Universitat Autònoma de Barcelona

Estrategias para Prevenir y Controlar el Sesgo de Diseminación de los Ensayos Clínicos con Distribución Aleatoria

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TESIS DOCTORAL

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Cita

“Que vuestra gentileza sea conocida delante de todas las personas”.

Libro de los Filipenses 4, 5

ÍNDICE

1. Resumen

1.1 Resumen

1.1.1. Antecedentes

El sesgo en el reporte de los ensayos clínicos con distribución aleatoria (ECA) surge por una tendencia de los investigadores a reportar y las revistas a publicar resultados positivos, estadísticamente significativos, o que coincidan con la hipótesis de los investigadores. El sesgo de reporte más común es el de diseminación de los ECAs, definido como "la publicación o no publicación de los resultados de estudios de investigación dependiendo de la naturaleza y/o dirección de los resultados". Estudios llevados a cabo en los últimos cinco años demuestran que el sesgo de diseminación continúa ocurriendo. Por tanto, se hace necesario el diseño y la implementación de estrategias adicionales para prevenir su aparición y controlar sus consecuencias.

1.1.2. Objetivos

El objetivo principal de este proyecto de tesis es desarrollar estrategias para prevenir y controlar el sesgo de diseminación de los ECAs.

1.1.3. Métodos

Se han llevado a cabo cuatro estudios con diferentes metodologías: 1) Una encuesta entre agencias europeas que financian investigación biomédica para explorar su opinión y posibles soluciones acerca del sesgo de publicación de los ECAs, así como desarrollo de recomendaciones para reducir la incidencia y el efecto del sesgo de diseminación, ambos realizados dentro del proyecto OPEN, *To Overcome failure to Publish nEgative fiNdings*, cofinanciado por la Unión Europea a través del *Seventh Framework Programme*; 2) Un estudio observacional y descriptivo para identificar y describir de manera exhaustiva las revistas que publican investigación original en España y Latinoamérica en lengua castellana; 3) Un estudio observacional y descriptivo para identificar a través de búsqueda manual y electrónica los ECAs publicados en revistas españolas de Fisioterapia, así como para proveer sus principales características y 4) El

desarrollo de una base de datos para facilitar el diseño, gestión y análisis de resultados de proyectos de búsqueda manual, así como el envío de referencias de los ECAs identificados a CENTRAL, la base de datos mundial de ECAs de la Colaboración Cochrane.

Asimismo, se presentan cuatro estudios anexos. Primero, un reporte en el que se explica, dentro del contexto del desarrollo de la Colaboración Cochrane en Latinoamérica, el inicio y progreso de la iniciativa de búsqueda manual de ECAs en España y Latinoamérica. Por otra parte, los resultados de dos estudios observacionales y descriptivos de identificación de ECAs publicados en revistas de Ginecología y Obstetricia españolas y en revistas de Dermatología españolas (una publicación) y latinoamericanas (dos publicaciones), respectivamente.

1.1.4. Resultados

1) A través de la encuesta entre agencias europeas que financian investigación biomédica se encontró que más de dos tercios adoptaban medidas para prevenir o controlar el sesgo de diseminación. Sin embargo, menos de un cuarto tenían conocimiento del estatus de publicación de proyectos financiados en el año 2005. A partir de los resultados globales de esta encuesta y de otros estudios llevados a cabo dentro del proyecto OPEN se desarrollaron recomendaciones específicas para estas agencias, entre las que destacan requerir la difusión de los resultados de la investigación en todas las convocatorias ofrecidas, solicitar un plan de difusión de los proyectos financiados y crear una base de datos accesible al público de todas las subvenciones concedidas y de la forma en que se difundieron sus resultados.

2) Se identificaron 1 498 revistas biomédicas que publican investigación original en España y Latinoamérica en lengua castellana, la mayor parte de ellas editadas en España, México y Argentina. A pesar de que más de un tercio se encontraban indexadas en al menos una base de datos, solo 4,1% y 3,7% se encontraban indexadas en MEDLINE y EMBASE, respectivamente. Asimismo, 45 revistas (3,0%) tenían factor de impacto en el año 2012. Poco más de la mitad de

estas revistas tienen una página web, que generalmente permiten buscar contenidos sin costo a los usuarios.

3) Se identificaros 78 ECAs en 10 revista de Fisioterapia de España, ninguna de las cuales se encontraban indexadas en MEDLINE o EMBASE. La mayoría de estos ECAs se centraban en aspectos relacionados con el dolor de espalda, Fibromialgia y Artrosis. Aproximadamente dos tercios de estos ECAs presentaron un alto riesgo de sesgo.

4) Se ha desarrollado la Base de Datos de Ensayos y Revistas Iberoamericanos (BADERI). BADERI es una herramienta gratuita gestionada desde el Centro Cochrane Iberoamericano que permite el seguimiento de diferentes aspectos de proyectos de búsqueda manual, incluyendo el aporte de cada participante o equipo investigador, las revistas a las que se las hecho búsqueda manual y los ECAs identificados con sus principales características. BADERI permite generar reportes para analizar los resultados de las actividades de búsqueda manual, así como archivos específicamente diseñados para su exportación a CENTRAL. A la fecha, hay más de 6 000 ECAs en BADERI.

Finalmente, a través de los estudios anexos 1) se explica el inicio y alcance de las actividades de búsqueda manual en España y Latinoamérica desarrollados desde el Centro Cochrane Iberoamericano, 2) Se identificaron 235 ECAs en 16 revistas de Ginecología y Obstetricia de España, y 3) Se identificaron 144 ECAs en 21 revistas de Dermatología de España y Latinoamérica.

1.1.5. Conclusiones

Aunque existe conciencia sobre el problema que supone el sesgo de diseminación, así como buenas intenciones para reducirlo y controlarlo, la mayoría de las agencias que financian investigación biomédica en Europa no implementan estrategias rigurosas para verificar la diseminación de los ECAs financiados.

Hay un número significativo de revistas biomédicas que publican investigación original en España y Latinoamérica. Sin embargo, la mayoría no tiene factor de impacto o no están indexadas en bases de datos de la literatura, lo que puede desalentar a los investigadores locales a la hora de publicar su trabajo en estas revistas.

El número de ECAs publicados en revistas españolas de Fisioterapia es limitado. Estos ECAs presentan una baja calidad metodológica. Dado que ninguna de las revistas españolas de Fisioterapia están indexadas en las principales bases de datos de la literatura, la identificación de estos ECAs y su posterior inclusión en CENTRAL contribuye a reducir el sesgo de publicación en el desarrollo y la actualización de futuras revisiones sistemáticas.

La base de datos BADERI se ha convertido en una herramienta invaluable para gestionar la identificación manual de ECAs y para facilitar su envío a CENTRAL para su posible inclusión en revisiones sistemáticas y otros documentos de síntesis.

1.2 Resum

1.2.1. Antecedents

El biaix de notificació en els assajos clínics amb distribució aleatòria per una tendència dels investigadors a disseminar i les revistes a publicar resultats positius, estadísticament significatius, o que coincideixin amb la hipòtesi dels investigadors. El biaix de notificació en ACAs més comú és el biaix de disseminació, definit com "la publicació o no publicació dels resultats d'estudis de recerca depenent de la naturalesa i/o direcció dels resultats". Estudis duts a terme en els últims cinc anys demostren que el biaix de disseminació continua succeint. Per tant, es fa necessari el disseny i la implementació d'estratègies addicionals per prevenir la seva aparició i controlar les seves conseqüències.

1.2.2. Objectius

L'objectiu principal d'aquest projecte de tesi és desenvolupar estratègies per prevenir i controlar el biaix de disseminació dels ACAs.

1.2.3. Mètodes

S'han dut a terme quatre estudis amb diferents metodologies: 1) Una enquesta entre agències europees que financen recerca biomèdica per explorar la seva opinió i possibles solucions sobre el biaix de publicació dels ACAs, així com el desenvolupament de recomanacions per reduir la incidència i l'efecte del biaix de disseminació, tots dos realitzats dins del projecte OPEN, *To Overcome failure to Publish nEgative fiNdings*, cofinançat per la Unió Europea a través del *Seventh Framework Programme*; 2) Un estudi observacional i descriptiu per identificar i descriure de manera exhaustiva les revistes que publiquen recerca original a Espanya i Llatinoamèrica en llengua castellana; 3) Un estudi observacional i descriptiu per identificar a través de la cerca manual i electrònica els ACAs publicats en revistes espanyoles de Fisioteràpia, així com per proveir les seves principals característiques i 4) El desenvolupament d'una base de dades per facilitar el disseny, gestió i anàlisi de resultats de projectes de cerca manual, així com l'enviament de referències dels ACAs identificats a CENTRAL, la base de dades mundial d'ACAs de la Col·laboració Cochrane.

1.2.4. Resultats

1) A través de l'enquesta entre agències europees que financen recerca biomèdica es va trobar que més de dos terços adoptaven mesures per prevenir o controlar el biaix de disseminació. No obstant això, menys d'un quart tenien coneixement de l'estatus de publicació de projectes finançats l'any 2005. A partir dels resultats globals d'aquesta enquesta i d'altres estudis duts a terme dins del projecte OPEN, es van desenvolupar recomanacions específiques per a aquestes agències, entre les quals destaquen requerir la difusió dels resultats de la recerca en totes les convocatòries ofertes, sol·licitar un pla de difusió dels projectes finançats i crear una base de

dades accessible al públic de totes les subvencions concedides i de la forma en què es van difondre els seus resultats.

2) Es van identificar 1 498 revistes biomèdiques que publiquen recerca original a Espanya i Llatinoamèrica en llengua castellana, la major part d'elles editades a Espanya, Mèxic i Argentina. A pesar de que més d'un terç es trobaven indexades en almenys una base de dades, només el 4,1% i 3,7% es trobaven indexades en MEDLINE i EMBASE, respectivament. Així mateix, 45 revistes (3,0%) tenien factor d'impacte l'any 2012. Poc més de la meitat d'aquestes revistes tenen pàgina web, que generalment permeten buscar continguts sense cost als usuaris.

3) Es van identificar 78 ACAs en 10 revistes de Fisioteràpia d'Espanya, cap de les quals es trobaven indexades en MEDLINE o EMBASE. La majoria d'aquests ACAs se centraven en aspectes relacionats amb el dolor d'esquena, Fibromiàlgia i Artrosis. Aproximadament dos terços d'aquests ACAs van presentar un alt risc de biaix.

4) S'ha desenvolupat la Base de Dades d'Assajos i Revistes Iberoamericans (BADERI). BADERI és una eina gratuïta gestionada des del Centre Cochrane Iberoamericà que permet el seguiment de diferents aspectes de projectes de cerca manual, incloent l'aportació de cada participant o equip investigador, les revistes en les quals s'ha fet cerca manual i els ACAs identificats amb les seves principals característiques. BADERI permet generar informes per analitzar els resultats de les activitats de cerca manual, així com arxius específicament dissenyats per a la seva exportació a CENTRAL. En l'actualitat, hi ha més de 6 000 ACAs a BADERI.

Finalment, a través dels estudis annexos 1) S'explica l'inici i importància de les activitats de cerca manual a Espanya i Llatinoamèrica desenvolupades des del Centre Cochrane Iberoamericà, 2) Es van identificar 235 ACAs en 16 revistes de Ginecologia i Obstetrícia d'Espanya, i 3) Es van identificar 144 ACAs en 21 revista de Dermatologia d'Espanya i Llatinoamèrica.

1.2.5. Conclusions

Encara que existeix consciència sobre el problema que suposa el biaix de disseminació, així com bones intencions per reduir-ho i controlar-ho, la majoria de les agències que financen recerca biomèdica a Europa no implementen estratègies rigoroses per verificar la disseminació dels ACAs que van ser finançats.

Hi ha un nombre significatiu de revistes biomèdiques que publiquen recerca original a Espanya i Amèrica Llatina. No obstant això, la majoria no té factor d'impacte o no estan indexades en bases de dades de la literatura, la qual cosa pot descoratjar als investigadors locals a l'hora de publicar el seu treball en aquestes revistes.

El nombre d'ACAs publicats en revistes espanyoles de Fisioteràpia és limitat. Aquests ACAs presenten una baixa qualitat metodològica. Donat que cap de les revistes espanyoles de Fisioteràpia està indexada en bases de dades bibliogràfiques, la seva identificació i posterior inclusió en CENTRAL contribueix a reduir el biaix de publicació en el desenvolupament i l'actualització de futures revisions sistemàtiques.

La base de dades BADERI s'ha convertit en una eina inavaluable per gestionar la identificació manual d'ACAs i per facilitar el seu enviament a CENTRAL per a la seva possible inclusió en revisions sistemàtiques i altres documents de síntesis.

1.3 Abstract

1.3.1. Background

Reporting bias in randomised clinical trials (RCTs) arises from a tendency among researchers to report and journals to publish results that are positive, statistically significant, or that coincide with the hypothesis of the researchers. The most common type of reporting bias is dissemination bias, defined as "the publication or non-publication of the results of research studies depending on the nature and/or direction of the results". Studies carried out in the last

five years show that dissemination bias is still a problem to be solved. Therefore, it is necessary to design and implement additional strategies to prevent and control dissemination bias.

1.3.2. Objectives

The main objective of this thesis project is to develop strategies to prevent and control the dissemination bias of RCTs.

1.3.3. Methods

Four studies with different methodologies have been carried out: 1) A survey among European agencies that fund biomedical research to explore their opinion and possible solutions about dissemination bias, as well as the development of recommendations to reduce the incidence and effect of dissemination bias. This study was carried out within the OPEN project, "To Overcome failure to Publish nEgative fiNdings," co-financed by the European Union under the Seventh Framework Programme; 2) An observational and descriptive study to identify and describe the journals that publish original research in Spain and Latin America in Spanish language; 3) An observational and descriptive study to identify, via hand and electronic searching, RCTs published in Spanish Physiotherapy journals, as well as to provide their main characteristics; and 4) The development of a database to facilitate the design, management and analysis of results of handsearching projects, as well as the submission of references of identified RCTs to CENTRAL, the Cochrane Collaboration global database of RCTs.

There were three additional supplemental studies. First, a report that explains, within the context of the development of the Cochrane Collaboration in Latin America, the early beginnings and progress of the handsearching of RCTs initiative in Spain and Latin America. Also, the results of two observational and descriptive studies for identifying RCTs published in Spanish Gynaecology and Obstetrics journals and in Spanish and Latin American Dermatology journals, respectively.

1.3.4. Results

1) Through the survey of European agencies that finance biomedical research, it was found that more than two thirds adopted measures to prevent or control the dissemination bias. However, less than a quarter were aware of the publication status of projects funded in 2005. Based on the overall results of this survey and of other studies carried out within the OPEN project, specific recommendations were developed for these agencies. The main ones include requiring the dissemination of research results in all calls for proposals, demanding a dissemination plan for all projects financed, and creating a publicly accessible database of all grants awarded and how their results were disseminated.

2) A total of 1498 biomedical journals that publish original research in Spain and Latin America in Spanish were identified, mostly from Spain, Mexico and Argentina. Despite the fact that more than a third were indexed in at least one database, only 4,1% and 3,7% were indexed in MEDLINE and EMBASE, respectively. Likewise, 45 journals (3,0%) had an impact factor in 2012. Just over half of these journals have a web page, which generally allow users to search for content at no cost.

3) A total of 78 RCTs were retrieved from ten Physiotherapy Spanish journals, none of which were indexed in MEDLINE or EMBASE. Most of the identified RCTs focused on aspects related to back pain, Fibromyalgia and Arthrosis. Approximately two thirds of these RCTs presented a high risk of bias.

4) BADERI (Database of Iberoamerican Clinical Trials and Journals, by its initials in Spanish) has been developed. BADERI is a free tool that allows the tracking of different aspects of handsearching projects, including the contribution of each participant or research team, the journals that have been handsearched, and the RCTs identified with their main characteristics. BADERI also allows generating reports to analyse the results of handsearching activities, as well

as files specifically designed for exporting references to CENTRAL. To date, there are over 6000 references to RCTs in BADERI.

Lastly, through the supplemental studies, 1) the early beginnings, scope and progress of handsearching activities coordinated by the Iberoamerican Cochrane Centre in Spain and Latin America are explained, 2) 230 RCTs were identified in 16 Gynaecology and Obstetrics journals from Spain, and 3) 144 RCTs were identified in 21 Dermatology journals from Spain and Latin America.

1.3.5. Conclusions

Although there is awareness of the issue of dissemination bias, as well as good intentions to reduce and control it, most funding agencies of biomedical research in Europe do not implement rigorous strategies to verify the dissemination of funded RCTs.

There is a significant number of biomedical journals that publish original research in Spain and Latin America. However, most of these journals do not have an impact factor or are not indexed in literature databases, which may discourage local researchers from publishing their work in these journals.

The number of RCTs published in Spanish Physiotherapy journals is limited. These RCTs present a low methodological quality. Given that none of the Spanish Physiotherapy journals handsearched are indexed in any of the major literature databases, the identification and subsequent inclusion in CENTRAL of these RCTs contributes to reducing dissemination bias in the development and update of future systematic reviews.

BADERI has become an invaluable tool for coordinating handsearching projects of RCTs, as well as for facilitating the submission of references to the identified RCTs to CENTRAL for their potential inclusion in systematic reviews and other documents of synthesis.

2. Introducción

2. Introducción

2.1. Los ensayos clínicos con distribución aleatoria

Los ensayos clínicos con distribución aleatoria (ECA) son la fuente más fidedigna y confiable de nuevos conocimientos científicos para evaluar la eficacia de intervenciones terapéuticas o de prevención en la investigación médica en humanos (1, 2). Se trata de estudios llevados a cabo con un diseño en el que participantes con condiciones basales homogéneas son adjudicados de manera prospectiva y aleatoria a uno de entre dos o más grupos a los que se les administran diferentes tratamientos activos, placebo y/o ningún tratamiento (3). Los tratamientos pueden incluir intervenciones de tipo farmacológico, quirúrgico, psicológico, educacional, informacional o terapias manuales, así como cambios en procesos o en el uso de aparatos o productos sanitarios (4-6). Su finalidad puede ser terapéutica, preventiva, rehabilitadora o paliativa. La aleatorización no se limita a la asignación de pacientes de manera individual (sin duda, la modalidad más frecuente de ECA), sino que puede incluir la aleatorización de grupos de pacientes (ECAs grupales o *cluster*). La aleatorización también se puede desarrollar de manera estratificada, en la que la población se agrupa de acuerdo a diferentes factores como edad, sexo, entre muchos otros. Asimismo, los participantes pueden recibir una única intervención a lo largo del estudio (ECA paralelos), o bien primero uno y luego la otra, asignadas en orden aleatorio (ECAs cruzados) o recibir una, dos o más intervenciones a la vez (ECAs factoriales).

La ventaja de los ECAs sobre otros tipos de estudio es que permiten eludir factores de confusión que puedan comprometer los resultados de la investigación acerca de la eficacia de las intervenciones. Por tanto, la validez interna de un ECA depende de que se haya llevado a cabo una distribución equitativa de cualquier determinante del resultado del estudio diferente de las intervenciones bajo investigación (1, 2, 5). Si la aleatorización de los participantes en un ECA se lleva a cabo de manera adecuada, dichos determinantes, independientemente de si son

conocidos *a priori* o no, serán distribuidos uniformemente entre los diferentes grupos de estudio.

Los ECAs se deben llevar a cabo siguiendo una metodología rigurosa que garantice la ausencia de sesgos, definidos como desviaciones sistemáticas en los resultados o en las inferencias derivados de un ECA (figura 1) (7, 8). Durante las fases iniciales del estudio, y con tal de prevenir los sesgos de selección de participantes, se requiere una adecuada generación de la secuencia aleatoria, con la cual asignar a los participantes reclutados para el estudio a los diferentes grupos de intervención. Esta secuencia debe ser oculta, para garantizar que no se pueda saber de antemano el grupo de intervención asignado. Durante el desarrollo del estudio, se requiere controlar los sesgos de realización y de detección a través del cegamiento a la intervención, en la medida de lo posible, de los participantes, investigadores y/o evaluadores de variables de interés. Asimismo, el sesgo de deserción se puede controlar a través de un análisis de resultados por intensión a tratar (4).

También es necesario garantizar la transparencia en el análisis de los resultados de los ECAs y permitir que los usuarios y la comunidad científica lleven a cabo una evaluación objetiva de los mismos. Se requieren por tanto medidas adicionales que incluyen el registro prospectivo del protocolo del ECA, la declaración de cualquier tipo de conflicto de interés por parte de los investigadores y el correcto y completo reporte de la metodología y los resultados de los ECAs independientemente de la dirección y magnitud de sus resultados.

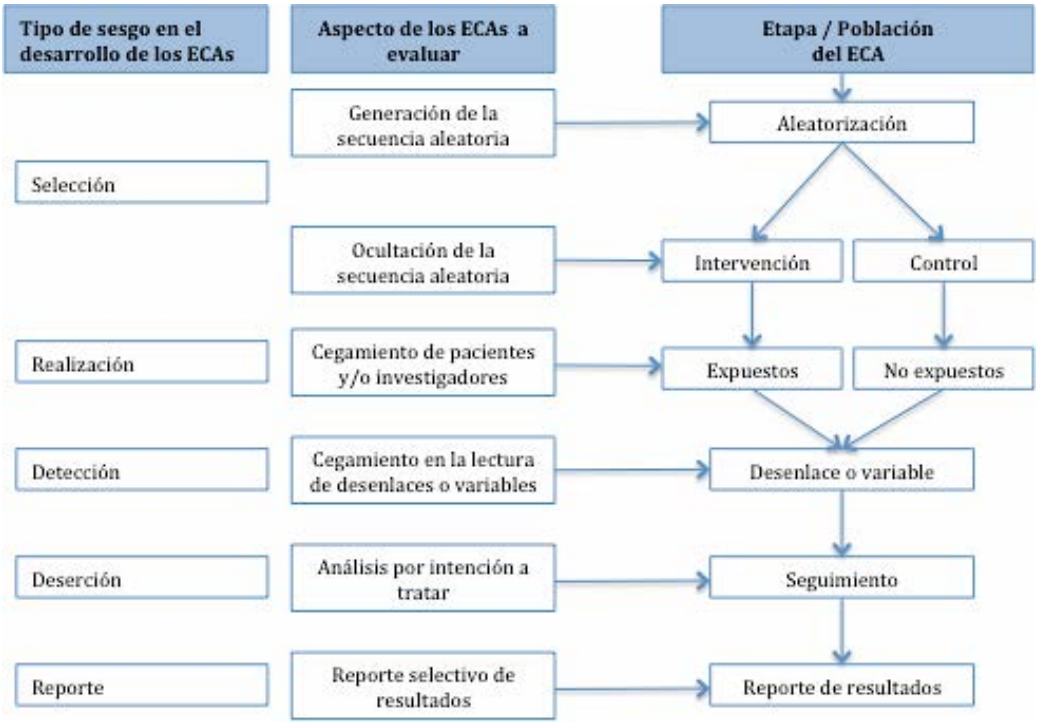

Figura 1: Tipos de sesgos durante el durante el desarrollo de los ECAs

2.1.1. Registro Prospectivo de los ensayos clínicos con distribución aleatoria

El registro prospectivo de los ECAs consiste en consignar en un registro de libre y gratuito acceso el protocolo del estudio antes de que se inicie el reclutamiento de pacientes o participantes (9). Entre los registros más reconocidos internacionalmente se encuentra *clinicaltrials.gov*, coordinado por el *National Institute of Health* en los Estados Unidos (10, 11) y la Plataforma de registros internacionales de ensayos clínicos (ICTRP por sus siglas en inglés) de la Organización Mundial de la Salud (12) (13). Esta medida busca promover la transparencia en el reporte y en el desarrollo de los ECAs. El registro prospectivo de ECAs permite que los investigadores y el público en general puedan comparar los aspectos pre-especificados en el protocolo con los resultados que se reportan subsecuentemente en las publicaciones asociadas al estudio. Asimismo, el registro prospectivo de ECAs es una medida útil para detectar estudios registrados y llevados a cabo pero que no se publican. Así, el *International Committee of Medical*

Journal Editors (ICMJE) requiere que todos los ECAs iniciados después del 1 de julio del 2005 sean registrados prospectivamente como requisito para su publicación.

No obstante este requerimiento, el registro prospectivo de ECAs es aun deficiente. El grupo de trabajo de nuestro centro, fundamental para el desarrollo de este trabajo de tesis, tiene amplia experiencia en la investigación del registro prospectivo de los ECAs y de su tasa de publicación, entre otros aspectos. Cabe destacar dos estudios a través de los cuales se llevó a cabo una descripción de 303 protocolos de ECAs sobre cáncer autorizados por la Agencia Española del Medicamento y de Productos Sanitarios entre 1999 y 2003 (14). Se determinó que la tasa de publicación de estos protocolos fue del 55% (168/303) (9). Otros proyectos han encontrado tendencias similares pero valoradas en el sentido contrario. Estudios transversales de ECAs publicados e indexados en MEDLINE o reportados en las revistas de medicina general de mayor factor de impacto reportaron tasas de registro prospectivo del 53% (523, 1122) (15) y del 28% (40/144) (16) respectivamente.

2.1.2. Declaración de conflictos de interés

El conflicto de interés se presenta cuando la opinión sobre un interés primario puede estar influenciada por un interés secundario, bien sea de carácter intelectual, económico, o de otra naturaleza, incluyendo la afiliación profesional o la fuente de financiación de los estudios (11, 17). Como evidencia de la influencia que pueden tener los conflictos de interés (reales o percibidos) existen diversos estudios que han relacionado su existencia con la dirección de los resultados de diferentes estudios. Por una parte, los estudios financiados por la industria farmacéutica tienen más probabilidades de reportar resultados positivos ($p<0,01$) o de superioridad para nuevos fármacos que los estudios financiados por instituciones gubernamentales (18-20). Asimismo, los estudios financiados por la industria farmacéutica son más propensos a reportar desenlaces de interés que favorecen a la intervención y tamaños de efecto más altos (21, 22).

2.1.3. Correcto reporte de los ensayos clínicos con distribución aleatoria

Con tal de garantizar que los ECA pueden ser evaluados, replicados y/o incorporados en la práctica clínica, es indispensable que los autores reporten con suficiente detalle los métodos y los resultados de los mismos (23). No obstante, diferentes estudios han encontrado que el reporte es a menudo insuficiente (24, 25). Esta problemática impulsó el desarrollo de la Declaración CONSORT, un listado de 25 ítems que deben ser considerados durante el reporte de los ECAs (*Consolidated Standards of Reporting Trials* por sus siglas en inglés) (26). Estos ítems incluyen información acerca de los participantes y las intervenciones evaluadas, los desenlaces de interés especificados *a priori*, los mecanismos para la generación y ocultación de la secuencia aleatoria, las medidas para asegurar el enmascaramiento de participantes e investigadores, los diferentes análisis estadísticos llevados a cabo en el estudio, los resultados para cada uno de los desenlaces preespecificados, los efectos adversos que se presentaron entre los participantes, las fuentes de financiación del estudio, los conflictos de interés de los investigadores y prueba del registro prospectivo del ECA (26) (Tabla 1).

Sección	Tema	Ítem CONSORT
Título y resumen	*Titulo*	Identificación como ECA
Título y resumen	*Resumen*	Resumen estructurado
Introducción	*Antecedentes*	Antecedentes científicos y justificación
Introducción	*Objetivos*	Objetivos específicos o hipótesis
Métodos	*Diseño del ensayo*	Descripción del diseño del ensayo
Métodos	*Diseño del ensayo*	Cambios en los métodos después de iniciar el ECA
Métodos	*Participantes*	Criterios de selección
Métodos	*Participantes*	Procedencia (centros o instituciones)
Métodos	*Intervenciones*	Intervenciones para cada grupo con suficientes detalles para permitir replicación
Métodos	*Resultados*	Desenlaces (variables de respuesta) primarios y secundarios definidos *a priori*
Métodos	*Resultados*	Cambios en los desenlaces después de iniciar el ECA
Métodos	*Tamaño de la muestra*	Cómo se determinó el tamaño de la muestra
Métodos	*Tamaño de la muestra*	Análisis intermedio y reglas de interrupción (si aplica)
Métodos	*Generación de la secuencia aleatoria*	Método para generar la secuencia aleatoria

Métodos	*Generación de la secuencia aleatoria*	Detalles de restricción de la secuencia aleatoria
Métodos	*Ocultación de la asignación aleatoria*	Métodos para ocultar la asignación de la secuencia hasta el inicio de las intervenciones
Métodos	*Implementación*	Quién generó la secuencia y realizó las asignaciones
Métodos	*Enmascaramiento*	Si se realizó, a quién se mantuvo cegado, y como.
Métodos	*Enmascaramiento*	Si es relevante, descripción de la similitud de las intervenciones
Métodos	*Análisis estadístico*	Métodos usados para comparar grupos en cuanto a desenlaces
Métodos	*Análisis estadístico*	Métodos de análisis adicionales (como de subgrupos)
Resultados	*Flujo de participantes*	Número de participantes en cada grupo
Resultados	*Flujo de participantes*	Pérdidas y exclusiones después de la aleatorización
Resultados	*Reclutamiento*	Fechas de reclutamiento y seguimiento
Resultados	*Reclutamiento*	Causas de finalización o interrupción del ensayo
Resultados	*Datos basales*	Tabla con características demográficas y basales para cada grupo
Resultados	*Números analizados*	Número de participantes incluidos en cada análisis
Resultados	*Resultados y estimación*	Resultados para cada grupo, tamaño del efecto y precisión
Resultados	*Resultados y estimación*	Para variables dicotómicas, tamaños del efecto absolutos y relativos
Resultados	*Análisis secundarios*	Resultados de análisis de subgrupos y análisis ajustados
Resultados	*Daños (perjuicios)*	Todos los daños o efectos no deseados
Discusión	*Limitaciones*	Limitaciones del estudio y posibles sesgos
Discusión	*Generalización*	Posibilidad de generalización
Discusión	*Interpretación*	Interpretación consistente con los resultados
Otra información	*Registro*	Número de registro y nombre del registro de ensayos
Otra información	*Protocolo*	Dónde puede accederse al protocolo del ECA
Otra información	*Financiación*	Fuentes de financiación y otras ayudas

Tabla 1: Ítems de la herramienta CONSORT (26)

CONSORT es, por tanto, una herramienta invaluable para garantizar el reporte completo, claro y transparente de los ECAs. Diferentes estudios han demostrado que la calidad y extensión del reporte de los ECAs ha mejorado a raíz de la adopción por parte de las revistas biomédicas de la Declaración CONSORT como requisito para publicación (27-30).

