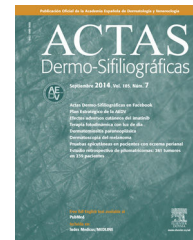




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ORIGINAL ARTICLE

Analysis of the Quality of Clinical Trials Published in Spanish-Language Dermatology Journals Between 1997 and 2012[☆]



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KEYWORDS

Randomized clinical trial;
Bias;
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Spanish

Abstract

Introduction: The value of randomized clinical trials (RCTs) undertaken to identify an association between an intervention and an outcome is determined by their quality and scientific rigor.

Objective: To assess the methodological quality of RCTs published in Spanish-language dermatology journals.

Methods: By way of a systematic manual search, we identified all the RCTs in journals published in Spain and Latin America between 1997 (the year in which the CONSORT statement was published) and 2012. Risk of bias was evaluated for each RCT by assessing the following domains: randomization sequence generation, allocation concealment, blinding of patients and those assessing outcomes, missing data, and patient follow-up. Source of funding and conflict of interest statements, if any, were recorded for each study.

Results: The search identified 70 RCTs published in 21 journals. Most of the RCTs had a high risk of bias, primarily because of gaps in the reporting of important methodological aspects. The source of funding was reported in only 15 studies.

Discussion and conclusions: In spite of the considerable number of Spanish and Latin American journals, few RCTs have been published in the 15 years analyzed. Most of the RCTs published had serious defects in that the authors omitted methodological information essential to any evaluation of the quality of the trial and failed to report sources of funding or possible conflicts of interest for the authors involved. Authors of experimental clinical research in dermatology published in Spain and Latin America need to substantially improve both the design of their trials and the reporting of results.

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PALABRAS CLAVE

Ensayo clínico aleatorizado; Sesgos; Metodología; Revistas dermatológicas; Español

Análisis de la calidad de los ensayos clínicos publicados en revistas dermatológicas publicadas en español entre 1997 y 2012**Resumen**

Introducción: La relevancia del ensayo controlado con asignación aleatoria (ECA) para determinar si existe una asociación entre una intervención y un desenlace está determinada por su calidad y rigor científico.

Objetivo: Evaluar la calidad metodológica de los ECA publicados en revistas dermatológicas en español.

Métodos: Se realizó una búsqueda manual y sistemática de los ECA publicados en las revistas de Dermatología españolas y latinoamericanas entre 1997 (publicación de los criterios CONSORT) y 2012. Se determinó el riesgo de sesgo de cada ECA, evaluando los siguientes dominios: generación de la secuencia aleatoria, ocultamiento de la asignación, cegamiento de los pacientes/evaluadores de desenlaces, datos faltantes y seguimiento de pacientes. Se identificaron la fuente de financiación de los estudios y el reporte de conflictos de interés.

Resultados: Se identificaron 70 ECA publicadas en 21 revistas. La mayoría de los ECA tuvo un alto riesgo de sesgo, principalmente por falta de reporte de los aspectos metodológicos importantes. Solo 15 estudios declararon fuentes de financiación.

Discusión y conclusiones: A pesar del número considerable de revistas existentes en España y Latinoamérica, en los 15 años estudiados se han publicado pocos ECA. La mayoría de los estudios presentó problemas de calidad importantes, al carecer de información metodológica que permitiera evaluar su calidad y a las falencias en el reporte de las fuentes de financiación y de los conflictos de interés de los autores. La investigación clínica experimental dermatológica que se publica en Ibero-Latinoamérica debe mejorar ostensiblemente tanto en su diseño como en su reporte de resultados.

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Introduction

The randomized controlled trial (RCT) is the most rigorous type of methodological design and the best way of determining whether a cause-effect relation exists between an intervention and the result or outcome being assessed. RCTs also provide the raw material for systematic reviews and meta-analyses. However, the value of such studies depends on the quality and methodological rigor of their design and implementation.

