
Received 24 May 2014; accepted in revised form 2 June 2014

Compliance with trial registration in five core journals of clinical geriatrics: a survey of original publications on randomised controlled trials from 2008 to 2012

EVA MANN1, NATALIE NGUYEN2, STEFFEN FLEISCHER2, GABRIELE MEYER2

1Institute of General Medicine, Family Medicine and Preventive Medicine, Paracelsus Medical University, Strubergasse 21, Salzburg 5020, Austria
2Institute of Health and Nursing Science, Medical Faculty, Martin-Luther-University Halle-Wittenberg, Halle (Saale), Germany

Address correspondence to: E. Mann. Tel: (+43) 664 2621397; Fax: (+43) 5522 431339. Email: evamann@vol.at

Abstract

Objective: to assess the proportion of registered randomised controlled trials in five core clinical geriatric journals and to analyse whether registered study outcomes correspond with published outcomes.
Design: survey of original papers published 2008 to 2012.

Methods: two independent reviewers retrieved the sample through search in the web-based archives of Age and Ageing, the Journal of the American Geriatric Society, the American Journal of Geriatric Psychiatry, the Journal of the American Medical Directors Association and International Psychogeriatrics. Data extraction was performed by two independent reviewers using a pre-tested 13-item checklist. Registration status was checked and information provided in registers compared with information presented in the original publication. A third reviewer was consulted if no consensus could be reached.

Results: the sample comprised 220 original publications on randomised controlled trials. A total of 140 (63.6%) were registered. Registration was in accordance with the ICMJE; requirements in 54 out of 140 registered trials (38.6%). Less than one-third of registered papers \( n = 40 \) reported on all study outcomes listed in the study register. In 74 out of the 80 non-registered trials, the missing registration was not declared in the publication. There was no consistent upward trend towards higher registration compliance throughout journals and years.

Conclusion: our survey shows that prospective trial registration and compliance between outcomes declared in the registry and reported in the publication is poor. Concerted action of authors, editors and peer-reviewers is overdue aimed to irreversibly implement the imperative of registration of randomised controlled trials and complete outcome reporting.

Keywords: registries, publication bias, patient outcome assessment, geriatrics, randomised controlled trials, older people

Background

Selective publication of randomised controlled trials (RCTs) and incomplete reporting of outcomes have shown to be major sources of bias which may distort the medical evidence base and thus lead to skewed treatment recommendations and guidelines [1]. As a safeguard against publication bias, the International Committee of Medical Journal Editors (ICMJE) requests mandatory registration of all RCTs as a precondition of publication and declares that member journals would only publish trials if they were properly registered. This policy published in 2004 required registration by 13 September 2005 for trials that started enrolment prior to 1 July 2005 and registration before the onset of patient enrolment for any clinical trial starting enrolment after 1 July 2005 [2].

Prospective trial registration in publicly accessible trial registers including administrative and scientific information as well as citation of registration in the publication are considered as prerequisites to guarantee transparency.

Despite the initial positive response to the ICMJE policy [3], less than one-third of journals require trial registration according to their instructions for authors. Reasons for journals’ reluctance to require registration are competition between journals and perception that ICMJE policy is not relevant to all journals or to small and exploratory studies and submissions from developing countries [4].

Quite a few studies have assessed the compliance with registration and predictors of non-compliance to registration and transparent reporting [5–8]. Even for leading journals with high-impact factors, the overall registration prevalence of RCTs has shown to be low although variation between the journals was pronounced ranging from 8 to 45% [7, 9, 10]. Deviation of outcome reporting in full papers from registered information is common [11–15]. Statistically significant outcomes have a higher likelihood of being reported [16, 17].

Objective

To the best of our knowledge, compliance with trial registration in geriatric research has not been investigated so far. Therefore, the objectives of our study are (i) to assess how often randomised controlled trials published in core journals of clinical geriatrics are registered in publicly accessible study registers, (ii) to assess whether registration took place prospectively, i.e. before participants’ enrolment in the study, (iii) to analyse whether study outcomes reported in the original publication agree with outcomes listed in the study register.

Methods and material

Design

We conducted a survey of original publications on randomised controlled trials published between January 2008 and December 2012 in Age and Ageing, the Journal of the American Geriatric Society (JAGS), the American Journal of Geriatric Psychiatry (AJGP), the Journal of the American Medical Directors Association (JAMDA), and International Psychogeriatrics (Int Psychogeriatr). These five journals were chosen since they have a strong clinical research perspective and a comparatively high-impact factor (all ranked within top 20 in the journal category Geriatrics & Gerontology by Journal Citation Reports in 2012). We restricted our search to these journals because a high-impact factor is usually considered as a predictor for high quality in reports and underlying methodology. We included either individual or cluster randomised trials reporting on preventive, therapeutic or diagnostic interventions. All other study designs, animal studies and cost-effectiveness studies were excluded.

