Trial Registration in Rheumatology: The Next Step

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Randomized controlled trials (RCTs) provide the clearest evidence of whether health care interventions, including interventions for patients with rheumatic diseases, have the desired effect on patient outcomes (1, 2). RCTs are prioritized in the evaluation of evidence for clinical guidelines and, thus, play a major role in determining clinical practice standards (2). However, the extent to which publications that describe the results of RCTs accurately portray what would occur in practice depends on the completeness and transparency of trial reports (1, 3, 4).

In order to provide valid, replicable answers to clinical questions, trials should ideally be designed with one major question in mind and, prior to initiating a trial, investigators should identify a single primary outcome variable that will be used to test the primary study hypothesis (1, 5). In some cases, more than one primary outcome may be specified with appropriate statistical adjustment, although this introduces complexity related to the interpretation of potentially contradictory results. Key secondary outcomes, which may address other important outcome variables or subgroups, should also be specified *a priori* (1, 5).

If outcomes are not completely and precisely declared prior to initiating a trial or if they are not fully reported post-trial in a manner consistent with the pre-specified plan for testing the trial hypothesis, reporting biases can exaggerate the benefits of therapies and potentially mislead policymakers, clinicians, and patients about the likely benefits of interventions (4, 6, 7). Biases related to trial reporting may include (1) study publication bias, in which studies with statistically significant or positive results are more likely to be published than studies with negative findings; (2) selective outcome reporting bias, in which statistically significant, or positive, outcomes from a study are published, whereas non-significant outcomes from the same study are not; (3) selective analysis reporting bias, in which data analyses are conducted using multiple methods, but only those that generate positive results are reported; and (4) other biases, such as the relegation of a non-statistically significant primary outcome to secondary status when results are published and describing a positive
outcome that was intended to be secondary as the primary outcome (4, 6-8). A Cochrane review of publication bias, which examined 5 reviews that investigated trials registered in national trial registries or with research ethics boards, found that trials with non-statistically significant results were only half as likely to be published as trials with positive results (3). With respect to selective outcome reporting, it has been estimated that 40-62% of all published studies include at least one primary outcome that has been changed, omitted, or introduced post hoc (6).

Clinical trial registration has been proposed as a way to reduce the influence of reporting biases on the evidence base and to ensure that all research results are made available to research participants, clinicians and researchers, and the public. In 2004, the International Committee of Medical Journal Editors (ICMJE) announced a policy, which stated that clinical trials intended to influence clinical practice initiated on or after July 1, 2005 would only be considered for publication if they were registered in a publically accessible trial registry prior to enrolment of patients. Trials that were ongoing as of July 1, 2005 were required to have registered by September 13, 2005 (9). The ICMJE trial registration policy includes a priori specification of the primary trial outcome and key secondary trial outcomes (9). In 2005, the editors of Arthritis Care & Research announced a similar policy, which took effect in January 2007 and required trial registration in either www.ClinicalTrials.gov or www.controlled-trials.com (10).

Clinical trial registration goes a long way towards solving the problem of entire studies remaining unpublished due to disappointing results. While negative studies may still not get published, at least there is a record of their existence. The ability of trial registration policies to rein in other reporting biases, however, depends on the degree that trial registration records adequately define primary and secondary outcomes prior to the initiation of trials. As described in the 2013 Standard Protocol Items: Recommendations for Interventional Trials (SPIRIT) Statement (11), fully adequate trial registrations must include specification of a single primary outcome (e.g., depressive
symptoms) or multiple primary outcomes with appropriate adjustment, the specific measurement variable (e.g., Patient Health Questionnaire – 9), the analysis metric (e.g., change from baseline, final value), the method of aggregation (e.g., mean, proportion above a pre-specified cutoff threshold), and the time point of assessment. Without adequate outcome specification at registration, rather than a single hypothesis test, a very large combination of analyses can potentially be conducted via different combinations of measurement variables, metrics, aggregation methods, and assessment points, leading to a high risk of reporting exaggerated or otherwise misleading results.