2.2. Las revisiones sistemáticas

Las revisiones sistemáticas son documentos que compilan toda la evidencia disponible sobre una pregunta específica de investigación. Se llevan a cabo siguiendo unos criterios explícitos

para evitar los posibles sesgos, incluyendo una búsqueda sistemática de la evidencia disponible seleccionada siguiendo unos criterios de elegibilidad preestablecidos, una evaluación de los sesgos de los estudios identificados y una presentación organizada de los resultados, con o sin metanálisis (4). Dada su exhaustividad y rigor metodológico, las revisiones sistemáticas facilitan una estimación de la confianza que se puede depositar en sus conclusiones tal y como propone el enfoque GRADE (*Grading of Recommendations Assessment, Development and Evaluation* por sus siglas en inglés) (31). No obstante, tener acceso a la información completa sobre todos los ECAs completados sobre un tema de interés es la base indispensable para la realización de una revisión sistemática (4).

Los autores de revisiones sistemáticas deben ser conscientes de las dificultades y limitaciones de los métodos actualmente existentes para identificar la literatura científica, lo cual amenaza la validez de los resultados de las mismas (4, 32). Los autores pueden tener serias dificultades identificando ECAs publicados en revisas no indexadas en las principales bases de datos de literatura científica, aquellos publicados en bases de datos a las que no tengan acceso, los publicados en literatura gris y en idiomas diferentes al inglés o aquellos que sencillamente no se hayan publicado (33-35). Estas dificultades surgen debido al sesgo de reporte de los ECAs en todas sus formas, aunque en especial al sesgo de publicación o de diseminación (36, 37).

2.3. Sesgo de reporte de los ensayos clínicos con distribución aleatoria

El sesgo en el reporte de los ECAs surge por una tendencia de los investigadores a reportar y las revistas a publicar resultados positivos, estadísticamente significativos, o que coincidan con la hipótesis de los investigadores (4, 37). El sesgo de reporte se origina a partir de la percepción, real o percibida, de que este tipo de resultados tendrán un mayor impacto en la comunidad científica y en la práctica clínica, con sus potenciales réditos académicos y económicos, así como una más alta de citación, con su potencial efecto en el factor de impacto de las revistas, entre otros factores. Existen diferentes tipos de sesgo de reporte de los ECAs (Tabla 2), incluyendo el

sesgo de publicación o diseminación, de retraso en la publicación de resultados, de localización, de lenguaje, de múltiples publicaciones y de citación y de reporte selectivo de desenlaces de interés (4, 36).

Tipo de sesgo de reporte	Definición
Sesgo de publicación o de diseminación	Publicación o no publicación de los resultados de estudios de investigación dependiendo de la naturaleza y/o dirección de los resultados
Sesgo de retraso en la publicación de resultados	Publicación acelerada o tardía de los resultados de los ECAs en función de la naturaleza y dirección de los resultados
Sesgo de localización	Publicación de resultados de ECAs en revistas con mayor o menos visibilidad en función de la naturaleza y dirección de los resultados
Sesgo de lenguaje	Publicación de resultados de ECAs en un idioma específico (en especial el inglés) en función de la naturaleza y dirección de los resultados
Sesgo de múltiples publicaciones y citación	Publicación de resultados de ECAs en múltiples artículos y a citación de dichos artículos en función de la naturaleza y dirección de los resultados
Sesgo de reporte selectivo de desenlaces de interés	Reporte de ciertos desenlaces pero no de otros en función de la naturaleza y dirección de los resultados de los mismos

Tabla 2: Tipos y definición de los sesgos de reporte (36)

2.3.1. El sesgo de publicación o de diseminación

El sesgo de publicación o de diseminación se define como "la publicación o no publicación de los resultados de estudios de investigación dependiendo de la naturaleza y/o dirección de los resultados." (4). No existe, sin embargo, consenso acerca de cómo definir cuándo un ECA se considera publicado, dado el amplio espectro de publicaciones que existen. Los autores de ECAs pueden diseminar los resultados en revistas revisadas por pares; en literatura gris, que incluye reportes de tesis y resúmenes o abstracts presentados a congresos o conferencias; o en registros o bases de datos de agencias regulatorias o de la industria. En cualquier caso, es indispensable que los datos diseminados a través de cualquiera de estos medios se puedan acceder para, por ejemplo, identificar información relevante para el desarrollo de revisiones sistemáticas y otros documentos de síntesis (36). Dada estas circunstancias, hay una reciente tendencia a reemplazar el término sesgo de publicación por el de sesgo de diseminación (37). Este último será el implementado en esta tesis.

El sesgo de diseminación tiene serias implicaciones. Al limitar la visibilidad y potencial impacto de los ECAs no publicados, desconoce la contribución de los pacientes que han participado en los ECAs, muchas veces invirtiendo tiempo y recursos económicos sin garantía de recibir un beneficio clínico. Los participantes también aceptan una importante carga asociada a las visitas e intervenciones, así como a la incertidumbre y de posibles riesgos asociados con la aleatorización a tratamientos o no tratamientos, al cegamiento o a la posibilidad de efectos adversos. El sesgo de diseminación también se traduce en desperdicio de recursos económicos, al desembocar en investigación redundante si las preguntas de investigación no publicadas son abordadas nuevamente por otros investigadores (38-40). Más aún, el sesgo de diseminación reduce la eficiencia del proceso investigativo al limitar el acceso a datos indispensables para el desarrollo y actualización de investigación secundaria (como las revisiones sistemáticas) y para la toma de decisiones en la asistencia sanitaria (41). Finalmente, y dado que se ha vinculado con intereses económicos y otros conflictos de interés (42), el sesgo de diseminación reduce la confianza de los pacientes y el público en general en la investigación clínica (37).

El sesgo de diseminación se puede determinar a través de la identificación de las publicaciones que se deberían haber generado en base a información obtenida a partir de las diferentes etapas del desarrollo de los ECAs, (34) (figura 2) que incluyen: 1) el inicio del ECA, en especial los protocolos sometidos a comités de ética o a comités de evaluación institucional, 2) el envío del protocolo del ECA para aprobación por parte de agencias regulatorias (si fuera necesario) o para su registro prospectivo en registros de libre acceso, 3) la diseminación preliminar de los resultados de los ECAs a través de resúmenes o abstracts presentados e conferencias o congresos y 4) el proceso de publicación de resultados en revistas revisadas por pares y otros medios.

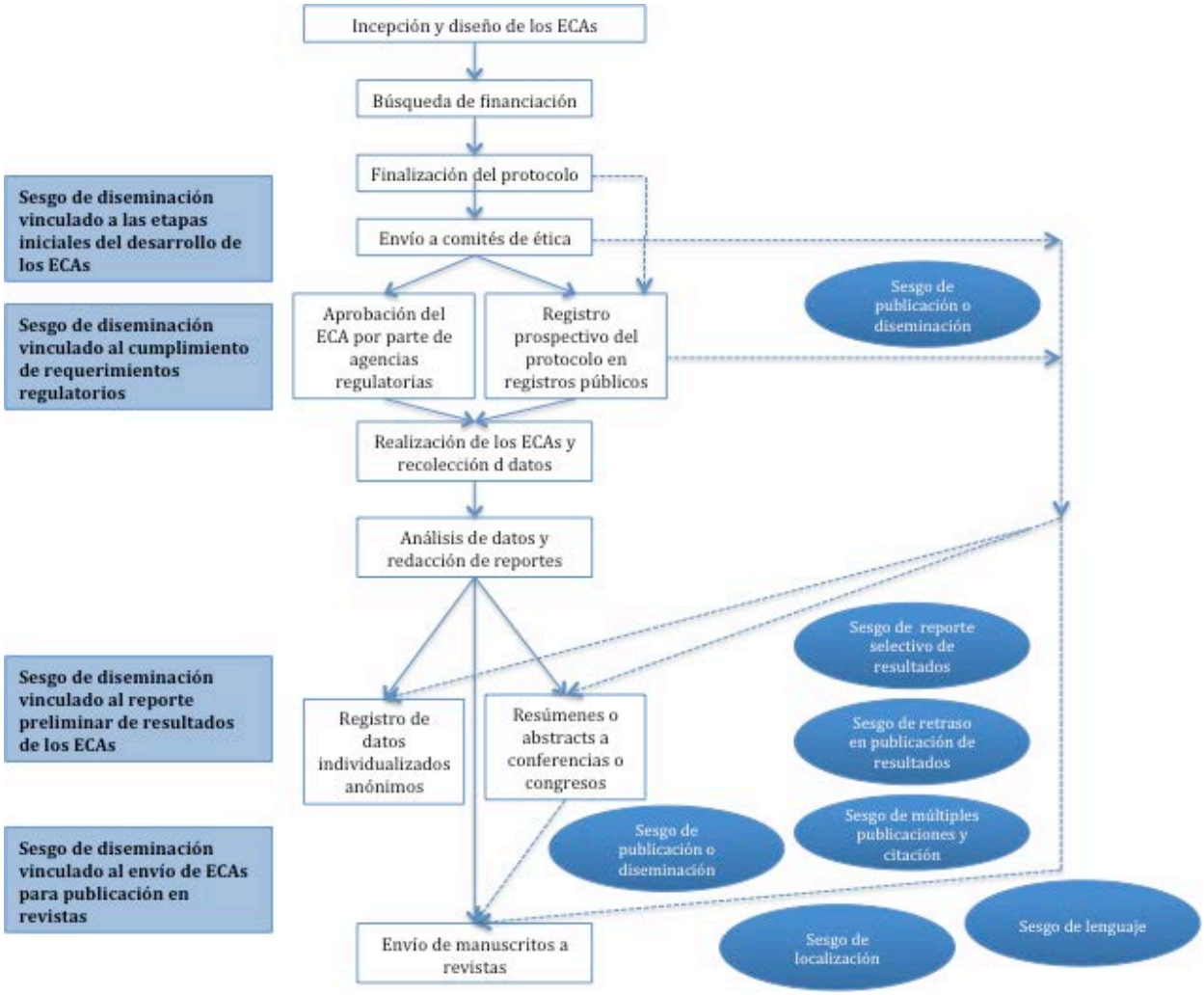

Figura 2: Etapas en el desarrollo de ECAs en el que se pueden presentar los diferentes tipos de sesgo de reporte(36, 43)

2.3.1.1. El sesgo de diseminación vinculado al inicio de los ensayos clínicos con distribución aleatoria

Una amplia variedad de estudios han investigado el sesgo de diseminación de ECAs en base a la información disponible a partir de los primeros pasos requeridos durante el desarrollo de un ECA, incluyendo la aprobación de comités de ética y de comités de evaluación institucional. Se ha reportado que la tasa de publicación de ECAs determinados a partir de estas etapas oscila entre el 60 y el 98% para estudios con resultados estadísticamente significativos y entre 20 y 85% para estudios con resultados no estadísticamente significativos (34), con un odds ratio

agrupado de 2,40 (1,18 a 4,88) favorable a la publicación de resultados estadísticamente significativos y de 2,78 (2,01 a 3,69) favorable a la publicación de resultados positivos (34).

2.3.1.1.1. Protocolos sometidos a comités de ética

A parte de los resultados reportados por Song et al, hay una revisión sistemática más reciente de estudios de cohortes que siguieron ECAs desde su aprobación por parte de comités de ética, sin límite de fecha hasta su publicación. Esta revisión identificó 17 publicaciones que reportaron intervalos de predicción de tasas de publicación que oscilaron entre el 22% y el 72%, con una proporción ponderada agrupada de 46% (95%CI 40,2% – 52,4%). Asimismo, reportaron que los estudios con resultados estadísticamente significativos, con resultados positivos o los financiados por agencias gubernamentales eran más propensos a ser publicados (44).

Dos estudios incluidos en esta revisión sistemática investigaron la tasa de publicación de 451 protocolos aprobados entre 1988 y 1998 por parte de un comité de ética en un hospital universitario en Suiza (45) y de 355 protocolos aprobados por la universidad de Friburgo en Alemania (46). La tasa de publicación de los ECAs analizados fue de 52% (233/451) y 57% (201/355), respectivamente. Estos estudios encontraron que los ECAs con un tamaño de muestra más grande, con colaboración internacional y multicéntricos tenían más posibilidades de publicarse.

2.3.1.1.2. Ensayos clínicos con distribución aleatoria discontinuados

A partir de la información identificada de los protocolos sometidos a comités de ética, se ha encontrado que los ECAs discontinuados tienen una alta probabilidad de no ser publicados. El estudio DISCO analizó 1 017 protocolos de ECAs aprobados por seis comités de ética en Suiza, Alemania y Canadá entre los años 2000 y 2003 (47). Luego de un seguimiento promedio de casi 12 años, se encontró que 38% de estos ECAs fueron discontinuados (253/1017). Los motivos para discontinuar los ECAs incluyeron las bajas tasas de reclutamiento, futilidad o inutilidad del estudio, efectos adversos entre los participantes, evidencia de beneficio evidente e inapelable en alguno de los brazos del ECA, dificultades administrativas, entre otros. Se estimó la tasa de

publicación de estos estudios y se encontró que los estudios discontinuados tienen posibilidades mucho más altas que aquellos que se terminan de no ser publicados (55,1% vs 33,6%; OR 3,19 (95%CI 2,29-4,43), p< 0,001).

Se han llevado a cabo subanálisis adicionales a partir de los datos recolectados en este estudio. En referencia a pacientes distribuidos de manera aleatoria en estudios que incluían procedimientos quirúrgicos, se encontró una tasa de publicación del 66% (208/314) que, aunque más alta que la del resto del estudio, es preocupante debido al alto riesgo al que se someten los participantes en este tipo de ECAs y a su alto costo económico (48). Similarmente, en ECAs discontinuados con pacientes en necesidad de cuidados críticos o en el departamento de urgencias, la tasa de publicación fue igualmente subóptima, de 58% (37/64) (49). Con respecto a ECAs que incluyeron poblaciones pediátricas, la tasa de publicación fue de 63% (54/86) (50).

2.3.1.2. El sesgo de diseminación vinculado al cumplimiento de requerimientos regulatorios

El sesgo de diseminación durante esta etapa se puede determinar a través de un seguimiento de las publicaciones que se deberían haber generado a partir de las solicitudes sometidas a agencias regulatorias y, más ampliamente, a partir de los protocolos registrados prospectivamente en registros de libre acceso.

2.3.1.2.1. Envío a agencias regulatorias

Diferentes estudios han cuantificado el sesgo de diseminación en solicitudes de aprobación para ECAs sometidos a autoridades reguladores en Suecia, Estados Unidos, Países Bajos y España. En general, estos estudios reportan que los estudios que obtuvieron resultados positivos tuvieron probabilidades más altas de ser publicados.

Melander *et al* siguió 42 ECAs controlados con placebo que estudiaban inhibidores selectivos de la recaptación de serotonina financiados por la industria farmacéutica y que se sometieron para aprobación a la Agencia Regulatoria de Medicamentos de Suecia. Se identificó una tasa de

publicación del 90% (38/42), generalmente a favor los ECAs con resultados que favorecieron el nuevo medicamento (42).

Por otra parte, dos estudios de cohortes obtuvieron las tasas de publicación de ECAs sometidos a la *Food and Drug Administration* (FDA por sus siglas en inglés) en los Estados Unidos para la aprobación de nuevos fármacos. El primero encontró que de 909 ECAs relacionados con 90 nuevos fármacos sometidos entre 1998 y 2000 a la FDA, 43% (394/909) fueron publicados. Los autores destacan que los ECAs con resultados estadísticamente significativos y con tamaños de muestra más elevados eran más propensos a ser publicados (51). El segundo estudio hizo un seguimiento de 164 ECAs de eficacia sometidos a la FDA para aprobación de nuevos entes moleculares, de los cuales 78% (128/164) fueron publicados. Destaca que los estudios que reportan resultados favorables para el desenlace de interés primario tuvieron más probabilidades de ser publicados (52).

Asimismo, se llevó a cabo un estudio de todos los ECAs con productos farmacéuticos sometidos para aprobación de los 28 comités de revisión institucional de los Países Bajos en 2007. De 574 ECAs que habían sido terminados, 58% fueron publicados (334/574). Los estudios multicéntricos e internacionales tuvieron más posibilidades de ser publicados, mientras que los que fueron discontinuados por algún motivo tuvieron menos posibilidades (53).

Con respecto a España, un estudio reciente llevado a cabo en nuestro centro determinó la tasa de publicación de 303 ECAs registrados en la Agencia Española del Medicamento y de Productos Sanitarios para la aprobación de fármacos oncológicos. Se encontró que 55% de estos ECAs fueron publicados (168/303); los ECAs llevados a cabo únicamente en España y los que reportaron resultados positivos tuvieron más posibilidades de ser publicados (9).

2.3.1.2.2. Registro prospectivo de los ensayos clínicos con distribución aleatoria

La gran mayoría de los estudios que han investigado el sesgo de diseminación en ECAs registrados de manera prospectiva en registros de libre acceso lo han hecho en base a los datos

existentes en *clinicaltrials.gov*. Una revisión sistemática de 2014 de estudios de cohortes que siguieron estudios desde su inclusión en registros prospectivos de libre acceso, sin límite de fecha, hasta su publicación, encontró 22 artículos que reportaron intervalos de predicción de tasas de publicación con una proporción ponderada agrupada del 54% (95%CI 42,0% - 65,9%) (44).

Estudios recientes no incluidos en esta revisión sistemática confirman sus resultados. Entre ECAs registrados prospectivamente por parte de centros académicos especializados en medicina en los Estados Unidos entre 2007 y 2010, se encontró que de 4 347 ECAs protocolos, el 66% fue publicado (2 892/4 347) (10). Con referencia a ECAs sobre cáncer de mama registrados en *clinicaltrials.gov* y con fecha de terminación anterior a julio del 2013, el 54% fueron publicados (159/297) (54). Entre ECAs sobre intervenciones quirúrgicas, de 314 registrados entre 2008 y 2009 y que fueron completados, 66% fueron publicados (208/314); los estudios financiados por la industria farmacéutica tuvieron menos probabilidades de ser publicados (48). Finalmente, un estudio que hizo un seguimiento de 352 ECAs de fase II y 74 de fase III de cáncer de mama avanzado, todos registrados en *clinicaltrials.gov* entre los años 2000 y 2012 reporta que tasas de publicación de resultados del 47% (165/352) para los primeros y de 58% (43/74) para los segundos. En general, se encontró que los estudios con resultados estadísticamente significativos tenían más probabilidades de ser publicados.

2.3.1.2.3. La revisión sistemática de Dwan 2008 y 2013 sobre el sesgo de diseminación

La revisión llevada a cabo por Dwan *et al* en el 2008 y actualizada en el 2013 ofrece una amplia perspectiva del sesgo de diseminación de ECAs con protocolos registrados prospectivamente en comités de ética, agencias regulatorias o sometidos para financiación por parte de agencias gubernamentales con carácter regulatorio. Los autores identificaron un total de 20 estudios de cohortes de protocolos de este tipo y encontraron que la tasa de publicación total osciló entre 21% y 93%, entre el 60% y el 98 para ECAs con resultados positivos y entre 19% y 85% para ECAs con resultados negativos (6, 32).

2.3.1.3. El sesgo de diseminación vinculado al reporte preliminar de los ensayos clínicos con distribución aleatoria a través de resúmenes o abstracts presentados a conferencias o congresos

La mayor parte de estudios que han analizado las tasas de publicación de resúmenes o abstracts presentados a conferencias o congresos en artículos de texto completo en revistas lo han hecho centrándose en especialidades médicas específicas. La revisión sistemática de Song et al identificó 30 estudios de cohortes que estudiaron el sesgo de diseminación en este tipo de documentos. Estos estudios reportaron tasas de publicación de entre 37% y 81% para resúmenes o abstracts con resultados estadísticamente significativos y de entre 22% y 70% para aquellos sin resultados estadísticamente significativos (34). Los odds ratios agrupados de publicación en texto completo fueron de 1,62 (1,34 a 1,96) favorable a la publicación de resultados estadísticamente significativos y de 1,70 (1,44 a 2,02) favorable a la publicación de resultados positivos (35).

Una revisión sistemática más reciente identificó reportes que evaluaron los motivos de autores de resúmenes o abstracts para no diseminar los resultados de los estudios en texto completo. Se identificaron 24 estudios con información acerca de la tasa de publicación de resultados, resultando en una proporción media ponderada de resúmenes o abstracts publicados de 55,9% (95%CI 54,8% - 56,9%) (55).

En referencia a resúmenes o abstracts presentados a conferencias de odontología, una revisión sistemática identificó 16 estudios que siguieron 10 365 resúmenes o abstracts presentados en 52 conferencias de esta especialidad. La proporción agrupada de publicación de ECAs en artículos de texto completo fue de 52% (95%CI 43,2% - 60,7%) (56).

Dos estudios recientes no incluidos en ninguna de estas revisiones sistemáticas dan una visión más amplia del problema. Uno de ellos hizo un seguimiento de 513 resúmenes o abstracts de ECAs presentados en las conferencias de la Asociación para la Investigación en Visión y Oftalmología de Estados Unidos de los años 2011 al 2004. Se encontró una tasa de publicación de 45% (230/513). Los autores que reportaron conflictos de interés eran más propensos a

publicar en texto completo (57). Un segundo estudio, que aunque no se centra en ECAs, es interesante al investigar resúmenes o abstracts presentados en las reuniones anuales del 2009 al 2014 de la *International Society for Medical Publication Professionals,* una asociación comprometida con "avanzar la profesión de la publicación médica a nivel global a través de una mayor transparencia e integridad en las publicaciones médicas, y en la implementación de mejores estándares prácticas". Este estudio reporta que solo cuatro de 164 resultaron en publicaciones de texto completo (58).

2.3.1.4. El sesgo de diseminación vinculado al envío de los ensayos clínicos con distribución aleatoria para su publicación en revistas

Las revistas biomédicas y sus políticas de publicación juegan un papel preponderante en determinar la publicación o no de manuscritos sobre ECAs. Tienen pues un efecto directo en el sesgo de diseminación aun después de que los autores hayan decidido publicar los resultados de sus estudios. La revisión sistemática de Song et al reporta que, en general, los ECAs sometidos para publicación que presentan resultados estadísticamente significativos y positivos tienen una mayor tendencia a ser publicados, con odds ratios agrupados de 1.15 (0,64 a 2,10) favorable a los primeros y de 1,06 (0,80 a 1,39) favorable a los segundos (35).

A pesar de estos resultados, estudios recientes sugieren que en la actualidad el sesgo de diseminación a nivel de publicación está menos relacionado con resultados positivos y más con la significancia estadística de los mismos. Por una parte, van Lent *et al* revisó las decisiones editoriales de 472 manuscritos de ECAs sometidos a publicación en el *British Medical Journal* y siete otras revistas de diferentes especialidades médicas. De estos manuscritos, el 61% (287/472) reportaban resultados positivos mientras que el restante 39% (185/472) reportaban resultados negativos. No se encontraron diferencias entre las tasas de publicación de ECAs con resultados positivos, que fue del 21% (60/287) y de ECAs con resultados negativos, que fue del 20% (38/185) (59).

Por otra parte, dos estudios que analizaron la distribución estadística de los valores p publicados en la literatura científica encontraron que dicha distribución no corresponden a lo que se esperaría de una muestra aleatoria de los mismos. En ECAs publicado en el año 2016 en las revistas de medicina general de mayor factor de impacto, se encontró una alta proporción de valores p<0,01, así como el doble de valores p<0,05 comparados con aquellos p>0,05 (60). Asimismo, otro estudio llevado a cabo en una muestra aleatoria de 1 000 artículos en psicología encontró una prevalencia desmedidamente alta de valores p que superaban el umbral de significancia (61).

2.3.1.5. Otras instancias donde se presenta el sesgo de diseminación

2.3.1.5.1. Investigación en animales

Los estudios de investigación pre-clínica, en particular aquellos *in vivo* con animales, son precursores que influencian e informan la agenda de la investigación clínica (62). A pesar de su importancia, hay evidencia limitada acerca del sesgo de diseminación en este tipo de estudios. Una encuesta llevada a cabo entre 454 investigadores afiliados con laboratorios de investigación en animales en los Países Bajos reporta que se estima que alrededor del 50% de los estudios llevados a cabo en estos laboratorios no se reportan (63). No obstante estos resultados, un estudio que recopiló e investigó la calidad metodológica de 512 revisiones sistemáticas de estudios en animales publicadas entre los años 2009 y 2013 encontró que 88% (448/512) no evaluaron el riesgo de sesgo de diseminación (62). Asimismo, dos recientes revisiones sistemáticas en investigación en animales que evaluaron el riesgo de sesgo de diseminación usando gráficos de embudo, métodos de recortar y llenar y el test de Egger, encontraron evidencia de estudios no financiados por la industria que no fueron publicados (64).

2.3.1.5.2. Ensayos clínicos de fase I

La mayoría de los estudios que han investigado el sesgo de diseminación se han enfocado en los ECAs fase II y III. Sin embargo, y al igual que los estudios de investigación pre-clínica, los ECAs de fase I tienen una influencia directa en la investigación que se lleva a cabo con pacientes en los

ECAs de eficacia. El estudio de van den Bogert *et al,* de todos los ECAs con productos farmacéuticos sometidos para aprobación de los 28 comités de revisión institucional de los Países Bajos en 2007, reporta que 35% de los ECAs fase I fueron publicados (41/119), una tasa significativamente menor a los ECAs fase II y III, del 60% y 73%, respectivamente (53).

2.3.1.5.3. Estudios de pruebas diagnósticas

En referencia a estudios de precisión diagnóstica, existe evidencia que confirma la existencia de sesgo de diseminación en este campo. Un estudio que hizo un seguimiento de 418 protocolos registrados en *clinicaltrials.gov* entre 2006 y 2010 que comparaban la precisión de una prueba diagnóstica contra un patrón estándar encontraron tasas de publicación de 54% (224/418), favoreciendo la publicación de estudios de más larga duración (65). Otro estudio que determinó la tasa de publicación de 250 resúmenes o abstracts presentados en conferencias sobre la precisión de pruebas diagnósticas en demencia encontró que 39% (97/250) fueron publicados en texto completo. Los estudios con resultados positivos, con un tamaño de muestra más alto o llevados a cabo en Europa o Norte América tenían más posibilidades de ser publicados (66).

2.3.1.5.4. Investigación cualitativa y de ciencias sociales y del comportamiento

Dado que el campo de metasíntesis de estudios cualitativos es relativamente nuevo, existe escasa evidencia sobre la prevalencia del sesgo de diseminación en estudios cualitativos (67). Un estudio de cohorte que siguió 224 estudios cualitativos presentados en una conferencia de sociología médica en 1998 y 1999 encontró tasas de publicación del 44% (99/224) (12). Adicionalmente, una encuesta entre 859 investigadores de este campo encontró que el 68% (585/859) habían llevado a cabo al menos un estudio que subsecuentemente no se había publicado (68). Por otra parte, una revisión sistemática en el campo de las ciencias sociales y del comportamiento sobre intervenciones breves para prevenir el consumo de alcohol entre jóvenes y adolescentes encontró evidencia, a través de la distribución del tamaño del efecto de los estudios incluidos, evidencia de sesgo de diseminación en este campo (69).

2.3.1.5.4. Sesgo de diseminación en revisiones sistemáticas

El sesgo de diseminación de revisiones sistemáticas se puede evaluar comparando la tasa de protocolos que resultan en publicaciones de revisiones terminadas. Un estudio retrospectivo de una cohorte de 411 protocolos de revisiones Cochrane publicados en los años 2000 y 2001 encontró que, de 372 protocolos relevantes de revisiones que fueron empezadas, el 81% fueron finalizadas y publicadas (301/372) (70). Adicionalmente, una encuesta entre 348 autores principales de revisiones sistemáticas publicadas en el año 2005 encontró que, en total, estos autores tenían 1 405 revisiones publicadas (mediana 2,0, rango 1-150) comparado con 199 sin publicar (mediana 2,0, rango 1-33) (71).

2.3.2. Otros tipos de sesgo de reporte de los ensayos clínicos con distribución aleatoria

2.3.2.1. Sesgo de retraso en la publicación de resultados

El sesgo de retraso en la publicación de resultados se ha definido como la publicación acelerada o tardía de los resultados de los ECAs en función de la naturaleza y dirección de los resultados (4). El sesgo de retraso en la publicación de resultados se puede valorar de manera similar a los estudios que valoran el sesgo de diseminación, siempre que exista una fecha de registro prospectivo o de envío a comités de ética y agencias regulatorias que se pueda comparar con la fecha de diseminación de resultados.

La revisión sistemática de Schmucker *et al* del 2014 de estudios de cohortes que siguieron ECAs desde su aprobación por parte de comités de ética, sin límite de fecha, hasta su publicación, encontró que los estudios con resultados positivos se publican en promedio entre 12 y 18 meses antes que aquellos con resultados negativos (44). En referencia a los ECAs registrados entre 1999 y 2003 en la Agencia Española del Medicamento y de Productos Sanitarios para la aprobación de fármacos oncológicos, los ECAs con resultados positivas tenían tendencia a publicarse más rápidamente (9). Con respecto a los resúmenes o abstracts de ECAs presentados en las conferencias de la Asociación para la Investigación en Visión y Oftalmología de los años 2011 al 2004, un tiempo de publicación más corto se asoció también con autores que

reportaron conflictos de interés (57). Tiempos de publicación más cortos también se han reportado para estudios de pruebas diagnósticos con estimadores más altos de sensibilidad y especificidad (Korevaar2016) y de ECAs que reportan desenlaces de interés primarios con resultados positivos y significativos (72).

2.3.2.2. Sesgo de localización

El sesgo de localización consiste en la publicación de resultados de ECAs en revistas con mayor o menos visibilidad en función de la naturaleza y dirección de los resultados (4)(Higgins2011). Así, se ha encontrado que los resultados de estudios considerados de menos interés tienen menos posibilidades de ser diseminados en revistas revisadas por pares (67)(Toews2017).