In recent decades, the field of dermatology has seen a substantial increase in experimental clinical research. However, this upturn in the volume of research has not been accompanied by a corresponding improvement in trial design and methodology. Several studies have reported that the RCTs published in the dermatology literature tend to fall below acceptable standards.¹⁻⁴

The Consolidated Standards of Reporting Trials (CONSORT) statement was first published in 1996 to improve the quality of reporting of clinical trials worldwide.⁵ The CONSORT statement includes a checklist designed to improve the reporting of RCTs, which also, indirectly, throws light on the study's quality and scientific rigor.

An improvement in the scientific quality and reporting of RCTs might have been expected following the implementation of CONSORT and the publication of the Medical Research Council Guidelines for Good Clinical Practice in Clinical Trials (available from: <http://www.fda.gov/downloads/Drugs/>

<http://www.mrc.ac.uk/documents/pdf/good-clinical-practice-in-clinical-trials/>).

However, the evidence reveals the continued presence after 1997 of serious flaws in the design and reporting of clinical trials.⁶ The problem has also been observed in trials in the Spanish-language dermatology literature published after 1997. A study carried out in Spain found that only 6 (25%) of the 24 clinical trials found in the dermatology journal with the highest impact in that country—*ACTAS Dermo-Sifiliográficas*—were classified as being of high quality.³

In this context, the aim of the present study was to assess the methodological quality of the experimental clinical research in dermatology published in Spanish to facilitate an analysis of the strengths of these studies and the challenges that must be overcome. We analyzed the RCTs identified by a recent study that handsearched Spanish-language dermatology journals.⁷

The present study complements that work by analyzing the methodological quality of the RCTs published between 1997 and 2012 using the appropriate Cochrane Collaboration tools and a review of the reporting of conflicts of interest and funding sources.

Objective

To assess the methodological quality of the RCTs published in Spanish-language dermatology journals between 1997 and 2012.

Materials and Methods

Journal Identification: Manual and Electronic Search

The methodology used to identify the RCTs published in Spanish-language dermatology journals has already been described in an earlier article.⁷

In a preliminary phase, all eligible journals were identified in the framework of a project led by the Iberoamerican Cochrane Centre (IbCC) in Barcelona, Spain. Using the IbCC protocol, journals were located through the following search engines and databases: MEDLINE (through PubMed), EMBASE, LILACS (Latin American Index of Scientific and Technical Literature), SciELO, Periódica, Latindex, Índice Médico Español, Catálogo Nacional de Publicaciones Periódicas en Ciencias de la Salud Españolas (C-17), as well as in other catalogues of health sciences publications in Spain. This initial search strategy was then complemented by a search of the Spanish health sciences indexes (IBECS and IMBIOMED), by free-text Internet searches using Google, by contacting the Dermatology societies in each of the countries studied, and through direct contact with dermatologists.

Each journal identified was then handsearched to identify all the RCTs published. This retrospective review was carried out in accordance with the Cochrane Collaboration's manual for handsearching archives and identifying clinical trials (available from <http://www.cochrane.es/~cochrane/?q=es/node/140>). Each journal was searched from 2012 back to the first issue published (provided full texts were still available).⁷

In addition to handsearching for RCTs, we also conducted an electronic search of MEDLINE (using PubMed), EMBASE, LILACS and IBECS, as well as the search engines of the Biblioteca Virtual en Salud hosted by the Latin American and Caribbean Center on Health Sciences Information (Bireme), the Pan American Health Organization, and the World Health Organization.

Data Extraction

A database was created to store each of the RCTs retrieved, to facilitate the handsearch of each journal, and to ensure that data was gathered and processed in an organized and systematic manner. We also identified journals specifying CONSORT reporting in their instructions to authors and journals indexed on MEDLINE or EMBASE.

Analysis of Quality and Risk of Bias

Only RCTs published between 1997 (the first year the CONSORT statement was implemented) and 2012 were included in the review of scientific rigor and methodological quality. The appraisal was performed twice, and any resulting discrepancies were resolved by a third assessor. The review was carried out using the Cochrane Collaboration tool for assessing risk of bias (high/medium/low).⁸ This tool assesses the methodological aspects of clinical trials, including sequence generation, concealment of the sequence of patient allocation to the different arms of the study, blinding

of participants and outcome assessors, incomplete data, and patient follow-up. The reviewer assesses each one of these domains and assigns one of the following answers: "yes", "no", or "unclear/not reported".

