ELSEVIER

Journal of Clinical Epidemiology 66 (2013) 948−954

Journal of Clinical Epidemiology

REVIEW ARTICLE

No differential attrition was found in randomized controlled trials published in general medical journals: a meta-analysis

Rik Crutzen[a,*], Wolfgang Viechtbauer[b], Daniel Kotz[a,c], Mark Spigt[a,d]

[a]*CAPHRI School for Public Health and Primary Care, Maastricht University, PO Box 616, 6200 MD Maastricht, The Netherlands*

[b]*MHeNS School for Mental Health and Neuroscience, Maastricht University, PO Box 616, 6200 MD Maastricht, The Netherlands*

[c]*Department of Epidemiology and Public Health, Cancer Research UK Health Behaviour Research Centre, University College London, WC1E 6BT, UK*

[d]*Department of General Practice, Tromso University, Norway*

Accepted 12 March 2013; Published online 21 June 2013

Abstract

Objective: Differential attrition is regarded as a major threat to the internal validity of a randomized controlled trial (RCT). This study identifies the degree of differential attrition in RCTs covering a broad spectrum of clinical areas and factors that are related to this.

Study Design and Setting: A PubMed search was conducted to obtain a random sample of 100 RCTs published between 2008 and 2010 in journals from the ISI Web of Knowledge[SM] category of medicine, general and internal. Eligibility criteria for selecting studies were primary publications of two-arm parallel randomized clinical trials, containing human participants and one or multiple follow-up measurements whose availability depended on the patients' willingness to participate.

Results: A significant amount of differential attrition was observed in 8% of the trials. The average differential attrition rate was 0.99 (95% confidence interval: 0.97−1.01), indicating no general difference in attrition rates between intervention and control groups. Moreover, no indication of heterogeneity was found, suggesting that the occurrence of differential attrition in the published literature is mostly a chance finding, unrelated to any particular design factors.

Conclusion: Differential attrition did not generally occur in RCTs covering a broad spectrum of clinical areas within general and internal medicine.

Keywords: Differential attrition; RCT; Internal validity; Meta-analysis; Bias; Loss to follow-up

1. Introduction

Attrition or loss to follow-up after randomization is a common problem in randomized controlled trials (RCTs) [1,2], which complicates the statistical analyses and can lead to bias in the findings [3]. When the degree of attrition differs between the various treatment groups that are being compared in an RCT, then this is typically called differential attrition. Because these groups are, if random allocation is undertaken properly, comparable at baseline (e.g., in terms of the study's primary outcome), differential attrition can be assumed to be a consequence of differences between the groups that arose at some point after randomization (e.g., because of perceived treatment efficacy, safety, or tolerability) [4]. For example, patients in the control group who improve in terms of the study's primary outcome might be more prone to complete follow-up measures than those who do not improve, or treated patients (i.e., those in the intervention group) may feel a general obligation to complete follow-up measures [5]. Therefore, differential attrition is usually regarded as a major threat to the internal validity of a study (i.e., whether the intervention really did cause a change in the outcome) [6], but insight into the degree of differential attrition occurring in RCTs is limited.

Previous meta-analyses focusing on a single clinical area found no differential attrition in trials regarding interventions aimed at self-monitoring of blood glucose in type 2 diabetes [7] and the use of serotonin-specific reuptake inhibitors in treatment of posttraumatic stress disorder [8] but did find differences when comparing atypical and typical antipsychotic medications [9]. In a convenience sample of 10 trials evaluating interventions for the treatment of musculoskeletal disorders, all trials showed some level of differential attrition between the treatment arms, ranging from 1% to 14% [10]. A systematic review of comprehensive cohorts and two-stage trials that measured or recorded patient or physician

Conflict of interest/Financial disclosure: Neither conflict of interest nor financial support regarding the present study was reported.

* Corresponding author. Tel.: +31-43-3882828; fax: +31-43-3671032.
E-mail address: Rik.Crutzen@maastrichtuniversity.nl (R. Crutzen).

0895-4356/$ - see front matter
http://dx.doi.org/10.1016/j.jclinepi.2013.03.019

What is new?