2.3.2.3. Sesgo de lenguaje

El sesgo de lenguaje, específicamente de la lengua inglesa, explica la tendencia de publicar resultados de ECAs en este idioma en función de la naturaleza y dirección de los resultados (4). Esto a su vez se traduce en una mayor visibilidad del ECA y una mayor probabilidad de ser incluido en revisiones sistemáticas y otros documentos de síntesis (67). Aunque sin analizar si los resultados eran positivos o estadísticamente significativos, un estudio encontró que la calidad metodológica y de reporte de resultados de los ECAs publicados sobre el asma entre 1987 y 1997 en revistas españolas fue más bajo que los de ECAs similares publicados en revistas anglosajonas en el mismo periodo de tiempo (73).

2.3.2.4. Sesgos de múltiples publicaciones y de citación

Estos dos sesgos se explican por la tendencia a diseminar los resultados de ECAs en múltiples publicaciones y a citar dichas publicaciones en función de la naturaleza y dirección de los resultados (4). Existe evidencia de que los ECAs con resultados positivos y estadísticamente significativos tienen más probabilidades de ser diseminados a través de más de un artículo en revistas revisadas por pares, lo que acarrea una consecuente posibilidad más alta de citación (42). Asimismo, los estudios publicados en revistas con mayor factor de impacto cuentan en general con publicaciones secundarias en otras revistas (74).

2.3.2.5. El reporte selectivo de desenlaces de interés

Un importante componente del sesgo de reporte de los ECAs se centra en el reporte selectivo de desenlaces de interés entre los estudios que acaban siendo publicados. El reporte selectivo de desenlaces de interés se define como el reporte de ciertos desenlaces pero no de otros en función de la naturaleza y dirección de los resultados (4). El reporte selectivo de desenlaces de interés resulta pues en efectos favorables a la intervención y en ECAs que se pueden clasificar como positivos o estadísticamente significativos (20). Los requerimiento por parte de la ICMJE de registrar prospectivamente los ECAs en registros de libre acceso persigue precisamente crear mecanismos que permitan comparar los desenlaces reportados en las publicaciones de resultados de ECAs con los preestablecidos en el protocolo.

Un revisión sistemática de publicaciones que cuantifican el sesgo de reporte selectivo de desenlaces identificó 27 estudios que reportan que un promedio de 31% de los ECAs presentan discrepancias entre los desenlaces de interés preestablecidos y los reportados en las publicaciones (75).

2.4. El efecto del sesgo de diseminación en las revisiones sistemáticas

El sesgo de diseminación se relaciona generalmente con resultados que favorecen la hipótesis del estudio. Por tanto, el sesgo de diseminación tiende a resultar en una sobreestimación de los efectos reportados en revisiones sistemáticas y en errores de tipo 1, cuando se detecta un efecto que en realidad no está presente (4, 32, 76). Por tanto, el sesgo de diseminación socava la validez de las revisiones sistemáticas y reduce la confianza en la evidencia proveniente de los ECAs (32).

2.4.1. Métodos para detectar el sesgo de diseminación en revisiones sistemáticas

El manual Cochrane de revisiones sistemáticas propone una serie de estrategias para detectar el sesgo de diseminación en revisiones sistemáticas. El más importante y comúnmente implementado es el gráfico de embudo, que ilustra la dispersión de las estimaciones de los efectos de la intervención, cuya precisión aumenta a medida que aumenta el tamaño de la muestra del estudio. Así, las estimaciones derivadas de estudios pequeños se dispersan en la base de la gráfica (la boca del embudo) mientras que las estimaciones derivadas de los estudios grandes se centran en la parte superior. Una apariencia asimétrica de esta gráfica confirmada por métodos estadísticos como las pruebas de Begg o de Egger pueden sugerir las presencia de sesgo de diseminación (4).

Alternativamente, el método de recortar y rellenar identifica y corrige la asimetría del gráfico de embudo. A través de este método, se "recortan" los estudios más pequeños del embudo y se pegan o "rellenan" para estimar el centro verdadero del embudo, reemplazando los estudios omitidos y sus contrapartes no identificadas. Finalmente, el método del cálculo del N a prueba de fallos permite evaluar la influencia del sesgo de diseminación en los resultados de los metanálisis. El N en este método representa los estudios con resultados negativos que se necesitarían para aumentar el valor de los valores p por encima de 0,05. Estos dos métodos son cada vez menos usados en favor del gráfico de embudo (62, 77).

2.4.2. Métodos para prevenir el sesgo de diseminación en revisiones sistemáticas

La Colaboración Cochrane propone, a través del Manual de Expectativas Metodológicas de las Revisiones de Intervención Cochrane (estándares MECIR, *Methodological Expectations of Cochrane Intervention Reviews* por sus iniciales en inglés), una serie de medidas destinadas a controlar el sesgo de diseminación. En general, estas medidas se pueden resumir bajo la premisa de incluir todos los ECAs potencialmente elegibles independientemente de su estado de publicación (78).

2.4.2.1. La búsqueda electrónica de ensayos clínicos con distribución aleatoria

La primera medida propuesta por los estándares MECIR es la de diseñar y ejecutar estrategias de búsqueda para diferentes bases de datos bibliográficas utilizando filtros de búsqueda y términos específicos para la pregunta de interés. Como mínimo, estas búsquedas se deben llevar a cabo en los registros especializados para cada grupo Cochrane (si existiera), en CENTRAL, la base de datos mundial de ECAs de la Colaboración Cochrane (*Central Register of Controlled Trials* por sus siglas en inglés) (79, 80), así como en MEDLINE y Embase. Además, se deben buscar bases de datos relevantes para el tema de interés, como CINAHL para temas de Enfermería o PsychINFO para intervenciones en Psicología, así como bases de datos regionales, como LILACS. Por otra parte, se recomienda buscar los registros prospectivos de ECAs *ClinicalTrials.gov* y la ICTRP. También se debe indagar la literatura gris, incluyendo los registros de tesis doctorales y los reportes de resúmenes o abstracts sometidos a congresos médicos. Finalmente, se recomienda revisar la bibliografía de estudios que se identifiquen como potencialmente incluibles en la revisión sistemática en desarrollo.

A pesar de la exhaustividad de esta lista de bases de datos y fuentes para identificar ECAs, las búsquedas electrónicas de literatura científica están limitadas por diferentes motivos. Por una parte, el termino ECA fue incluido en las bases de datos en la década de los noventa, por lo que los estudios publicados previamente pueden no estar bien clasificados. Por otra parte, existe evidencia que los términos de indexación disponibles no son siempre aplicados fielmente. Finalmente, los autores a menudo reportan de manera errónea la metodología de sus ECAs, imposibilitando su correcta indexación (81-83).

2.4.2.2. La búsqueda manual de ensayos clínicos con distribución aleatoria

La búsqueda manual de ECAs se define como la evaluación progresiva, página por página, de todas las secciones de una revista determinada, evaluando cada artículo para poder calificarse o no como un ECA (4, 84). Así, la implementación de una estrategia de búsqueda manual de ECAs permite solventar las limitaciones de las búsquedas electrónicas, en especial las relacionadas a

la indexación deficiente de los estudios. Asimismo, la búsqueda manual facilita la detección de estudios publicados en revistas no indexadas en bases de datos o publicadas en diferentes idiomas (4, 82). Por tanto, la búsqueda manual es un complemento indispensable para las búsquedas electrónicas durante el desarrollo de revisiones sistemáticas (85).

El Centro Cochrane Iberoamericano ha llevado a cabo durante las últimas dos décadas diferentes estudios de búsqueda manual de ECAs, descritos en la Tabla 3. Además de los estudios en esta tabla, en la actualidad se están realizando proyectos de búsqueda manual de ECAs publicados en revistas de Oncología, Neurología, Neumología, Salud Pública, pediatría, anestesiología y medicina familiar.

Revista o especialidad médica	País	ECAs encontrados	Comparación de búsqueda manual y electrónica
Medicina Interna y General (1971-1995)(85)	España	215	Cuatro revistas indexadas en PubMed. No se encontraron ECAs de manera electrónica que no se habían encontrado de manera manual. La búsqueda electrónica identificó solo 146 de los 215 ECAs identificado por búsqueda manual.
Dermatología (Actas Dermatológicas)(86)	España	24	No se llevó a cabo
Farmacología (*Methods and Findings*)(87)	España	189	No se encontraron ECAs de manera electrónica que no se habían encontrado de manera manual. La búsqueda electrónica identificó solo 121 de los 189 ECAs identificado por búsqueda manual.
Anestesiología (Revista Española de Anestesiología)(88)	España	640	No se encontraron ECAs de manera electrónica que no se habían encontrado de manera manual. La búsqueda electrónica identificó solo 285 de los 640 ECAs identificado por búsqueda manual.
Seguridad del Paciente(89)	Todos los países	131	No se encontraron ECAs de manera electrónica que no se habían encontrado de manera manual. La búsqueda electrónica identificó solo 89 de los 131 ECAs identificado por búsqueda manual.
Odontología (sometido a publicación)	España, Latinoamérica	244	No se llevó a cabo

Oftalmología (sometido a publicación)	España	105	Solo una revista indexada en PubMed. Se encontraron 3 ECAs no encontrados por búqueda manual pero no se econtraron 12 ECAs identificados en búsqueda manual
Traumatología (sometido a publicación)	España, Latinoamérica	57	No se llevó a cabo
Geriatría y gerontología (en curso)	España, Latinoamérica	78	Solo una revista indexada en PubMed. No se encontraron ECAs de manera electrónica que no se habían encontrado de manera manual

Tabla 3: Sumario de actividades de búsqueda manual coordinadas desde el Centro Cochrane Iberoamericano

2.4.2.3. Comparación de las búsquedas manuales y las búsquedas electrónicas

Estudios que han comparado la proporción de estudios identificados a través de la búsqueda manual con los identificados adoptando estrategias de búsqueda electrónica en revistas de Medicina General e Interna (85), Oftalmología (82) y Seguridad del Paciente (89) confirmaron la superioridad del método de búsqueda manual. En general, se ha encontrado que la sensibilidad y especificidad de las búsquedas electrónicas es del 77% y 50% respectivamente, mientras que para la búsqueda manual es prácticamente del 100% en ambos casos.

2.5. Justificación de la tesis

Como se ha explicado hasta este punto, el sesgo de diseminación en los ECAs:

1. Se relaciona con serias implicaciones éticas,
2. reduce la confianza de los pacientes y el público en general en la investigación clínica,
3. afecta el proceso de toma de decisiones en asistencia sanitaria,
4. disminuye la eficiencia del proceso investigativo y
5. genera un uso inadecuado de los recursos económicos.

Estudios llevados a cabo en los últimos cinco años demuestran que el sesgo de diseminación continúa ocurriendo (9, 10, 44, 48, 53, 54, 56-58, 60, 61). Por tanto, se hace necesario el diseño y la implementación de estrategias adicionales para prevenir su aparición y controlar sus consecuencias.

Este trabajo de tesis pretende contribuir a este objetivo aportando conocimiento en diferentes ámbitos relacionados con el sesgo de diseminación. Primero, se buscó obtener la opinión de los organismos europeos de financiación de investigación biomédica sobre el sesgo de diseminación y sus procedimientos en vigor para reducirlo o prevenirlo. Los resultados de este estudio se combinaron con otros obtenidos a través del proyecto OPEN, *To Overcome failure to Publish nEgative fiNdings*, entre instituciones de investigación, registros prospectivos de ECAs, autores de artículos de ECAs, revistas biomédicas, agencias reguladoras, comités de ética y compañías farmacéuticas, para formular recomendaciones que podrían ser implementadas a nivel europeo para reducir el sesgo de diseminación.

En segundo lugar, se buscó impulsar la iniciativa del Centro Cochrane Iberoamericano de búsqueda manual de ECAs publicados en revistas de España y Latinoamérica. El primer paso lógico para llevar a cabo esta iniciativa es la identificación de todas las revistas biomédicas en lengua castellana editadas en España y Latinoamérica que publican investigación original. A través del segundo estudio de esta tesis se buscó alcanzar precisamente este objetivo, proporcionando además un análisis descriptivo de las principales características de estas publicaciones y, cuando los hubo, los sitios web donde se puede acceder a sus contenidos.

La identificación de revistas biomédicas en lengua castellana sirvió de punto de partida para diseñar un proyecto de búsqueda manual en Fisioterapia, un proyecto de crucial importancia dado que ninguna de las revistas españolas de Fisioterapia están indexada en las principales bases de datos de literatura científica. Por tanto, los ECAs publicados en estas revistas difícilmente se podían identificar para su potencial inclusión en revisiones sistemáticas y otros documentos de síntesis. El tercer estudio de esta tesis tuvo como objetivo identificar a través de búsqueda manual todos los ECAs publicados en revistas de Fisioterapia en España. Estas referencias serían sometidas a CENTRAL, la base de datos mundial de ECAs de la Colaboración

Cochrane (79, 80) para su posible inclusión en revisiones sistemáticas y otros documentos de síntesis.

Finalmente, se buscó desarrollar una plataforma basada en Internet desde la cual sistematizar y monitorizar proyectos de búsqueda manual. Se buscó crear una herramienta que sirviera como repositorio de las revistas que se han buscado manualmente y de los ECAs que se han identificado. Además, se esta herramienta debería facilitara la coordinación de las actividades de varios equipos de búsqueda manual localizados en diferentes países e instituciones así como acelerar el envío de los ECAs identificados a CENTRAL para su posible inclusión en revisiones sistemáticas y otros documentos de síntesis.

3. Objetivos

3. Objetivos

3.1. Objetivos generales

1. Desarrollar estrategias para prevenir y controlar el sesgo de diseminación de ensayos clínicos con distribución aleatoria (ECA)

3.2. Objetivos específicos

1. Describir las políticas actualmente existentes para prevenir y controlar el sesgo de diseminación por parte de organismos de financiación de investigación biomédica europeos.

2. Conocer la opinión sobre el impacto del sesgo de diseminación y las medidas que se podrían implementar para prevenirlo y controlarlo por parte de organismos de financiación de investigación biomédica europeos para formular recomendaciones orientadas a limitar la incidencia y el efecto del sesgo de publicación.

3. Identificar revistas científicas a través de las cuales los resultados de ECAs son divulgados y evaluar su accesibilidad.

4. Identificar el mayor número posible de ECAs publicados en revistas españolas de Fisioterapia, describiendo sus características y aspectos metodológicos para detectar posibles sesgos.

5. Implementar una plataforma electrónica para coordinar las actividades de búsqueda manual de ECAs y que facilite su identificación para su inclusión en revisiones sistemáticas y otros documentos de síntesis.

4. Métodos

4. Métodos

Esta tesis se presenta como compendio de publicaciones originales. Los métodos corresponden al diseño de cada una de las publicaciones de esta tesis.

4.1. Métodos del primer estudio

El objetivo del primer estudio fue describir las políticas actualmente existentes para prevenir y controlar el sesgo de diseminación por parte de organismos de financiación de investigación biomédica europeos así como formular recomendaciones orientadas a limitar la incidencia y el efecto del sesgo de diseminación. Se realizó una encuesta organismos de financiación de investigación biomédica 34 países europeos, incluyendo a los 28 miembros de la Unión Europea (UE), países candidatos (Islandia, Macedonia, Montenegro y Turquía), Noruega y Suiza.

Esta investigación fue parte del Proyecto OPEN: *Overcoming Failure in the Publication of Negative Findings*. Este proyecto fue una iniciativa de 24 meses cofinanciada por la Unión Europea a través del *Seventh Framework Programme*, cuyo objetivo principal era identificar las actuales evidencias disponibles sobre el sesgo de publicación en Europa (90). Un total de once instituciones de seis países participaron en el proyecto, bajo la dirección del Centro Cochrane Alemán, así como un consejo asesor de expertos mundiales en el campo del sesgo de publicación y la presentación de informes de los resultados de la investigación. El proyecto OPEN se centró en la investigación de las políticas y procedimientos seguidos por agencias de financiamiento, instituciones de investigación, registros de pruebas, autores e investigadores, revistas biomédicas, agencias reguladoras, comités de ética y compañías farmacéuticas.

4.1.1. Identificación de los organismos de financiación elegibles

Los organismos de financiación elegibles incluían agencias públicas, privadas o mixtas que apoyaban la investigación biomédica en los países antes mencionados. Se incluyeron agencias

que operaban a nivel estatal o internacional, excluyendo las que operaban sólo a nivel local o regional (por ejemplo, ciudades, provincias o regiones).

Con el fin de identificar las agencias elegibles, se intentó localizar directorios completos de agencias de financiamiento en toda Europa, similares a los disponibles en los Estados Unidos (91). Sin embargo, como tal lista no estaba disponible, se buscó en los sitios web de organizaciones que proporcionaban información sobre cómo financiar diferentes tipos de proyectos, así como los de agencias europeas dedicadas a apoyar a investigadores, bibliotecas locales y otras organizaciones. También se contactó con la *Europe Direct Office*, que forma parte del Departamento de Comunicaciones de la Unión Europea. También se llevaron a cabo búsquedas exhaustivas en los sitios web de los Ministerios de Salud, Educación y/o Investigación de cada país; Instituciones europeas, como el Espacio Europeo de Investigación, CORDIS (Servicio de Información Comunitario sobre Investigación y Desarrollo), ALLEA (*All European Academies* según sus siglas en inglés), EURAXESS y el Centro Europeo de Fundaciones; y universidades y otros centros que regularmente reciben fondos para la investigación científica.

4.1.2. Encuesta electrónica

Se creó una encuesta electrónica con 29 preguntas cuantitativas y cualitativas cerradas y abiertas. La validez del diseño de la encuesta fue evaluada por parte de seis miembros del Centro Cochrane Iberoamericano y por otros socios del proyecto OPEN. La encuesta fue y administrada entre septiembre de 2012 y enero de 2013 utilizando la plataforma en línea *Surveymonkey.com*.

4.1.3. Contacto con las agencias elegibles

Para cada agencia elegible, se identificó personal que pudiera tendría acceso a los datos necesarios para responder a la encuesta. Se obtuvo esta información revisando sitios web y

otras fuentes, con especial énfasis en secciones como las de personal, de descripción de los departamentos que forman cada agencia, "quiénes somos" y "contacto". La información sobre cómo y dónde completar la encuesta fue enviada por correo electrónico con una carta personalizada (en inglés) en membrete institucional

4.1.4 Análisis estadístico

Se realizaron análisis descriptivos utilizando la versión SPSS 17,0 (SPSS, Inc., Chicago, IL, USA).

4.1.5. Desarrollo de recomendaciones

Se utilizaron los resultados de esta encuesta, así como los resultados de los demás paquetes de trabajo del Proyecto OPEN, para redactar una serie de recomendaciones generales y específicas para reducir el sesgo de diseminación. Cada socio OPEN desarrolló una serie de borradores de medidas que inicialmente se discutieron con el consorcio en su conjunto. Estos proyectos de recomendaciones fueron presentados y discutidos con un grupo de expertos y profesionales interesados de diferentes países e instituciones europeas durante un taller celebrado en Friburgo, Alemania, en 2013. Las recomendaciones se clasificaron como "recomendaciones sólidas" o simplemente "recomendaciones" basadas en criterios adaptados del enfoque GRADE (92). Estos criterios fueron: confianza en la efectividad de la medida propuesta, balance de beneficios y riesgos, posible oposición a las recomendaciones, uso de recursos, implementabilidad y factibilidad.

4.1.6. Conflictos de interés y fuentes de financiación

Una de las autoras de este estudio, Elizabeth Wager, imparte clases sobre publicación de artículos científicos, provee servicios de consultoría y ha trabajado para diferentes universidades. Ningún otro autor tenía conflictos de interés. Este estudio fue financiado

parcialmente a través del *European Union Seventh Framework Programme* (FP7 - HEALTH.2011.4.1 - 2), contrato número 285453.

4.2. Métodos del segundo estudio

El objetivo del segundo estudio fue identificar revistas científicas a través de las cuales los resultados de ECAs son divulgados, así como llevar a cabo una apreciación de su accesibilidad. Para ello se llevó a cabo un estudio descriptivo en los 19 países que forman parte de la Red Cochrane Iberoamericana y que tienen como idioma oficial el español. Estos países son Argentina, Bolivia, Chile, Colombia, Costa Rica, Cuba, Ecuador, El Salvador, España, Guatemala, Honduras, México, Nicaragua, Panamá, Paraguay, Perú, República Dominicana, Uruguay y Venezuela. A pesar de que Andorra y Portugal también son parte de la Red Cochrane Iberoamericana, fueron excluidos porque el español no es su idioma oficial.

4.2.1. Identificación de las revistas

Se realizó una búsqueda secuencial en PubMed, LILACS, SciELO, Periódica y Latindex, con el objetivo de identificar todas las revistas biomédicas publicadas en español en los países mencionados. Para ser elegibles, las revistas tuvieron que ser periódicas y publicar trabajos originales de investigación clínica. Se excluyeron las revistas de salud mental y enfermería, que forman parte de proyectos independientes. El país de origen de las revistas fue definido como aquel donde se encontraba la editorial, editor o entidad u organización responsable de la publicación. Una vez completada esta búsqueda, el siguiente paso fue determinar la elegibilidad de cada revista y, si procedía, recopilar toda la información de interés.

4.2.2. Envío a miembros de la Red Cochrane Iberoamericana

Los resultados de esta búsqueda fueron posteriormente enviados a colaboradores en cada país, quienes en general eran miembros activos del Red Cochrane Iberoamericana. Los colaboradores recibieron indicaciones claras en las que se les pedía comprobar que las revistas identificadas para sus países correspondientes y los datos asociados con ellas fuesen exactos y completos, así como actualizar y/o complementar los resultados si fuera necesario. Para lograr este objetivo, estos colaboradores revisaron catálogos nacionales, colecciones de bibliotecas y otras fuentes en las que se encontraron publicaciones que cumplían con los criterios de elegibilidad.

4.2.3. Análisis

Una vez que se verificaron todos los resultados, se realizó un análisis descriptivo utilizando SPSS versión 17.0 (SPSS, Inc., Chicago, IL, EE.UU.). Las variables se expresaron como media (desviación estándar) o mediana (rango inter cuartil). Los valores categóricos se expresaron como porcentajes.

4.2.4. Aspectos éticos

Dado que este estudio no incluyó pacientes ni información confidencial, no se necesitó aprobación de los comités de ética en ninguna de las instituciones participantes.

4.2.5. Conflictos de interés y fuentes de financiación

Los autores no tuvieron ningún conflicto de interés. Este estudio fue financiado parcialmente a través de la beca PI 99/1333 del Instituto de Salud Carlos III.

4.3. Métodos del tercer estudio

A través del tercer estudio se buscó identificar el mayor número posible de ECAs publicados en revistas españolas de Fisioterapia, describiendo sus características y aspectos metodológicos

para detectar posibles sesgos. Se realizó un estudio observacional descriptivo de dos partes: identificación de revistas de Fisioterapia publicadas en España y búsqueda manual de ECAs publicados con un análisis descriptivo y de riesgo de sesgo correspondiente de los estudios identificados.

4.3.1. Identificación de revistas

El primer paso de este estudio consistió en seleccionar las revistas que debían ser búsquedas de manera manual. Los criterios de elegibilidad incluyeron revistas de Fisioterapia publicadas en España que difundían la investigación original. Las revistas fueron identificadas a partir del estudio dos de esta tesis, que buscó en PubMed (MEDLINE), el Índice Médico Español (IME), el Catálogo Nacional de Periódicos en Ciencias de la Salud en Español C-17 (editado por el Centro de Información y Documentación Científica (CINDOC)), Latindex, Periódica, LILACS y SciELO. Se excluyeron las revistas que no publicaban la investigación original y que se enfocaban en difundir contenidos educativos, promocionales o comerciales.

4.3.2. Identificación de ensayos clínicos controlados

La búsqueda manual de las revistas identificadas se llevó a cabo siguiendo las directrices proporcionadas por la Colaboración Cochrane. Estas recomiendan que cada artículo publicado en las revistas debe ser revisado cuidadosamente, incluyendo no sólo artículos originales, sino también otros tipos de estudios, cartas al editor, resúmenes y abstracts presentados a congresos o conferencias. Además, se planificó una búsqueda electrónica en PubMed (MEDLINE) con el fin de identificar ECAs publicados en las revistas elegibles de este estudio y comparar los resultados con los de la búsqueda manual.

4.3.3. Criterios de inclusión y exclusión

Con el fin de ser considerado un ECA, y en línea con los criterios propuestos por la Colaboración Cochrane, un estudio debía 1) Comparar tratamientos en humanos; 2) Ser prospectivo: las intervenciones debían haber sido planificadas antes de que el estudio hubiera tenido lugar 3) Comparar dos o más tratamientos o intervenciones de fisioterapia, uno de los cuales podía ser un grupo de control sin tratamiento y 4) Tener un método aleatorio o semialeatorio de asignación al tratamiento. Se excluyeron artículos que eran referencias o traducciones de trabajos publicado en otras revistas. La búsqueda manual se llevó a cabo individualmente. Dos autores verificaron que todos los ECAs potenciales identificados eran realmente elegibles. Las discrepancias se resolvieron por consenso o consultando a un tercer autor.

4.3.4. Extracción de datos

Se desarrolló un libro de registro de recolección de datos que incluía todos los resultados de interés. Se realizó una evaluación del riesgo de sesgo (alto/medio/bajo) de los ECAs identificados, utilizando la herramienta proporcionada por la Colaboración Cochrane para ese propósito (4). Además, se registró si los autores se adhirieron a la herramienta CONSORT para intervenciones no farmacológicas (herramienta CONSORT-NPT) (93) al informar los resultados de sus proyectos de investigación.

4.3.5. Análisis

Se realizó un análisis descriptivo de los resultados de interés utilizando SPSS versión 17.0 (SPSS, Inc., Chicago, IL, USA).

4.3.6. Conflictos de interés y fuentes de financiación

Los autores no tuvieron ningún conflicto de interés para declarar. Este estudio no recibió ninguna financiación.

4.4. Métodos del cuarto estudio

El objetivo final de este trabajo de tesis fue implementar una plataforma electrónica para coordinar las actividades de búsqueda manual de ECAs y que facilite su identificación para su inclusión en revisiones sistemáticas y otros documentos de síntesis. Se llevó a cabo, pues, un estudio basado en el desarrollo de bases de datos y análisis descriptivo de ECAs.

4.4.1. Desarrollo de la base de datos

El proceso de desarrollo de la base de datos comenzó en septiembre de 2013. A través de una lluvia de ideas y discusión entre el personal y las partes interesadas involucradas en proyectos de búsqueda manual, se identificaron necesidades que debían resolverse para asegurar la viabilidad de los proyectos de búsqueda manual. Se contrató una empresa de tecnología de la información (TI) para crear una página web que alojaría la base de datos propuesta. El proceso de desarrollo duró 18 meses, hasta que la base de datos estuvo lista para pilotaje entre diferentes equipos de búsqueda manual, en marzo de 2015.

4.4.1.1. Pilotaje de la base de datos

Se reclutaron tres equipos de búsqueda manual para pilotar la base de datos. Estos equipos llevaban a cabo actividades de búsqueda manual de Ginecología, Oftalmología, Ortopedia y Traumatología. Se les pidió que introdujeran las referencias de ECAs identificados cono parte de sus actividades en la base de datos, incluyendo los autores del estudio; revista de publicación; volumen, año y número de publicación; entre otros datos.

4.4.1.2. Actualización de la base de datos

Basándose en los comentarios recibidos por parte personal que pilotó la base de datos, fueron incorporadas nuevas características y se modificaron las ya existentes, una vez más mediante

discusiones reiterativas entre las partes interesadas y el personal de la Red Cochrane Iberoamericana.

4.4.2. Inauguración de la base de datos y actividades iniciales

Una vez aprobada la versión final de la base de datos, se procedió a proporcionar capacitación al personal involucrado en proyectos de búsqueda manual. Las actividades de búsqueda manual se llevaron a cabo siguiendo las directrices proporcionadas por la Colaboración Cochrane (4, 84).

4.4.2.1. Criterios de elegibilidad

Se incluyeron ECAs, independientemente de si fueron publicados como artículos de texto completo o simplemente como resúmenes o abstracts presentados a congresos o conferencias. Se excluyeron los artículos que eran traducciones de estudios publicados en otros idiomas con el fin de evitar duplicados una vez que estas referencias fueran enviadas a CENTRAL.

4.4.2.2. Extracción de datos

Para cada título de revista incluido en BADERI, se registró la siguiente información: ISSN, país de origen, especialidad médica y años de publicación. La base de datos permite hasta dos especialidades médicas por revista. Cada ECA identificado se introdujo en la base de datos y se archivó en la correspondiente revista. La siguiente información fue registrada para cada ECA identificado: Título en español e inglés (si estaba disponible); autor/es, en un formato compatible con los requisitos de CENTRAL; año, volumen, número de publicación y páginas de publicación (cuando correspondía); y método de asignación aleatoria.

4.4.3. Análisis de datos

Se utilizaron estadísticas descriptivas para analizar el progreso de la implementación de la base de datos para diferentes proyectos de búsqueda manual. Este análisis se realizó utilizando informes generados por la base de datos, que fueron exportados en formato Excel, versión 2010, Microsoft Office, Redmond, WA, Estados Unidos. Además, todas las referencias introducidas en

BADERI pueden ser exportadas en formato ProCite y enviadas a CENTRAL para su posible inclusión en revisiones sistemáticas y otros documentos de síntesis (79, 80).

4.4.4. Conflictos de interés y fuentes de financiación

Los autores no tuvieron ningún conflicto de interés para declarar. Este estudio fue financiado parcialmente a través del *Discretionary Fund* del año 2014 de la Colaboración Cochrane.