Studies were categorized as having a "high risk of bias" if they had 1 flaw that affected the generation of the allocation sequence or had more than 1 flaw affecting any of the other methodological aspects analyzed. If the necessary information was unavailable, the study was categorized as "unclear risk/not reported". The results of the assessment and scoring of these methodological aspects were recorded using version 5.2 of the application Review Manager (Copenhagen, the Nordic Cochrane Centre, The Cochrane Collaboration, 2012). Information on sources of funding and the reporting of potential conflicts of interest on the part of authors were also logged.

Statistical Analysis

Descriptive statistics of the resulting information were compiled, using univariate analysis to determine the frequencies of the variables. Appropriate summary measures were calculated for the continuous variables. Absolute and relative frequencies and their percentages were determined for qualitative variables. When appropriate, the confidence interval was calculated for proportions. The data were recorded on Review Manager and also in an Excel spreadsheet (Microsoft Office 2010). The software package SPSS (version 19, IBM) was used to analyze the data.

Results

Of the 28 journals that fulfilled the criteria for eligibility, 21 were eventually included in the study: 5 from Spain and 16 from Latin American countries. Of these 21 journals only *ACTAS DERMOSIFILIOGRÁFICAS* is currently indexed on both MEDLINE and EMBASE. Four others are indexed on EMBASE: *Dermatología Revista Mexicana*, *Argentina de Dermatología*, *Medicina Cutánea Ibero Latinoamericana* and *Piel*.⁷

The total number of journals included and excluded, and the reasons for the choices made have been described in an earlier article (Fig. 1).⁷

Identification of Clinical Trials

Seventy RCTs published between 1997 and 2012 were identified in the 21 journals studied: 73% (51) in the 16 Latin American journals and 27% (19) in the 5 Spanish journals (Table 1) (Appendix 1). The Latin American journals that published the largest number of RCTs were *Dermatología Revista Mexicana* (16), *Dermatología Peruana* (9), and *Revista Chilena de Dermatología* (5) (Table 1). The Spanish journals that published the most RCTs were *ACTAS DERMOSIFILIOGRÁFICAS* and *Piel*, with 8 each (Table 1).

Most of the trials reviewed were classified as having a high risk of bias because the authors failed to report the information needed to assess the quality and methodological rigor of the trial (Table 2). A small percentage of trials had a low risk of bias in the domains assessed (Table 2) (Fig. 2).

The authors of 15 RCTs reported sources of funding and only 2 did so in the required manner (Ramirez-Bosca et al. and Pinto et al.) (Appendix 1). The authors of 5 studies

