits of gonadotropin dosing on clinical pregnancy outcomes. Due to recruitment issues - including a shortage of gonadotropin-releasing hormone (GnRH)-antagonists twice for 2 months, and an unfortunate patient death related to an undisclosed autoimmune disorder that was deemed unrelated to the trial procedures based on the coroner’s exam - the enrollment was extended to 1.5 years. Finally, with no additional resources to maintain the mandated insurance requirement per the Ethics Committee, the joint decision was made amongst the site-investigators to terminate the study prior to meeting our planned sample size.

Overall, of the planned enrollment, 190 participants were randomized, with 98 receiving lower-dose treatment and 92 receiving higher-dose treatment. Analysis of the study’s outcomes revealed the same conclusion of previous RCTs: use of increased dose gonadotropin did not correlate to greater stimulation, embryology, or clinical pregnancy outcomes in expected poor responders undergoing IVF [3]. As a result, rather than a definitive efficacy trial, our RCT was peer-reviewed as an exploratory study, as we failed to show any differences in cCPR in poor responders using either low-dose or high-dose gonadotropins, with a high probability of a type II error.

Challenges of RCTs

RCTs have become increasingly complex and expensive to conduct. The Consolidated Standards of Reporting Trials (CONSORT) guidelines can serve as a roadmap when the study steps are planned and help identify specific roles for the study, which may vary depending on funding [11] (Table 1). Farrell et al compared the development and execution of an

RCT to a business plan, putting forward five basic stages of running a clinical trial. Briefly, these are: 1) initiation, including hypothesis generation and identification of co-investigators; 2) planning, involving preparation of a research plan and finding study personnel at each site; 3) execution, with training of study personnel and subject enrollment; 4) monitoring and control, including follow-up at each site and enrollment of new sites if required; and 5) analysis and reporting [12].

Nonetheless, we, as well as many others, failed to meet enrollment goals, which are commonly encountered in RCTs. In a review of a cohort of 114 trials, Campbell et al reported that less than one-third recruited their target participants within their original timeline, and approximately one-third needed an extension to meet the study goals [13].

In retrospect, stage 1 of our “business plan” posited challenges regarding our hypothesis. The lack of universally agreed-upon inclusion criteria has led to difficulty comparing data across existing studies [14]. Two criteria, the Bologna criteria and the POSEIDON classification, have spearheaded enhanced universal identification of poor responders [10, 15]. Despite this, both criteria have faced disapproval among reproductive endocrinologists. The Bologna criteria is a binary classification system that classifies patients as being poor responders or not based on meeting at least two criteria (advanced maternal age ≥ 40 years or other risk factor for poor ovarian reserve, previous evidence of poor ovarian reserve, abnormal ovarian reserve testing), but excludes classifying younger women with abnormal ovarian reserve testing as poor responders [16]. The POSEIDON criteria is a more nuanced stratified classification system that separates expected and unexpected poor responders based on age, ovarian reserve testing, and ovarian response [16]. It includes young women with an unexpected poor ovarian response (POSEIDON 1), whose treatment outcome (pregnancy) may not be different from other normal responders not otherwise classified by POSEIDON. This contrasts with expected poor responders (POSEIDON 3 and 4) [17]. As inclusion criteria such as POSEIDON have been further enhanced, this has led to limitations in recruitment due to the stringent inclusion criteria. While restricting to unexpected poor responders defined as POSEIDON 3 and 4 allowed us to enhance external validity and the generalization of our results, we needed to be more realistic about its impact on study recruitment and consider less stringent criteria for inclusion. Furthermore, as we identified motivated co-investigators, we needed to anticipate and address provider reluctance to prescribe follitropin- δ , which at the time was a new fertility medication potentially limiting their willingness to enroll study patients.

With respect to stages 2, 3, and 4, we lacked dedicated study personnel at each site to assist with execution, monitoring, and follow-up, including enrollment of new sites. Though a collegial relationship was in place with our co-investigators, in hindsight it would have been critical to assess in advance how many subjects a co-investigator realistically was able to enroll based on the characteristics of their patient population and over a defined timeline. In contrast to pharma-sponsored trials, where feasibility questionnaires are often utilized, going by one’s word proved to be inadequate. Considering that IVF services in Hungary are fully reimbursed up to age 45, the

Table 1. Responsibility Related to Trial Associated Activities in Pharma-Sponsored, Investigator-Initiated Trials and Our Own RCT