5. Resultados

5. Resultados

Esta tesis se presenta como compendio de publicaciones originales. Los resultados corresponden a los resultados reportados en cada una de las publicaciones de esta tesis, que son:

1. *H. Pardo-Hernandez, G. Urrútia, J.J. Meerpohl, A. Marušić, E. Wager, X. Bonfill*. **Opinions and potential solutions regarding dissemination bias from funding agencies of biomedical research in Europe.** J Eval Clin Pract. 2017 Jan 16. doi: 10.1111/jep.12692. Factor de impacto 2016 (último disponible): 1,25. Segundo cuartil en revistas de la categoría "Salud pública, ambiental y ocupacional".
2. *X. Bonfill, D. Osorio, M. Posso, I. Sola, G. Rada, A. Torres, M. Garcia Dieguez, M. Pina-Pozas, L. Diaz-Garcia, M. Tristan, O. Gandarilla, D.A. Rincon-Valenzuela, A. Marti, R. Hidalgo, D. Simancas-Racines, L. Lopez, R. Correa, A. Rojas-De-Arias, C. Loza, O. Gianneo and H. Pardo*. **Identification of biomedical journals in Spain and Latin America**. Health Info Libr J. 2015;32(4):276-86. Factor de impacto 2015: 0,71. Primer cuartil en revistas de la categoría "Ciencias bibliotecarias y de información".
3. M*. Turrillas, M. Sitjà-Rabert, H. Pardo, J. Vilaró Casamitjana, A. Fort-Vanmeerhaeghe, A. Morral Fernández, M.À. Cebrià I Iranzo, X. Bonfill*. **Identification and description of controlled clinical trials published in Physiotherapy journals in Spain**. J Eval Clin Pract. 2017 Feb;23(1):29-36. Factor de impacto 2015: 1,05. Segundo cuartil en revistas de la categoría "Salud pública, ambiental y ocupacional".
4. H*. Pardo-Hernandez, G. Urrútia, L.A. Barajas-Nava, D. Buitrago-Garcia, J.V Garzón, M.J. Martínez-Zapata, X. Bonfill*. **BADERI: An online database to coordinate handsearching activities of controlled clinical trials for their potential inclusion in systematic reviews.** Trials 2017 18:273 DOI: 10.1186/s13063-017-2023-3. Factor de impacto 2016 (último disponible): 1,97. Primer cuartil entre revistas de la categoría "Medicina – Misceláneas".

5.1. Sumario de resultados

5.1.1. Resultados del primer estudio

La encuesta se envió a 245 agencias de financiación, de las cuales 64 respondieron (tasa de respuesta del 26%).

5.1.1.1 Información básica sobre las agencias participantes

Se recibieron respuestas de la mayoría de países, excepto Chipre, Grecia, Letonia, Luxemburgo, Macedonia, Montenegro y Turquía. Francia (seis agencias), Reino Unido (cinco agencias), Finlandia, Alemania, Irlanda y Países Bajos (4 agencias cada uno) proporcionaron la mayor cantidad de respuestas. De las 64 agencias que respondieron, ocho declararon que financiaban investigación únicamente a nivel local. Por tanto, solo los 56 restantes, que financiaban investigación a nivel nacional y/o internacional, respondieron la encuesta completa.

De estas 56 agencias, 33 (58,9%) eran públicas, mientras que 6 (10,7%) contaban con fondos públicos y privados. Las restantes agencias eran privadas (8, 14,2%) o de otro tipo (9, 16,0%). La mayoría eran instituciones gubernamentales (27, 48,2%) o fundaciones (16, 28,6%), con diversas áreas de interés en investigación. Los ensayos clínicos de fase III y IV fueron financiados por 17 agencias (30,4%), mientras que 29 (51,8%) no lo hicieron. 10 (17,9%) de los encuestados no sabían la respuesta a esta pregunta.

5.1.1.2. Investigación financiada en 2005

Sólo 13 (23,2%) de las agencias de sabían el número de publicaciones resultantes de la investigación que habían financiado en 2005, y de los 43 restantes (76,8%), sólo la mitad pudo proporcionar una estimación. Por lo tanto, 20 (35,7%) de las agencias no tenían información sobre el número de publicaciones relacionadas con la investigación que financiaron en 2005. A pesar de esto, 33 (58,9%) agencias encuestadas declararon que tenían políticas para promover la publicación de resultados en 2005.

5.1.1.3 Políticas sobre el sesgo de difusión en 2012

En 2012, 38 (67,8%) de los organismos participantes declararon que tenían políticas para fomentar la publicación de resultados, que podían encontrarse principalmente en las convocatorias de propuestas, en los sitios web de la agencia, en las directrices éticas de las convocatorias, entre otras. Aproximadamente dos tercios de las agencias hicieron un seguimiento para asegurar que se habían publicado los resultados de la investigación financiada, aunque menos de la mitad lo hizo activamente (por ejemplo, durante la evaluación de los proyectos en lugar de simplemente requerir copias de los artículos correspondientes una vez estuvieran publicados). 13 (23,2%) de las agencias declararon no realizar ningún seguimiento sobre este asunto.

5.1.1.4 Opiniones y opiniones sobre el sesgo de diseminación

En cuanto a consideraciones y opiniones sobre el sesgo de diseminación, la mayoría de los participantes coincidieron en que el sesgo de diseminación era un problema para la investigación en salud. Sin embargo, 16 (28,6%) de los encuestados consideraron que los investigadores deberían decidir si los resultados de la investigación deberían publicarse, mientras que 22 (39,3%) afirmaron que los estudios observacionales y experimentales sólo debían publicarse si tenían resultados relevantes. 32 (57,1%) de los participantes coincidieron en que la publicación obligatoria de los resultados de la investigación disminuiría el sesgo de diseminación. La mayoría (41, 73,2%) opinó que todos los resultados de la investigación deberían estar disponibles como documentos de acceso abierto.

5.1.1.5. Recomendaciones para controlar el sesgo de diseminación

Las siguientes recomendaciones para las agencias de financiación, basadas en los resultados de esta encuesta y del estudio de estudios del proyecto OPEN, fueron acordadas por el Consorcio OPEN y los participantes en un taller que se llevó a cabo en mayo de 2013 en Friburgo, Alemania:

1. Las agencias de financiación deberían incluir una declaración sobre el sesgo de diseminación requerir la diseminación de los resultados de la investigación en todas las convocatorias (recomendación fuerte).

2. Las agencias de financiación deberían requerir que se proporcione un plan de diseminación de los resultados de los proyectos financiados en todas las convocatorias de financiación (recomendación fuerte).

3. Las agencias de financiación deberían requerir que se declare explícitamente que los resultados de la investigación financiada se difundirían, independientemente de la naturaleza de los resultados, en todos los contratos de financiación (recomendación fuerte).

4. Las agencias de financiación deberían adoptar medidas para garantizar que el proceso de evaluación de los proyectos financiados no termine con el informe final del proyecto, sino que continúe hasta que se hayan diseminado todos los datos resultados (recomendación).

5. Las agencias de financiación deberían considerar la posibilidad de ofrecer incentivos a los investigadores que diseminen sus resultados o, alternativamente, retener una parte de la financiación hasta que los resultados del proyecto se diseminen adecuadamente (recomendación).

6. Las agencias de financiación deberían crear una base de datos accesible de libre acceso con información sobre las subvenciones concedidas y la forma en que se diseminaron los resultados a fin de mantener un registro preciso de los proyectos financiados y la diseminación correspondiente de resultados (recomendación).

También se recomendó que las agencias de financiación solicitaran a los potenciales beneficiarios que correlacionen explícitamente los proyectos ya cerrados con las publicaciones

correspondientes. Esta información puede ser considerada al decidir qué candidatos recibirán financiación. Además, se recomendó que las agencias requieran que el protocolo completo de los proyectos de investigación financiados y las enmiendas correspondientes estén libremente disponibles, así como que alentaran el intercambio de datos individuales anónimos de los estudios cuando se solicite.

5.1.2 Resultados del segundo estudio

Se identificaron inicialmente 2457 revistas biomédicas publicadas en la lengua española. De esta lista, 959 fueron eliminadas porque eran duplicados o porque se centraron en publicar contenidos educativos, promocionales o comerciales. Se observó que en muchos casos, la información proporcionada por las bases de datos buscadas difería de la que se encontraba en los sitios web de las revistas, cuando estaba disponible. Por tanto, al final 1 498 revistas fueron elegibles para este estudio.

5.1.2.1. Información básica sobre las revistas identificadas

El año de inicio de actividades de las revistas, que fue analizado en períodos de cinco años, varió desde 1858 (Revista Farmacéutica, editado por la Academia Argentina de Farmacia y Bioquímica) hasta 2012. Un total de 1 316 (87,9%) revistas estaban activas (definidas como las que habían publicado al menos una edición durante los dos últimos años) a partir de 2012, mientras que 125 (8,3%) estaban inactivas.

Un total de 509 (34,0%) revistas no fueron indexadas en ninguna base de datos bibliográfica. Las restantes 989 (66,0%) fueron indexadas en al menos una base de datos según la siguiente distribución: 522 (34,8% de las revistas indexadas) en una base de datos, 173 (11,5%) en dos, 106 (7,1%) en tres, 64 (4,3%) en cuatro y 124 (8,3%) en cinco o más. LILACS y Periódica, con 17,4% y 10,5% de las revistas, respectivamente, fueron las bases de datos que más revistas indexaron., mientras que 4,1% se encontraban indexadas en MEDLINE y 3,7% en EMBASE. Cabe mencionar que 1 213 (82,0%) revistas fueron encontradas en Latindex, un directorio con

información de revistas científicas, profesionales y culturales de Latinoamérica, pero donde el contenido de las revistas no se indexa (94). De estas 1 213 revistas, 439 (29,3% del total) solo se encontraban en esta fuente.

5.1.2.2. Acceso a las revistas identificadas

Hubo 845 revistas con sitios web (56,4%), de los cuales 815 (96,4%) están actualmente activos y proporcionan información sobre el contenido de la revista. De los 845 sitios web, 681 (80,6%, que representa 45,5% de todas las revistas identificadas) ofrecían acceso gratuito o proporcionaban información básica de contacto. Ya fuera gratuito o no, 700 (82,8%, que representa 46,7% de todas las revistas identificadas) de los sitios web fueron consultables, 424 (50,2%, que representa el 28,3% de todas las revistas identificadas) tenían acceso a la totalidad del contenido de las revistas y 276 (32,7%, que representa el 18,4% de todas las revistas identificadas) permitían acceso parcial al contenido.

Las revistas identificadas se centraron en 65 especialidades médicas diferentes. El ISSN se encontró para 1 318 (87,8%) de las revistas identificadas. Un total de 45 de las revistas identificadas (3,6%) tuvieron un factor de impacto en 2012 según el *Journal Citation Reports*®. La mayoría de ellas (26, 57,7%) fueron de España, siendo el resto de Argentina (5, 11,1%), Chile (4, 8,9%), Colombia (3, 6,7%), México (3, 6,7%) y Venezuela (4, 8,9%). La mayoría de las revistas se clasifican en el cuarto cuartil de sus respectivas categorías.

5.1.3. Resultados del tercer estudio

5.1.3.1. Revistas y ensayos clínicos con distribución aleatoria identificados

Se identificaron diez revistas de Fisioterapia publicadas en España, ninguna de las cuales estaba indexada en PubMed (MEDLINE), EMBASE o CINAHL. Se llevó a cabo búsqueda manual en 451 números de revistas con 3 775 artículos publicados. De estos, 78 (2,1%) fueron ECAs.

5.1.3.2. Características de los ensayos clínicos identificados

La mayoría de los ECAs se realizaron en un centro (65, 83,3%), mientras que el 16,7% fueron multicéntricos. Las instituciones donde más comúnmente se desarrollaron los ECAs fueron

hospitales (28 ECAs, 35,9%), seguidas por universidades (12 ECAs, 15,4%), otras instituciones (como gimnasios, asociaciones de pacientes, etc.; 11 ECAs, 14,1%), centros de fisioterapia (10 ECAs , 12,8%), residencias de personas de la tercera edad (6 ECAs, 7,7%) y centros de atención primaria (4 ECAs, 5,1%). En cuanto a la subespecialidad médica, Traumatología y Ortopedia fue los campo más estudiado (33,3%) seguido de Neurología (15,4%).

La edad de los participantes varió en gran medida, oscilando de 13 a 80 con una media de 82,3. Esta variable, sin embargo, no se reportó en 34 ECAs, 43,6% de los estudios identificados. En 59 ECAs (75,6%), se informó del sexo de los participantes; para los que lo hicieron, los hombres representaron el 40,9% del total (SD 29,4) comparado con 59,1% de mujeres. Los problemas de salud más estudiados fueron el dolor de espalda (cervical y lumbalgia, 17,24%) seguido de Fibromialgia, Artrosis y accidente cerebrovascular (6,8% cada uno), lesiones de la médula espinal, Osteoartritis de rodilla y reemplazo de rodilla (3,8% cada uno). Sin embargo, la mayoría de los estudios identificados se realizaron en sujetos sanos (centrándose en los efectos de la electroterapia, la terapia manual o los efectos del fortalecimiento muscular). El resultado principal más común en los estudios identificados fue el control del dolor, seguido de movilidad funcional, rango de movimiento y calidad de vida.

Un total de 27 de los estudios identificados (34,6%) se clasificaron como con distribución aleatoria, mientras que 51 fueron pseudoaleatorios (65,4%). La mayoría de los ECAs tenían un alto riesgo de sesgo (64,1%). Respecto a la herramienta CONSORT, dos ECAs (2,6%) informaron utilizarlo en la redacción del informe. En cuanto a la fuente de financiación, el 91,1% de los autores no especificaron si recibían fondos para realizar su investigación. Los conflictos de interés fueron informados por 39,7% de los autores.

5.1.3.3. Comparación de la búsqueda manual con estrategias de búsqueda electrónica

La búsqueda electrónica llevada a cabo en PubMed (MEDLINE) recuperó 175 ECAs en Fisioterapia de autores afiliados a instituciones españolas. Sin embargo, estos estudios se

encontraron en revistas publicadas en otros países o en revistas que no se centraron exclusivamente en Fisioterapia. Estos estudios serán analizados en un futuro proyecto de investigación.

5.1.4. Resultados del cuarto estudio

5.1.4.1. Desarrollo de la base de datos (diseño y actualización)

La base de datos propuesta se denominó BADERI (Base de Datos de Ensayos Clínicos y Revistas Iberoamericanas). BADERI inició actividades en octubre de 2015 y se puede acceder en www.baderi.com/login.php (se necesita nombre de usuario y contraseña, que se generan a petición). BADERI es gratuito para todos los usuarios.

Después de la lluvia de ideas y las sesiones de discusión se consensuaron las características que se incorporarían en BADERI, el flujo que los usuarios seguirían para introducir nuevas referencias en la base de datos y el formato de los informes. Posteriormente se evaluó diferentes versiones de la base de datos y se aprobó la interfaz propuesta por la empresa de TI que diseñó BADERI.

A partir de marzo de 2015 y durante tres meses, BADERI fue sometido a pilotaje. Tres equipos de búsqueda manual introdujeron 203 referencias de ECA, realizaron búsquedas de texto libre de una muestra conveniente de referencias para verificar que se habían introducido correctamente y generaron los informes disponibles para rastrear el trabajo que habían llevado a cabo. Este ejercicio permitió incorporar cambios importantes a BADERI, los más relevantes de los cuales fueron: 1) la adición de campos para el registro de información adicional de ECA identificados (por ejemplo, el nombre de la persona que había identificado el ECA), 2) la integración de menús desplegables para algunos campos (por ejemplo, el método de asignación aleatoria), 3) cambiar la ubicación de los enlaces (por ejemplo, los enlaces para generar una nueva revista o una nueva referencia), y 4) sugerir formatos o datos que se incluyeran en los informes (por ejemplo, informes que pudieran ser filtrados por revista, país o especialidad médica).

5.1.4.2. Principales características

La página de inicio solicita a los usuarios que introduzcan un nombre de usuario y una contraseña, que se generan desde el Centro Cochrane Iberoamericano. Los usuarios pueden ser asignados a uno o más proyectos de búsqueda manual (especialidad médica) o a búsqueda manual en países específicos y recibir diferentes roles de acuerdo con sus responsabilidades en los proyecto de búsqueda manual.

BADERI se divide en cuatro subsecciones a las que se puede acceder haciendo clic en las diferentes pestañas de la página principal: "Administración", "Referencias", "Informes" y "Buscar". La subsección "Administración" permite asignar a cada usuario diferentes roles y proyectos de búsqueda manual, específicamente por país y especialidad médica. Esta subsección se supervisa centralmente desde la sede del Centro Cochrane Iberoamericano en Barcelona, España, así como por administradores locales ubicados en diferentes países. La subsección "Referencias" proporciona dos subsecciones en las que se pueden introducir referencias de ECA publicados y no publicados (es decir, literatura gris). La subsección "Informes" permite exportar hojas de cálculo en formato Excel para monitorear las actividades de búsqueda manual. Los informes proporcionan toda la información disponible para las revistas y los ECA registrados en la base de datos y pueden ser filtrados por revista/s, país/es o especialidad/es médica/s. Por último, la subsección "Buscar" contiene un motor de búsqueda que permite recuperar referencias a través de búsquedas de texto libre para título de la revista, autor o título del artículo.

BADERI tiene una función incorporada, disponible también bajo la subsección "Informes", que permite exportar toda la información bibliográfica disponible en la base de datos en un archivo ProCite. Este archivo se puede cargar directamente en CENTRAL.

5.1.4.3. Resultados de las actividades iniciales de BADERI

A partir de agosto de 2016, un total de 6 284 referencias de ECAs fueron incluidas en BADERI. Estas referencias correspondieron a diferentes proyectos de búsqueda manual realizados por

miembros de la Red Cochrane Iberoamericana. Los ECAs identificados se publicaron en un total de 420 revistas de 46 especialidades médicas. Se encontraron muy pocos ECA con títulos traducidos al inglés; dos traductores profesionales registraron la información correspondiente en BADERI. Por último, se generó un informe de todos los ECA identificados en formato ProCite y se enviaron para su inclusión en CENTRAL.

5.2. Publicaciones presentadas para este proyecto de tesis

5.2.1. Primera publicación

Opinions and potential solutions regarding dissemination bias from funding agencies of biomedical research in Europe. J Eval Clin Pract. 2017 Jan 16. doi: 10.1111/jep.12692. Factor de impacto 2016 (último disponible): 1,25. Segundo cuartil en revistas de la categoría "Salud pública, ambiental y ocupacional".

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ORIGINAL ARTICLE

Opinions and potential solutions regarding dissemination bias from funding agencies of biomedical research in Europe

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Abstract

Rationale, aims, and objectives Several studies have found that about half of research results from clinical trials are never published. Until now, there has been little information on the views that funding agencies of biomedical research in Europe have regarding this issue and its possible solutions.

Methods An electronic survey was conducted among funding agencies from 34 European countries. Participants were asked about their opinions, policies, and potential solutions regarding dissemination bias. On the basis of the results of this survey and the input of the OPEN Consortium and of representatives of stakeholder groups in the knowledge generation process, we formulated recommendations for funding agencies to reduce dissemination bias.

Results We received responses from 64 funding agencies of biomedical medicine from most European countries, out of 245 that were contacted (26%). Of these, 56 funded research at the national and/or international level and were therefore eligible to participate. Policies encouraging publication increased over time: 33 (58.9%) of agencies enforced them in 2005 compared to 38 (67.6%) in 2012. However, only 13 (23.2%) had knowledge of the publications related to research funded in 2005, 23 (41.1%) were able to provide only an estimate, and 20 (35.7%) did not know at all. Regarding recommendations to control dissemination bias, we propose that funding agencies request the dissemination of research results irrespective of the direction of findings. We also call for measures that allow evaluating funded projects past the contractual period and until dissemination of results. Funding agencies should create publicly accessible databases with information on funded projects and dissemination efforts.

Conclusion Despite having policies to encourage publication of results, most funding agencies fail to implement such measures or to ensure compliance. We propose recommendations that could be incorporated in the blueprint of calls for proposals and contracts agreed upon by funding agencies and grant recipients.

KEYWORDS

clinical trials, dissemination bias, evaluation, medical ethics, publication bias, the OPEN Project

1 | BACKGROUND

Full information about completed clinical trials is the indispensable base for medical decision-making.[1,2] Despite the importance of considering all relevant trials, studies that have tracked the publication of results of clinical trials either approved by ethics committees or registered in trial registers have found clear evidence that the results of about half of clinical trials are never published.[3–13] Another concern is that a high proportion of research, both clinical trials and other types of studies, presented in the form of abstracts at biomedical conferences is never reported in full.[14]

The nondissemination of research results is known as publication bias —or more broadly, dissemination bias.[15,16] One of the main reasons for this phenomenon is that authors tend to submit—and journal editors to accept —articles on the basis of the direction and strength of findings.[10,17,18] It has been shown that positive and/or statistically significant results are more likely to be published than negative or inconclusive ones.[6,16] In addition, discontinued clinical trials may contribute to dissemination bias and such failed studies have both ethical and economic implications.[8,9]

Dissemination bias is worrisome for many reasons. It reduces public trust in clinical research, as it has been linked to vested economic interests that researchers and sponsors may have.[19] Dissemination bias also disregards the contribution made by patients who participate in clinical studies, who often do so accepting research-related risks and burdens. And, most importantly, it reduces the efficiency of research by limiting access to findings which, as mentioned above, is indispensable for decision-making in health care.[2,20]

Several studies have shown the extent and impact of dissemination bias in Europe.[21–23] There have also been some enquiries into the views and positions of key players in the knowledge generation process, including research ethics committees,[11] journal editors and publishers,[24] and authors of biomedical research.[25] Further work has investigated research funding institutions' guidelines for grantees regarding publication of results.[26] However, to date, there has been little or no information on the opinions that European funding agencies of biomedical research have about publication bias and its possible solutions.

This study aimed to capture the views of European clinical research funding agencies on dissemination bias and survey the policies and procedures in place in these agencies in 2005 and 2012 to reduce or prevent dissemination bias. We also sought to question these agencies on the feasibility of different initiatives to control dissemination bias. The results of this project were used to formulate recommendations, which could be implemented by funding agencies to reduce dissemination bias. In this article, we present the results of our survey, describe how the recommendations were developed, and present recommendations for funding agencies to prevent and control dissemination bias.

2 | METHODS

We conducted a survey of funding agencies from 34 European countries, including the 28 members of the European Union, candidate countries (Iceland, Macedonia, Montenegro, and Turkey), Norway, and Switzerland.

This research was part of the OPEN Project: To Overcome failure to Publish nEgative fiNdings. This project was a 24-month initiative cofunded by the European Union through the Seventh Framework Programme that aimed primarily at identifying the current evidence available on publication bias across Europe.[15,27,28] A total of 11 institutions from 6 countries participated in the project (Appendix 1), under the leadership of the German Cochrane Centre, and an advisory board of world experts in the field of publication bias and reporting of research results (Appendix file 2). The OPEN Project focused on researching the policies and procedures adhered by funding agencies, research institutions, trial registries, authors and researchers, biomedical journals, regulatory agencies, ethics committees, and pharmaceutical companies.

2.1 | Identification of eligible funding agencies

Eligible funding agencies included public, private, or mixed agencies that support biomedical research in the aforementioned countries. We included agencies that operated at the state (national) or international level, to capture those that, because of the scope of their work, were more likely to be familiar with national and international regulations regarding dissemination bias. Agencies that operated only at the local or regional level (eg, city, provinces, or regions) were therefore excluded, because we considered that such agencies and/or foundations would not necessarily reflect the policies on dissemination bias in their countries.

We planned to select between 5 and 15 agencies per country, adjusted by country population (15 agencies for countries with over 20 million inhabitants; 12 for those with 10-20 million; 10 for those with 5-10 million; and 5 for countries with less than 5 million inhabitants) (Table 1). To identify eligible agencies, we tried to locate comprehensive directories of funding agencies across Europe, similar to those available in the United States.[29] However, as such a list was not available, we searched the websites of organisations that provide information on how to fund different types of projects, as well as those of European agencies dedicated to support researchers, local libraries, and other organisations. We also contacted the Europe Direct Office, part of the Communications Department of the European Union. While these sources allowed us to identify a group of eligible funding agencies, we were not able to identify all the target agencies that we aimed to survey.

Therefore, in a second step, we conducted exhaustive searches of the websites of Ministries of Health, Education, and/or Research in each country; institutions at the European level, such as the European Research Area, Community Research and Development Information Service, All European Academies, EURAXESS, and the European Foundation Centre; and universities and other centres that regularly receive funding for scientific research. For countries such as Germany, France, the UK, and Spain, for which several funding agencies were identified, we made a final selection based on the advice of other OPEN Project partners or members of the Cochrane Collaboration based in these countries. The aim was to ensure the inclusion of the most important research funding agencies in each country, as well as those that fund clinical trials. For other countries, the search was stopped once the target number of research funding agencies was met.

2.2 | Electronic survey

We created an electronic survey with 29 closed- and open-ended quantitative and qualitative questions (Appendix 3). These questions addressed 5 specific areas: basic information on the agency, including

TABLE 1 Number of agencies planned and identified per country

Country	Planned	Identified
Germany	15	15
Turkey	15	6
France	15	15
UK	15	16
Italy	15	15
Spain	15	15
Poland	12	12
Romania	12	12
The Netherlands	12	12
Greece	12	13
Belgium	10	10
Portugal	10	10
Czech Rep.	10	5
Hungary	10	2
Sweden	8	8
Austria	8	10
Switzerland	8	8
Bulgaria	8	4
Denmark	7	9
Slovakia	7	2
Finland	7	7
Norway	5	6
Ireland	5	5
Croatia	5	3
Lithuania	5	3
Latvia	5	1
Macedonia	5	2
Slovenia	5	5
Estonia	5	5
Cyprus	5	2
Montenegro	5	0
Luxembourg	5	4
Malta	5	2
Iceland	5	1
Total	**296**	**245**

whether it is a private or public funding agency and the type of research it funds (6 questions); information on projects funded in 2005, including whether they know the publication status of funded projects (8 questions); information on the agency's more recent (2012) policies regarding dissemination bias (3 questions); information on the agency's views and opinions on dissemination bias (7 questions); and a final section with demographic questions about the person completing the survey and open questions for comments (5 questions). We selected the year 2005 to allow ample time for studies to be completed and for results to have been published, and this information recorded by the agency, given that such processes may take several years.[12,30]

The survey was designed in line with the recommendations of the Cochrane Collaboration systematic review on methods to increase response rates in electronic questionnaires, including length of the survey, format and presentation of the questions, styles, and ways of submitting the survey.[31] The survey was tested for face validity by 6 staff members at our centre and by other partners in the OPEN Project and administered between September 2012 and January 2013 using the Surveymonkey.com online platform.

2.3 | Contacting eligible agencies

For each eligible agency, we identified personnel who would likely have access to the data needed to answer the survey. We obtained this information by reviewing websites and other sources, focusing specifically on sections such as staff, description of departments, and "who we are" and "contact us" tabs. This process took a substantial amount of time because we encountered language barriers, ambiguous descriptions of departments and units within each agency, and because the needed information was often found in different sections of the website. When this information was unavailable, the survey was sent to the email provided at the website for contact, either a personal address or common domains such as info@agency.com or webmaster@agency.com.

Information on how and where to complete the survey was sent via email with a personalised letter (in English) on our institutional letterhead that was worded carefully to avoid biasing respondents to responding 1 way or another (Appendix 4). The letter briefly explained the project, the reason why their agency was being contacted, and a link where the survey could be completed. The letter was signed by the director of the Iberoamerican Cochrane Centre and was sent from an institutional email account. If an email bounced back, a second person within that agency was identified and a new personalised mail was sent. Agencies that did not respond were sent 2 further invitations, giving a total of 3 rounds of mailing.

2.4 | Statistical analysis

We conducted descriptive analyses using SPSS version 17.0 (SPSS, Inc, Chicago, Illinois).

2.5 | Development of recommendations

We used the results of this survey, as well as the results of the remaining work packages of the OPEN Project, to draft a series of general and targeted recommendations to reduce dissemination bias. Each OPEN partner developed a series of draft measures that were initially discussed with the consortium as a whole. To formalise agreement, the definition of key several terms were agreed upon, including the term "clinical trial," defined as "any research study that prospectively assigns human participants or groups of humans to one or more health-related interventions to evaluate the effects on health outcomes. Clinical trials may also be referred to as interventional trials". This definition includes phase I-IV trials.[28,32] These draft recommendations were presented and discussed with a group of stakeholders from different countries during a workshop held in Freiburg, Germany, in 2013 (Appendix 5). The recommendations were classified as "strong recommendations" or simply "recommendations" on the basis of adapted criteria from the Grading of Recommendations Assessment, Development and Evaluation approach.[33] These criteria were confidence in effectiveness of the proposed measure, balance of benefits and downsides, likelihood of opposition, resource use, implementability, and feasibility.

3 | RESULTS

We were able to identify 245 of the 296 funding agencies from the initial sample. Table 1 shows the number of agencies identified for each country.

The survey was sent to 245 funding agencies and 64 replied. For the first contact, a sizable number of contact staff at agencies replied indicating that they did not have the knowledge to answer the survey and suggesting alternative people. For these contacts, new letters were drafted and readdressed either to those suggested by the participants or to others identified from the agency's website. The second mailing brought in additional responses. After the final round of mailing, which included an appeal to participate and a mention that this was the last mailing of the project, the response rate was 26% (Figure 1).

3.1 | Basic information about participating agencies

We received responses from most countries, except for Cyprus, Greece, Latvia, Luxembourg, Macedonia, Montenegro, and Turkey. France (6 agencies), UK (5 agencies), Finland, Germany, Ireland, and the Netherlands (4 agencies each) provided the most responses.

Of the 64 agencies that answered the survey, 8 stated that they funded research only at the local level. Only the remaining 56, which funded research at a national and/or international level were asked to continue answering the full survey.

According to the survey, 33 of 56 (59%) of respondents were male, 15 (26%) were either the director, chair or the president of the agency, 6 (10%) held an executive position, 1 (2%) was a researcher, 16 (29%) were managerial staff, 7 (13%) were support staff, and 11 (20%) held other positions.

Of these 56 institutions, 33 (59%) were public while 6 (11%) had both public and private funds. The remaining agencies were either private (8, 14%) or self-classified as other (9, 16%). Most were government institutions (27, 48%) or foundations (16, 29%), with varied areas of research interest. Phase IV clinical trials were funded by 17 agencies (30%), while 29 (52%) did not. Ten (18%) of respondents were unsure/did not know the answer to this question (Table 2).

TABLE 2 Characteristics of participating funding agencies

Type of research centre	n (%)
Government institutions	27 (48)
Foundation	16 (29)
Academic institution	7 (13)
Scientific society	1 (2)
Other	5 (8)
Funding	
Public	33 (59)
Private	8 (14)
Mixed (public and private)	6 (11)
Other	9 (16)
Research field(s)*	
Basic research	24 (43)
Clinical research trials	17 (30)
Pharmacological trials	11 (20)
Public health trials	21 (38)
Not health care	7 (13)
Other	22 (39)
Clinical trials (phases I-IV)	
Yes	17 (30)
No	29 (52)
Do not know/unsure	10 (18)
Grants awarded for research (2005)	
<€1 000 000	21 (38)
€1 000 001 to €10 000 000	10 (18)
€10 000 001 to €25 000 000	10 (18)
>€25 000 001	15 (26)

*Respondents could indicate multiple fields.

