Methodological quality and reporting of ethical requirements in clinical trials

Miguel Ruiz-Canela, Jokin de Irala-Estevez, Miguel Ángel Martínez-González, Enrique Gómez-Gracia and Joaquin Fernández-Crehuet
University of Navarre and University of Malaga, Spain

Abstract
Objectives—To assess the relationship between the approval of trials by a research ethics committee (REC) and the fact that informed consent from participants (ICP) was obtained, with the quality of study design and methods.

Design—Systematic review using a standardised checklist.

Main measures—Methodological and ethical issues of all trials published between 1993 and 1995 in the New England Journal of Medicine, the Lancet, the Journal of the American Medical Association and the British Medical Journal were studied. In addition, clinical trials conducted in Spain and published by at least one Spanish author during the same period in any other journal were also included.

Results—We studied the published articles of 767 trials and found the following indicators of lower methodological quality to be independent predictors for failure to disclose REC approval or ICP: absence of concealment of allocation, lack of justification for unblinded trials, not using a treatment for the patients in the control group, absent information on statistical methods, not including sample size estimation, not establishing the rules to stop the trial, and omitting the presentation of a baseline comparison of groups.

Conclusion—Trials of higher methodological and scientific quality were more likely to provide information about their ethical aspects.

Methods
Two short preliminary reports, including some of our methods, have been published elsewhere. We studied the published articles of 767 trials and found the following indicators of lower methodological quality to be independent predictors for failure to disclose REC approval or ICP: absence of concealment of allocation, lack of justification for unblinded trials, not using a treatment for the patients in the control group, absent information on statistical methods, not including sample size estimation, not establishing the rules to stop the trial, and omitting the presentation of a baseline comparison of groups.

Conclusion—Trials of higher methodological and scientific quality were more likely to provide information about their ethical aspects.

Keywords: Clinical trials; informed consent; research ethics committee; research design

Introduction
Methodological quality is the first ethical requirement in clinical trials. Moreover, the approval of a research ethics committee (REC) and obtaining informed consent from patients (ICP) could be considered the main issues in the ethics of research with human beings.

Both methodological and ethical aspects should be adequately reported to enable readers to make an accurate assessment of the clinical research about which they are reading. However, there are several studies that have found deficiencies in reporting the design and conduct of trials. It has also been shown that disclosure of the ICP and REC approval in published reports is sometimes incomplete, and sometimes omitted. Nevertheless, very few studies have assessed the relationship between omission of REC or ICP and methodological quality of trials. We present the main results of a systematic evaluation of 767 clinical trials where the disclosure of REC approval and ICP was assessed, as well as the association between reporting these aspects and the methodological quality of the trials.
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A multivariable logistic regression model was fitted to assess the methodological characteristics independently related to disclosing those ethical requirements (REC/ICP). In this model, we considered the failure to report that either REC or ICP had been obtained, or the explicit disclosure in the original paper that any of these requirements were not obtained, as the outcome. Multivariable analysis was performed with the aim of controlling for several variables that could be considered as potential confounders. In addition, we considered all indicators of methodological quality with a p value ≤0.25 in the univariate analysis as candidate variables for the multivariable model. After including these potential predictors and/or confounders in one multivariable model, the final model was obtained by gradually removing non-significant variables using the likelihood ratio test and by evaluating potential confounding with the criterion of a 10% change between crude and adjusted estimates of the odds ratios.

Our study was not approved by an REC, nor did we request informed consent from the authors of the articles because our research did not involve an experimental design using human beings.

Table 1 Characteristics of the trials associated with not reporting any or both ethical issues (REC approval and/or request of informed consent from participants). Logistic regression analysis. Odds ratios (OR) and 95% confidence intervals (CI)