The practice of “data dredging” and selective reporting of positive outcomes and analyses may be particularly high in trials of non-pharmacological interventions, including the psychological, educational, and rehabilitation interventions that are most often considered for publication in *Arthritis Care & Research*. In these kinds of trials, multiple outcome variables are typically measured, and there is usually not a standard outcome measure that is expected to be primary across studies. If one assumes that many trials test interventions with some effect, albeit smaller than the effect sizes that are published, then selectively choosing outcomes to publish from multiple outcome options or possible analysis methods could easily lead to exaggerated estimates of effect. Consistent with this, the proportion of published studies with statistically significant results is substantially higher in psychological or behavioral research compared to other areas (12-14).

Examination of trial registration patterns suggests that selective outcome and analysis reporting likely contribute substantially to the publication of exaggerated numbers of non-pharmacological trials with positive results. A 2009 study investigated trial registrations and outcomes from all trials, including pharmacological trials, published in high-impact general and specialty medical journals in 2008 and found that of 186 studies that had been registered prior to trial initiation, 147 (79%) were adequately registered with a clear description of the primary outcome measure (15). On the other hand, among 63 RCTs published in four top behavioral health journals
between 2008 and 2009, only 1 RCT (< 2%) was adequately registered, and for that RCT, a non-statistically significant outcome that was registered as primary was not published as the primary outcome (4).

How useful are registration records of RCTs of non-pharmacological interventions in rheumatology for determining the primary study outcome and comparing pre-specified testing plans to published results? We searched ClinicalTrials.gov for records of ongoing non-pharmacological trials in rheumatic diseases for which data collection was not yet complete, registered between January 1, 2013 and December 31, 2013. RCT registrations were included if they evaluated the effect of a psychological, educational, rehabilitation, or organizational intervention to improve a health outcome. Two investigators independently reviewed trial registrations for eligibility with any disagreements resolved by consensus. For included trials, registration adequacy was coded using a method described by Mathieu et al. (13), which is consistent with the SPIRIT criteria (11). Adequately registered trials were defined as trials that registered a single primary outcome (or multiple primary outcomes with appropriate statistical adjustment) and specified the primary outcome measure, the time point when it would be assessed, and the method of aggregation (see Appendix for search terms and coding manuals).

Our search yielded 269 RCT registrations for review, of which 34 met inclusion criteria (see Figure 1). Of these 34 registrations, 24 described trials of rehabilitation interventions (e.g., physical therapy), 8 described psychological or educational interventions (e.g., disease self-management), and 2 described organizational interventions (e.g., a referral model). As shown in Table 1, 22 of the 34 registered trials (65%) specified a single primary outcome construct, but only 18 (53%) described a single primary outcome measure. Only 10 trials (29%) pre-specified the outcome measure and time of assessment, and no trials were fully adequately registered, including method of aggregation. Compared to RCTs published in top behavioral health journals, registrations of RCTs of non-
pharmacological interventions in the rheumatic diseases are more likely to specify a primary outcome measure. On the other hand, none of the registrations we examined fully met criteria for adequate registration per SPIRIT guidelines (11).

Adequate trial registration can help ensure that results accurately reflect what has occurred in a trial rather than our desire for a positive trial that confirms effectiveness, regardless of reality. Non-statistically significant trials that are presented otherwise can lead to the propagation of interventions that are not effective and the consumption of resources that could be better used to offer health care strategies of actual benefit to patients. Inappropriate reporting of effectiveness can also mislead us into assuming that we have solutions to important patient problems, when in reality, we may still have work to do. Going forward, it is incumbent upon all health professionals who work to improve care for people with rheumatic diseases, including researchers, peer reviewers, journal editors, and clinicians and patients who are consumers of research, to insist that trials are adequately registered. By doing this, we will move closer to being able to make clinical practice decisions that are indeed evidence-based and more likely to improve the lives of patients.
REFERENCES