3.2 | Research funded in 2005

In the amount of research funded in 2005, most agencies funded research worth less than €1 million, with a more or less even spread of middle-size agencies (€1-€10 and €10-€25 million) and larger agencies (funding over €25 million) (Table 2). Only 13 (23%) of responding funding agencies knew the number of publications resulting from the research they had funded in 2005, and of the remaining 43 (77%), only about half were able to provide an estimate. Accordingly, 20 (36%) of

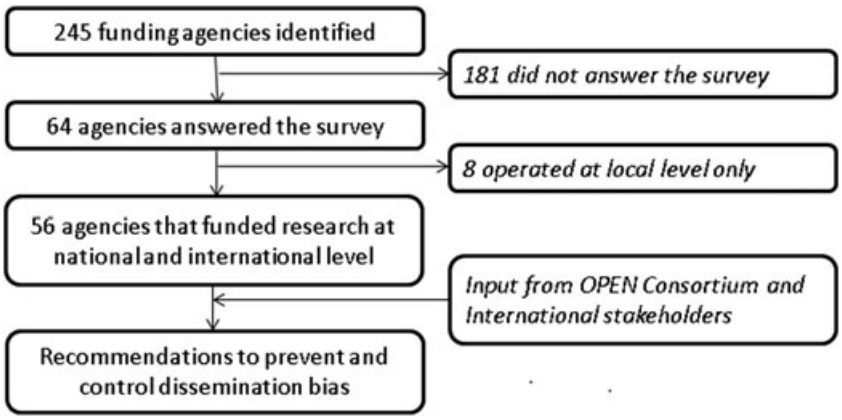

FIGURE 1 Study flow diagram

agencies did not have any information about the number of publications related to the research they funded in 2005. Despite this, 33 (59%) of surveyed agencies stated that they had policies in place to encourage publication of results in place in 2005.

We asked participants to send a copy of their institution's call for funding proposals for 2005. Only a single respondent agreed to this, however, we never received this document at the email address provided.

3.3 | Policies regarding dissemination bias in 2012

In 2012, 38 (68%) of participating agencies stated that they had policies in place to encourage the publication of results, which could be found mostly on the actual calls for proposals, the agency's websites, program blueprints, ethical guidelines, and other sources. About two-thirds of the agencies followed up with grantees to ask whether they have published the results of the research for which they were funded, although less than half did so actively (eg, during evaluation as opposed to simply asking grantees to send their publications once they are ready). Thirteen (24%) of funding agencies stated that they do not follow up with grantees at all on this matter.

3.4 | Views and opinions on dissemination bias

Regarding views and opinions of dissemination bias, most participants agreed that dissemination bias is a problem for health care research (Table 3).

However, 16 (29%) of respondents considered that grantees should decide whether research results should be published, while 22 (39%) stated that both observational and experimental studies should be published only when they have relevant results. Only 18 (32%) of funding agencies stated that both observational and experimental studies should be published regardless of their results. No agency advocated publishing results of experimental studies only. Thirty-two (57%) of participants agreed that mandatory publication of research results would decrease dissemination bias. The majority (41, 73%) believed that all research results should be available as open access documents. When asked about the aspects of studies that should be disseminated to reduce dissemination bias, participants favoured a scientific publication, access to full dataset, and summary of the protocol, among others (Figure 2).

When asked to suggest initiatives or ideas to control dissemination bias, only 3 agencies (5%) provided answers, which were "mandatory registration of trials," "retraction watch blog," and "funding agencies should be more careful". Only 13 (23%) of respondents agreed that policies aimed at reducing dissemination bias are fit for purpose and implementable.

TABLE 3 Extent to which publication bias is a problem to health care research

Extent to which publication bias is a problem to health care research	n (%)
Not a problem at all	8 (14)
Somewhat a problem	20 (36)
A problem	18 (32)
A serious problem	8 (14)
A very serious problem	2 (4)
Total	**56 (100)**

3.5 | Recommendations to control dissemination bias

The following recommendations for funding agencies, based on the results of this survey and of the work of the remaining work packages of the OPEN Project, were agreed upon by the OPEN Consortium and a group of international stakeholders during the May 2013 workshop in Freiburg, Germany (Figure 1, Appendixes 1 and 5):

1. Funding agencies should include a statement on dissemination bias and the requirement for the dissemination of research results in all calls for proposals (strong recommendation)
2. Funding agencies should include the requirement for grantees to provide a dissemination plan for funded projects in all calls for proposals (strong recommendation)
3. Funding agencies should include the requirement for grantees to explicitly declare that the results of funded research will be disseminated, regardless of the nature of findings, in all funding contracts (strong recommendation)
4. Funding agencies should implement measures to ensure that the evaluation process of funded projects does not end with the project's final report, but instead is followed up until all agreed data have been disseminated (recommendation)
5. Funding agencies should consider providing incentives for researchers who disseminate their results, or, alternatively, withhold a part of the funding until a project's results are adequately disseminated (recommendation)
6. Funding agencies should create a publicly accessible database of all grants awarded and on how their results were disseminated to keep an accurate record of funded projects and publication outcomes (recommendation)

We also recommend that funding agencies request potential grantees to explicitly correlate past projects with corresponding publications or dissemination efforts. This information can then be taken into account when deciding which applicants will receive funding. In addition, we recommend that funding agencies require that the full protocol of any research projects funded and the corresponding amendments be publicly available, as well as that they encourage sharing of anonymised individual participant data upon request.

4 | DISCUSSION

Despite the disappointing response rate, we will attempt to draw some general conclusions from our study. The responses to our survey suggest that medical funding agencies in Europe are, in theory, aware of the issue of dissemination bias. However, most are doing little or

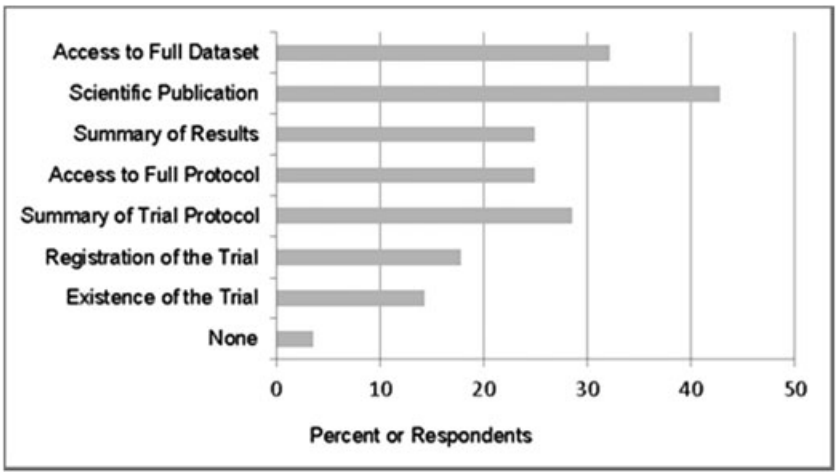

FIGURE 2 Aspects of clinical trials that should be publicly available to reduce dissemination bias

nothing to address it. We found that, among our respondents, most were uncertain of the publication status of the research they fund. Nevertheless, most agencies that participated in our study stated that they had policies to ensure publication of results and, at least in principle, try to follow up with grant recipients to ensure compliance. In addition, there is a lack of consensus on the type of measures that need to be taken to reduce or eliminate dissemination bias.

Our survey showed that 59% of respondents had policies in 2005 that encouraged or made it mandatory for grantees to publish the results of the research for which they had been funded. That number went up to 68% in 2012. Most agencies try to follow up with grant recipients on this matter, especially by asking for proof of publication of academic articles. However, these same agencies report difficulties upholding these policies, as less than a quarter knew the number of publications resulting from the research projects they had funded in 2005.

This inconsistency may be explained by less than a quarter of surveyed agencies had faith in the effectiveness of measures taken to control dissemination bias, whereas an even lower percentage were able or willing to articulate further measures to tackle the problem. These findings coincide with those of other OPEN Project partners. As part of the work conducted on research ethics committees,[11] journal editors and publishers,[24] and researchers[25] Strech et al[34]and Panteli,[35] it was found that most of these stakeholders acknowledge the deleterious effects of dissemination bias on health care research but are unwilling or unable to implement measures to control the problem. In addition, a recent systematic review concluded that while implementation of measures to reduce dissemination bias is on the rise, they are not adequately conducted.[36]

Among surveyed agencies, there was wide support for making several aspects of clinical trials publicly available to reduce dissemination bias. These include access to the corresponding scientific publications, full dataset, full protocol, and summary of results. Only a small proportion of respondents opposed these ideas. In addition, respondents endorsed the dissemination of research results in open access format, as well as agreeing that dissemination of research results should not be limited to experimental trials but also to observational studies. However, these agencies appear to be taking little or no action to implement these measures. In addition, this information came from agencies that took the time and effort to answer a survey on dissemination bias. The situation may well be even worse among agencies that did not reply to our call to participate in this study.

Our survey focused on projects funded by surveyed agencies in 2005. We selected this year to control for research projects often take several years to complete, with the associated lag in dissemination of results via academic articles, which also take time to be prepared, accepted, and published.[12,30] We are aware that the policies and measures that agencies adhere to ensure publication of results of funded work may have changed through time. However, the results for 2005 and 2012 regarding policies to control dissemination bias were similar. This suggests that no major shifts in these policies took place during these years.

We developed a series of recommendations for funding agencies to control dissemination bias. In general, the main recommendations that apply to all stakeholders focus on raising awareness of the issue of publication bias, as well as supporting initiatives such as trial registration and posting of results, which help reduce dissemination bias. In addition, there is a call to promote and implement the recommendations targeted at each specific stakeholder.[28] Regarding funding agencies, we aimed to formulate recommendations that could be incorporated in the blueprint of calls for proposals and contracts agreed upon by funding agencies and grant recipients. Because of the relationship between funding agency and grantee, the recommendations could represent contractual conditions that must be met to receive financing. As far as we are concerned, to date, very few recommendations specifically tailored for funding agencies on how to control and prevent dissemination bias had been developed.

The OPEN Consortium endorsed, in 2012, the AllTrials campaign, an initiative committed to raising awareness on the issue of publication bias and possible solutions.[37] This campaign advocates that "All trials, past and present, should be registered, and the full methods and the results reported. We call on governments, regulators and research bodies to implement measures to achieve this". We hope that the measures we present in this article are supportive to the achievement of these goals, as well as with those of other initiatives, such as Reduce research Waste And Reward Diligence,[38] the Code of Conduct of the Committee on Publication Ethics,[39] the Declaration of Helsinki,[40] and others.[41]

One of the main strengths of this study is that we received responses from a diverse sample of funding agencies, including public,

private, and mixed-funding agencies with varied research interests and budget. In addition, the OPEN Consortium provided ample methodological and logistic support, which facilitated the participation of a diverse sample of stakeholders in the development of the recommendations. The results of our work were contrasted and compared with those of other OPEN partners, and the proposed recommendations were discussed and agreed upon with actual funding agencies representatives and with experts in the field, which gives us confidence in the feasibility of their implementation.

This work is subject to some limitations. We did intend to gather information from a representative sample of agencies from all countries in Europe. However, to identify the agencies that were to be surveyed, we had to consult a variety of sources because, to our knowledge, there is no directory or comprehensive list of agencies at the European level that fund biomedical research. These lists are available in other countries, such as the United States (Fogarty International Center 2006). Despite this shortcoming, we believe that the agencies that participated in our study provided answers that allow us to draw some interesting conclusions. As such, we obtained answers from most countries and from agencies with varied research interests and volume of funded research projects. Staff members who actually answered our survey represented all levels of management within the agencies. While most agencies were public, there was a sizeable representation of private and mixed agencies.

The response rate was low, despite several attempts to increase it. Participation in the study was voluntary, which may have been a factor in the low-response rate. In addition, we faced language barriers when trying to find people to contact in every agency, as well as when attempting to verify some of the answers provided in the surveys, especially regarding websites where agencies posted their policies on dissemination bias. We cannot rule out either that, since the survey was administered in English, some respondents may have been discouraged from providing more elaborate answers in the open-ended questions. The information gathered from the survey to inform the development of the recommendations is therefore reflective of the views of a limited sample that may not be representative of all agencies in Europe. Likewise, as mentioned earlier in the discussion, in the survey we included question for research funded in 2005; our findings for these and other questions may have been compromised by participants' poor recall. We hope to have overcome these shortcomings by including the input of the entire OPEN Consortium and of different stakeholders when drafting the proposed recommendations.

In conclusion, while there seems to be some awareness about the issue of dissemination bias, as well as good intentions to reduce and control it, most funding agencies fail to implement rigorous strategies to achieve this. We hope that the recommendations we present in this paper and in other publications of the OPEN Consortium, which were discussed with and supported by representatives of funding agencies and by other experts in the field, will facilitate this task. Furthermore, the findings of this study and of the remaining OPEN partners provide a clearer picture of the problem of dissemination bias, as well as general strategies that can be implemented by any stakeholder. We hope that this work will further raise awareness about the harmful effects of dissemination bias.

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CONFLICT OF INTEREST

Elizabeth Wager provides publication training and consultancy and has worked for a number of universities.

ETHICAL APPROVAL

Research ethics approval was waived by the Sant Pau Biomedical Research Institute (IIB Sant Pau) because this study did not involve any patients.

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SUPPORTING INFORMATION

Additional Supporting Information may be found online in the supporting information tab for this article.

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5.2.2. Segunda publicación

Identification of biomedical journals in Spain and Latin America. Health Info Libr J. 2015;32(4):276-86. Factor de impacto 2015: 0,71. Primer cuartil en revistas de la categoría "Ciencias bibliotecarias y de información"

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Identification of biomedical journals in Spain and Latin America

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Abstract

Objectives: Journals in languages other than English that publish original clinical research are often not well covered in the main biomedical databases and therefore often not included in systematic reviews. This study aimed to identify Spanish language biomedical journals from Spain and Latin America and to describe their main features.

Methods: Journals were identified in electronic databases, publishers' catalogues and local registries. Eligibility was determined by assessing data from these sources or the journals' websites, when available.

Findings: A total of 2457 journals were initially identified; 1498 met inclusion criteria. Spain (27.3%), Mexico (16.0%), Argentina (15.1%) and Chile (11.9%) had the highest number of journals. Most (85.8%) are currently active; 87.8% have an ISSN. The median and mean length of publication were 22 and 29 years, respectively. A total of 66.0% were indexed in at least one database; 3.0% had an impact factor in 2012. A total of 845 journals had websites (56.4%), of which 700 (82.8%) were searchable and 681 (80.6%) free of charge.

Conclusions: Most of the identified journals have no impact factor or are not indexed in any of the major databases. The list of identified biomedical journals can be a useful resource when conducting hand searching activities and identifying clinical trials that otherwise would not be retrieved.

Keywords: America, South; citation analysis; clinical trials; database searching; Europe, South-West; journals

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Key Messages

- There are 1498 biomedical journals that publish original clinical research in Spanish language in Spain and Latin America.
- Of these, few have an impact factor (3.0%) or are indexed in MEDLINE (4.1%) or EMBASE (3.7%) as of 2012.
- The list of identified journals available in online supporting information Appendix S1 and in the Iberoamerican Cochrane Network website can be a useful resource to conduct handsearching activities for identifying clinical trials that otherwise would not be retrieved.
- Databases and repositories should make an effort to maintain the information they provide up-to-date.

Background

Reporting bias occurs when the dissemination of research results is influenced by the nature and direction of results. Publication bias, which arises from a tendency to overvalue research with positive findings and results that are statistically significant, is a classic example.[1,2] Several studies have found that research results that do not favour the effectiveness of the studied interventions, as well as those that report side-effects or other undesirable outcomes, are less likely to be published and disseminated.[3] To control and reduce the effects of publication bias when conducting systematic reviews, the Cochrane Collaboration promotes the identification of all clinical trials that are published in indexed and non-indexed biomedical journals, as well as of trials that have not been published or that are currently underway.[1]

One of the most effective strategies to identify all clinical trials as thoroughly as possible in the available literature is to combine electronic searches and handsearching.[4,5] While the former is a widely used and efficient practice that is made possible by an improvement in the indexation of documents in bibliographic databases, several studies have revealed that it may not be enough to retrieve all clinical trials on a given subject.[6–8] Handsearching may help overcome this problem, for it involves a page-by-page examination of journal issues, allowing the identification of clinical trials even when they are not included in electronic databases or when they are not indexed using the appropriate search terms.[1,6,9] Therefore, it becomes an indispensable complement to electronic searches to identify trials that are not indexed using the right terms or simply not retrieved electronically because they are not indexed in any searchable database. The superiority of handsearching over searches conducted strictly electronically has been observed in studies aimed at identifying clinical trials in Anaesthesiology,[10] General and Internal Medicine,[11] and patient safety.[12] The results of these studies show that the proportion of studies identified via electronic search over those identified via handsearch is low, as well as the truly eligible studies among all those retrieved via the electronic search strategy.

Given that many journals are not indexed in any major database, it is very difficult to efficiently identify and consequently to handsearch them.[13,14] In such cases, there are various options, such as consulting libraries, publishers' catalogues, national publication catalogues and specialised registries. These resources, nevertheless, are not known or accessible to everybody and are rarely exhaustive, which hampers the proper and systematic identification of journals. In the case of Spanish language publications, it is imperative to address this problem for two main reasons. First, because the Spanish language has over 500 million speakers worldwide in Spain and several different countries in Latin America, and therefore with many publications to serve such a large audience.[15] And second, because during the last decade the output of scientific literature from Spanish-speaking countries has increased significantly.[13]

While there are several databases, directories and registries that allow searching for biomedical journals published in Spain and Latin America, including LILACS, SCIELO, PERIODICA, LATINDEX and PUBMED, none of them are all-inclusive as they do not contain, in any case, all existing journals. In addition, and some may provide information that is outdated and/or incomplete,[4,5,9] that is inactive journals are still marked as active, and contact information or data related to publishers is not up-to-date. These resources may also leave out lesser-known journals or those that are not indexed. This study aimed to compile a list as comprehensive as possible of biomedical journals from Spain and Latin America by drawing information from a diverse pool of sources. In addition, the main characteristics of these publications were described, to provide readers with a tool that would allow them to find all information associated with these journals in a single place.

Objectives

- To identify biomedical journals published in Spanish, both in Spain and Latin America, and to provide a single source where this body of publications can be found.
- To describe the main features of the identified journals in order to stimulate further research on this field and to facilitate the planning and completion of projects that rely on this information, such as handsearching of journals or literature searches in journals that are not indexed in any database.

Methods

This was a descriptive study conducted in the 19 countries that are part of the Iberoamerican Cochrane Network (IbCN) and that have Spanish as their official language. These countries are Argentina, Bolivia, Chile, Colombia, Costa Rica, Cuba, Dominican Republic, Ecuador, El Salvador, Guatemala, Honduras, Mexico, Nicaragua, Panama, Paraguay, Peru, Spain, Uruguay and Venezuela. Despite the fact that Andorra and Portugal are also part of the IbCN, they were excluded because Spanish is not their official language.

A search was conducted sequentially in PUBMED, LILACS, SCIELO, Periódica and Latindex, with the aim to identify all biomedical journals published in Spanish language in the aforementioned countries. To be eligible, journals had to be periodic and publish original clinical research papers. Mental health and nursing journals were excluded and will be part of future independent projects. Country of origin for journals was defined as that where the publisher, editor or entity or organisation responsible for publication was located. If this information was not available, journals were assigned to the country listed under the database as country of origin.

This search was conducted by trained researchers at the Iberoamerican Cochrane Centre (IbCC, Barcelona, Spain), who had previous experience in completing studies that required identifying all journals (and available literature) on given medical specialties or conditions.[10–12] Once this search was completed, the next step was to determine eligibility of each journal and, if applicable, to collect all information of interest. For all the identified journals, each of the aforementioned sources were consulted to determine whether they were a periodical and published original clinical research. This search was completed by looking at the available links to journals' websites. When they were not available, the websites were looked up in Google using both the name and ISSN of the journal (when available). For eligible journals, the following information was collected: journal title, ISSN, inception year, current publication status, bibliographic databases where it is indexed, publisher or entity responsible for publication, medical specialty, whether they had a website and, given the case, if this website was active, offered access free of cost and had searchable contents. Journals with a generic/general scope were assigned to 'General Medicine'. In addition, the impact factor and the ranking within their respective medical categories, both in 2012, were collected for those journals included in the *Journal Citation Reports*®.[16]

The results of this search were subsequently sent to corresponding country collaborators, who in general were active members of the IbCN. If any of these collaborators were unable to

participate in this study, results were sent to colleagues from neighbouring countries. They received clear instructions requesting that they verify and identify journals for their corresponding countries and the data associated with them were accurate and complete, as well as to update and/or complement the results if needed. Emphasis was made on journals with no ISSN, to verify that they were indeed serial publications. To achieve this goal, these collaborators, who have ample experience in bibliographic searches, were given directions to review national catalogues, library collections and other sources where publications that met the eligibility criteria could be found.

Once all results had been verified, a descriptive analysis was performed using SPSS version 17.0 (SPSS, Inc., Chicago, IL, USA). Variables were expressed as mean (standard deviation) or median (interquartile range) when appropriate. Categorical values were expressed as percentages.

As this study did not involve patients or confidential information, no approval from ethics committees in any of the participating institutions was needed.

Results

A total of 2457 biomedical journals published in the Spanish language were initially identified. From this list, 959 were eliminated either because they were duplicated in different databases or because they did not publish original research and focused instead on educational, promotional or commercial contents. It was noted that in many cases, the information provided by the searched databases differed from that found on the journals' websites, when available. In such cases, the information provided by the journals' website was the one that was recorded. As a result, a total of 1498 eligible journals were included (for a total list of the identified journals, please see online supporting information Appendix S1 or visit the IbCC website, www.cochrane.es).

The distribution of the identified journals by country of origin is presented in Table 1.

Year in which journals were launched, which was analysed in 5-year periods, ranged from 1858 (Revista Farmacéutica, edited by the Argentinean Academy of Pharmacy and Biochemistry) to 2012.

Table 1 Number of journals according to country of origin

Country	*n* (%)
Spain	409 (23.3)
Mexico	240 (16.0)
Argentina	226 (15.1)
Chile	179 (11.9)
Colombia	94 (6.3)
Venezuela	70 (4.7)
Cuba	54 (3.6)
Ecuador	52 (3.5)
Peru	52 (3.5)
Uruguay	32 (2.1)
Costa Rica	23 (1.5)
Dominican Republic	23 (1.5)
Bolivia	18 (1.2)
Guatemala	7 (0.5)
El Salvador	6 (0.4)
Panama	5 (0.3)
Paraguay	4 (0.3)
Honduras	3 (0.2)
Puerto Rico	1 (0.1)
Total	1498 (100.0)

These data were unavailable for 63 (4.2%) journals. By 1992, 50% had already started publishing. During the period from 1996 to 2000, 264 (17.6%) journals began publication, the most of any 5-year period, followed by the periods between 1991 and 1995 and between 2001 and 2005, with 195 (13.0%) and 190 (12.7%) new journals, respectively (Figure 1).

A total of 1316 (87.9%) journals were active (defined as having published at least one issue during the past 2 years) as of 2012, while 125

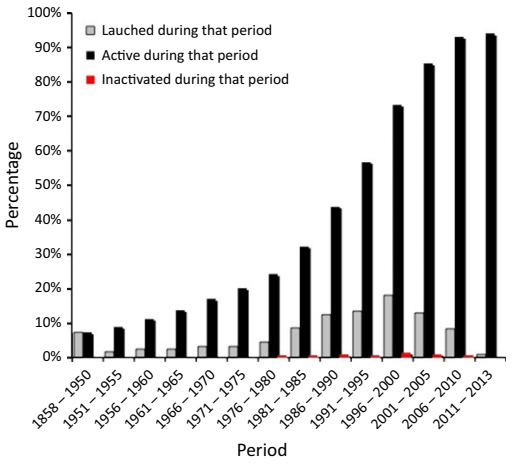

Figure 1 Time evolution of launching of biomedical journals in Spain and Latin America

(8.3%) were inactive. For 57 (3.8%) journals, it was not possible to determine the status of publication. The median length of publication for the journals with this information available was 22 years (interquartile range: 1981–2000), whereas the mean was 29 years (SD 20.6).

A total of 509 (34.0%) journals were not indexed in any bibliographic database. The remaining 989 (66.0%) are indexed in at least one database according to the following distribution: 522 (34.8% of indexed journals) in one database, 173 (11.5%) in two, 106 (7.1%) in three, 64 (4.3%) in four and 124 (8.3%) in five or more. LILACS and Periódica, with 17.4% and 10.5% of the journals, respectively, are the databases that index the most journals, whereas 5.9% can be found in SCIELO, 4.1% in MEDLINE and 3.7% in EMBASE. Figure 2 shows the percentage of publications indexed in each of the main databases. It should be mentioned that 1213 (82.0%) journals can be found in Latindex, which is a directory with information from scientific, professional and cultural journals from Latin America, but where the content of journals is not indexed.[17] Of these journals, 439 (29.3% of the total) can be found exclusively in this source, which are represented together with journals not indexed in any database (or in Latindex) under the 'none' category in Figure 2.

There were 845 journals with websites (56.4%), of which 815 (96.4%) are currently active and provide information about the scope of the journal, current status and type of articles published. Of the 845 websites, 681 (80.6%, 45.5% of all the identified journals) offer access free of charge or by simply providing basic contact information. Whether free of access or not, 700 (82.8%, 46.7% of all the identified journals) of the websites were searchable, 424 (50.2%, 28.3% of all the identified journals) for the entirety of the contents of the journals and 276 (32.7%, 18.4% of all the identified journals) for a portion of the contents. Links to each of the websites can be found in online supporting information Appendix S1 or at the IbCC website, www.cochrane.es.

The journals identified focused on 65 different medical specialties; the most frequent ones are shown in Figure 3.

Information on the publisher, entity or organisation responsible was available for 1250 (83.4%) of the journals, which were most commonly professional or scientific societies, publishers or academic institutions (see Table 2). The ISSN was found for 1318 (87.8%) of the identified journals. The remaining 180 (12.2%) journals were confirmed to be eligible publications despite not having an ISSN. These journals had active websites or were included in databases with searchable summaries that confirmed that they were published periodically and that included original research in their comments.

A total of 45 of the identified journals (3.60%) had an impact factor in 2012 according to the *Journal Citation Reports*®.[11] Most of these (26, 57.7%) are from Spain, the remaining being from Argentina (5, 11.1%), Chile (4, 8.9%), Colombia (3, 6.7%), Mexico (3, 6.7%) and Venezuela (4, 8.9%). Most journals rank in the fourth quartile of their respective categories, although five of them

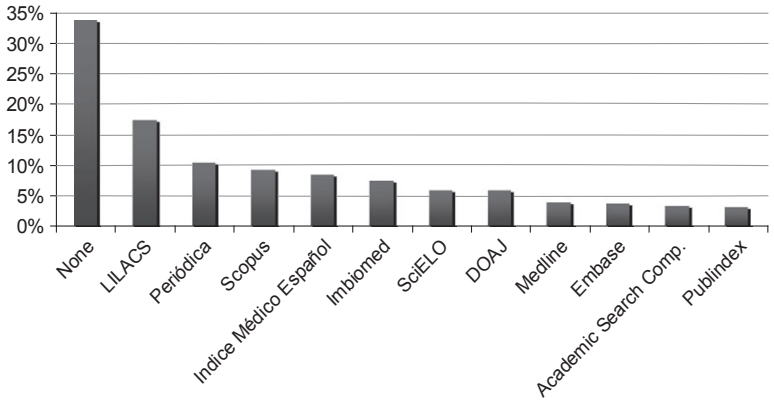

Figure 2 Percentage of journals published in each database

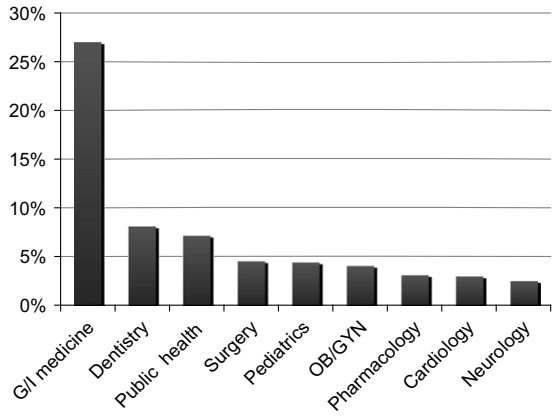

Figure 3 Distribution of journals according to most common medical specialties

Table 2 Type of agency responsible for publication

Type of agency	*n* (%)
Professional or scientific associations	452 (36.2)
Publishers	289 (23.1)
Academic Institutions	233 (18.7)
Public or governmental agencies	61 (4.9)
Health centres	55 (4.4)
Private agencies	53 (4.2)
Foundations and NGOs	45 (3.6)
Research centres	43 (3.4)
Others	19 (1.5)
Total	1250 (100.0)

(9.3%), all from Spain, ranked within the first or second quartile of their categories (Appendix 1).

