Since the last update of the International Committee of Medical Journal Editors (ICMJE) recommendations, which we at REVISTA ESPAÑOLA DE CARDIOLOGÍA adopted,\textsuperscript{1-3} one of the most important contributions to this field has been the suggestion that all clinical trials (CT) should be “registered” prior to definitive publication in biomedical journals.\textsuperscript{6-11} The ICMJE believes that from their very inception CTs need to be registered in public databases that are easily accessible both to authors, researchers, and regulatory agencies as well as the general public. The principal objective of this initiative is to improve the trials’ credibility when finally published and guarantee that the methodology employed, results, and scientific information generated should be freely available for analysis by the international scientific community.\textsuperscript{6-11}

The very definition of CTs has raised controversy. A CT could be defined broadly as “a research study in human volunteers to answer specific health questions.”\textsuperscript{7} This initial definition would include observational trials and interventional trials without control groups, too. However, from the editorial point of view, and bearing in mind the implications we shall now consider, the definition proposed by the ICMJE is more pragmatic and also more acceptable.\textsuperscript{11} Thus, the CT is defined as any research project that prospectively allocates subjects to a particular intervention or comparison group to study the cause-effect relationship between a medical intervention and a health outcome.\textsuperscript{11}

Such interventions include drugs, surgical procedures, and devices, as well as behavioral treatments or process-of-care changes.\textsuperscript{11}

In the present article we review: a) principal biases in medical research that affect CTs; b) recommendations to improve the description of CTs in biomedical journals; c) general implications derived from the initiative to register CTs; and d) adapting REVISTA ESPAÑOLA DE CARDIOLOGÍA editorial policy.

**EDITOR’S PAGE**

**Publication of Clinical Trials in Scientific Journals: Editorial Issues**

Fernando Alfonso,a Javier Segovia,b Magda Heras,c and Javier Bermejo\textsuperscript{b}

\textsuperscript{a} Editor-in-Chief.

\textsuperscript{b} Associate Editor.

\textsuperscript{c} Supplements Editor.

Since the last update of the International Committee of Medical Journal Editors (ICMJE)\textsuperscript{1} recommendations, which we at REVISTA ESPAÑOLA DE CARDIOLOGÍA adopted,\textsuperscript{2-3} one of the most important contributions to this field has been the suggestion that all clinical trials (CT) should be “registered” prior to definitive publication in biomedical journals.\textsuperscript{6-11} The ICMJE believes that from their very inception CTs need to be registered in public databases that are easily accessible both to authors, researchers, and regulatory agencies as well as the general public. The principal objective of this initiative is to improve the trials’ credibility when finally published and guarantee that the methodology employed, results, and scientific information generated should be freely available for analysis by the international scientific community.\textsuperscript{6-11}

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**CLINICAL TRIALS AND BIAS IN RESEARCH AND PUBLICATION**

Many publications with “false positive” results have been a consequence of the pressure experienced by different research groups competing in the same field to publish results that confirm the most attractive physiopathologic hypotheses. Ioannidis\textsuperscript{12} analyzed the results of trials that, after publication in medical journals with the highest impact factors, were later the most cited. One third of these articles were questioned by subsequent studies—which were better designed or included a greater number of patients—that rejected or significantly diminished the effects of the intervention analyzed. Larger trials and those with randomized designs were better able to withstand the passage of time.\textsuperscript{12}