	Pharma-sponsored	Investigator-initiated	Our own RCT
Hypothesis generation	By sponsor	By investigator	By chief investigator
Preparation of the protocol	By sponsor	By investigator	By chief investigator
Recruitment of co-investigators: feasibility questionnaire	By sponsor/monitoring company	By investigator in person/online discussion	Pre-study online discussion
Determining the interventions/arms	By sponsor	By investigator	By chief investigator
Setting up the inclusion-exclusion criteria	By sponsor	By investigator	By chief investigator
Determining the 1° and 2° outcomes	By sponsor	By investigator	By chief investigator
Sample size calculation	By sponsor	By investigator	By chief investigator
Randomization	By sponsor; central list, proper concealment	By investigator; central list, concealment may be an issue	Randomization list prepared by statistician, central access, concealment problematic
Blinding	Arranged by sponsor if blinding is needed/possible	Often problematic	Providers/patients not blinded to treatment
Placebo group	If required, arranged by sponsor	Rarely used; Who prepares the placebo? Who pays for it?	There was no placebo group
Statistical methods	By sponsor	By investigator/statistician	By statistician
Single-center vs. multi-center RCT	Almost always multi-center	Mostly single center	Multicenter
IRB approval	Monitoring company	By investigator	By chief investigator
Local ethical procedures	Monitoring company	By investigator	By chief investigator
Insurance	By investigator	By investigator or no extra insurance	Additional insurance was mandated by regulatory authorities
Trial registration	By sponsor	By investigator	By chief investigator in ClinicalTrials
Funding	By sponsor	None or through funds	None
Data collection	By sponsor and monitoring company	By investigator(s)	Chief and local investigators
Patient enrollment/maintenance	Local investigators	By investigator(s)	Local investigators
Periodic follow-up	By sponsor and monitoring company	By chief investigator or none	Only <i>ad hoc</i> follow-up, no regular follow-up
Statistical analysis	By sponsor	By investigator/statistician	By chief investigators
Publication - publication expenses	By sponsor	By investigator	By investigator, no funding, open access publication not an option

IRB: Institutional Review Board; RCT: randomized controlled trial.

incorrect notion among co-investigators was that recruitment would not be an issue.

Unlike investigator-initiated studies, pharma-sponsored studies routinely have investigator meetings detailing the rationale, review of the protocol, and procedures for the study. Furthermore, regular site visits by monitors allow for assessment of enrollment progress and could offer solutions to improve subject recruitment. Successful trial recruitment has been shown to correspond to having a dedicated study nurse [13]. Sully et al reported that involving clinical trial units increased overall recruitment and saved time and costs by assessing efficacy and determining trial progress [18]. In our investigator-initiated clinical trial, despite good intentions with a second online meeting with the goal of re-reviewing the study

protocol, this was not enough. Further, updates were not provided at regular intervals, and contact would have provided a constant reminder to enroll patients and to identify barriers that limited subject recruitment. Instead, contact was *ad hoc* due to a lack of study support personnel. This is particularly imperative when unforeseen events occur, as in our study, which included a medication shortage and an untimely death.

Tools and strategies to aid participant recruitment include local outreach, digital platforms, enhanced patient education, increased amount of time spent with patients answering questions, and utilization of recruitment companies. Further, Paramasivan et al developed the Quanti-Qualitative Appointment Timing (Q-QAT) technique to identify and address challenges with recruitment [19]. Others have used the Quintet Recruit-

ment Intervention (QRI) tool, which helps participants make informed decisions and overall increases RCT recruitment [20]. They both thoroughly assess the consenting process and provide feedback on how to make it more efficient. Utilizing these tools proactively in the early phase of an RCT before recruitment difficulties came to light in future studies should be considered to enhance subject numbers and study results [21].

Difficulties in achieving participant recruitment goals for RCTs can mainly be attributed to under-calculation of financial needs, limited financial resources from grants or pharma support, and improper utilization and spending of financial resources [22]. High costs associated with an RCT's planning phase are often underestimated. In our study, the only incentive was co-authorship for site investigators, and the study was planned to avoid extra clinic visits without compromising care. This, nonetheless, was not enough to secure adequate enrollment.

Challenges of Conducting Infertility-Related RCTs

Infertility-related clinical trials present unique challenges, including methodology, ethical and emotional questions, and financial and operational issues. The sequential stages of fertility treatments (stimulation, egg retrieval, and embryo transfer) create statistical challenges, including what to measure and how to handle patients who undergo multiple treatment attempts within the same study. Live birth is the most important outcome of fertility treatments, but due to long follow-up between treatment and birth, one needs to take into consideration the potential for considerable drop-out rates. Patients who undergo multiple treatment attempts within the same study represent further statistical challenges. For example, if study participants “crossover” from one treatment group to another, particularly if they do not conceive early in the study, it can compromise the study's randomization and dilute the treatment's effect. Other methodological issues include the use of a total number of randomized participants versus total number of participants who complete the study. In a 2016 review of 142 IVF RCTs published in 2013 and 2014, approximately one out of three trials reporting live birth rates reported results using a post-randomization denominator, while intention-to-treat analysis (initial total number of randomized participants) should have been used making the data more reliable [23]. This issue is well illustrated by an example regarding different stimulation protocols for ovarian stimulation. Instead of including all participants who initiated treatment, the primary outcome would only be calculated in those who underwent oocyte retrieval or embryo transfer, excluding participants who may have been cancelled for a poor response and never underwent an oocyte retrieval or embryo transfer, thus introducing a bias towards those who responded to a particular stimulation protocol. While this does not represent an intentional manipulation of data, this may occur in infertility studies that may have several different secondary outcomes and treatment milestones, making various combinations of numerators and denominators available to use in data analysis [23]. Additionally, infertility patients frequently pursue complementary and

alternative therapies including nutritional supplements, herbal therapies, acupuncture, and ovarian platelet-rich plasma therapy, often concurrently with conventional treatment. This may introduce potential unmeasured confounding factors into fertility research outcomes [24, 25].