Discussion

To our knowledge, this is the first study that aimed to compile a list as comprehensive as possible of biomedical journals that publish original research in Spain and Latin America, as well as the first that describes and analyses the distribution of these publications according to their main characteristics. This information, especially the list of journals and their websites provided in online supporting information Appendix S1 (also at the IbCC website), is invaluable to map out the current status of biomedical publications in the Spanish language and to gauge the relevance and accessibility of this body of scientific literature. In addition, it provides another tool that can be useful when searching for clinical trials from journals not indexed in any database for their inclusion in systematic reviews and other evidence synthesis documents.[4,5,18]

The results of this study reveal that there are 1498 biomedical journals, excluding mental health and nursing journals, which publish original clinical research in the Spanish language. While there are no direct criteria to judge whether the amount of journals published in a country or region is too high, indirect measures such as being indexed in databases and impact factor can be considered. In the case of Spain and Latin America, this study found that only about one-third of biomedical journals are indexed in more than one bibliographic database. At this current moment, no database acts as a primary source to conduct a literature search in Spanish and Latin American journals; the most active ones, LILACS and Periódica, index 17.4% and 10.5% of the identified journals, respectively. Moreover, the poor percentage of journals indexed in MEDLINE (4.1%) and EMBASE (3.7%) is worrisome, given the wide use and recognition associated with these databases by the international scientific community.[19]

In addition, only 45 of the identified publications (3.0%) have an impact factor as of 2012, generally ranking in the fourth quartile within their medical categories. Regional inequalities are evident, with only six of the 19 countries in the IbCN having journals with an impact factor. Spain accounts for over a half of these journals and presents a significantly higher mean impact factor (1.089, SD: 0.682) than the rest of the countries with impact factor journals: Argentina, 0.261 (SD 0.218); Chile, 0.237 (SD 0.172); Colombia, 0.186 (SD 0.093); Mexico, 0.251 (SD 0.087); and Venezuela, 0.187 (SD 0.142). It is likely that the low impact factor of these journals discourages many Spanish and Latin American authors from publishing their research in local journals.[20] Correspondingly, a recent exploratory electronic search in PUBMED (Nov. 2013) reveals that there are 576 references to studies indexed as a randomised controlled trial published by first or contact authors affiliated to Spanish or Latin American institutions in journals in the Spanish language. Conversely, there are

8035 randomised controlled trials of authors with a Spanish or Latin American affiliation published in journals in other languages. This as a trend raises some concerns, as the majority of the volume of research produced in Spain and Latin America is disseminated through publications written in different languages that are not always accessible to health care professionals in the region, depriving them of much needed access to this body of locally relevant knowledge.

Despite the fact that to be eligible for this study journals had to publish original clinical research, many of the identified publications belong to medical societies and professional associations that focus more on educational and promotional activities and less on disseminating original research.[21] In addition, 12.3% of the identified journals do not meet the minimal criteria required of academic journals: even though they are indeed periodical journals that publish some original research, they do not have an ISSN number, which is an internationally accepted code for identifying periodical publications.[22] Another study recently published determined that just 19.8% of a sample of 101 trials published in 2011 in 56 Latin American journals mentioned trial registration.[23] Of these journals, only 68% endorsed guidelines from the International Committee of Medical Journals Editors, and 36% required trial registration. An even lower percentage provided advice on the use of reporting guidelines such as CONSORT, PRISMA or STROBE.

In general, and in the light of the aforementioned data, the results of this study suggest that there may be an over-emphasis on launching new publications rather than on increasing the quality, visibility and accessibility of already-existing ones. The latter is of importance for Spanish and Latin American investigators as it would encourage them to disseminate their work in journals published in the Spanish language, facilitating access to local professionals who would benefit the most from such body of knowledge.[20]

As Figure 1 shows, there was a clear increase in the number of new journals starting in the 1980s, reaching a peak in the year 2000. From that point on, the number of newly appearing journals has been decreasing, especially during the last five analysed years. The distribution of active versus inactive journals, however, does not follow a similar pattern, and of the 1498 journals identified, only 156 are currently inactive, even though 173 of the total started activities over 50 years ago.

The distribution of journals according to country of origin reveals that over 70% (1148 or 70.4%) come from only four countries, namely Spain (27.3%), Mexico (16.0%), Argentina (15.1%) and Chile (11.9%). Conversely, Central America and the Caribbean have a very modest output, with 122 journals or 8.1% of the total. Interestingly, these data correlate directly with expenditure in research and development by each country. As reported in the UNESCO Science report, the GDP expenditure in research and development to GDP ratio in 2007 was highest in Spain (1.27), followed by Chile (0.67), Argentina (0.51) and Mexico (0.46). In terms of total expenditure, the same countries stand out, with Spain spending 15.7 US$ billions in 2007, followed by Mexico (3.5 US$ billions), Argentina (1.3 US$ billions) and Chile (0.6 US$ billions). The remaining Latin American countries spent a combined 2.9 US$ billions.[24]

The list of journals identified in this study and available in online supporting information Appendix S1 (and on the IbCC website) can serve as a starting point for projects that aim at handsearching scientific literature. One of such initiatives is currently being conducted at the IbCC, with the objective of identifying all controlled clinical trials published in Spain and Latin America by medical specialty to carry out a descriptive analysis of their main characteristics and potential risk of bias. In addition, these articles are made available in CENTRAL, the Cochrane Collaboration registry of controlled clinical trials.[25]

This study has several strengths. First, it covers the main scientific literature databases, which were searched systematically using a protocol that ensures the reproducibility of the process and adds external validity. Contributors at the IbCC who participated in this study have experience in conducting this type of searches, and have published articles that required the identification of all journals on a given medical specialty or condition.[10–12,26] In addition, this search was complemented by members of the IbCN in Latin America, who have a vast amount of experience in the completion of scientific reviews and other

documents of synthesis, and therefore solid knowledge on conducting comprehensive scientific literature searches.

This study, however, may have also been subject to some limitations. There were different teams in each country participating in this study. While this was necessary to optimise the journal identification process, it may have introduced heterogeneity. In addition, there may be journals that are currently active but that were missed because they were not indexed or included in any of the databases or sources consulted. However, the search for journals was complemented by collaborators in each country, who looked at libraries and other local repositories, probably overcoming this limitation. In addition, it is fair to assume that if such journals still exist, their use is very limited. Lastly, information on the main features of publications found in databases and repositories such as LILACS, Periódica or Latindex is sometimes outdated, especially regarding to whether journals are currently active and the type of research they publish.

Conclusions

In summary, there are a significant number of biomedical journals that publish original research in Spain and Latin America. However, most rate low in different indicators of quality AND/OR ARE NOT indexed in major databases, which may discourage local investigators from publishing their work in these journals. Geographical differences in number of journals, indexing and impact factor are significant. Information provided by the existing databases was incomplete and, at times, outdated, compared to the information provided by the available journals' websites. Having access to a list of biomedical journals such as the one compiled in this study (Appendix S1 or the IbCC website, www.cochrane.es) can be a useful resource to conduct handsearching activities for identifying clinical trials that otherwise would not be found for their eventual inclusion in systematic reviews.

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Competing interests

None declared.

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Supporting Information

Additional Supporting Information may be found in the online version of this article:

Appendix S1 List of identied journals, ISSN, country, websites

Received *20 June 2014*; Accepted *19 May 2015*

Appendix 1
Journals with an impact factor in the JCR classified per country and ranking within category

Country	Journal title (abbreviated)	ISSN	I.F.	Category	Ranking within category	Quartile within category
Argentina	Rev Argent Microbiol	0325-7541	0.543	Microbiology	108/116	Q4
	Medicina-Buenos Aire	0025-7680	0.423	Medicine, General and Internal	121/155	Q4
	Arch Argent Pediatr	0325-0075	0.323	Pediatrics	114/122	Q4
	Salud Cienc	1667-8982	0.018	Medicine, General and Internal	153/155	Q4
	Rev Nefrol Dial Trs	0326-3428	0.0	Urology and Nephrology	73/73	Q4
Chile	Rev Chil Infectol	0716-1018	0.452	Infectious Diseases	69/70	Q4
	Rev Med Chile	0034-9887	0.360	Medicine, General and Internal	124/155	Q4
	Rev Chil Cir	0718-4026	0.075	Surgery	197/199	Q4
	Acta Bioeth	1726-569X	0.061	Medical Ethics	18/18	Q4
Colombia	Biomedica	0120-4157	0.315	Tropical Medicine	20/22	Q4
	Vitae-Columbia	0121-4004	0.149	Pharmacology and Pharmacy	255/261	Q4
	Colomb Medica	1657-9534	0.094	Medicine, General and Internal	147/155	Q4
Mexico	Cir Cir	0009-7411	0.316	Surgery	180/199	Q4
	Rev Invest Clin	0034-8376	0.310	Medicine, General and Internal	128/155	Q4
	Gac med Mex	0016-3813	0.128	Medicine, General and Internal	144/155	Q4
Spain	Rev Esp Cardiol	0300-8932	3.204	Cardiac and Cardiovascular Systems	39/124	Q2
	Emergencias	1137-6821	2.578	Emergency Medicine	3/25	Q1
	Rev Esp Enferm Dig	1130-0108	1.652	Gastroenterology and Hepatology	53/74	Q3
	Enferm Infec Micr Cl	0213-005X	1.478	Infectious Diseases	58/70	Q4
				Microbiology	89/116	Q4
	Med-Clin Barcelona	0025-7753	1.399	Medicine, General and Internal	65/155	Q2
	Arch Bronconeumol	0300-2896	1.372	Respiratory System	41/50	Q4
	Med Intensiva	0210-5691	1.323	Critical Care Medicine	23/27	Q4
	Neurologia	0213-4853	1.322	Clinical Neurology	143/193	Q4
	Nutr Hosp	0212-1611	1.305	Nutrition and Dietetics	57/76	Q4
	Nefrologia	0211-6995	1.274	Urology and Nephrology	55/73	Q4
	Allergol Immunopath	0301-0546	1.229	Allergy	16/23	Q3
				Immunology	120/137	Q4
	Rev Neurologia	0210-0010	1.179	Clinical Neurology	154/193	Q4
	Actas Urol Esp	0210-4806	1.144	Urology and Nephrology	57/73	Q4
	Gac Sanit	0213-9111	1.116	Public, Environ. And Occupational Health	115/161	Q3
	Med Oral Patol Oral	1698-6946	1.017	Dentistry, Oral Surgery and Medicine	53/83	Q3
	Aten Prim	0212-6567	0.957	Primary Health Care	13/18	Q3
				Medicine, General and Internal	86/155	Q3
	Cir Espan	0009-739X	0.871	Surgery	137/199	Q3
	An Pediatr	1695-4033	0.867	Pediatrics	91/122	Q3
	Rev Esp Med Nucl Ima	2253-654X	0.863	Radiology, Nuclear Medicine, and Medical Imaging	100/120	Q4
	Gastroent Hepat-Barc	0210-5705	0.567	Gastroenterology and Hepatology	69/74	Q4
	An Sist Sanit Navar	1137-6627	0.351	Public, Environ. And Occupational Health	153/161	Q4
	Neurocirugia	1130-1473	0.343	Neurosciences	242/252	Q4
				Surgery	177/199	Q4

(continued)

Appendix 1 *(continued)*

Country	Journal title (abbreviated)	ISSN	I.F.	Category	Ranking within category	Quartile within category
	Med Paliativa	1134-248X	0.326	Health Care Sciences and Services	83/83	Q4
	Rev Int Androl	1698-031X	0.256	Andrology	6/6	Q4
	Rev Int Med Cienc Ac	1577-0354	0.205	Sports Sciences	81/84	Q4
	Aten Farm	1139-7357	0.125	Pharmacology and Pharmacy	257/261	Q4
Venezuela	Invest Clin	0535-5133	0.394	Medicine, Research and Experimental	108/121	Q4
	Arch Latinoam Nutr	0004-0622	0.241	Nutrition and Dietetics	73/76	Q4
	Kasmera	0075-5222	0.071	Tropical Medicine	21/22	Q4
	Arch Latinoam Nutr	0004-0622	0.241	Nutrition and Dietetics	73/76	Q4

5.2.3. Tercera publicación

Identification and description of controlled clinical trials published in Physiotherapy journals in Spain. J Eval Clin Pract. 2017 Feb;23(1):29-36. Factor de impacto 2015: 1,05. Segundo cuartil en revistas de la categoría "Salud pública, ambiental y ocupacional".

Journal of Evaluation in Clinical Practice
International Journal of Public Health Policy and Health Services Research

Journal of Evaluation in Clinical Practice ISSN 1365-2753

Identification and description of controlled clinical trials published in Physiotherapy journals in Spain

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Keywords
evidence-based medicine, medical research, structured reviews

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Abstract

Rationale and objectives The quantity and quality of research in physiotherapy has increased exponentially during the past decades. However, retrieving publications associated with this field of research is difficult. The aim of this study is to identify and describe controlled clinical trials (CCT) published in Spanish physiotherapy journals using electronic and handsearching strategies.

Method Observational study through which we identified eligible journals in order to retrieve CCTs using electronic and handsearching strategies, as proposed by the Cochrane Collaboration. A descriptive analysis of the main characteristics of these CCTs was completed.

Results Seventy-eight CCTs were identified in 10 eligible journals, none of which were indexed in the major databases. 16.7% of the identified studies were multicentric. Traumatology and orthopaedics was the most studied field (33.3%) followed by neurology (15.4%). The most researched health problems were back pain (17.24%) fibromyalgia, arthrosis and stroke (6.8% each). Measured outcomes varied greatly, including pain control, functional mobility and quality of life. Most CCTs (64.1%) had a high risk of bias.

Conclusions The number of CCTs published in Spanish physiotherapy journals is limited. Handsearching these journals is essential, since none is indexed in major databases. In general, the identified CCTs carry a high risk of bias.

Introduction

Ever since the first controlled clinical trial (CCT) on physiotherapy was published in 1930, the quality and quantity of publications on this field has grown exponentially [1–3]. Nowadays, if a search of CCTs on physiotherapy is conducted in PubMed, over 17 000 references will be retrieved. PEDro (Physiotherapy Evidences Database), an evidence-based physiotherapy database, also presents a significant increase in activity, doubling the number of CCTs and systematic reviews every three and a half years [4].

Evidence-based medicine is defined as 'the conscious, explicit and judicious use of the best clinical evidence available to make decisions of the healing of patients' [5]. Applied to physiotherapy, this approach is known as evidence-based physiotherapy [6]. Evidence-based physiotherapy enables a structured approach to research and practice in this field, improving the understanding of research methods, providing scientific support to clinical and managerial decision making, reducing the variability of interventions and facilitating access to more effective practices [1–7].

The best clinical evidence of the effect of a health care intervention is provided by CCTs [4,8]. It is imperative to base decision making not only on one's own knowledge but also on the results of research projects, bearing in mind at all times that CCTs with an inadequate methodology may involve exaggerated estimates of the effects of interventions [9].

Evidence-based physiotherapy relies on having access to the entire body of evidence provided by CCTs, which is achieved with an electronic search of the available literature complemented with a handsearching strategy [10]. The former, which relies on electronic filters and keywords, presents low sensitivity and precision [11,12]. Handsearching of literature, which involves progressive, page-by-page examination of all issues of a given journal [10], is a tool that allows circumventing these shortcomings.

Several studies that aimed at identifying CCTs combining electronic and handsearching strategies conducted in anaesthesiology [13], general and internal medicine [14], and patient safety [15] journals confirm these results. Through these projects, it has been found that the sensitivity of the electronic searches (proportion of all studies identified via electronic search over those identified via handsearch) does not exceed 69%, while the specificity (truly eligible studies among all those retrieved via the electronic search strategy) does not exceed 50%.

Nevertheless, access to clinical evidence and the time needed to scrutinize it are two key limitations that block the practice of evidence-based physiotherapy [10]. A survey in the UK and Australia shows that between 20% and 44% of physiotherapists reported difficulties to access scientific literature, and between 31% and 61% stated that they had no time to read scientific articles [16,17].

This study aimed to identify all CCTs conducted in physiotherapy and published in physiotherapy journals in Spain. Additionally, and in order to obtain a clearer picture of the strengths and challenges of research in physiotherapy, a description of the methodological aspects of CCTs identified was performed, including an assessment of potential risk of biases and quality of reporting results [18,19]. Lastly, the identified articles will be submitted for inclusion in the Cochrane Central Register of Controlled Trials (CRS).

Methods

We conducted a descriptive observational study that consisted of two parts: identification of eligible journals and handsearching of CCTs with a corresponding descriptive and risk of bias analysis of the retrieved studies.

Identification of journals

The first step of this study consisted of selecting the journals that were to be handsearched. Eligibility criteria included physiotherapy journals published in Spain that disseminate original research. Journals were identified through PubMed (MEDLINE), the Spanish Medical Index (IME), the National Catalogue of Periodicals in Spanish Health Science Libraries C-17 (edited by *Centro de Información y Documentación Científica* (CINDOC), Latindex, Periodic, LILACS and SciELO. We excluded journals that do not publish original research and that focus instead on educational, promotional, or commercial contents.

Identifications of controlled clinical trials

Handsearching of the identified journals was conducted following the guidelines provided by the Cochrane Collaboration. These state that each journal article must be carefully reviewed, including not only original articles but also other types of studies, letters to the editor, abstracts, and conference presentations. The recommended steps for handsearching a journal are: (1) reading the table of contents; (2) locating keywords in the title of the article (e.g. randomized, random, blinded, etc.); (3) reading the abstract; and (4) reading the methods section in the full text of the article.

Handsearching of journals has to be performed retrospectively, starting backwards with the latest issue published. If no CCTs are identified in five consecutive years in a given journal, the handsearch can be stopped for that journal since it is assumed that no CCTs will be found from that point onward.

In line with the recommendation from the Cochrane Collaboration, each reviewer conducted a pilot test consisting of reviewing a volume of a journal that had been previously handsearched by experts in this field.

Furthermore, an electronic search was planned in PubMed (MEDLINE) in order to identify CCTs published in the eligible journals of this study and to compare results with those of the handsearching strategy.

Inclusion and exclusion criteria

In order to be considered a CCT, and in line with the criteria proposed by the Cochrane Collaboration, a study had to

1 Compare treatments in humans.

2 Be prospective: interventions must have been planned before the study took place.

3 Compare two or more physiotherapy treatments or interventions, one of which can be a no-treatment control group or a placebo. The interventions can be of any type: diagnostic, rehabilitative, educational, etc.

4 Have a random method of allocation to treatment.

- Randomized CCTs: authors explicitly state that compared groups were formed by random assignment, generally describing the allocation method.
- Quasi-randomized CCTs: authors attempt to form intervention groups with similar characteristics. Methods to achieve this end include allocation by date of birth, day of the week or month of the year, even and odd numbers, medical record number, etc.

We excluded articles that were references to or translations into Spanish of work published elsewhere.

Handsearching of journals was conducted individually. Two authors (MT and MS) verified that all potential CCTs identified were indeed eligible. Discrepancies were resolved by consensus or by consulting a third author (HP).

Data extraction

In order to ensure that data were collected in an orderly and systematic fashion, a database was created to record each CCT identified and to track the progress of the project. A data collection logbook including all outcomes of interest was also developed.

An assessment of risk of bias (high/medium/low) of the identified CCTs was also conducted, using the tool provided by the Cochrane Collaboration for this purpose [20]. This instrument evaluates aspects of CCTs methodology such as random sequence generation, allocation concealment, blinding of patients or investigators, and reasons for missing data (if applicable). In addition, it was recorded whether the authors adhered to the CONSORT tool

for non-pharmacological interventions (CONSORT-NPT tool) [18] when reporting the results of their research projects.

Analysis

A descriptive analysis of the outcomes of interest was performed using SPSS version 17.0 (SPSS, Inc., Chicago, IL, USA).

Results

Ten physiotherapy journals published in Spain were identified, none of which were indexed in PubMed (MEDLINE), CENTRAL, EMBASE or CINAHL. A total of 451 issues with 3775 articles were handsearched. Of these, 78 (2.07%) were CCTs (see Fig. 1, Table 1). Ten reviewers participated in this stage of the project.

The first CCT was published in 1980 in the journal *Rehabilitación* (Salvador E, Alvarado AG. La infiltración epidural en el tratamiento de las lumbalgias. *Rehabilitación*. 1980;14(2): 165–174.), which evaluated the efficacy of kinesiotherapy plus electrotherapy with and without lumbar spinal traction in low back pain. Thereafter, a progressive increase in the number of CCTs published was observed. The highest number of CCTs were published in 2011 (20.5% of all identified studies), followed by 2012 (19.2%). Between 2008 and 2012 alone, over 64% of the identified articles were published. Figure 2 shows the number of publications of CCTs per 5-year interval.

The journal with the most CCTs was *Rehabilitación*, with 28 CCTs representing 35.9% of the total, followed by *Fisioterapia* with 25 CCTs (32.1%). Most CCTs were conducted in one centre (65, 83.3%), whereas only 16.7% were multicentre. The most common settings were hospitals (28 CCTs, 35.9%), followed by universities (12 CCTs, 15.4%), others institutions (such as fitness centres, associations, etc.;11 CCTs, 14.1%), physiotherapy centres (10 CCTs, 12.8%), nursing homes (6 CCTs, 7.7%) and primary

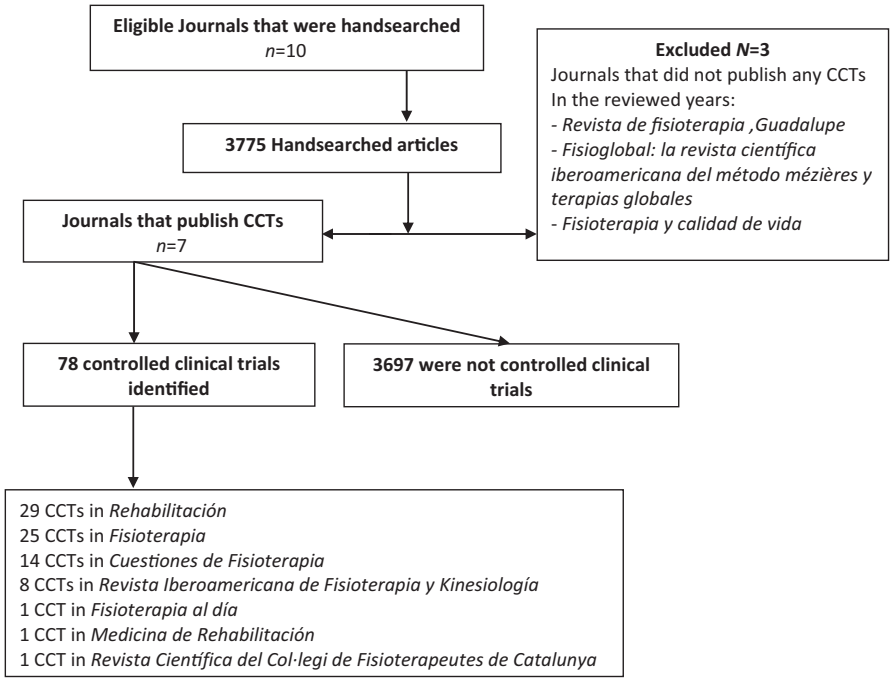

Figure 1 Journals and CCTs eligibility flow chart.

Table 1. Identified journals and Clinical Controlled Trials found

Journal (revision period)	No. of revised articles	No. of CCTs found	% of total CCTs
■ Cuestiones de Fisioterapia (2003–2012)	154	14	17,9
■ Fisioglobal: La revista científica Iberoamericana del Método Mézières y terapias globales (2008–2011)	24	0	0
■ Fisioterapia (1985–2012)	895	25	32,1
■ Fisioteràpia al día (2003–2012)	92	1	1,3
■ Fisioterapia y calidad de vida (2008–2012)	67	0	0
■ Medicina de Rehabilitación (1999–2004)	167	1	1,3
■ Rehabilitación (1975–2012)	2157	28	35,9
■ Revista científica del colegio de fisioterapeutas de Catalunya (2011–2012)	13	1	1,3
■ Revista de Fisioterapia (Guadalupe) (2007–2011)	61	0	0
■ Revista Iberoamericana de Fisioterapia y Kinesiología (1998–2011)	145	8	10,3
TOTAL:	3775	78	100

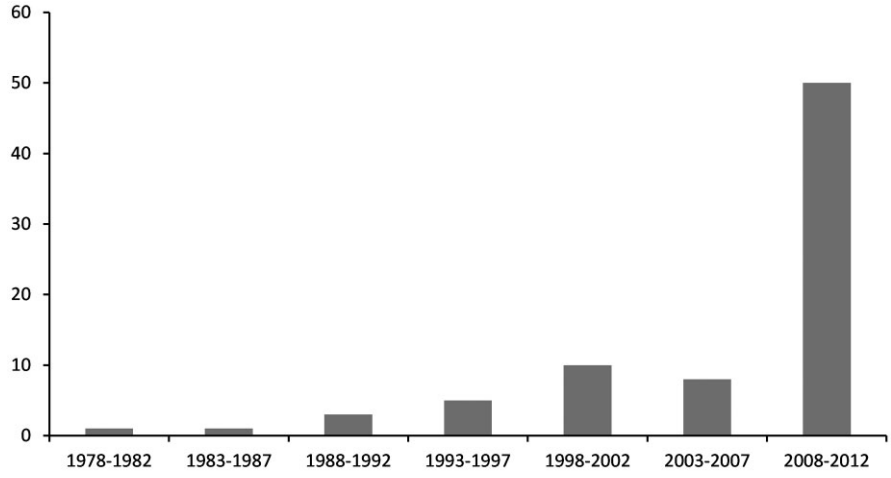

Figure 2 Number of CCTs published in 5-year intervals.

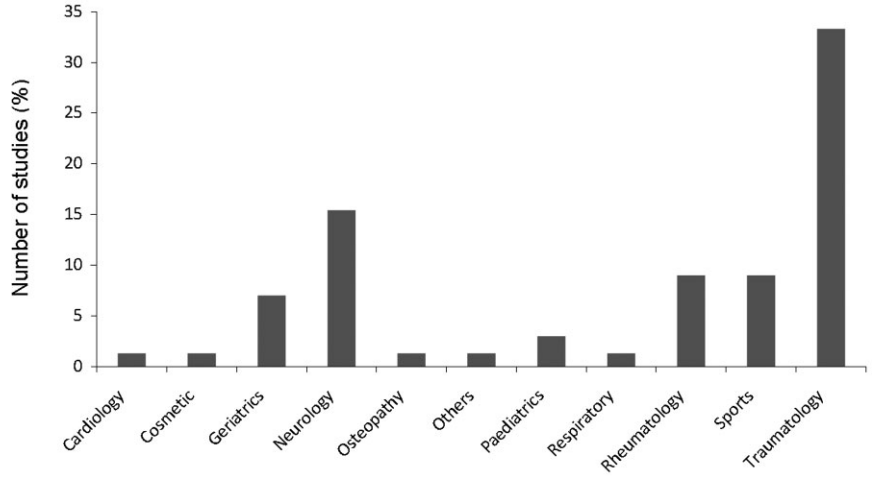

Figure 3 Medical subspecialty.

care centres (4 CCTs, 5.1%). Regarding medical subspecialty, traumatology and orthopaedics was the most studied field (33.3%) followed by neurology (15.4%) (see Fig. 3).

Age of participants varied greatly, ranging from 13 to 80 with a mean of 82.3, but this variable was not reported in 34 CCTs, or 43.6% of the identified studies. In 59 CCTs (75.6%), the sex of participants was reported; for those that did, men accounted for 41.0% of the total (SD 29.4) compared to 59.1% of women.

The most studied health problems were back pain (cervical and low back pain; 17.24%) followed by fibromyalgia, arthrosis and stroke (6.8% each) spinal cord injuries, knee osteoarthritis and knee replacement (3.8% each; see Fig. 4). Nevertheless, the majority of the identified studies were performed on healthy subjects (focusing on the effects of electrotherapy, manual therapy or the effects of muscle strengthening).

The most common main outcome in the identified studies was pain control, followed by functional mobility, range of movement and quality of life. Measures used to evaluate outcomes are shown in Appendix S1 online (also available at the Iberoamerican Cochrane Centre website, http://www.cochrane.es).

Fifty-six (71.8%) of the identified CCTs reported total treatment duration. Most CCTs lasted a day or a period of 2–3 weeks (19.6%, 11 CCTs each), followed by 8 weeks (17.9%, 10 CCTs), 4 weeks (16.1% or 9 CCTs), 12 weeks (14.3% or 8 CCTs) and 12 weeks or more (12.5%, 7 CCTs; see Appendix S1 online, also available at the Iberoamerican Cochrane Centre website, http://www.cochrane.es).

Forty-eight CCTs (61.5%) reported number of sessions of physiotherapy intervention held weekly during the treatment period. 16 (20.5%) reported more than three sessions per week, another 16 (20.5%) conducted two or three sessions, and 16 (20.5%) with a single weekly session (or simply a single session). However, 30 RCTs (38.5%) did not report this information (see Appendix S1 online, also available at the Iberoamerican Cochrane Centre website, http://www.cochrane.es).

The duration of each session of physiotherapy intervention was not reported in 45 CCTs, representing (57.7%). Among those that did, 77.4% lasted less than one hour, 19.4% lasted between 1 and 2 hours, and 3.2% lasted over 2 hours (see Appendix S1 online, also available at the Iberoamerican Cochrane Centre website, http://www.cochrane.es). Follow-up of patients varied greatly, from less than 1 month (3 CCTs, 3.9%), to 1 month (9, 11.5%), 2–6 months (19, 24.4%), or over 6 months (2, 2.6%). This information was not reported in 45 CCTs 57.7%.

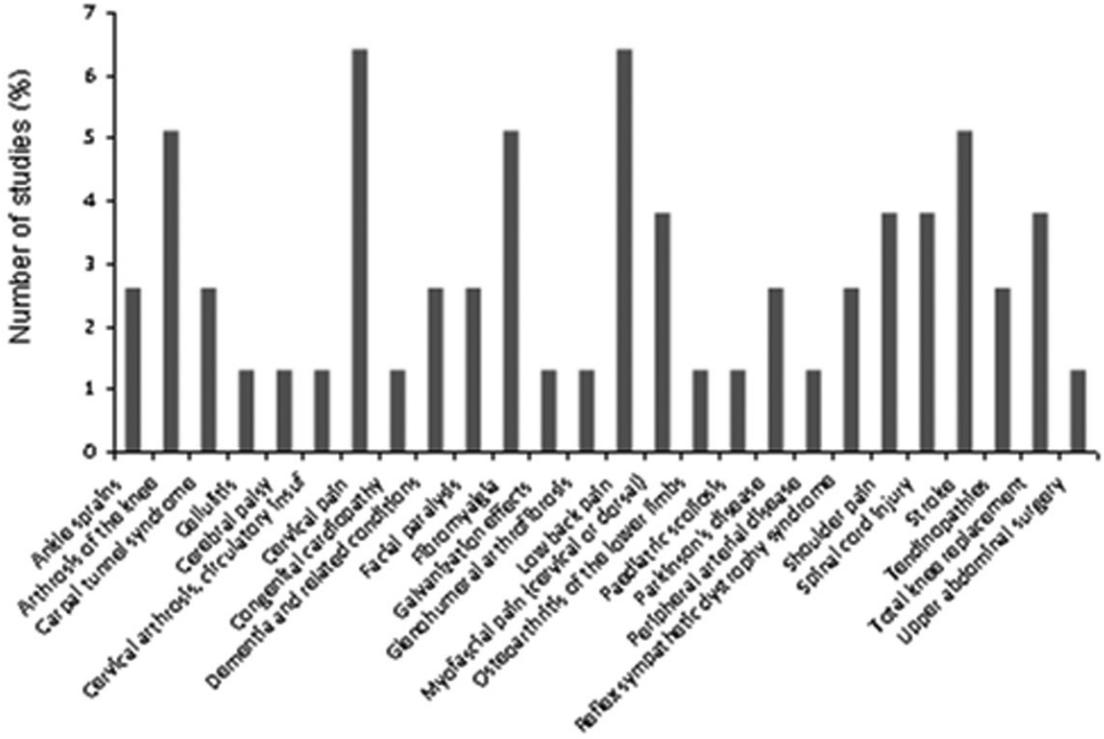

Figure 4 Researched health problem.