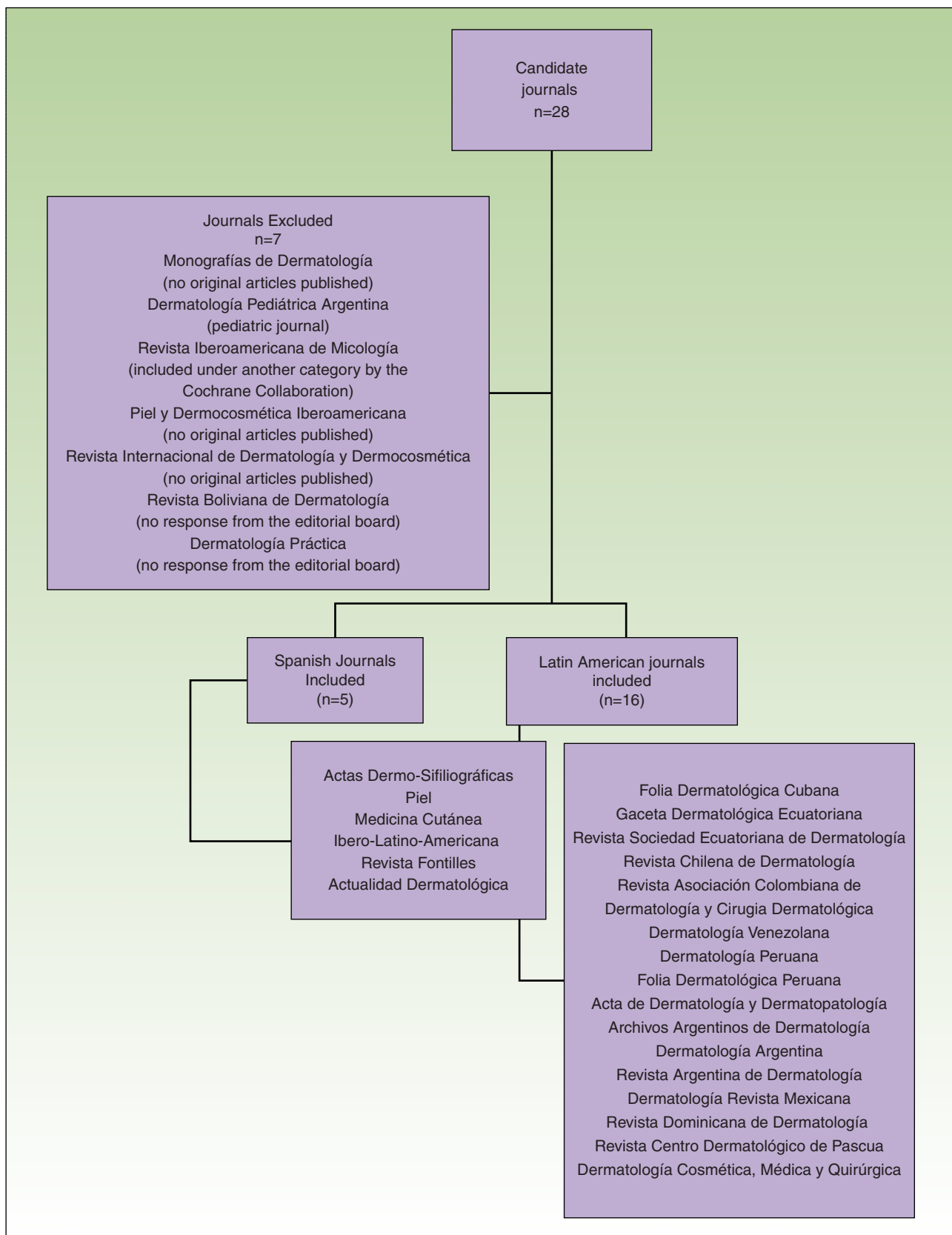


Figure 1 Flow chart showing the process used to select dermatology journals according to inclusion and exclusion criteria. Source: Sanclemente G, Pardo H, Sánchez S, Bonfill X. Identificación de ensayos clínicos en revistas dermatológicas publicadas en español. *Actas Dermosifiliogr.* 2015;106:415-422).

Table 1 Randomized Controlled Trials (RCTs) Identified in Spanish and Latin American Dermatology Journals.

| | Journal Name | Periods Not Assessed Because No Copies (Print or Electronic) Available | Number of RCTs Identified |
|----|--|--|---------------------------|
| 1 | <i>Dermatología Revista Mexicana</i> | – | 16 |
| 2 | <i>Dermatología Peruana</i> | – | 9 |
| 3 | ACTAS DERMO-SIFILOGRÁFICAS | – | 8 |
| 4 | <i>Piel</i> | – | 8 |
| 5 | <i>Revista Chilena de Dermatología</i> | – | 5 |
| 6 | <i>Dermatología Cosmética, Médica Y Quirúrgica</i> | – | 4 |
| 7 | <i>Revista del Centro Dermatológico Pascua</i> | – | 4 |
| 8 | <i>Revista Asociación Colombiana de Dermatología</i> | – | 4 |
| 9 | <i>Medicina Cutánea Ibero-Latino-Americana</i> | – | 3 |
| 10 | <i>Folia Dermatológica Peruana</i> | – | 2 |
| 11 | <i>Dermatología Argentina</i> | – | 2 |
| 12 | <i>Folia Dermatológica Cubana</i> | – | 2 |
| 13 | <i>Dermatología Venezolana</i> | – | 2 |
| 14 | <i>Revista Argentina de Dermatología</i> | – | 1 |
| 15 | <i>Archivos Argentinos de Dermatología</i> | – | 0 |
| 16 | <i>Actas de Dermatología y Dermatopatología</i> | – | 0 |
| 17 | <i>Revista Dominicana de Dermatología</i> | 1997-2009 | 0 |
| 18 | <i>Revista Sociedad Ecuatoriana de Dermatología</i> | 1997-2002, 2005, 2008, 2009, 2011, 2012 | 0 |
| 19 | <i>Gaceta Dermatológica Ecuatoriana</i> | 1999-2012 | 0 |
| 20 | <i>Actualidad Dermatológica</i> | – | 0 |
| 21 | <i>Revista Fontilles</i> | 1997-2002 | 0 |
| | Total | | 70 |

