Original Article

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Reporting of pre-enrolment screening with randomized clinical trials: A small item that could impact a big difference

Abstract

Introduction: Randomized controlled trials (RCTs), when conducted using ethical and transparent methods, become the ultimate standard for producing evidence-based knowledge in the field of medical research. We sought to determine the proportion of RCTs in which the number of screened patients is reported, and also to ascertain what predicted efficient screening (i.e., a high number of screened participants being enrolled). **Materials and Methods:** Thirty-five RCTs from the Journals Clinical Infectious Diseases and The Lancet Infectious Diseases were reviewed from the time period of January 2012 to July 2013 using standardised criteria. **Results:** From the 35 RCTs, 9 of 35 (26%) did not report the number of patients screened prior to recruitment. From the 26 studies that reported this screening figure, 10,215 (47%; range: 2-98%) of the screened participants (21,862) were subsequently enrolled. About 18.3% of those screened and not enrolled, met inclusion and exclusion criteria yet did not wish to participate in an RCT. Studies performed in developed countries and pediatric populations were more likely to have low rates of enrolment compared with the screened population although there was no statistical significance to these associations (P = 0.2 for both variables). **Conclusion:** Many reports of RCTs do not report screening figures, even though these add useful information about the feasibility of future trials.

Key words: Clinical trials, enrolment, participant recruitment, randomized controlled trials, research methodology, screening

INTRODUCTION

The science and evidence-based knowledge provided by conducting and publishing a randomized controlled trial (RCT) in any clinical setting is vital to the advancement of theory and practice in that field. When RCTs are developed and reported in a clear, factual and ethical manner, they can become the gold standard when evaluating a clinical intervention.[1] Reporting on all aspects of the trial, from the preenrolment screening to the end data analysis of the indicated outcomes, should be seen as warranted information for providing a transparent trail for the reader and also for aiding in the development of subsequent future trials of a similar nature.

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Information deemed essential when reporting on an RCT has been evaluated by many authors and has even reached an element of standardized requirement by organizations such as the International Committee of Medical Journal Editors,[2] and the World Health Organization through their trial registration minimum dataset.[3] The SPIRIT 2013 Statement,[4] an updated version of the original statement introduced in 2007, developed a checklist of recommended items that should be provided in a clinical trial's protocol and affiliated study documents. Within this checklist, the reporting of the investigator's

strategies for recruitment and successfully achieving the targeted sample size is identified. Corresponding with a study's recruitment methodology is the initial identification of a preenrolment recruitment screening figure. Identifying how many potential participants were approached for recruitment prior to enrolment can provide the reader and future investigator with an essential level of detail, especially in resource-limited clinician-initiated trials.

In this article, we evaluate how often reporting of preenrolment recruitment screening figures occur and what role this can potentially play in determining a trial's success.

MATERIALS AND METHODS

Thirty-five RCTs were selected for review from the Journals Clinical Infectious Diseases and The Lancet Infectious Diseases from January 2012 to July 2013.[5-39] These two journals were selected for review for their high-impact factor and level of academic preeminence within the field of infectious diseases. A review of each journal's archive database starting from most recent was performed to identify these RCTs. The only search criteria used was to identify solely published RCTs from these two journals within the demonstrated timeframe.

Through each article's review, the primary aim was to evaluate preenrolment screening. We asked two questions: (1) Was the number of screened patients reported in the study results?; and (2) what predicted a high proportion of screened patients being enrolled?

Firstly, studies were identified as to whether or not a preenrolment screening figure was reported either within the methods/results or an illustrated flow diagram figure. From this given figure a percentage was calculated for each trial to demonstrate what number of participants were enrolled from those that had been screened, and what percentage were excluded. Next, reasons for exclusion from enrolment post-screening were identified. These reasons were further broken down into the categories of: "did not meet inclusion criteria," "met exclusion criteria", or "other." The reasons for exclusion that were identified as "other" were further reviewed if provided by the article.

Additional variables were also evaluated. Each of the 35 articles that were reviewed discussed a range of infectious diseases topics from human immunodeficiency virus (HIV), hepatitis C virus (HCV), respiratory tract infections (RTIs) to antimicrobial prophylaxis. The trials assessed exemplified characteristics of both paediatric (≤18 years of age) and adult populations, pharmaceutical and nonpharmaceutical support, and geographic diversity within the United States (US), non-US countries and combined international collaborations. The variable of the trial being conducted in a developed versus a developing setting was also evaluated, with the classifications modelling those provided by The World Bank.[40]

Variables associated with "efficient" rates of enrolment compared to the screened population (arbitrarily defined as >75% of those screened were enrolled) were assessed using the Fisher's exact test.

RESULTS

In total 57,400 (mean: 1640 and range: 48-43,802) participants were enrolled across the 35 RCTs. A range of subject areas were discussed throughout the studies: (20%) HIV, (17%) tropical diseases, (14%) vaccines, (11%) HCV, (6% each) for sexually transmitted infections, RTIs, skin and fungal infections, and (3% each) for sepsis, urinary tract and viral infections, *Clostridium difficile* infections, and prophylaxis treatments. Studies whose participant age criteria were adults (≥18 years of age) accounted for 23 of 35 (66%) and pharmaceutical supported studies accounted for 19 of 35 (54%). The most prevalent geographic location was studies conducted solely in non-US countries, 20 of 35 (57%), with international combined (including US) representing 8 of 35 (23%) and US only accounting for 7 of 35 (20%). The studies conducted in developed settings 25 of 35 (71%), out-numbered those performed in developing settings.[40] The mean duration of study length among the 35 trials was 26 months (range 1.2-84 months).