However, the fact that the bulk of research has been seen to move from academic and university centers to direct contracts between sponsors and private organizations for research by contract\textsuperscript{13,14} highlights the gradual loss of the scientific-academic establishment’s influence in controlling the “research agenda.” A recent study\textsuperscript{15} has shown that, although the most cited articles continue in the main to be the products of authors with academic affiliations, the number of trials financed exclusively by industry has increased spectacularly. The potential danger of this change is double-edged. On the one hand, scientifically relevant issues are left out in the cold and are increasingly less likely to be investigated. On the other, a plethora of authors\textsuperscript{16-19} have demonstrated that, by comparison with non-sponsored research, sponsored trials are published less frequently and, moreover, have a three-fold greater probability of obtaining favorable results than their non-sponsored counterparts.\textsuperscript{16-19} Curiously, these differences do not appear to be due to inferior methodology in the trials financed by industry. Specifically, this problem has been analyzed in the context of cardiology, too. In a provocative study that included 324 cardiovascular CTs published between 2000 and 2005 in the 3 medical journals with the
highest impact factors, Ridker et al analyzed the probability of results being positive according to the source of finance. Trials financed by industry more frequently presented results favorable to the drug or device analyzed than those financed by not-for-profit organizations. Moreover, results were more favorable in CTs using surrogate endpoints than in those using clinical endpoints.

According to the Declaration of Helsinki, CTs can only be conducted with volunteers and, therefore, medical progress is based on the generosity of people who freely agree to participate in trials. Although these individuals assume risks, their participation in CTs permits them to opt for greater clinical benefits or, at least, means the results obtained can lead to improved treatment for others. As the fundamental objective of research is to extend knowledge, it seems ethically reprehensible to withhold knowledge generated by CTs from the public domain. However, in corporate research, bias can arise when issues of image or, above all, economic motives take precedence over scientific interest. The former frequently underlie the problems of selective publication of results and concealment of data. One recent review showed that 91% of protocols specified limitations in researchers’ rights of publication. In more than half the cases, data were identified as the property of the sponsor who, moreover, had to approve the manuscript prior to its submission for publication. Many contracts signed between sponsors and researchers prohibit the latter from disclosing or commenting on results that have been presented to them in private. Not even the powerful US Food and Drug Administration (FDA) can publish all the data it examines. These biases limit the information available, condition our knowledge—which particularly affects evidence-based medicine—and, what is more important, can prejudice the care patients receive. Unfortunately, it has taken revelations of the scandalous concealment of serious adverse events to shake the foundations that underpin the regulation of financing and publishing CTs. Although criticism has centered fundamentally on trials sponsored by pharmaceutical companies, substantial problems have also been found in many trials financed by government agencies. Chan et al showed that in trials conducted in the 1990s in Canada there were notable differences between initial protocols and final publications. They found incomplete data on efficacy outcomes and harm outcomes in 31% and 59% of the trials, respectively. More worrying was their demonstration of differences in descriptions of primary outcomes in protocols sent to ethics committees and those in the definitive publications. The same authors conducted a similar study with data from ethics committees in Denmark. More than half of the efficacy or harm outcomes were communicated in an incomplete form so as to favor the results of the intervention and conceal adverse effects.

All of the above highlights the problem of publication bias. Some analyses of drug efficacy have found positive results when only evaluating published trials, whereas the inclusion of all trials conducted (published and unpublished) has very often shown that the prejudicial effects can even surpass the benefits. Metaanalyses especially suffer the consequences of publication bias.

Medical journal editors should favor the publication of correctly designed and conducted trials on topics that are clinically relevant to their readers, whether the trial results are negative or positive. The latest ICMJE recommendations stress aspects of authorship, conflict of interests and control of data that should be analyzed and interpreted directly by the researchers conducting the trial. Moreover, they remind us that failure to submit for publication—on the part of authors—or non-acceptance—on the part of editors—simply because the trials concerned present negative results, constitute publication bias. These issues notwithstanding, many negative studies are simply inconclusive and, logically, should be low priorities for publication. Some institutions (Cochrane Library) have shown themselves to be especially interested in gathering data from all these trials. The policy of registering all CTs seeks to facilitate public access to all scientifically relevant information that, for different motives, may not find its way into conventional publications.