reported conflicts of interest, but only 1 of these reports conformed to accepted standards (Ramirez-Bosca et al.) (Appendix 1). Of all the journals assessed, only ACTAS DERMO-SIFILOGRÁFICAS, since 2008, requires authors to report trials in accordance with the CONSORT guidelines; however, none of the authors reported in the body of the article whether or not the CONSORT checklist had been used to guide the reporting of the study.

Figure 2 is a summary of the risk of bias for the RCTs identified.

Discussion

The objective of this study was to assess the methodological quality of the RCTs published in Spanish-language dermatology journals between 1997 and 2012. Our findings

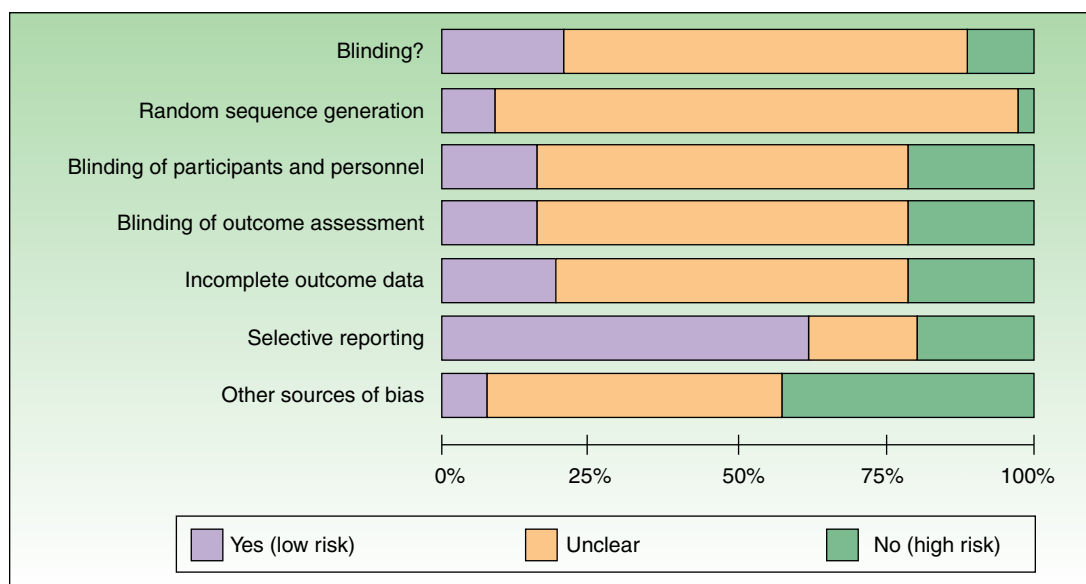


Figure 2 Risk of bias of the RCTs analyzed (graphic designed using Review Manager, version 5.2, Copenhagen, The Nordic Cochrane Centre, The Cochrane Collaboration, 2012).