Infertility-related studies may also pose ethical and emotional questions including the treatment of vulnerable participants and the potential future child undergoing infertility trials, which requires careful attention of all potential risks. For example, a multiple gestation pregnancy could be desired by the parents but poses significant health risks to both the pregnant woman and the infant(s). Some patients may feel that they are “experimented” with when they undergo their best chance at pregnancy and thus may elect not to participate, while others may agree to anything that promises a successful outcome. Patients undergoing fertility treatment often may feel a mix of hope and desperation, which can compromise their ability to give fully informed consent. Cultural or financial pressures can complicate the decision-making process. While women bear the burden of the treatment, the decision to participate in a trial is shared with the partner or family, thus creating privacy issues. Infertility-related studies are rife with ethical quandaries, including what to do with surplus embryos after a trial, determining fair compensation for participants without exploiting them, and establishing appropriate age limits and inclusion criteria for treatments, which often vary widely based on individual assessment or public funding.

Lastly, regarding financial and operational challenges, recruiting patients is notoriously difficult, and many trials fail to meet their enrollment goals. Reasons include strict eligibility criteria, patient fear of receiving a placebo, and the heavy financial and time burden on participants. Additionally, the financial demands of infertility trials are significant. The high cost of treatment, combined with extensive monitoring and long-term follow-up required to track live births, creates major financial and logistical burdens. In many places, funding is limited, and industry sponsorship has declined, making these trials exceedingly difficult. Finally, clinical trials are subject to an increasing regulatory burden, including extensive paperwork for human subject research. These regulations are designed to protect participants but can significantly increase the cost and time required to launch and complete a trial.

Reasons for Publishing Underpowered RCTs

Most journals prioritize significant findings while rejecting studies with negative results, representing a potential for publication bias. We implore to all investigators that underpowered RCTs should be published as they may provide valuable data that can be combined with other studies in systematic reviews and meta-analyses, contributing to the collective body of evidence and influencing clinical practice. Rather than being reluctant to pursue publication, authors should focus on different aspects of their datasets that highlight interesting features of the study population, even if they do not achieve statistical significance based on the primary outcome. Furthermore, such studies may be valuable for demonstrating important

findings about the rarity or ubiquity of events, which can be a significant outcome in themselves. Finally, publishing results regardless of outcome, including trials with null results, helps to counteract the publication bias that can skew the perceived body of evidence by masking the true effects of treatments, and it can often serve as pilot studies and provide important information on feasibility, develop realistic estimates of effect sizes, and refine study designs for larger, more powerful trials.

Considerations for authors who want to publish their work include pre-registered protocols that pre-specify analyses and make data publicly available by demonstrating full reporting, regardless of outcome. Investigators should also commit to data-sharing agreements in their protocols to facilitate meta-analyses and individual data pooled analyses, even from under-enrolled trials. Reporting should also emphasize responsible interpretation of the data itself rather than focusing solely on the lack of statistical significance, acknowledging that “underpowered analyses” can be more problematic than “underpowered datasets.” Findings such as ours, even if not statistically significant, can serve to help design future, adequately powered trials by revealing issues with implementation or providing better estimates of effect sizes.

Conclusions

Recruitment, conducting, and publishing an RCT have numerous challenges, as highlighted by our own RCT study investigating treatments particularly in an infertile population. These difficulties are not unique to our study. Despite these challenges, RCTs are necessary for advancing clinical care in the field of infertility care. It is critical to address these barriers and to conduct these studies and to encourage publication in order to support clinically applicable advancements in medical treatments, including infertility treatment. Through the lens of our own investigation, strategies to optimize an RCT include the use of a business model approach, implementation of standardized recruitment tools, and utilization of a dedicated clinical team for recruitment and tracking progress. Despite the shortcomings of our RCT, our findings have significant value in lessons learned with respect to study execution and serve to encourage publication to contribute to systematic reviews and meta-analyses in the future.

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Conflict of Interest

The authors declare no conflict of interest that could inappropriately influence or bias this work.

Author Contributions

Peter Kovacs: conceptualization, investigation, writing - review and editing, supervision. Summer Crawford: investigation, writing - original draft preparation. Saira Kothari: investigation, writing - original draft preparation. Nigel Pereira: investigation, writing - review and editing. Jose Carugno: investigation, writing - review and editing. Steven Lindheim: conceptualization, investigation, writing - review and editing, supervision.

Data Availability

Any inquiries regarding supporting data availability of this study should be directed to the corresponding author.

Abbreviations

RCT: randomized clinical trial; IVF: *in vitro* fertilization; cCPR: cumulative clinical pregnancy rate; GnRH: gonadotropin-releasing hormone; CONSORT: Consolidated Standards of Reporting Trials; Q-QAT: Quanti-Qualitative Appointment Timing; QRI: Quintet Recruitment Intervention

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