RECOMMENDATIONS FOR THE PUBLICATION OF CLINICAL TRIALS (CONSORT RECOMMENDATIONS)

In spite of their limitations, randomized trials represent the benchmark approach to learning about the “efficacy” of a particular treatment. In fact, in the era of evidence-based medicine, the CT has been enthroned at the very highest level of the hierarchy of what has been proven. However, the “quality” of information in controlled trials has been shown to be frequently deficient. When analyzing trials, readers can become frustrated as they realize that information on relevant aspects is missing. Moher et al and Schulz et al showed that inadequate description of randomized trials is associated with a bias in estimating the effects of the interventions being evaluated that tended to overestimate the effects of the treatment.

The CONSORT declaration (Consolidated Standards of Reporting Trials) was made by a group of researchers, epidemiologists, statisticians, and biomedical journal editors to improve the presentation of randomized clinical trials. The proposal included a flowchart (Figure) during the process of writing, revising and analyzing CTs. In great detail, the
<table>
<thead>
<tr>
<th>Variable (Number)</th>
<th>Description</th>
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<tr>
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<td>How participants were allocated to interventions (“random allocation,” “randomized,” or “randomly assigned”)</td>
</tr>
<tr>
<td>Introduction</td>
<td>Scientific background and explanation of hypothesis</td>
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<td>Results (6)</td>
<td>Clearly-defined primary and secondary outcome measures and, when applicable, results of methods used to enhance measurement quality (e.g., multiple observations, training of assessors)</td>
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<tr>
<td>Sample size (7)</td>
<td>How sample size was determined and, when applicable, explanation of any interim analyses and stopping rules</td>
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<tr>
<td>Randomization</td>
<td>Method used to generate random allocation sequence, including details of any restrictions (e.g., blocking, stratification)</td>
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<tr>
<td>– Sequence generation (8)</td>
<td>Method used to generate random allocation sequence, including details of any restrictions (e.g., blocking, stratification)</td>
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<tr>
<td>– Allocation concealment (9)</td>
<td>Method used to implement random allocation sequence (e.g., numbered containers or central telephone), specifying whether sequence was concealed until interventions were assigned</td>
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<tr>
<td>– Implementation (10)</td>
<td>Who generated the allocation sequence, who enrolled participants, and who assigned participants to their respective groups</td>
</tr>
<tr>
<td>Blinding (masking) (11)</td>
<td>Specifying whether or not participants, those administering or allocating interventions, and those assessing outcomes were blinded to group allocation and, if so, how the success of masking was evaluated</td>
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<td>Statistical methods (12)</td>
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<tr>
<td>Results</td>
<td>Flow of participants through each stage (a diagram is strongly recommended)</td>
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<tr>
<td>Participant flow (13)</td>
<td>Flow of participants through each stage (a diagram is strongly recommended)</td>
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<tr>
<td>Numbers analyzed (16)</td>
<td>Number of participants (denominator) in each group included in each analysis, specifying whether analysis was by “intention-to-treat.” When feasible, stating results in absolute numbers (e.g., 10/20, not 50%)</td>
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<tr>
<td>Outcomes and estimations (17)</td>
<td>For each primary and secondary outcome, summarize results for each group and the estimated effect size and its precision (e.g., 95% confidence interval)</td>
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<tr>
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<td>Assess the presence of multiplicity by reporting any other analyses performed, including subgroup analyses and adjusted analyses, indicating those that were prespecified and those that were exploratory</td>
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<td>Adverse events (19)</td>
<td>Interpretation of results, taking into account study hypotheses, sources of potential bias or imprecision, and the dangers associated with multiplicity of analyses and outcomes</td>
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<td>General interpretation of results in the context of currently available evidence</td>
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An additional column (right) should specify the page on which each variable is described. Adapted from Moher et al.33