Table 2 Assessment of Methodological Aspects of Randomized Controlled Trials (RCTs) Published in Spanish and Latin American Dermatology Journals.

| Methodological Aspect | No. (%) | 95% CI |
|-------------------------------|--------------|---------------|
| <i>Allocation concealment</i> | | |
| Unclear/Not reported | 48 (68.6) | 57.73%-79.47% |
| Yes | 14 (20) | 10.63%-29.37% |
| No | 8 (11.4) | 3.95%-18.85% |
| Unclear/Not reported | 62 (88.6) | 81.15%-96.05% |
| Yes | 6 (8.6) | 2.03%-15.17% |
| No | 2 (2.8) | -1.06%-6.66% |
| Unclear/Not reported | 44 (62.8) | 51.48%-74.12% |
| Yes | 11 (15.7) | 7.18%-24.22% |
| No | 15 (21.5) | 11.88%-31.12% |
| Unclear/Not reported | 44 (62.8) | 51.48%-74.12% |
| Yes | 11 (15.7) | 7.18%-24.22% |
| No | 15 (21.5) | 11.88%-31.12% |
| Unclear/Not reported | 42 (60) | 48.52%-71.48% |
| Yes | 13 (18.5) | 9.4%-27.6% |
| No | 15 (21.5) | 11.88%-31.12% |
| Unclear/Not reported | 12 (17.2) | 8.36%-26.04% |
| No | 44 (62.8) | 51.48%-74.12% |
| Yes | 14 (20) | 10.63%-29.37% |
| Unclear/Not reported | 35 (50) | 38.29%-61.71% |
| No | 5 (7, 15, 8) | 7.26%-24.34% |
| Yes | 30 (42.9) | 31.31%-54.49% |
| Not reported | 55 (78.6) | 68.99%-88.21% |
| Reported | 15 (21.4) | 11.79%-31.01% |
| Not reported | 65 (92.8) | 86.74%-98.86% |
| Reported | 5 (7.2) | 1.14%-13.26% |

show that the risk of bias was high in the clinical trials published in the Spanish-language dermatology literature in that period, primarily because authors failed to report on important methodological aspects of their work. Although this shortcoming had already been described in earlier studies focusing on specific dermatology journals in Spanish,⁹ this is the first comprehensive analysis that covers all the dermatology journals publishing RCTs in Spain and Latin America. Our findings are similar to those of authors who studied RCTs in the English-language dermatology literature or RCTs on diseases such as perioral dermatitis and atopic dermatitis.^{4,10,11}

The presence of such flaws in RCTs is of particular concern because this type of study is considered to be a gold standard for the assessment of the efficacy and safety of an intervention. Consequently, the implication is that dermatological practice today (at least that predicated on evidence from

the studies assessed) may be based on information gathered in a non-systematic manner or on clinical experiments lacking control groups.¹² We also detected a mismatch between the outcomes typically assessed and those that might interest patients. For example, many dermatology studies now incorporate variables relating to quality-of-life because of the considerable interest of patients in this outcome in relation to dermatological treatments.¹³⁻¹⁵ However, it is striking that quality-of-life was assessed in only 1 of the 70 RCTs identified.

The methodological aspects least often reported were random sequence generation and allocation concealment; authors also failed to report on sources of funding and possible conflicts of interest. Our findings, which are similar to those observed by other authors in journals that endorse CONSORT reporting as well as in those that do not,^{6,16,17} highlight shortcomings in the scientific rigor with which the

RCTs were designed and reported. In the future, experimental clinical research published in Spain and Latin America in the field of dermatology needs to be considerably improved both in the design and the reporting of results (endorsement and application of the CONSORT guidelines).

The starting point for an unbiased study is the use of a mechanism that ensures that all the patients have the same probability of belonging to one group or the other, and that adequate concealment of the allocation sequence prevents selective recruitment of patients according to prognostic factors (guidelines available from <http://handbook.cochrane.org/>). In fact, it has been shown that inadequate random sequence generation in an RCT can result in an overestimation of the effect of the treatment of up to 12%,¹⁸ while inadequate allocation concealment may increase the effect up to 18%. Furthermore, the fact that a clinical experiment is classified as randomized does not, in and of itself, guarantee that the study fulfils the methodological standards associated with this type of study.¹⁹

The only journal included in this study that requires authors to comply with the CONSORT statement when reporting clinical trials is *ACTAS DERMATO-SIFILIOGRÁFICAS*. This endorsement may explain the higher methodological quality of the RCTs published recently by that journal. However, it has been observed that, despite improvements in reporting of RCTs when this tool is used, the completeness of reporting of trials continues to be suboptimal in terms of ensuring a better quality of study.⁶