The quality of the included studies presented several shortcomings that are described in Table 2. A total of 27 of the identified studies (34.6%) were classified as randomized CCTs, whereas 51 were quasi-randomized (65.4%). Most CCTs had a high risk of bias (64.1%). A total of 61.5% did not generate the randomization sequence adequately and 67.9% did not conceal allocation of patients to treatments or interventions. Blinding was adopted by 36 CCTs, equivalent to 46.2% of the total. Regarding the CONSORT tool, two CCTs (2.6%) reported using it in the drafting of the report. Groups at the beginning of the study were comparable in 74.4% of the studies. In 65.4%, there was no missing relevant data. For the remaining studies, 24.4% specified reasons for such omissions, while 10.3% did not.

Concerning source of funding, 91.1% of authors did not specify whether they received funds to conduct their research. Of those that did, 6.4% received private funding compared to 2.6% who received public funding. Conflicts of interest were reported by 39.7% of authors.

Figure 5 provides a summary that allows assessing the overall risk of bias of the identified CCTs at a glance.

The electronic search conducted in PubMed (MEDLINE) retrieved 175 CCTs on physiotherapy conducted by authors affiliated to Spanish institutions. However, these studies were found either in journals published in other countries or in journals that did not focus exclusively on physiotherapy. These studies will be analysed in a future research project. It should be noted that since none of the journals handsearched in this study were indexed in PubMed, there was no overlap between the CCTs identified through both searches.

Discussion

The main aim of this article was to identify and describe all the CCTs published in Spanish physiotherapy journals, to assess their methodological quality, and to, subsequently, incorporate them into CRS.

Despite an increase in physiotherapy research in recent years [1,3], the number of CCTs identified in Spanish physiotherapy journals is low. A total of 78 CCTs published between 1980 and 2012 were found, corresponding to an average of 2.4 CCTs per year.

Most CCTs were published in *Rehabilitación* (35.9%) and *Fisioterapia* (32.1%). Thus, these journals stand as leaders in the dissemination of research on physiotherapy in Spain.

Regarding researched health problems, back pain, including low back and cervical pain, was the condition that gathered the most attention from investigators. This was expected since, according to the Spanish National Health Survey in 2011–2012, back pain is one of the most common health ailments in the country [21], with a high impact on quality of life and sick leaves, and its corresponding effect on productivity [22]. Back pain is closely associated with body posture and a sedentary lifestyle, both of which can be targeted using physiotherapy interventions [23].

Another commonly addressed health issue was hypertension, which is also identified as a serious public health problem among adults in Spain [21]. Additionally, there was a marked interest on researching the effects of physiotherapy interventions on functional mobility of patients after a stroke.

However, there is a lack of studies that investigate the impact of physiotherapy intervention on other chronic diseases such as diabetes, obesity or hypercholesterolemia. In addition, and despite the fact that Spain is one of the countries with a higher proportion of elderly citizens [24], research on geriatric populations remains scant.

Most studies were conducted in hospitals. However, there was almost no research conducted on surgical patients, which is the most common reason for hospitalization in Spain [21]. It would therefore be of invaluable importance to research the effect of physiotherapy interventions on the recovery of post-surgical patients and on reducing costs associated with hospital stays.

Table 2 Methodological quality of identified studies

Category	*n*	%
Funding		
Public	2	2,6
Private	5	6,4
Not reported	71	91,0
Conflicts of interest		
Reported	31	39,7
Not reported	47	60,3
Risk of bias		
Low	6	7,7
Moderate	22	28,2
High	50	64,1
Comparable groups at study beginning		
Yes	58	74,4
No	3	3,8
Not reported	17	21,8
Adequate randomization		
Yes	25	32,1
No	48	61,5
Not reported	5	6,4
Assignment concealment		
Yes	13	16,7
No	53	67,9
Not reported	12	15,4
Blinding		
Yes	36	46,2
No	34	43,6
Not reported	8	10,3
Reasons for missing data		
Yes	19	24,4
No	2	2,6
Not applicable	51	65,4
Not reported	6	7,7
Use of CONSORT recommendations		
Yes	2	2,6
No	76	97,4

Pain control and quality of life are the main outcome of interest in the identified studies. Physiotherapy interventions that address these variables can also have an effect on other conditions associated with chronic diseases, such as depression, insomnia and anxiety [25]. The lack of research on these variables highlights the need to include them in future studies, which would both broaden the field of action of physiotherapy interventions and incorporate new tools to assess the efficacy of these interventions.

This study underlines the variety of interventions that physiotherapists implement treating patients. In addition, while over 40% of studies conducted two or more weekly sessions per intervention, in general, treatment period was short (3 months or less). This may be reflective of budgetary restrictions or that studies focused on short-term results.

The overall methodological quality of the included studies was low. In over 60%, the randomization sequence was not generated adequately and in 67.9%, this sequence was not concealed. As a result, the fact that a study is classified as randomized does not guarantee that it meets the methodological standards associated with this type of studies [23]. Additionally, 65.4% of CCTs were classified as quasi-randomized.

A method for masking physiotherapy interventions was reported by 46.2% of CCTs. This result is encouraging given the difficulties of blinding researchers or patients in this field. Most studies reported all the data they had planned to disseminate; when they did not, they provided reasons for such omissions. This good practice ensures transparency in the flow of patients throughout the study and decreases the chance of biased results.

Authors provided information on sources of funding in only seven CCTs (9.0%) compared with 71 CCTs (91.0%) that did not report any information on this matter. This finding is in line with García-Alamino *et al.* [23], who observed that, in a high percentage of cases, authors did not specify the source of funding for their studies. Likewise, there was no mention of potential conflicts of interest, or lack thereof, in over half of the CCTs identified.

Only two authors mentioned adhering to the CONSORT-NPT tool. Given the deficiencies in the reporting of results in the identified CCTs, it is essential to promote the dissemination of this tool among physiotherapists, which will undoubtedly have a positive impact on the quality of their publications.

One of the major strengths of this study is the large number of documents reviewed, a total 451 numbers published in 10 journals

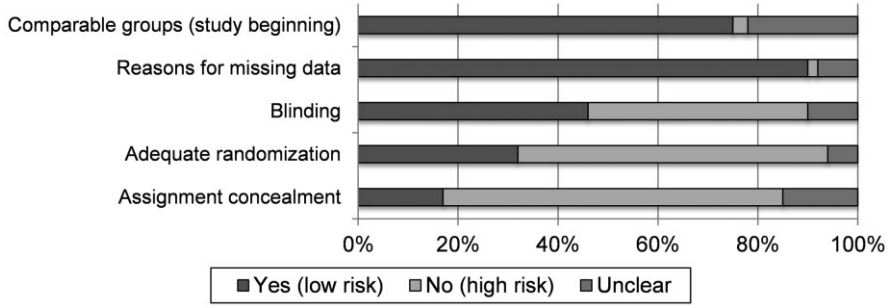

Figure 5 Risk of bias summary.

(until 31 December 2012). Handsearching – always in accordance with the criteria of the Cochrane Collaboration – was systematic and exhaustive for all volumes and supplements, including letters to the editor, abstracts, conferences and monographs.

The CCTs identified in this study would not have been retrieved through an electronic search in PubMed (MEDLINE), as the reviewed journals were not indexed in this database. This is further evidence of the limitations of searches conducted exclusively electronically [21] and the invaluable role of handsearching to identify CCTs, especially those reported as abstracts, letters to the editor or reported in languages other than English [22].

One possible limitation of this study is that the review of journals was conducted individually and without corroboration from another author, which might have resulted in eligible CCTs being discarded. However, the possibility of false positives was minimized since the 78 identified CCTs were verified by at least two of the authors. In addition, this paper focused only on Spanish physiotherapy journals and excluded international publications. Future studies currently underway at the Iberoamerican Cochrane Centre will focus on Latin American physiotherapy journals and on journals that publish physiotherapy original research articles indexed in bibliographic databases.

For future research, similar studies could be carried out in international publications, which would permit a wider analysis of the current status of research in the field of physiotherapy. It would also be interesting to consider other types of study designs to assess the effect of health interventions, such as systematic reviews, as well as to expand this work to fields that are closely associated with physiotherapy, such as osteopathy.

In conclusion, the number of physiotherapy CCTs published in the identified Spanish journals is limited. Handsearching these journals is essential for the identification of such CCTs, as eligible Spanish physiotherapy journals are not indexed in PubMed (MEDLINE).

Most studies investigated the effect of physiotherapy interventions on back pain, fibromyalgia, arthrosis and stroke, assessing outcomes such as pain control, functional mobility and quality of life. These studies, however, were conducted on healthy patients in a majority of cases and had short follow-up periods.

In general, the identified CCTs carry a high risk of bias. Therefore, it is recommended that authors adhere to the CONSORT-NPT tool and to standard recommendations to reduce risk of bias when conducting CCTs and to improve the quality of future research.

Conflict of interest

The authors declare no conflict of interest.

Ethical approval

No ethical approval required for this study.

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Supporting information

Additional supporting information may be found in the online version of this article at the publisher's web site.

5.2.4. Cuarta publicación

BADERI: An online database to coordinate handsearching activities of controlled clinical trials for their potential inclusion in systematic reviews. Trials 2017 18:273 DOI: 10.1186/s13063-017-2023-3. Factor de impacto 2016 (último disponible): 1,97. Primer cuartil entre revistas de la categoría "Medicina – Misceláneas".

Pardo-Hernandez et al. Trials (2017) 18:273
DOI 10.1186/s13063-017-2023-3

Trials

RESEARCH Open Access

BADERI: an online database to coordinate handsearching activities of controlled clinical trials for their potential inclusion in systematic reviews

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Abstract

Background: Systematic reviews provide the best evidence on the effect of health care interventions. They rely on comprehensive access to the available scientific literature. Electronic search strategies alone may not suffice, requiring the implementation of a handsearching approach. We have developed a database to provide an Internet-based platform from which handsearching activities can be coordinated, including a procedure to streamline the submission of these references into CENTRAL, the Cochrane Collaboration Central Register of Controlled Trials.

Methods: We developed a database and a descriptive analysis. Through brainstorming and discussion among stakeholders involved in handsearching projects, we designed a database that met identified needs that had to be addressed in order to ensure the viability of handsearching activities. Three handsearching teams pilot tested the proposed database. Once the final version of the database was approved, we proceeded to train the staff involved in handsearching.

Results: The proposed database is called BADERI (Database of Iberoamerican Clinical Trials and Journals, by its initials in Spanish). BADERI was officially launched in October 2015, and it can be accessed at www.baderi.com/login.php free of cost. BADERI has an administration subsection, from which the roles of users are managed; a references subsection, where information associated to identified controlled clinical trials (CCTs) can be entered; a reports subsection, from which reports can be generated to track and analyse the results of handsearching activities; and a built-in free text search engine. BADERI allows all references to be exported in ProCite files that can be directly uploaded into CENTRAL. To date, 6284 references to CCTs have been uploaded to BADERI and sent to CENTRAL. The identified CCTs were published in a total of 420 journals related to 46 medical specialties. The year of publication ranged between 1957 and 2016.

Conclusions: BADERI allows the efficient management of handsearching activities across different countries and institutions. References to all CCTs available in BADERI can be readily submitted to CENTRAL for their potential inclusion in systematic reviews.

Keywords: Information storage and retrieval, Database searching, Database development, Systematic reviews, Randomized controlled trial, Handsearching

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Background

Systematic reviews and meta-analyses of randomized controlled trials (RCTs) provide the best evidence on the effect of health care interventions [1]. They review and integrate the available evidence through an assessment of research results, the methodological quality, and the risk of bias of the corresponding studies, facilitating an estimation of the confidence that can be placed on its conclusions [2], as proposed by the Grading of Recommendations Assessment, Development and Evaluation (GRADE) approach [3, 4]. Systematic reviews rely on a comprehensive and unbiased identification of available studies [5, 6]; developers must therefore be aware of the possibility of dissemination bias when conducting their literature searches. Dissemination bias has been defined as "the publication or non-publication of research findings, depending on the nature and direction of the results" [1].

Several initiatives around the world are currently committed to raising awareness and addressing the issue of dissemination bias, including AllTrials [7] and REWARD (Reduce research Waste And Reward Diligence) [8], as well as the Declaration of Helsinki [9], the World Health Organization' (WHO's) standards and operational guidance for ethics review of health-related research with human participants [10], the Code of Conduct of the Committee on Publication Ethics [11], and the ethical resources provided by the World Association of Medical Editors [12, 13], among others [14].

An approach to potentially address the issue of dissemination bias involves handsearching journals in order to identify controlled clinical trials (CCTs). Handsearching is defined as a progressive, page-by-page examination of all issues of a given journal, assessing all sections until each article can either be dismissed or classified as a CCT [15]. By implementing a handsearching strategy, issues of poor indexation and non-detection of studies published in journals not indexed in major databases or published in different languages can be overcome. Studies that have compared the proportion of studies identified via handsearching against those identified adopting electronic search strategies confirm the superiority of the handsearching approach [16–19].

One of the main promoters of handsearching worldwide is the Cochrane Collaboration, through different initiatives coordinated among review groups and Cochrane centres. As such, the Iberoamerican Cochrane Centre (IbCC), in collaboration with the Iberoamerican Cochrane Network (IbCN), conducts an initiative aimed at identifying all CCTs published in Spain and Latin America [20]. The project consists of handsearching journals of several medical specialties, obtaining the full text of any CCT that has been published, and carrying out a descriptive analysis of the main characteristics and potential risk of bias of the identified CCTs [17, 20, 21]. Through this effort, more than 4000 articles have been identified to date in more than 300 journals that have been handsearched completely or partially. Additionally, references to the CCTs identified are submitted to the Central Register of Controlled Trials (CENTRAL), the Cochrane Collaboration repository of CCTs [22, 23]. The results of these efforts have been disseminated in several publications, including studies on handsearching of CCTs in Dermatology [24, 25], Physiotherapy [26], Gynaecology [17], patient safety [16], General and Internal Medicine [27], Anaesthesiology (one journal in Spain) [28], and Dentistry (Villanueva J, Delgado I, Saldarriaga J, García Gargayo M, Amaro Y, Zapata S, Núñez L, Zamorano G, Pardo-Hernandez H, Bonfill, X, Martin C: Identification and description of controlled clinical trials in Spanish language dentistry journals, submitted), among others. Likewise, handsearching activities are underway again for Anaesthesiology, as well as for Geriatrics, Neurology, Oncology, Paediatrics, and Orthopaedics and Traumatology.

In order to address these challenges, we aimed to develop an Internet-based platform from which the handsearching activities could be coordinated. This tool would serve as a secure database for registering the journals that have been handsearched and the CCTs that have been identified. Additionally, it would facilitate coordinating the activities of several handsearching teams in different countries and institutions in Spain and Latin America, tracking the completed work to avoid duplication, verifying results, classifying and storing the CCTs identified, and planning future undertakings. Lastly, this platform would expedite the submission of the identified CCTs to CENTRAL for potential inclusion in systematic reviews and other documents of synthesis. In this article we present the methodology adopted to design and create this database and the results of its launching and implementation.

Methods

The methods include database development and descriptive analysis of CCTs.

Database development

The database development process started in September 2013. Through brainstorming and discussion among staff and stakeholders involved in handsearching projects, we identified needs that should be solved in order to ensure the viability of the handsearching enterprise. We contracted the services of an information technology (IT) company to set up a webpage that would host the proposed database, incorporating features that would address the identified needs. The development process of the database is summarized in Fig. 1.

We iteratively assessed and tested different versions of the database, proposing at each time changes and add-ons to improve its accessibility, practicality, and

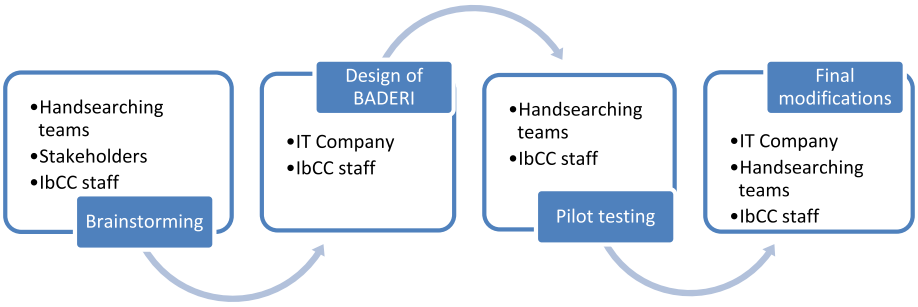

Fig. 1 Flowchart for the development of BADERI: tasks and personnel responsible

usefulness. We uploaded the titles of more than 1500 journals, which had been identified in a previous study [21], that were potentially eligible for handseaching. In order to be included in this database, journals had to publish original articles on biomedical research, regardless of language or country of origin and of whether they were indexed in any database or had an impact factor. Journals that focussed exclusively on academic or promotional activities were excluded. The entire development process lasted 18 months until the database was ready for pilot testing among different handsearching teams in March 2015.

Pilot testing of the database

Three handsearching teams were recruited for pilot testing the database. They were involved in handsearching activities for Gynaecology, Ophthalmology, and Orthopaedics and Traumatology. They were asked to enter references of identified CCTs into the database, including study authors, journal of publication, and volume, year, and issue number where the CCT was published, among other data as described below. They were also required to verify that the data had been entered correctly using the built-in search engine and to create reports to track the progress of their handsearching activities.

Database updating

Based on the feedback received from the staff that pilot tested the database, we incorporated new features and modified existing ones, once again through iterative discussion among stakeholders and staff at the IbCC. Additionally, it was planned that the design and features of the database will be revisited continuously as more users give us feedback about their experience in implementing their handsearching activities.

Launching of the database and early activities

Once the final version of the database was approved, we proceeded to train the staff involved in handsearching projects. As reported elsewhere, the handsearching activities are conducted following the guidelines provided by the Cochrane Collaboration [1, 15]. These require that each journal issue be carefully inspected, assessing not only original articles but also editorials, letters to the editor, abstracts, and conference presentations. The recommended steps are (1) reading the table of contents, (2) locating keywords in the title of the article (e.g. randomized, random, blinded, etc.), (3) reading the abstract, and (4) reading the methods section in the full text of the article. Handsearching must be conducted retrospectively starting with the latest available issue of the corresponding journal. All personnel involved in handsearching are required to complete a pilot test, consisting of identifying CCTs in a volume of a journal that had previously been handsearched by personnel expert in the field.

Eligibility criteria

In order to be eligible for inclusion in the database, studies had to meet the following criteria, as per the guidelines provided by the Cochrane collaboration to classify studies as CCTs: they had to (1) compare treatments in humans, (2) be prospective; interventions must have been planned before the study took place, (3) compare two or more interventions, one of which can be a no-treatment control group or a placebo, and (4) have a random or quasi-random method of allocation to treatment [1]. Random allocation was defined as the explicit adoption of random methods for assignment of participants to study arms, such as computer-generated random numbers. Quasi-random allocation was defined as the adoption of less stringent methods that can be used to generate comparable groups for the study arms, such as assignment by date of birth, even and odd numbers, or medical record number [28].

We included CCTs regardless of whether they were published as full-text articles or just in abstract format (such as in reports of conference proceedings). We excluded articles that were translations of studies published

in other languages in order to avoid duplicates once these references are sent to CENTRAL.

Data extraction

For each journal title included in BADERI, we recorded the following information: International Standard Serial Number (ISSN), country of origin, medical specialty, and years of publication. The database allows up to two medical specialties per journal. Each identified CCT was entered in the database and filed under the corresponding journal. We recorded the following information for each identified CCT: title in Spanish and English (if available); author(s), in a format compatible with the requirements of CENTRAL; year, volume, issue number, and pages of publication (when appropriate); and method of randomization. The name of the person who identified the CCT, the year when it was identified, and whether the corresponding full text is available were also recorded. There was a field where comments could be entered as needed. Lastly, we translated into English the titles of CCTs that were available only in Spanish.

Data analysis

We used descriptive statistics to analyse the progress of the implementation of the database for different handsearching projects. This analysis was performed using reports generated by the database, which are exported in Excel® format, version 2010, Microsoft Office, Redmond, WA, USA. Additionally, all references entered in BADERI can be exported in ProCite format and submitted for inclusion in CENTRAL for their potential inclusion in systematic reviews and other documents of synthesis [22, 23].

Results

Database development (design and updating)

The proposed database was named BADERI (Database of Iberoamerican Clinical Trials and Journals, by its initials in Spanish). BADERI was officially launched in October 2015 and can be accessed at www.baderi.com/login.php (login and password needed, which can be generated upon request). BADERI is free of cost to all users.

After the brainstorming and discussion sessions, we agreed upon the features that were added to BADERI, the flow that users would follow to enter new references into the database, and the format of the reports. We subsequently assessed different versions of the database and approved the interface proposed by the IT company that set up BADERI.

Starting in March 2015 and during the next 3 months, BADERI was pilot tested. Three handsearching teams entered 203 references to CCTs, performed free text searches for a convenience sample of references to verify they had been correctly entered, and generated the available reports to track the work they had completed. This exercise allowed us to incorporate important changes to BADERI, the most relevant of which were (1) adding fields for recording additional information from identified CCTs (e.g. name of the person who had identified the CCT), (2) integrating drop-down menus for some fields (e.g. for method of randomization), (3) changing the location of links (e.g. links for generating a new journal or a new reference), and (4) suggesting formats or data to be included in reports (e.g. reports that could be filtered by journal, country, or medical specialty).

Since the database has been launched, we have received further feedback from users on how to improve the usability of BADERI. We update the database on a regular basis accordingly.

Main characteristics

The login page prompts users to enter a username and password, which are assigned upon request. Users can be assigned to one or more handsearching projects (medical specialty), to handsearch journals from specific countries, and be granted different roles according to their responsibilities in the team. These roles include general administrator, or overall coordinator for all handsearching activities; local administrator, or coordinator at the country or medical specialty level; and reviewer (user/handsearcher), responsible for uploading references to identified CCTs. This distribution of tasks encourages teamwork while allowing team leaders to oversee the progress of the project.

Once signed in, users are prompted to a home page with general instructions on how to complete different tasks. The home page also includes acknowledgement to the entities that have financially supported BADERI as well as to the IT company responsible for its development. Lastly, users can find contact information for submitting inquiries or reporting issues with BADERI.

BADERI is divided into four subsections that can be accessed by clicking on different tabs in the home page: 'Administration', 'References', 'Reports', and 'Search'.

The 'Administration' subsection allows one to assign each user different roles and handsearching projects, specifically per country and medical specialty. It also provides a list of all registered users. This subsection is centrally overseen from the IbCC headquarters in Barcelona, Spain, as well as by remotely situated local administrators.

Next, the 'References' subsection provides two subsections where references to published and non-published CCTs (i.e. grey literature) can be entered. The process to enter a new reference can be summarized as follows. First, users can determine, through a free text search in the upper section of the page, if the journal where the reference was published is already registered in BADERI.

Users can choose to create a new journal title and enter all relevant information or to modify existing information. The same process is followed for selecting the year, volume, and issue of publication. Users can then click the 'new article' button within the corresponding issue, which prompts them to enter all information related to the CCT and its identification. BADERI automatically records the user person who entered this information, as well as the date and time.

The 'Reports' subsection allows spreadsheets to be exported in Excel format to monitor handsearching activities. The reports provide all available information for the journals and the CCTs registered in the database and can be filtered per journal(s), country(ies), or medical specialty(ies). There are three types of reports: handsearched journals, identified CCTs, and overall report of activities.

Lastly, the 'Search' subsection contains the search engine. This engine allows retrieving references through free text searches for journal title, author, or title of the article.

BADERI has a built-in feature, also available under the 'Reports' subsection, which allows the exportation of all bibliographic information available in the database in a ProCite file. This file can then be directly uploaded into CENTRAL. Additional file 1 provides screenshots of each of the four subsections in BADERI.

Results of BADERI early activities

As of August 2016, a total of 6284 references to CCTs had been uploaded to BADERI. These references correspond to a variety of handsearching projects completed by members of the IbCN. Table 1 provides a sorting of these references per country of publication.

Table 1 CCTs in BADERI per country of publication

Country	No. of CCTs (*n*)	Percentage
Spain	4745	75.5
Chile	676	10.8
Mexico	249	4.0
Colombia	190	3.0
Cuba	183	2.9
Argentina	94	1.5
Peru	64	1.0
Uruguay	42	0.66
Ecuador	15	0.23
Venezuela	12	0.19
Guatemala	8	0.13
El Salvador	4	0.06
Paraguay	2	0.03
Total	6284	100.0

The year of publication ranged between 1957 and 2016. The distribution of articles published per 5-year period reveals that most of the articles currently in BADERI were published between 1987 and 2001 (4379, 69.7%) (Fig. 2).

The identified CCTs were published in a total of 420 journals related to more than 46 medical specialties (Table 2).

The most common journals and countries of precedence are listed in Table 3.

Authors of a large proportion of the identified CCTs (3050, 48.4%) did not specifically describe the method they implemented for achieving randomization of participants. Among the remaining authors, 2105 (33.5%) implemented random allocation, whereas 1129 (18.1%) implemented quasi-random allocation. We found very few CCTs with titles translated into English; two professional translators recorded the corresponding information in BADERI. Lastly, a report of all the identified CCTs was generated in ProCite format and uploaded to CENTRAL.

Discussion

We have developed BADERI, an online database to facilitate the management of handsearching of CCT projects. BADERI has several features that address the logistic challenges of this type of undertaking. Through a user-friendly interface, BADERI allows maintaining a repository of the journals that have been handsearched, the number of articles reviewed, and full bibliographic references to the identified CCTs. This information can be easily exported in Excel format for descriptive analyses or in ProCite format for its inclusion in CENTRAL. Users can be assigned to one or more handsearching projects (medical specialty or by country/ies) and be granted general administrator, local administrator (at the country level), or handsearching roles. This distribution of tasks encourages teamwork while allowing team leaders to oversee the progress of the project.

The development of BADERI relied on input from experts with first-hand knowledge of the challenges that handsearching projects entail. In addition, the database was pilot tested by personnel with ample experience completing handsearching projects. The involvement of these stakeholders guarantees that BADERI incorporates features and functions to expedite handsearching projects, while stimulating the participation of more volunteers working from remote locations. BADERI will also provide an entry door to people who may be interested in systematic reviews even before they receive the corresponding formal training by allowing them to participate in the identification of potentially eligible CCTs.

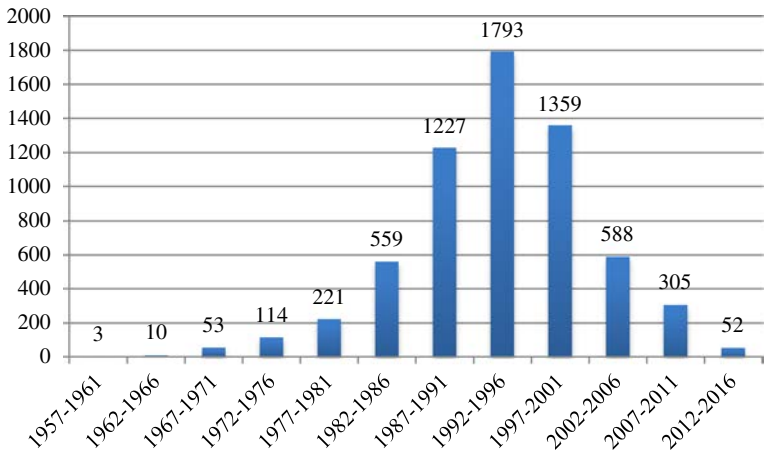

Fig. 2 CCTs in BADERI published per 5-year period

Most importantly, all the material contained in BADERI will be made available for its potential inclusion in systematic reviews and other documents of synthesis. BADERI contains all the information required by CENTRAL, and all data can be exported in ProCite format and uploaded directly into CENTRAL. Based on our previous experience, BADERI significantly simplifies the process of submitting data to CENTRAL. This year alone, we have been able to submit more than 3000 references, more than we had managed to in all previous years together, and we expect to send more than 2000 more within the upcoming semester.

To our knowledge, there are no other initiatives or studies that have addressed the challenges of hand-searching projects. As reported by several other studies [29–32], BADERI can help overcome some of the

Table 2 CCTs in BADERI per medical specialty

Medical specialty	No. of CCTs (*n*)	Percentage
General and Internal Medicine	915	14.5
Anaesthesiology	626	10.0
Cardiology	601	9.6
Gastroenterology	576	9.2
OB-GYN	372	5.9
Pulmunology	305	4.9
Paediatrics	287	4.6
Psychology	286	4.6
Oncology	264	4.2
Surgery (general)	188	3.0
Dentistry	153	2.4
Pharmacology	148	2.4
Immunology	139	2.2
Neurology	137	2.2
Nutrition	132	2.1
Dermatology	114	1.8
Public Health	111	1.8
All others	930	14.6
Total	6284	100.0

Table 3 CCTs in BADERI per journal of publication and country

Journal	Country	No. of CCTs (*n*)	Percentage
Revista Española de Anestesiología y Reanimación	Spain	438	7.0
Gastroenterología y Hepatología	Spain	388	6.2
Archivos de Bronconeumología	Spain	237	3.8
Revista Española de Cardiología	Spain	221	3.5
Medicina Clínica	Spain	177	2.7
Medicina Intensiva	Spain	154	2.5
Revista Chilena de Anestesia	Chile	140	2.2
Revista Clínica Española	Spain	124	2.0
Hipertensión	Spain	117	1.9
Nutrición Hospitalaria	Spain	113	1.8
Revista Médica de Chile	Chile	108	1.7
Alergología et Immunopathologia	Spain	97	1.5
Annals de Medicina	Spain	96	1.5
Revista Española de Enfermedades Digestivas	Spain	89	1.4
Cirugía Española	Spain	75	1.2
Sangre	Spain	68	1.1
Neurología (Barcelona)	Spain	66	1.1
Progresos de Obstetricia y Ginecología	Spain	64	1.0
Atención Primaria	Spain	62	1.0
All others		3450	54.9
Total		6284	100.0

shortcomings of literature searches by facilitating the implementation of handsearching initiatives on behalf of different institutions. BADERI will also give visibility to research published in non-indexed journals and journals published in the Spanish language by facilitating the inclusion of CCTs identified via handsearching into CENTRAL.