<table>
<thead>
<tr>
<th>Quality indicators (number of trials)</th>
<th>Proportion not reporting request of ICP</th>
<th>Proportion not reporting REC approval</th>
<th>Proportion not reporting both request of ICP and REC approval</th>
<th>Adjusted OR* (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>All sample (767)</td>
<td>19.8</td>
<td>29.2</td>
<td>12.9</td>
<td></td>
</tr>
<tr>
<td>Concealment of allocation</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes (264)†</td>
<td>14.8</td>
<td>24.2</td>
<td>8.0</td>
<td>1 (ref)‡</td>
</tr>
<tr>
<td>No (503)</td>
<td>22.5</td>
<td>31.8</td>
<td>15.5</td>
<td>1.66 (1.12–2.46)</td>
</tr>
<tr>
<td>Justification of unblinded trials</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes (36)†</td>
<td>8.3</td>
<td>19.4</td>
<td>5.6</td>
<td>1 (ref)‡</td>
</tr>
<tr>
<td>No (280)</td>
<td>26.1</td>
<td>41.1</td>
<td>18.2</td>
<td>2.70 (1.09–6.66)</td>
</tr>
<tr>
<td>Type of treatment for control group</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Placebo (273)†</td>
<td>11.7</td>
<td>18.7</td>
<td>7.0</td>
<td>1 (ref)‡</td>
</tr>
<tr>
<td>Alternative active treatment (366)</td>
<td>21.3</td>
<td>33.6</td>
<td>14.5</td>
<td>1.39 (0.88–2.20)</td>
</tr>
<tr>
<td>No treatment (105)</td>
<td>35.2</td>
<td>40.0</td>
<td>21.9</td>
<td>2.47 (1.37–4.47)</td>
</tr>
<tr>
<td>Not a proper control group (23)</td>
<td>21.7</td>
<td>34.8</td>
<td>17.4</td>
<td>1.73 (0.92–3.24)</td>
</tr>
<tr>
<td>Reporting of statistical methods</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes: some information reported (739)†</td>
<td>18.9</td>
<td>27.9</td>
<td>12.0</td>
<td>1 (ref)§</td>
</tr>
<tr>
<td>No information about statistical methods (28)</td>
<td>42.9</td>
<td>64.3</td>
<td>35.7</td>
<td>3.77 (1.42–9.98)</td>
</tr>
<tr>
<td>Sample size estimation</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Shown (320)†</td>
<td>14.4</td>
<td>23.1</td>
<td>6.9</td>
<td>1 (ref)‡</td>
</tr>
<tr>
<td>Not shown (447)</td>
<td>23.7</td>
<td>33.6</td>
<td>17.2</td>
<td>1.49 (1.02–2.19)</td>
</tr>
<tr>
<td>Rules to stop the trial</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Reported (269)†</td>
<td>12.1</td>
<td>21.6</td>
<td>6.4</td>
<td>1 (ref)‡</td>
</tr>
<tr>
<td>Not reported (498)</td>
<td>23.7</td>
<td>32.9</td>
<td>16.3</td>
<td>1.33 (0.99–1.78)</td>
</tr>
<tr>
<td>Baseline comparison of groups</td>
<td></td>
<td></td>
<td></td>
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</tr>
<tr>
<td>Presented (679)†</td>
<td>18.6</td>
<td>27.1</td>
<td>11.6</td>
<td>1 (ref)‡</td>
</tr>
<tr>
<td>Not presented (88)</td>
<td>29.5</td>
<td>45.5</td>
<td>22.7</td>
<td>1.80 (1.05–3.08)</td>
</tr>
<tr>
<td>Outcome</td>
<td></td>
<td></td>
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</tr>
<tr>
<td>Survival (166)†</td>
<td>22.9</td>
<td>30.7</td>
<td>13.9</td>
<td>1 (ref)§</td>
</tr>
<tr>
<td>Other (601)</td>
<td>19.0</td>
<td>28.8</td>
<td>12.6</td>
<td>0.52 (0.33–0.84)</td>
</tr>
</tbody>
</table>

Trials that acknowledged that they did not obtain the REC (Research Ethics Committee) approval or the ICP (informed consent from participants) are included together with those that did not disclose the information about these issues in the original report.

*A higher odds ratio (OR) means a higher probability of failing to provide information about either or both ethical issues in the original paper.

Odds ratios have been also adjusted for journal, country of authors, length of the report, number of participants and source of funding.

†This was the reference category (ref: reference category).
‡p<0.05 (Likelihood ratio test).
§p<0.01 (Likelihood ratio test).
Results
A brief descriptive assessment of the proportion of studies failing to report the ethical requirements has been published elsewhere. Table 1 shows the study quality indicators that were identified in the multivariable analysis as independent predictors of failure to report information about REC approval, ICP, or both. In addition to the variables shown in the table, the analysis was also adjusted for the length of the article, the journal in which the article was published, the country of authors, the number of participants and the source of funding.