flowchart guides the passage of participants through the 4 key phases of a trial: enrolment, allocation to intervention, follow-up, and analysis. The objective was to provide a flexible, regularly-updated working tool that would permit researchers to present CT results systematically and with total transparency, so readers could judge their validity adequately.34 The initial 1996 declaration was updated in 2003 when, moreover, an additional document was published with examples, explanations and a glossary of terms to guarantee correct application.34 The authors explained the scientific foundations for their choice of variables and highlighted the coherence of the final list. The most recently updated version of the CONSORT recommendations can be found on their website.35 Some important issues, which finally could not be incorporated into the list, provoked debate. Interesting variables (ethics committee approval, sources of finance,
and registry number) were not included. As we will see later, CT registries already facilitate this information. Some researchers noted the lack of a variable that made explicit the sponsor’s role in designing, conducting, analyzing, interpreting, and writing up the trial. Others suggested that the process that guarantees a systematic, structured review of the information available should be more detailed as only a minority of CTs analyzed prior information systematically. The presentation of a systematic review that justifies the trial guarantees to participants that the design is optimal. In some debates, it was suggested that all systematic reviews should be openly accessible. It was also proposed that the use of missing data and patients’ compliance with treatment should be explicitly defined. Finally, it was suggested that the list of variables should include a description of the economic analysis to determine if trials can be conducted on the efficiency of the interventions evaluated.

New Proposals

Probably, the most interesting advance to occur in this field is that of optimizing the description of harm, risk, and adverse effects in CTs. The CONSORT group has developed a list of 10 variables to improve the description of risk and complications that coincides perfectly with the initial 22 points. It is intended to raise awareness of the importance of informing more widely about the problems of safety detected in CTs.

The initial recommendations have also been adapted to cater for trials with specific designs. Thus, the CONSORT group has recently prepared a document for trials that randomize “groups” of patients (cluster trials) as these have been found to present specific problems (design, effective sample size, intragroup correlation coefficient, and selection after randomization). Other adaptations are aimed at equivalence or noninferiority trials, with crossover treatments or multiple intervention groups. Previously, deficiencies in the publication of noninferiority or equivalence trials had been detected. In these trials it is necessary to predefine margins of noninferiority or equivalence and their clinical justification, to mention confidence intervals and analyze results both for intention-to-treat and protocol.

Results and Challenges in Their Implementation

Implementation of the CONSORT criteria has been shown to improve the quality of published information on randomized trials. Mohr et al showed that quality of CT presentation improved notably on following these criteria. In particular, the incorporation of the flowcharts helped improve the quality of publications. Devereaux et al showed that journals that endorsed the CONSORT recommendations improved their quality criteria and increased the number of methodological aspects described. Yank et al compared the quality criteria of 300 CTs published before 1997 in 5 prestigious medical journals with 300 CTs published after 1997. Description of informed consent and ethics committee approval significantly improved during the study period. However, although descriptions of randomized trials correlate with methodological quality, substantial differences of quality continue to be found in well-presented trials.

Figure 1. Flowchart of subjects participating in the different phases of randomized trials. (1) Enrolment period; (2) Allocation to intervention; (3) Follow-up; (4) Analysis.
Hewitt et al.\(^5\) showed that description of concealing group allocation from patients was customary in journals that endorsed CONSORT\(^7\) but infrequent in other journals. This affects result credibility as CTS that omit mentioning allocation concealment more frequently present positive results for their primary outcome.\(^5\)

Recently, it has been reported that as many as 70% of randomized trials in cardiovascular disease use subgroup analyses and that these are not always conducted adequately.\(^8\) In spite of the fact that the CONSORT list specifically tackles this issue, few studies clearly state whether or not subgroups are presupposed, if statistical analysis considers multiple comparisons, or if interactions have been evaluated.\(^5\) Finally, Nuovo et al.\(^5\) have insisted that, despite all the recommendations, only a limited number of CTS specify the number of patients needed to treat and the absolute reduction in risk.

These data confirm that we should continue to strive to improve the presentation of randomized trials in biomedical journals. Altman\(^5\) reviewed the instructions for authors in 167 high-impact factor journals published in 2003. Only 23% of these mentioned the CONSORT recommendations and 43% cited the ICMJE recommendations, often with out-of-date references. General medicine journals were more rigorous than specialized journals, and those that adopted the CONSORT proposals also followed ICMJE recommendations.