- This study did not find evidence that differential attrition generally occurs in RCTs covering a broad spectrum of clinical areas.
- Potentially anticipatable sources of differential attrition (e.g., differences in the number of contact moments, additional advantages because of taking part in the intervention) should be taken into account when designing an RCT.
- The average overall attrition is 13%, which can be used as a rule of thumb in sample size calculations of future RCTs within general and internal medicine.

preference found little evidence that preference affects validity [11]. Furthermore, Puffer et al. [12] found evidence of differential attrition in 4 of 36 cluster randomized trials published in three general medicine journals. In only one of these trials did the authors comment on this in the discussion section.

To our knowledge, no study exists that has examined differential attrition in general (i.e., not focused on a single clinical area). This makes it impossible to draw any general conclusions about the degree of differential attrition in RCTs. We therefore conducted the present study to address the following key question: How often and to what degree does differential attrition occur in RCTs covering a broad spectrum of clinical areas within general and internal medicine, and which factors may be related to the degree to which differential attrition occurs in such studies?

2. Methods

A systematic review and meta-analysis of a random selection of RCTs published between 2008 and 2010 in journals from the ISI Web of Knowledge^{SM} category of medicine, general and internal was conducted.

2.1. Search strategy

To identify the trials, we obtained the impact factors (IFs) from the Journal Citation Reports Science Edition 2009 of ISI Web of Knowledge^{SM}. To obtain a representative sample of articles from both higher and lower impact journals, we selected the top 40 journals (IF: mean, 6.8; standard deviation [SD], 9.3; median, 2.9; range, 1.8–47.1), ranked these journals based on their IF, and created 4 groups of 10 journals, group 1 being the group with the highest IF and group 4 with the lowest. Subsequently, we searched PubMed for articles in each group with the following restrictions: ((''Randomized Controlled Trial'' [PT] OR ''Controlled Clinical Trial'' [PT] OR ''Clinical Trial'' [PT]) AND humans [MeSH Terms] AND English [LA] AND 2008:2010 [DP] AND random* [TIAB]). This resulted in 1,150 hits for group 1; 221 hits for group 2; 504 hits for group 3; and 99 hits for group 4; a total of 1,974.

2.2. Selection of trials

Each study identified in this manner then received a trial identification number and was randomly assigned to one of the investigators, who examined whether the article fitted the inclusion criteria. In particular, the article had to be the primary publication of a randomized clinical trial with an identifiable intervention and control/comparison group. Trials with more than two treatment groups or multifactor studies were included if groups could be collapsed in a logical manner (e.g., groups receiving varying dosages of a medication could be collapsed into a single intervention group). Furthermore, the trial should contain human participants and one or multiple follow-up measurements whose availability depended on the patients' willingness to participate (e.g., a trial that measured outcomes while patients stayed in the clinic was excluded because of the limited chance of loss to follow-up). If in doubt, inclusion of the article was discussed with the rest of the research team until a unanimous decision was reached. If an article did not fit the inclusion criteria, a new article was randomly selected based on the screening list.

This process was continued until the desired number of studies was selected from each group. Proportional stratified sampling (i.e., in proportion to the number of hits per group) was used to select articles, with the goal of obtaining approximately 5% of the trials within each group. Accordingly, we included articles until the following number of articles from each group was selected: 58 articles from group 1; 12 articles from group 2; 24 articles from group 3; and 6 articles from group 4; resulting in a total of 100 articles (Fig. 1).

2.3. Analysis of RCTs

The final set of 100 articles included a wide variety of trials, covering the following general categories: various types of medication for a variety of different medical conditions (e.g., uncomplicated acute cystitis, superficial vein thrombosis), the benefits of vitamin supplementation (e.g., vitamin K in postmenopausal women with osteopenia), surgical procedures (e.g., male circumcision, stent placement), vaccination (e.g., hepatitis B), behavioral/counseling interventions (e.g., computerized tailored physical activity reports), and policy evaluations (e.g., removing direct payment for health care). Each included RCT was independently scored on the items shown in Table 1 by two investigators (the one who initially examined the article for