12. Fanelli D. "Positive" results increase down the hierarchy of the sciences. PLOS ONE. 2010; 5: e10068.


<table>
<thead>
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<th>Number of Registrations</th>
<th>Number (%) of Adequately Registered RCTs</th>
<th>One Primary Outcome Specified</th>
<th>Outcome Measure specified</th>
<th>Timeframe Specified</th>
<th>Method of Aggregation Specified</th>
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<td>Rehabilitation</td>
<td>24</td>
<td>14 (58%)</td>
<td>12 (50%)</td>
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<td>Behavioral / Psychological / Educational</td>
<td>8</td>
<td>6 (75%)</td>
<td>4 (50%)</td>
<td>3 (38%)</td>
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<td>Organizational</td>
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<td>2 (100%)</td>
<td>2 (100%)</td>
<td>0 (0%)</td>
<td>0 (0%)</td>
</tr>
<tr>
<td>Total</td>
<td>34</td>
<td>22 (65%)</td>
<td>18 (53%)</td>
<td>10 (29%)</td>
<td>0 (0%)</td>
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</tbody>
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Figure 1. Flow Diagram of Selection of Trial Registrations of Randomised Controlled Trials (RCTs) of Non-pharmacological Interventions in Rheumatic Diseases

269 Unique trial registrations identified and screened for potential inclusion

235 Trial registrations excluded:
- Not rheumatic disease (n = 3)
- Not a non-pharmacological intervention (n = 221)
- Not a RCT (n = 8)
- No health outcomes (n = 3)
APPENDIX

Search strategy - www.ClinicalTrials.gov

Search terms: Arthritis

Recruitment: Open studies

Study results: Studies without results

Study type: Interventional studies

First received: 01/01/2013 to 12/31/2013

Coding manual for registration eligibility

No: not rheumatic disease. The registered trial does not include patients with rheumatic diseases.

No: not a non-pharmacological intervention. The registered trial does not evaluate the effects of a non-pharmacological intervention. Eligible interventions include psychological, educational, rehabilitation, and organizational (e.g., application of a specific referral model) interventions. Trials evaluating the effects of drug interventions, surgical procedures (e.g., cementing techniques, tourniquet pressure), and medical devices used in surgical procedures are excluded. Studies with any arm investigating the effects of medication are excluded. Eligible trials include non-pharmacological interventions delivered in a face-to-face, internet, telephone or self-guided (e.g., pamphlet) format.

No: not a randomized controlled trial (RCT) of non-pharmacological intervention. Not a RCT. Studies that are excluded include pre-post studies, case-control studies and observational studies, for example.

No: no health outcomes. No registered primary and secondary outcomes are health outcomes. Studies only investigating feasibility or acceptability of an intervention, for instance, are excluded.
**Yes.** Eligible trial registration.

**Coding manual for adequacy of registration**

**No: multiple primary outcomes:** Trial registration lists more than one primary outcome or does not make a distinction between primary and secondary outcomes. Trial registrations that have multiple primary outcomes, but include an adjustment plan for statistical significance are considered adequate.

**No: measure not specified:** Trial registry does not clearly specify the primary outcome measure. This would occur, for instance, if the outcome measure is described as “depression” instead of naming the measure (e.g., Beck Depression Inventory).

**No: timeframe not specified:** Trial registry does not specify the time point of the primary outcome assessment (e.g., “Beck Depression Inventory will be administered at intervals”). If multiple time points are listed, the time point of the primary outcome is considered specified only if one is identified as primary or if the outcome will be examined with a single analysis that examines change across all time points.

**No: method of aggregation not specified.** Trial registry does not specify the method of aggregation for the primary outcome measure (e.g., does not describe whether data will be analyzed as a continuous outcome variable versus a percentage of participants above or below an a priori determined cut-off).

**Yes. Adequate trial registration.**