Assessment and data handling

The journals’ archives were searched online. Full-text articles of included randomised controlled trials were assessed in
each case by two independent reviewers (E.M., N.N., G.M.) using a data extraction sheet with 13 items. The sheet was piloted in a sample of 10 publications. Registration status of the trial was determined by search of the WHO International Clinical Trials Registry Platform [18]. Data extraction covered three parts; items on the (i) registration including the date of registration, name of the registry and notation of sample size and funding, (ii) study protocol and (iii) full-text publication including name of the journal, date of submission, online publication and print publication, declaration of registration, country of recruitment, topic of the primary health condition or problem, sample size, funding, presentation on all study outcomes listed in the registry and/or published study protocol, and data about referral to further references on outcomes not presented in the publication assessed. Results were compared between two reviewers and a third reviewer was consulted in case consensus could not be obtained.

Data analysis
The final data after reviewers’ agreement were entered in an Excel database by one author (N.N.). Descriptive analysis was performed by another author (S.F.) using R. Data are reported as absolute numbers and percentages only. No further analysis was performed due to the limited sample of studies.

Results
Our search revealed 220 publications which were conducted in North America (44.1%), Europe (39.1%), Australia/New Zealand (7.7%), Asia (6.4%), Africa (0.9%) and multiple countries at different continents (1.8%). A range of geriatric topics was covered, e.g. dementia, delirium, depression, Parkinson syndrome, cardiovascular disease, stroke, sleeping disorders, nursing home care and hospital admission.

Trial registration
A total of 140/220 randomised controlled trials (63.6%) were registered. The proportion of registered trials across the journals was 27 out of 48 in Age Aging, 73 out of 104 in JAGS, 20 out 37 in JAGP, 11 out of 18 in JAMDA and 9 out 13 trials in Inter Psychogeriatr.

Out of all 140 registered trials, 19 (13.6%) were registered in 2008, 28 (20.0%) in 2009, 33 (23.6%) in 2010, 30 (21.4%) in 2011 and 30 (21.4%) in 2012. The majority of trials were registered in ClinicalTrials (62.1%), followed by ISRCTN (22.9%), ANZCTR (10.0%), Netherlands Trials (2.1%) and other registries (2.9%), respectively.

Table 1 displays the descriptive data of registered studies as presented in the registries compared with the original publications as well as descriptive data of non-registered studies as reported in the publications.

Out of the 140 registered studies, 89 trials enrolled participants prior/on 1 July 2005, and 51 trials enrolled participants after 1 July 2005. Registration was in accordance with the ICMJE requirements in 54 out of 140 registered trials (38.6%). Time of registration remained unclear in 7 (5%) of registered trials. Table 2 describes the time of registration according to the ICMJE requirements.

Study protocol
A study protocol was published in 35 out of 220 studies, i.e. 34 registered trials and one non-registered trial.

Full-text analysis
Reporting of results on study characteristics and predefined outcomes
In 74 out of the 80 non-registered randomised controlled trials, the missing registration was not declared in the publication. The start of participants’ enrolment was not reported in 41 (29.3%) of all registered and in 40 (50%) of all non-

Table 1. Sample characteristics of trials according to information in the study registries and publications

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Registered trials (n = 140)</th>
<th>Non-registered trials (n = 80)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Registration status stated</td>
<td>Register-based information</td>
<td>Publication-based information</td>
</tr>
<tr>
<td>Sample size mentioned</td>
<td>136 (97.1)</td>
<td>138 (98.6)</td>
</tr>
<tr>
<td>Participants, median (IQR)</td>
<td>213 (124.3–400)</td>
<td>191 (103.5–352)</td>
</tr>
<tr>
<td>Number of participants</td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;100</td>
<td>25/136 (18.4)</td>
<td>33/138 (23.9)</td>
</tr>
<tr>
<td>100 to &lt;500</td>
<td>83/136 (61.0)</td>
<td>83/138 (60.1)</td>
</tr>
<tr>
<td>500 to &lt;1000</td>
<td>13/136 (9.6)</td>
<td>10/138 (7.2)</td>
</tr>
<tr>
<td>≥1000</td>
<td>15/136 (11.0)</td>
<td>12/138 (8.7)</td>
</tr>
<tr>
<td>Source of funding declared</td>
<td>128/140 (91.4)</td>
<td>134/140 (95.7)</td>
</tr>
<tr>
<td>Government only</td>
<td>77/128 (60.2)</td>
<td>55/134 (41.0)</td>
</tr>
<tr>
<td>Government and other source</td>
<td>16/128 (12.5)</td>
<td>29/134 (21.6)</td>
</tr>
<tr>
<td>Other source</td>
<td>15/128 (11.7)</td>
<td>13/134 (9.7)</td>
</tr>
<tr>
<td>Pharmaceutical company or industry only</td>
<td>8/128 (6.3)</td>
<td>8/134 (6.0)</td>
</tr>
<tr>
<td>Co-financing by pharmaceutical company/industry</td>
<td>12/128 (9.4)</td>
<td>29/134 (21.6)</td>
</tr>
</tbody>
</table>

Values are numbers (percentage) unless stated otherwise.
Table 2. Time of registration according to the ICMJE requirements (n = 140)