Of note is the fact that almost none of the trials identified provided any information on sources of funding or conflicts of interest. Complete reporting of both of these aspects is essential since the results of the trial may be affected by the personal interests of the researcher or the funder of the study (very often a pharmaceutical company).^{20–22} Transparency is important because it is common in the dermatology literature to find selective reporting of endpoints, a practice which in most cases leads to the overestimation of positive outcomes.²³ This practice may be associated with the presence of conflicts of interest. Therefore, in the future careful assessment of these characteristics will be essential in the studies published in Spanish-language dermatology journals.²⁴

One of the principal strengths of the present study was that 21 dermatology journals published in Spanish were handsearched to identify RCTs. The clinical trials identified will shortly be included in the Cochrane Central Register of Controlled Trials (CENTRAL), making them available for future systematic reviews and other summary documents. As reported by the earlier article, which identified the RCTs⁷ analyzed in the present study, finding 70 RCTs and retrieving the full texts of those articles would have been impossible through an electronic search because only 1 journal is indexed on MEDLINE (*Actas Dermo-Sifiliográficas*) and only 4 are indexed on EMBASE⁷ (*Dermatología Revista Mexicana*, *Revista Argentina de Dermatología*, *Medicina Cutánea Ibero Latinoamericana* and *Piel*). Another strength of the present study was the duplicate analysis of the quality of the RCTs and the use of internationally-recognized and validated Cochrane tools. (Available from: http://handbook.cochrane.org/chapter_8/8_assessing_risk_of_bias_in_included_studies.htm).

The main limitation of this study was the impossibility of assessing all the volumes and issues of 3 journals: 2 published in Ecuador and 1 published in the Dominican Republic. However, it is unlikely that our results would have differed significantly with a complete analysis of these 3 journals since no RCTs were found in the issues we were able to review. Furthermore, none of those journals have endorsed the CONSORT statement or require its use. Another limitation was the variability of the endpoints and the way these were measured in the RCTs identified. This variability led to a high level of heterogeneity among the studies, making it difficult to quantitatively summarize the results in a meta-analysis

In conclusion, the risk of bias of the clinical trials published in Spanish-language dermatology journals between 1997 and 2012 was high, mainly because the study reports provided insufficient information on which to base any assessment of the quality and methodological rigor of the studies. Moreover, in many cases the authors failed to report on sources of funding and possible conflicts of interest. Complete reporting of all methodological aspects of trials is recommended, as this would allow readers to detect possible sources of bias and design flaws. A complete description of the study is important because it facilitates proper analysis of the evidence and because it ensures that a trial is not classified as having a high risk of bias solely because of omissions in the information provided. Complete reporting will benefit patients—the foundation of evidence-based dermatological practice—and will contribute to more effective decision-taking in this field of practice. Finally, and as a future strategy, we plan to contact the publishers of the dermatology journals analyzed with a view to standardizing prospective tools for the identification of the RCTs published in their journals. The implementation of such a system will facilitate continual updating of this work, thereby obviating the need to repeat the manual search in the future.

Ethical Disclosures

Protection of human and animal subjects. The authors declare that no experiments were performed on humans or animals during the course of this study.

Data confidentiality. The authors declare that no private patient data are disclosed in this article.

Right to privacy and informed consent. The authors declare that no private patient data are disclosed in this article.

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Conflicts of Interest

The authors declare that they have no conflicts of interest.

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(*Revista Dermatología Mexicana*), to Dr. Roberto Arenas and Dr. Jorge Ocampo-Candiani (*Revista Dermatología Cosmética Médica y Quirúrgica*), and to Dr. Edgardo Chouela for their help in the search and in sending full texts of the articles we requested.

Dr. Gloria Sanclemente is a PhD candidate in the department of pediatrics, obstetrics, gynecology, and preventive medicine of the Universitat Autònoma de Barcelona, Spain. This study was carried out with the help of the Group of Investigative Dermatology (GRID) of the Universidad de Antioquia, Medellín, Colombia.

Appendix 1.

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