From these studies, 9 of 35 (26%) did not provide a preenrolment and randomization recruitment screening figure. Within the 26 studies that did report a recruitment screening figure, 21,862 (mean: 841, and range: 74-6491) participants were screened and 10,215 (mean: 393 and range: 48-2061) were subsequently enrolled. The percentage of participants that were successfully enrolled from those screened was calculated for each of the 26 studies that provided a screened figure. From the 26 studies that provided a recruitment screening figure, 47% (range: 2-98%) of participants were enrolled. Exclusion figures and criteria were analyzed for those 26 studies that reported reasons for screened individuals not being enrolled. Rationale for nonenrolment was largely represented by screened participants not meeting all inclusion or exclusion criteria 8858 (40.5%) or "declined or refused to participate" 2135 (9.77% of all of those who were screened, but not enrolled).

From these 26 studies, 5 of 26 (19%) achieved <50% enrolment from participants who were screened, with 1 of the 5 studies achieving <10% enrolment from recruitment screening. Common factors identified from these studies

were all 5 had non-pharmaceutical involvement, 4 of 5 (80%) were paediatric populations, along with the same percentage being represented for studies occurring in non-USA locations.

The results in Table 1 demonstrate the variables that contributed to "efficient" enrolment, arbitrarily defined as >75% success in enrolment throughout the 26 studies. No variables significantly predicted "efficient" enrolment, although studies performed in developed countries and with pediatric populations were less likely to exceed >75% success in enrolment.

DISCUSSION

Recruitment is invariably an issue that requires attention within clinical trials. Many times investigators are faced with needing to re-visit and adjust a study's initial participant recruitment strategies. Difficulties with maintaining a study's timeline because of recruitment barriers can gravely jeopardise a study's financial and physical resources along with delaying the availability of its potentially beneficial outcomes.

Table 1: Predictors of enrolment in RCTs (efficient enrollers defined as >75% screened patients enrolled in the study)

Characteristics	Inefficient enrollers (*n*=15)	Efficient enrollers (*n*=11)	Fisher's exact *P*
Economic status			
Developed	11	5	0.22
Developing	4	6	
Setting			
USA	3	3	0.60
Non-USA	8	7	
Combined	4	1	
Age-group			
Adults	8	9	0.21
Paediatrics	7	2	
Primary sponsorship of study			
Pharma	6	4	1.0
Nonpharma	9	7	
Topic of RCT			
HIV	4	3	0.70
Tropical infections	2	4	
Vaccines	1	1	
HCV	3	1	
STI	1	1	
Skin infections	2	0	
RTI	1	0	
Fungal infections	1	0	
Sepsis	0	0	
UTI	0	0	
Viral infections	0	1	
Clostridium difficile infections	0	0	
Prophylaxis treatments	0	0	
Participant figures			
≥500 enrolled	3	3	1.0
<500 enrolled	12	8	

RCTs=Randomized controlled trials, HIV=Human immunodeficiency virus, HCV=Hepatitis C virus, STI=Sexually transmissible infections, RTI=Respiratory tract infections, UTI=Urinary tract infections

Reporting accurate participant recruitment and retainment figures, including those screened, enrolled and reasons for exclusion, are an essential component of performing clinical research. Yet we found that 9 of 35 (26%) RCTs published in high-impact infectious diseases journals did not demonstrate a preenrolment and randomization recruitment screening figure. These elements should be reported because they allow for a trial's infrastructure to be clearly visualized from commencement to final analysis. Any steps that will provide a clearer translation and greater knowledge-base of clinical research practices are valuable and essential to the future of health research.

We did not find statistically significant variables that predicted suboptimal enrolment to screening ratios, although there were trends to lower recruitment rates in developed countries and pediatric populations. Addressing recruitment strategies through conducting a pilot study can prove beneficial by identifying factors that may have gone undetected during a study's protocol development. One identified study looked at recruitment strategies when pilot studies were conducted in RCT's, and found that over 50% of the trials had to perform changes to their recruitment strategies and protocols because of issues highlighted during the formal pilot study. Having to modify study documents, inclusion criteria, sample sizes and adding additional study sites were commonly adjusted items that were identified from performing these pilot studies.[41]

When a clinical trial runs into unexpected recruitment and enrolment issues, maintaining momentum and the trial team's sense of ownership can be challenging. Poor recruitment, when met with financial and physical resource strain, can contribute to a decrease in trial staff morale and achieving expected outcomes. Developing the practice of documenting and identifying a preenrolment screening figure and associated exclusion reasons, especially when a formal pilot study is not performed, can aid investigators with determining a trial's shortfalls along with future recruitment predictions for trials of a similar nature.

Louis Lasagna, an American clinical pharmacologist, coined the theory of "Lasagna's law" observing that at the moment a trial's recruitment begins, the availability of suitable participants to recruit sharply decreases from what was assumed prior to the trial's commencement.[42] This theory could be interpreted however, as challenging the guidelines for good clinical practice set by the International Conference on Harmonisation (ICH), "4.2.1 - The investigator should be able to demonstrate (e.g., based on retrospective data)

a potential for recruiting the required number of suitable subjects within the agreed recruitment period".[43]

When underestimated barriers to recruitment are faced, severe consequences in the form of premature ethical termination and refusal of grant extensions can occur. We advocate careful consideration of barriers to recruitment in all trials, and publication of numbers both screened and enrolled in order to better understand all clinical trials.

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