Once adjusted for the other variables, an open randomisation procedure (failure to conceal allocation) was independently associated with not presenting information on ICP and/or approval by an REC. Among open trials, those that did not justify the unblinded assessment of the outcome were more likely not to report ICP/REC. Trials which did not use a treatment for the patients in the control group omitted this information significantly more often. Not disclosing information on statistical methods, nor on sample size estimation; not providing the rules to stop the trial, and not presenting a comparison of the distribution of baseline factors were characteristics independently and more frequently associated with the omission of ICP/REC. Trials with survival of patients as the outcome were less likely to provide information about these ethical issues.

When we fitted the logistic models using the actual responses of authors to our queries (mailed questionnaires) as the outcome, and reclassified the authors who replied that they had in fact obtained the ICP/REC in spite of not having reported it, the adjusted odds ratios for most of the indicators of lower quality remained high: no justification of unblinded trials (OR=2.62); no information about statistical methods (OR=1.62); omitting sample size estimation (OR=1.34), and not reporting the rules to stop the trial (OR=1.43).

When the two ethical issues were considered as separate outcomes, all associations maintained the same direction and most of them remained consistent and statistically significant (see table 2).

Discussion
The hypothesis of this study was that the higher the methodological and scientific quality of a trial, the more attention was given to its ethical aspects. Our findings suggest that, independently of the journal where they were published and the length of the report (among other descriptive variables), trials with higher standards of quality met the requirement of reporting ethical issues more frequently. Other authors have previously assessed some of these standards as indicators of quality (concealment of allocation, type of treatment for the control group, reporting of statistical methods, and justification of open trials) but have not...
related them to ethical aspects. Our results are consistent with those of another study regarding the association between lower quality and frequent omission of reporting REC approval in studies concerning cardiopulmonary resuscitation.

Nevertheless, the assessment of methodological quality in that study was only based on the randomisation scheme. The ethical requirements were not mentioned in some articles, even though the authors responded to our questionnaire that they had in fact requested them. However, we chose the statements in the original article (or lack thereof) over the actual response of the authors, in terms of the information provided on ICP requested or REC approval. This decision was based on several reasons: a) This may promote more reporting of ethical issues in publications of clinical trials in the future; b) Some authors did not respond to our questionnaires, and therefore we could not ascertain what they had actually done in their studies, and c) Failing to report the ethical requirements in the original article may already imply a lower concern for ethical issues in trials. When we fitted the logistic model using the actual responses of authors as the outcome, the adjusted odds ratios for most of the indicators of lower quality remained high. Therefore, not only the actual reporting of ethical issues in articles, but also the verified request for ICP or REC approval, showed an association with higher methodological quality.

We selected four journals that have had representatives on the International Committee of Medical Journal Editors (ICMJE) since its inception. This does not imply that these journals consistently follow the uniform requirements in all cases, but these are leading journals which publish research reports in all fields and have a broad readership. Medical journals which are published weekly also provide a large enough sample to assess the current trends in our topic of interest with precision. Reviewing trials with Spanish authors also has some advantages because it provides a subset of trials resembling a comparison (“pseudo-control”) group. Most trials in this group were published in specialised journals written in English. This does not imply that these journals may already imply a lower concern for ethical issues in trials.

The association between methodological quality and reporting of ethical requirements probably reflects the respect shown for patients during the whole research process.

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Miguel Ruiz-Canela, BPharm, PhD, is Associate Professor in the Department of Biomedical Humanities, University of Navarre, Spain. Joaquin de Irala-Estevez, MD, MPH, PhD, is Professor in the Department of Epidemiology and Public Health, University of Navarre. Miguel Angel Martinez-Gonzalez, MD, MPH, PhD, is Head of the Department of Epidemiology and Public Health, University of Navarre. Enrique Gomez-Gracia, MD, MPH, PhD, is Professor in the Department of Preventive Medicine and Public Health, University of Malaga, Spain. Joaquin Fernandez-Crehuet, MD, MPH, PhD, is Head of the Department of Preventive Medicine and Public Health, University of Malaga, Spain. Address for readers’ correspondence: Miguel Angel Martinez-Gonzalez, Epidemiologia y Salud Publica, Irunlarrea s/n, Facultad de Medicina, Universidad de Navarra, 31080 Pamplona, Spain. Fax: (34)-48-425649; tel: (34)-48-425600; e-mail: mamartinez@uman.es.

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