### REGISTRY OF CLINICAL TRIALS

The idea of registering CTS arose more than 30 years ago in an attempt to avoid publication bias.\(^1\) It has been calculated that only half of the 1 million CTS conducted in the last 50 years has been published and that of these, a considerable number are unavailable via MEDLINE.\(^4\) The net result is a clear bias towards the publication of positive results that systematically favor more innovative and more expensive treatments. Moreover, adverse effects are normally silenced or communicated after some delay. This problem affects clinical practice guideline recommendations\(^1\) and, ultimately, patients’ health.\(^5\) The question is fundamentally ethical: are CTS results the exclusive property of their sponsors or are they also the property of the international scientific community as they have direct repercussions on the health of citizens? From the editorial point of view the reply is clear.\(^6\) In fact, the ICMJE proposal has translated into a more effective stimulus to implement CT registries.\(^6\) The Declaration of Helsinki\(^21\) requires that trial designs should be available to the public. In the long term, no one wins with the selective dissemination of CT information.\(^5\) Consequently, researchers and sponsors hold the weighty responsibility of presenting findings —and possible adverse effects—within a reasonable period of time.\(^6\) Finally, ethics committees should cooperate by insisting on registering CTS prior to giving their definitive agreement.

Outstanding advantages of registering CTS\(^6\)-\(^11\) include: a) ethical aspects; b) avoiding harm to patients by allowing access to unpublished information about risks and adverse effects; c) avoiding duplicating research and thus optimizing the efficiency of the investigation and helping improve the design of new trials; d) avoiding publication bias; e) improving transparency, to prevent changes in CT design and favor better interpretation of results; and f) raising the overall quality of the research.\(^8\) At the same time, possible limitations of registering CTS include: a) lack of registers that meet all the required criteria; b) increased bureaucratic red-tape—complex enough in itself—for research; c) presentation of results prior to their analysis and criticized in the process of peer revision; d) incorrect interpretation of results—insufficiently explained—by the general public; e) loss of the advantages (and of the resulting economic benefits) for the companies and investment in research and innovation, to the benefit of their competitors; and f) lack of effective measures that penalize non-registration of CTS.\(^6\)

Since 2004, the world’s principal pharmaceutical companies have collaborated resolutely to favor registering CTS. In fact, many of them have developed proactive measures aimed at restoring the climate of confidence in research financed by the industry.\(^7\) Some initiatives have centered on developing private but easily accessible registers of all CTS sponsored by each pharmaceutical company. However, attempts by some associations in the industry to unify their registers have yet to produce the desired results.\(^8\) Moreover, due to the inherent conflict of interests, these initiatives do not seem to be the best solution to the problem and we can barely hope for a unification of these registers.

The latest ICMJE recommendations specify the “obligation” to register CTS\(^6\)-\(^11\).\(^8\) Thus, in 2004 the editors responded to a growing clamor for increased transparency in CTS. This registry would be universal, public, easily accessible (in electronic format) and free. It would remain open prospectively to permit the updating of data and should be managed by a non-profit making organization. Each CT would have a unique register number appearing at the end of the abstract. Finally, it should be possible to guarantee the validity of the data included. In Table 2, we present the ICMJE recommendations, adapted from the World Health Organization (WHO) proposal, with the minimum data for inclusion in each record.\(^8\)

These recommendations are less demanding than the much more ambitious Declaration of Ottawa proposals, with contributions from many organizations,
including the Cochrane Collaboration. These proposals suggested that all prospective trials should be registered, including phase I trials, with or without control group. Moreover, any alterations introduced in the trial should be detailed and final results presented, although some delay would be acceptable to allow for their publication.

### Currently Available Registries

1. The US clinicaltrials.gov registry meets all ICMJE requirements. This database, developed by the National Library of Medicine, is available on the internet and, although it depends on the FDA and the National Institute of Health, permits the inclusion of international trials. The registry has been criticized by some European researchers as being overly centered on US CTs and not incorporating information about final results.