<table>
<thead>
<tr>
<th>Registration characteristics</th>
<th>Registered trials (n = 140)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Registration for studies enrolling participants before 1 July 2005</td>
<td>89 (63.6)</td>
</tr>
<tr>
<td>In accordance with ICMJE requirements&lt;sup&gt;a,b&lt;/sup&gt;</td>
<td>36 (25.7)</td>
</tr>
<tr>
<td>Registration for studies enrolling participants later than 1 July 2005</td>
<td>51 (36.4)</td>
</tr>
<tr>
<td>In accordance with ICMJE requirements&lt;sup&gt;b&lt;/sup&gt;</td>
<td>18 (12.9)</td>
</tr>
</tbody>
</table>

Values are numbers (%).
<sup>a</sup>Time of registration unclear: 7 (5.0%) trials.
<sup>b</sup>The ICMJE policy published in 2004 required registration by 13 September 2005 for trials that started participant enrolment prior to 1 July 2005, and registration before the onset of patient enrolment for any clinical trial starting enrolment after 1 July 2005 [2].

registered studies. Comparison of full-text publications of registered and non-registered trials revealed smaller sample sizes for non-registered studies.

Funding sources differed somehow between registered-based information and publication-based information of registered studies indicating less often funding by government only and more often co-financing by pharmaceutical company/industry according to full-text publications compared with registers. The details are depicted in Table 1.

Out of all 140 registered trials, 40 (28.6%) reported on all study outcomes listed in the registry and 27 trials (19.3%) pointed to planned analyses or to references on outcomes not presented in the full-text article. The primary outcome was clearly stated in 109 out of 140 full-text articles of registered trials (77.9%) and in 52 out of 80 non-registered trials (65.0%), respectively.

Discussion

Our analysis of five core journals of clinical geriatrics revealed that approximately two-thirds of all randomised controlled trials were registered. Although trial registration numbers in our sample were higher in 2012 than in 2008, the upward trend was not consistent throughout the journals and over time. Only ~40% of registered trials were compliant with the requirements of the ICMJE. Outcome reporting was incomplete, a fact which is worrisome. Approximately, half of the registered trials reported on all study outcomes declared in the registry or referred to on-going or planned analyses or presented further references.

Our analysis revealed several important differences between registered and non-registered trials. The vast majority of non-registered studies did not declare their registration status in the full-text article, presumably to hide the failing registration. In contrast, two-thirds of full-text articles of registered trials contained information on the registration. Sample size was also different between registered and non-registered trials indicating higher participants’ numbers in registered trials. Strikingly, in every third of the 140 registered and in every second of the 80 non-registered trials the information about the start of patient enrolment remained unclear.

Recently, published literature confirms the findings of our study. Hannink et al. reported that registration was lacking in one-third of all reviewed surgical trials; one-fifth of the registered trials were registered after completion of the study and half of them showed discrepancies between outcomes registered and the outcomes published [19]. The study by Mathieu et al. revealed higher numbers with >50% of non-registered studies out of 323 reviewed from the areas of cardiology, rheumatology and gastroenterology. Only a half of the registered studies were registered before the end of the trial, and every third showed discrepancies between the outcomes registered and the outcomes published [9]. A recent systematic review examining whether registered primary outcomes in analgesic treatment trials corresponded with published primary outcomes showed that primary outcomes never matched precisely and that one-fifth failed to register or publish primary outcomes [11].

Recent findings demonstrated that only half of 55 urology-related journals provided some editorial advice about trial registration [20]. Another study indicated that only one-third of peer-reviewers examined trial registration and compared information provided in registries with results reported in full-text publications [21].

Our survey has limitations. First, we selected only trials published in core clinical geriatric journals. Thus, it can be suspected that our results underestimate the overall amount of non-existent or inadequate registration in geriatric journals. Second, we did not statistically investigate associations of compliance to registration since our sample was rather small. Therefore, any judgement about a possible relation between trial characteristics and non-registration and incomplete outcome reporting, respectively, must remain speculative.

Conclusion

The findings of our survey demonstrate that compliance with trial registration in core geriatric journals is insufficient. The policy needed to overcome reporting bias which is still present 10 years after the request of mandatory trial registration by the ICMJE is evident. Authors, journal editors and peer-reviewers alike are demanded to irreversibly implement the imperative of registration of randomised controlled trials.

Principal investigators must ensure that trials are registered before the enrolment of participants. Journal editors are highly requested to demand study registration as a prerequisite for publication or to justify publication of non-registered study. They also should instruct authors to provide the unique identification number of the trial registration at the time of submission. Finally, peer reviewers should be advised to check trial registration and any evidence for discrepancies between outcomes declared in the registry and described in the full-text publication.
Key points

- Registration of randomised controlled trials published between 2008 and 2012 in five core clinical geriatric journals is not complete and approximately one-third is not registered.
- Only ~40% of registered trials were compliant with the requirements of the ICMJE.
- Approximately half of the registered trial reported on all study outcomes declared in the registry or referred to ongoing or planned analyses or presented further references.
- The vast majority of non-registered studies did not declare their registration status in the full-text article, and in every second the start of participants’ enrolment remained unclear.

References

17. Ioannidis JP. Effect of the statistical significance of results on the time to completion and publication of randomised efficacy trials. JAMA 1998; 279: 281–4.