2. A British private company (Current Controlled Trials) developed the idea of the standard international registry number. In late 2005, ownership of this database was transferred to a non-profit making organization fulfilling ICMJE requirements. Now, this registry (International Standard Randomised Controlled Trial Number) is also valid from an editorial point of view.

3. The European Community, in a specific harmonization directive (2001/20/CT) introduced legislation that made it obligatory to register “clinical studies about medical products for human use” and developed the EudraCT database controlled by the European Medicines Agency. Although this database could be very useful for European researchers, at the moment it does not comply with some ICMJE requirements as it is a confidential register, only available to regulatory agencies and funding organizations.

4. Many countries, including Spain, have gathered information on all CTs although, again, these data are not available to the public.

5. Some medical specialties, such as pediatrics, have been particularly sensitive to the ethical problems in research. In 2004, a registry of drug evaluation in children (DEC-net) was established, sponsored directly by the European Union, which fully complies with ICMJE requirements.

6. Finally, the WHO has developed an international “platform” to organize CT registries and assume the leadership in this initiative. The WHO collaborates with other organizations on projects destined to guarantee consensus over the minimum data contained in the registry, the reliability of the information registered and the implementation of a single international system of numeration.

### Problems and Consequences of Application

Some issues have generated considerable discussion. According to the ICMJE, the registry should be public property and non-profit making. However, the editors...
we will improve the quality of the final publication of the British Medical Journal consider that public ownership of the registry, although desirable, could be an unnecessarily restrictive criterion and, in fact, this apparently minor difference led them to refrain from signing the latest ICMJE declaration.\textsuperscript{27} Moreover, although the ICMJE does not demand it, some researchers insist on the usefulness of extending the registries to phase I trials and, above all, on the need to present final results.\textsuperscript{28,29} Also, it is important to see how the WHO initiative\textsuperscript{60-61} and the Declaration of Ottawa\textsuperscript{30-31} evolve. Finally, from time to time, we must evaluate the results and implications of this new editorial policy.

Zarin et al\textsuperscript{27} confirm the important influence of the ICMJE initiative on registering CTs. The number of CTs registered clearly “peaked” in September 2005. A progressive improvement in the quality of the data registered was confirmed. This included the name of the intervention analyzed and the primary outcome. However, the authors observed different concerns at the time of revealing information and many studies were registered simply as “drug in research phase” instead of specifying the specific name of the intervention.\textsuperscript{30} While provision of full information for these fields was practically universal when CTs were financed by academic institutions, CTs sponsored by industry frequently used vague terms to describe these important variables.\textsuperscript{27}

\textbf{CONSIDERATIONS OF EDITORIAL POLICY}

At Revista española de cardiología we have conducted an editorial review of this issue. In contrast with some important American journals, no European publication dedicated to cardiovascular diseases yet insists CTs be registered. However, this issue was debated at the last meeting of national editors of the European Cardiology Society. Moreover, the HEART group (Heart Editors Action Round Table) is actively working to promote agreement among cardiovascular journal editors to facilitate an overall policy of registering CTs.

The number of randomized trials submitted to Revista española de cardiología in recent years has been as few as only 2-3 a year. However, during this period we have published a substantial number of sub-trials, analyses of subgroups and follow-ups of different CTs. From now on, the randomized trials published in this journal must comply with the CONSORT recommendations. Moreover, we are committed to adapting our instructions for authors to the advances that are occurring over the registering of CTs, in terms both of editorial requirements and of adapting to current legislation. We hope that the concerns we outline here help present CTs with the greatest methodological clarity possible. In this way, we will improve the quality of the final publication of these trials that are so essential to the advance of scientific knowledge. We trust that these editorial initiatives, together with those previously adopted,\textsuperscript{27,29} contribute to improve the quality and credibility of Revista española de cardiología.

\textbf{REFERENCES}