Strengths and limitations

The main strengths of our study include the expertise in handsearching of the personnel involved in the design, setup, and pilot testing of BADERI. Furthermore, these personnel have ample experience in completing systematic reviews and in developing research projects in the methodology of systematic reviews and clinical practice guidelines. Additionally, the database we propose is free of cost and user-friendly, which facilitates its adoption among handsearching teams. Lastly, BADERI's features to export data in spreadsheets and ProCite format are unique, streamlining the analysis of data registered in BADERI and its submission to CENTRAL.

Our work is subject to some limitations. BADERI may require input and pilot testing on behalf of other stakeholders, especially beyond projects conducted within the Cochrane Collaboration. Similarly, access to use BADERI is granted upon request to a local or general administrator, which may be a barrier to its uptake. However, we are committed to collaborating with any entity interested in learning how to use BADERI to meet their specific needs and to granting access to the database and its contents to any interested party.

Given that we are still in the process of uploading identified CCTs into BADERI, we cannot draw firm conclusions about the main characteristics of this body of work. We hope that as we complete the process of compiling in BADERI the results of all handsearching activities conducted so far, we will be better able to conduct descriptive studies regarding the features of these studies.

Implications for practice

The BADERI database will serve handsearching teams across several countries and institutions. All personnel involved in these activities will be granted access to BADERI free of charge. Furthermore, BADERI could be easily adapted to fulfil the handsearching management needs of other entities. BADERI can also be a useful resource for other initiatives or groups that need to register and monitor existing journals and corresponding handsearching activities.

We are currently providing training to several handsearching teams from Spain and Latin America on how to report the results of their work via BADERI. As they implement BADERI in their handsearching activities, they provide feedback that helps us to adjust and improve the database. We are also finishing the upload of handsearching projects that were conducted in the past but that have not been added to BADERI. Once this process is complete, this material will be readily available for consultation.

Implications for research

The handsearching of CCTs is a crucial complement to electronic searches in order to identify all the available evidence that can potentially be used in systematic reviews and other documents of synthesis. The IbCC has made it a top priority to foster current and future handsearching projects of biomedical journals in different medical fields, for which the BADERI database will be an invaluable aid. We are currently finishing the upload of references identified in previous handsearching projects and its submission to CENTRAL. There is also a need to critically assess the results and quality of the CCTs included in BADERI.

Conclusions

BADERI allows the efficient management of handsearching activities across different countries and institutions. References to all CCTs available in BADERI can be readily submitted to CENTRAL for their potential inclusion in systematic reviews. There is a need to critically assess the main characteristics and methodological quality of the CCTs included in BADERI.

Additional file

Additional file 1: BADERI subsections. (PDF 541 kb)

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Availability of data and materials

The dataset supporting the conclusions of this article is included within the article.

Authors' contributions

HPH, GU, and XB conceived the idea of the study. HPH, LBN, DBG, JVG, and MJMZ collected and classified study data. All study authors analysed the data. HPH, GU, and XB drafted the manuscript. All authors reviewed the manuscript for content and style and approved its final version.

Competing interests

The authors declare that they have no competing interests.

Consent for publication
Not applicable.

Ethics approval and consent to participate
Not applicable since this study did not involve any patients.

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6. Discusión

6. Discusión

6.1. Principales resultados derivados de las publicaciones

A través de las cuatro publicaciones que forman este trabajo de tesis se han desarrollado e implementado estrategias para contribuir a prevenir y controlar el sesgo de diseminación de los ECAs. Estas estrategias fueron diseñadas en base a la opinión de diferentes actores implicados en el proceso de diseminación del conocimiento, incluyendo organismos de financiación biomédica, profesionales que llevan a cabo búsquedas manuales de ECAs y miembros de la Red Cochrane Iberoamericana, entre otros. Así pues, se presentan recomendaciones específicas para que los organismos de financiación de investigación biomédica puedan incorporar medidas que les permita fomentar y evaluar el correcto reporte de los resultados de la investigación financiada. Además, se reporta el resultado de la implementación de iniciativas como la identificación exhaustiva de revistas que publican investigación biomédica en España y Latinoamérica, la búsqueda manual de ECAs y la base de datos BADERI.

Los resultados de la primera publicación sugieren que las agencias de financiación de investigación biomédica en Europa son, en teoría, conscientes del problema del sesgo de diseminación de los ECAs. Sin embargo, estos organismos toman pocas o nulas medidas para abordarlo. Se encontró que, entre los organismos encuestados, la mayoría no tenía conocimiento preciso del estado de publicación de los proyectos financiados por ellos a pesar de también declarar que implementan diferentes políticas para fomentar la publicación de resultados y, al menos en principio, hacer un seguimiento para asegurar su cumplimiento. Además, existía una falta de consenso sobre el tipo de medidas específicas que deben adoptarse para reducir o controlar el sesgo de diseminación. Con los resultados de esta encuesta se desarrollaron una serie de recomendaciones dirigidas a agencias de financiación de investigación biomédica a nivel europeo para prevenir y controlar el sesgo de diseminación. Estas recomendaciones se enmarcan dentro de los resultados generales del proyecto OPEN, a

través de los cuales se generaron recomendaciones adicionales para otros tipos de agencias y actores interesados.

A través del segundo estudio se identificó una lista lo más completa posible de revistas biomédicas que publican investigación original en España y Latinoamérica, una iniciativa vital para el desarrollo de actividades de búsqueda manual y que no se había realizado hasta la fecha. En total se encontraron 1 498 revistas, un número que se puede considerar alto en vista del bajo porcentaje de estas revistas que se encuentran indexadas en bases de datos bibliográficas internacionales o que tienen factor de impacto. A pesar de que para ser elegibles para este estudio las revistas debían publicar investigación original, muchas de las revistas identificadas pertenecen a sociedades médicas o asociaciones profesionales que se centran más en actividades divulgativas que en la difusión de estudios originales.

Por medio del tercer estudio se llevó a cabo una búsqueda manual de ECAs publicados en las diez revistas de Fisioterapia elegibles publicadas en España. Se identificaron un total de 78 ECAs publicados desde 1980, la mayor parte de los cuales en solo dos revistas, Rehabilitación y Fisioterapia. En general, estos ECAs presentaron un alto riesgo de sesgo y en muy contadas ocasiones se adhirieron a la declaración CONSORT-NPT para el reporte de resultados. Estos 78 ECAs no se habrían identificado a través de estrategias de búsqueda electrónica en PubMed, ya que se encontró que ninguna de las 10 revistas en las que se le hizo búsqueda manual estaban indexadas en esta base de datos.

Finalmente, se ha desarrollado una base de datos en línea que permite coordinar y monitorizar proyectos de búsqueda manual de ECAs. Esta base de datos, BADERI, permite llevar a cabo un seguimiento de las revistas en las que se ha hecho búsqueda manual, monitorizar el número de artículos revisados y de ECAs identificados, y almacenar las correspondientes referencias bibliográficas completas. La información contenida en BADERI se puede exportar en formato Excel® para llevar a cabo análisis descriptivos, o en formato ProCite para su inclusión en

CENTRAL. BADERI permite una distribución de tareas que fomenta el trabajo en equipo y facilita la supervisión del progreso de cada proyecto.

Este trabajo de tesis cuanta asimismo con cuatro publicaciones anexas. En la primera se explica, dentro del contexto del desarrollo de la Colaboración Cochrane en Latinoamérica, el inicio y progreso de la iniciativa de búsqueda manual de ECAs en España y Latinoamérica (95). En la segunda y la tercera se explican dos proyectos de búsqueda manual enmarcados dentro de esta iniciativa. Por una parte, se identificaron 235 ECAs en 16 revistas de Ginecología y Obstetricia publicadas en España (96). De estos, 29 ECAs investigaron métodos de reproducción asistida, los cuales presentaron una baja calidad en la metodología de los estudios y en el reporte de resultados. Por otra parte, se identificaron 144 ECAs en 21 revistas de Dermatología publicadas en España y Latinoamérica, de los cuales 66 (45,8%) se llevaron a cabo en España y 78 (54,2%) en Latinoamérica (97). Estos ECAs presentaron también una baja calidad metodológica y de reporte de resultados (98).

La gran mayoría de los ECAs identificados de manera manual en estas publicaciones anexas no se habrían identificado implementando una estrategia de búsqueda electrónica. En el caso de Ginecología y Obstetricia, una búsqueda de ECAs publicados en aquellas revistas indexadas en PubMed no arrojó ningún resultado. En el caso de Dermatología, se encontraron 4 ECAs en PubMed de 30 que se habían identificado de manera manual, mientras que en EMBASE se encontraron cuatro ECAs de 144 que se habían identificado de manera manual y dos que no se habían identificado de manera manual. Estos últimos estaban publicados en números correspondientes a revista a las que no se tuvo acceso al texto completo y en las que, por tanto, no se pudo llevar a cabo búsqueda manual.

6.2. Discusión de los aspectos generales en el contexto actual

Un reciente artículo sobre los logros de la Medicina Basada en la Evidencia durante los últimos 25 años subraya su contribución a la evaluación crítica de los resultados de la investigación

biomédica, a la incorporación de los valores y preferencias de los pacientes en la toma de decisiones, al desarrollo de las guías de práctica clínica y al estudio de métodos para generar recomendaciones que tengan un impacto directo en la práctica clínica, entre otros (99). Sin embargo, también resalta que uno de los desafíos inmediatos más importantes es no solo el reporte incorrecto y sesgado de los resultados de la investigación biomédica, sino también la persistente práctica de no diseminar los resultados de los ECAs en función de la dirección y magnitud de los resultados (100, 101). Durante las últimas décadas se ha desarrollado un gran número de estudios para determinar las causas y la prevalencia del sesgo de diseminación, así como para diseñar diferentes medidas para prevenir su aparición y limitar sus efectos. No obstante, el sesgo de diseminación continúa siendo una seria amenaza para el entendimiento y la aplicación de la evidencia disponible proveniente de los ECAs (102). Combatir el sesgo de diseminación es también uno de los pilares para evitar duplicidades en la investigación biomédica, como propone la iniciativa "*Increasing Value, Reducing Waste*" publicada por *The Lancet* (103), entre otros proyectos (102).

El proyecto OPEN buscó contribuir a atenuar esta problemática a través del desarrollo de diferentes iniciativas que buscaban sensibilizar a diferentes actor involucrados en la investigación biomédica a nivel europeo sobre los efectos negativos del sesgo de diseminación. Se desarrollaron una serie de recomendaciones globales y otras destinadas a cada actor para prevenir y controlar el sesgo de diseminación.

6.2.1. Opiniones y percepciones de diferentes agentes acerca del sesgo de diseminación

En concordancia con lo que se reporta en este proyecto de tesis, a través del proyecto OPEN se encontró que los investigadores (104), los miembros de comités de ética (105) y los editores de revistas biomédicas (106) son conscientes de la existencia y efectos negativos del sesgo de diseminación. Asimismo, existe un amplio apoyo para publicar o diseminar diferentes aspectos

de los ECAs a fin de reducir el sesgo de diseminación, incluyendo el registro prospectivo de los ECAs, el permitir acceso al protocolo de los ECAs y al conjunto completo de los datos obtenidos y la publicación o diseminación compulsoria de resultados en publicaciones científicas y otras fuentes.

Sin embargo, en cada caso, los diferentes actores son laxos en la implementación de estas y otras estrategias para prevenir y controlar el sesgo de diseminación. Por una parte, hay una percepción de que la responsabilidad de implementar medidas para controlar el sesgo de diseminación recae en otros agentes involucrados en el diseño y desarrollo de los ECAs. Por otra parte, estos actores a menudo no cuentan con los recursos logísticos o económicos necesarios para hacer un seguimiento activo y verificar la diseminación de los resultados de los ECAs que han financiado, autorizado o realizado. Por ejemplo, una encuesta llevada a cabo entre autores de revisiones Cochrane o que habían publicado en revistas de alto impacto encontró que 48 (36%) tenían proyectos sin publicar y que 40 (30%) habían publicado desenlaces de interés de manera selectiva. Sin embargo, estos mismos investigadores responsabilizan, entre otros, al sistema de publicación de resultados en artículos revisados por pares, que favorece la diseminación de resultados positivos ("espectaculares") a menudo sin adherirse a medidas básicas como el registro prospectivo de los ECAs (104). En contraste, según los editores de revistas biomédicas que publican ECAs, la aplicación de medidas tales como el registro de los ECAs de manera prospectiva como prerrequisito para publicación les puede ponerles en desventaja con respecto a otras revistas (106).

Los resultados del proyecto OPEN se refuerzan con dos revisiones sistemáticas llevadas a cabo posteriormente, específicamente de estudios que indagaron los motivos de investigadores para publicar o publicar selectivamente los resultados de ECAs (107) o de estudios presentados como resúmenes o abstracts presentados a conferencias o congresos (55). Estas revisiones encontraron que la percepción de que un estudio tuviera resultados negativos, de que fuera de bajo impacto o de que sería rechazado por las revistas a la que sería sometido, así como las

restricciones por parte de los promotores o la industria, como los principales motivos para estas prácticas.

6.2.2. Recomendaciones para prevenir y controlar el sesgo de diseminación

6.2.2.1. Recomendaciones del proyecto OPEN

Las recomendaciones globales del proyecto OPEN dirigidas a los diferentes actores involucrados en la investigación biomédica a nivel europeo se centran en la implementación de campañas para aumentar la conciencia sobre los efectos del sesgo de diseminación, la promoción del registro prospectivo de ECAs y el apoyo a las diferentes iniciativas y recomendaciones para controlar el sesgo de diseminación (37). En la tabla 4 se presentan las recomendaciones específicas para cada tipo de organismo o actor (37, 104-106, 108).

Recomendación	Agencias de financiación	Industria farmacéutica	Agencias de investigación	Investigadores	Comités de ética	Registros de ECAs	Revistas	Legisladores
Requerimientos para diseminar los resultados de todos los ECAs	x	x	x				x	x
Seguimiento para corroborar la diseminación de resultados	x				x			
Incentivos para investigadores que diseminen resultados de ECAs	x							x
Registro prospectivo de ECAs		x		x	x	x	x	x
Diseminación, registro prospectivo de protocolos de ECAs		x		x			x	x
Diseminación de sumarios de los principales resultados ECAs		x		x	x	x		x
Registro de reportes de ECAs o de datos individualizados, anónimos		x			x			x

Formación sobre cómo diseminar los resultados de ECAs	x	
Sanciones disciplinarias	x	

Tabla 4: Representaciones específicas del proyecto OPEN para cada tipo de agencia o actor responsable

La campaña *AllTrials* es una iniciativa que busca promover que todos los ECAs, pasados y presentes, sean registrados, y que los métodos y resultados correspondientes sean reportados. Esta iniciativa se añade a las campañas para publicar los resultados de los ECAs independientemente de la dirección y magnitud de los resultados por parte del proyecto REWARD (101), del Código de Conducta del Comité de Publicación Ética (109) y de la Declaración de Helsinki (110), entre otros (111).

No obstante, el éxito de estas recomendaciones requiere de un compromiso para realizar un seguimiento activo para determinar el cumplimiento de las mismas. Se ha encontrado que una inadecuada implementación de medidas para controlar el sesgo de diseminación compromete la eficacia de las mismas (43). Por ejemplo, a pesar de que algunas agencias de financiación incluyen cláusulas en los contratos de financiación requiriendo el completo reporte de los ECAs financiados, estas cláusulas a menudo no son lo suficientemente específicas, lo que dificulta su implementación (112). Asimismo, a fecha de 2017, los organismos de financiación del Reino Unido que se habían comprometido a desarrollar estrategias para optimizar el uso de recursos en la investigación médica no han incorporado medidas específicas al respecto (113). Finalmente, la existencia de intereses económicos puede comprometer la autonomía de los autores para diseminar los resultados de estudios que vayan en contra de la hipótesis inicial, como se refleja en la existencia de acuerdos que restringen la autonomía de los autores para decidir el contenido de las publicaciones o de los resultados que se diseminan (114).

6.2.3. La búsqueda manual de los ensayos clínicos controlados

Una de las principales estrategias que propone la Colaboración Cochrane para limitar el sesgo de diseminación de ECAs y su impacto negativo en las revisiones sistemáticas consiste en incorporar una estrategia de búsqueda manual de ECAs para complementar las búsquedas en las diferentes bases de datos bibliográficas. Dado que las actividades de búsqueda manual requieren de una importante inversión de recursos económicos y humanos, su implementación no es siempre viable durante el desarrollo de revisiones sistemáticas más allá de la revisión de la bibliografía de los estudios potencialmente elegibles.

Para solventar esta limitación en el ámbito de las revistas publicadas en lengua castellana, el Centro Cochrane Iberoamericano impulsa actividades de búsqueda manual de ECAs publicados en revistas biomédicas de España y Latinoamérica (95). Esta iniciativa no se había llevado a cabo hasta la fecha en estos países, con el valor agregado de que se trata de un proyecto que se debe llevar a cabo de manera retrospectiva solo una vez y complementado con una estrategia prospectiva que en la actualidad se está implementando en un conjunto de revistas. Además, el envío de estas referencias a CENTRAL proporciona una importante visibilidad a los ECAs publicados en revistas de España y Latinoamérica, en especial aquellos publicados en revistas no indexadas, y amplía la base de evidencia sobre la cual se desarrollan y actualiza las revisiones sistemáticas.

6.2.3.1. Calidad de las revistas biomédicas de España y Latinoamérica

En general, las revistas identificadas a través de la segunda publicación presentan deficiencias que pueden contribuir al sesgo de reporte, específicamente al sesgo de lenguaje y localización. Se encontró que 180 (12,2%) de las revistas identificadas a través de este trabajo de tesis no cumplieron con los criterios mínimos exigidos para que una publicación académica sea considerada como tal: aunque se trataba de revistas periódicas que publican investigación original, no tenían número ISSN, un código internacionalmente aceptado para identificar publicaciones periódicas (115). Además, sólo 45 (3,0%) tenían factor de impacto en el año 2012

(año en el que se llevó a cabo el estudio), generalmente clasificándose en el cuarto cuartil dentro de sus categorías.

Otro estudio que han valorado la calidad de las revistas latinoamericanas determinó que sólo el 19,8% de una muestra de 101 ensayos publicados en 2011 en 56 revistas latinoamericanas mencionó el registro prospectivo de ECAs (116). De estas revistas, 38 (68%) respaldaron las directrices del ICMJE y 20 (36%) solicitaban el registro prospectivo de ECAs. Un porcentaje aún menor proporcionó asesoramiento sobre el uso de listas de verificación ("*checklists*") para el reporte de resultados, como CONSORT para ECAs, PRISMA para revisiones sistemáticas o STROBE para estudios observacionales (116). No sorprende, por tanto, que otro estudio similar haya encontrado que entre los 526 ECAs indexados en PubMed y LILACS en el año 2010 y con un primer autor afiliado a una institución de Latinoamérica, solo el 17% (89/526) habían sido registrados en la ICTRP, 4% de los cuales (21/89) de manera prospectiva (117).

Una limitación adicional del conjunto de revistas biomédicas en España y Latinoamérica es su bajo nivel de indexación. Sólo alrededor de un tercio de las revistas biomédicas estaban indexadas en más de una base de datos de la literatura. LILACS y Periódica son las más usadas y aglutinan el 17,4% y 10,5% de las revistas identificadas, respectivamente, mientras que MEDLINE y EMBASE indexan el 4,1% y 3,7% de las revistas identificadas, respectivamente.

6.2.3.2. Contribución de los proyectos de búsqueda manual a reducir el sesgo de diseminación

En general, una amplia mayoría de los ECAs identificados en el proyecto de búsqueda manual de revistas de Fisioterapia publicadas en España, así como de revistas de Ginecología y Obstetricia de España y de Dermatología en España y Latinoamérica (ver anexos), no se habrían podido detectar a través de una estrategia de búsqueda electrónica dado el bajo nivel de indexación de las revistas revisadas. La inclusión de estos ECAs en una base de datos como BADERI es de vital importancia para facilitar la accesibilidad de este conjunto de evidencia a los autores de revisiones sistemáticas y otros documentos de síntesis.

Finalmente, durante los últimos años hay un creciente interés en el uso de nuevas tecnologías para facilitar el proceso de desarrollo de las revisiones sistemáticas. El uso de software de aprendizaje automático ("*machine learning*") permite generar estimadores de aprendizaje automático para identificar referencias potencialmente incluibles en revisiones sistemáticas y determinar si son relevantes (118). No obstante, los estimadores solo se pueden implementar en referencias que se encuentren indexadas en bases de datos de la literatura científica. La inclusión de los ECAs identificados a través de los proyectos de búsqueda manual en CENTRAL también asegura su visibilidad a través del uso de nuevas tecnologías para el desarrollo y actualización de revisiones sistemáticas.

6.2.4. Retos pendientes de las estrategias para prevenir y controlar el sesgo de diseminación

A pesar de la existencia de diferentes políticas para fomentar la diseminación de los resultados derivados de la investigación biomédica, la implementación de las mismas, la adherencia por parte de los diferentes actores involucrados y la evaluación de los resultados de su implementación continúan siendo un reto. La ICMJE, la FDA en Estados Unidos y la *European Medicines Agency* (EMA por sus siglas en inglés) se han adherido a dos de las medidas más ampliamente respaldadas para disminuir el sesgo de diseminación, el registro prospectivo de ECAs y la diseminación de un mínimo establecido de datos relacionados con los resultados de los estudios (36). Sin embargo, estas mismas normativas están condicionadas a la protección de los posibles intereses comerciales relacionados con los ECAs y al uso que se le vaya a dar a estos datos (119).

También se hace necesario velar por el correcto reporte prospectivo de ECAs en registros de acceso libre y gratuito. Un estudio retrospectivo de los datos registrados en *clinicaltrials.gov* relacionados con 152 ECAs publicados en revistas de la ICMJE entre 2005 y 2008 encontró, entre otras irregularidades, diferencias entre los datos registrados inicialmente en *clinicaltrials.gov* y los posteriormente publicados en 31 de los ECAs (25%)(120). Por su parte,

un estudio entre 265 protocolos de ECAs registrados en la ICTRP encontró que en menos del 10% de los casos se reportó adecuadamente la generación de la secuencia aleatoria, la ocultación de la secuencia, y cegamiento en estudios abiertos (121). No obstante, las estrategias para verificar la correcta adherencia al reporte prospectivo de ECAs son complejas, dado que a pesar de ser requerimientos legales en Estados Unidos y otros países, el registro prospectivo de ECAs no se verifica activamente por parte de las autoridades sino de manera pasiva, a través de la presión sociales y de otros investigadores o, en el mejor de los casos, como prerrequisito para la publicación o financiación de estudios (16, 122, 123).

La calidad en el reporte de los ECAs que sí se diseminan es otra tarea aún pendiente. Un estudio de mapeo que incluyó 20 920 ECAs incluidos en revisiones Cochrane publicadas entre 2011 y 2014 encontró que el 49% y 56% de los ECAs tenían un riesgo de sesgo indeterminado debido a falta de información detallada relacionada con la generación y ocultación de la secuencia aleatoria, respectivamente. A pesar de que la calidad del reporte de los estudios ha mejorado con el tiempo, se encontró que esta mejora se vio limitada a revistas de alto factor de impacto (24). Los autores resaltan la necesidad de adherirse de manera explícita a la declaración CONSORT y sus extensiones, incluyendo el envío compulsorio de una copia cumplimentada de CONSORT como prerrequisito para publicación.

La herramienta CONSORT y otras listas de verificación continúan siendo, por tanto, invaluables para facilitar el correcto reporte de la metodología y los resultados de los ECAs. Por su parte, la nueva herramienta ROBIS, desarrollada para evaluar el riesgo de sesgo en revisiones sistemáticas de intervenciones, contiene apartados específicos para permitir una valoración de la calidad en el reporte de los ECAs y de la manera cómo los sesgos identificados afectan la interpretación de las conclusiones de las revisiones (124).

Con referencia a la visibilidad de los ECAs que han sido publicados, durante los últimos años se ha implantado progresivamente un modelo de acceso abierto y gratuito a las revistas y a los artículos que traspasa los costos de publicación del lector a los autores. El acceso abierto puede

reducir el sesgo de diseminación al proveer de manera sostenible una oferta más amplia de espacios donde publicar, por ejemplo, ECAs con resultados negativos o de menor impacto. Por el contrario, el modelo de acceso abierto puede también exacerbar el problema al imponer una carga económica que, por ejemplo, podría no ser asumida por algunos investigadores de países en vía de desarrollo (43). La evidencia actualmente existente sobre el efecto del modelo de acceso abierto sobre el sesgo de diseminación es contradictoria e imprecisa (43).

Finalmente, se deben continuar promoviendo las prácticas que permiten una diseminación más exhaustiva y transparente de los resultados de los ECAs que la permitida por la publicación de artículos en revistas con revisión por pares (125). Una de las iniciativas que más interés genera es el depósito de los datos anónimos obtenidos a partir de los ECAs en registros de libre acceso o el compromiso de los investigadores de compartirlos si fuera requerido. Estos datos anónimos, que incluyen los reportes de estudios clínicos ("*clinical study reports*" o "*CRS*") o los datos individualizados de los pacientes provenientes de los formularios de informe de casos ("*case report forms*"), facilitan la reproducibilidad de los análisis y la constatación de los resultados obtenidos (126, 127). A pesar de que la OMS y la FDA ya han puesto en marcha estrategias para promover esta práctica, el camino por recorrer es aún largo. Más del 90% de las compañías farmacéuticas con mayores ingresos a nivel mundial se han comprometido a compartir reportes de estudios clínicos o datos individualizados de los pacientes, sin embargo, en la práctica este compromiso es de difícil cumplimiento dado que las cláusulas que lo regulan son confusas y contradictorias y contienen numerosas excepciones (126, 128, 129). También sobresale el reto de preservar la privacidad de los pacientes cuyos datos son compartidos y de legislar para determinar si los consentimientos informados para participar en ECAs incluyen o no autorización para compartir datos individualizados anónimos (122).

6.3. Fortalezas y limitaciones

6.3.1. Fortalezas

Con respecto al primer estudio de esta tesis, para la encuesta realizada se recibieron respuestas de una diversa muestra de organismos que financian investigación biomédica, incluyendo agencias públicas, privadas y de financiamiento mixto con intereses de investigación y presupuesto variados y provenientes de diferentes países. Además, el Consorcio OPEN brindó un amplio apoyo metodológico y logístico que facilitó la colaboración con otros miembros del consorcio OPEN y con los representantes de los organismos de financiación de investigación biomédica a nivel europeo y otros actores interesados para el desarrollo de las recomendaciones propuestas. Esto facilita su viabilidad e implementación.

En cuanto al estudio de identificación de revistas biomédicas de España y Latinoamérica, las fuentes consultadas abarcaron diferentes fuentes, incluyendo las principales bases de datos de la literatura científica, que se buscaron sistemáticamente mediante un protocolo que aseguraba la reproducibilidad del proceso y agregaba validez externa, así como bibliotecas y otras fuentes donde se pudo identificar revistas no indexadas. Los miembros del Centro Cochrane Iberoamericano que tomaron parte en este estudio tenían experiencia en la realización de este tipo de búsquedas y habían publicado artículos que requerían la identificación de todas las revistas en una especialidad o condición médica determinada (85, 87-89). Además, esta búsqueda fue complementada por miembros de la Red Cochrane Iberoamericana en Latinoamérica, quienes tenían experiencia en la realización de búsquedas exhaustivas de literatura científica. Los resultados de este estudio permitieron identificar fácilmente las revistas en Fisioterapia que se debían buscar de manera manual para el tercer estudio de este trabajo de tesis. En cuanto al tercer artículo, la búsqueda manual de ECAs se llevó a cabo siguiendo de manera sistemática las directrices de la Colaboración Cochrane: se revisaron más de 400 artículos publicados en las 10 revistas elegibles.

Finalmente, BADERI se desarrolló con personal experimentado en el diseño, coordinación y ejecución de proyectos de búsqueda manual, así como en la metodología de las revisiones sistemáticas y de búsquedas de ECAs en CENTRAL. Asimismo, BADERI es una base de datos

gratuita, sencilla y fácil de usar, lo que facilita su adopción en los proyectos de búsqueda manual. Por último, BADERI permite exportar datos en hojas de cálculo y de formato ProCite, simplificando el análisis de datos registrados y su incorporación en CENTRAL.

6.3.2. Limitaciones

Con respecto al estudio OPEN, se buscaba recopilar información de una muestra amplia y representativa de agencias de todos los países de Europa. Sin embargo, para identificar las agencias que debían ser encuestadas, se tuvo que consultar una variedad de fuentes ya que, a nuestro conocimiento, no existía un directorio ni una lista completa de agencias a nivel europeo que financiasen la investigación biomédica. Estas listas estaban disponibles en otros países, como en Estados Unidos (91). A pesar de esta limitación, se obtuvieron respuestas de la mayoría de los países y de agencias, con variados intereses de investigación y volumen de proyectos financiados. Los miembros de las agencias que respondieron a la encuesta pertenecían a todos los niveles de gestión.

La tasa de respuesta fue baja, a pesar de varios intentos de aumentarla. Además, se encontraron barreras lingüísticas que ralentizaron la identificación de personal para responder la encuesta y la recolección de datos de los sitios web donde las agencias publicaban sus políticas acerca del sesgo de diseminación. Tampoco se pudo descartar que, dado que la encuesta se administró en inglés, algunos encuestados pudieron renunciar a proporcionar respuestas más elaboradas en las preguntas abiertas. La información obtenida de la encuesta para informar el desarrollo de las recomendaciones reflejó, por tanto, las opiniones de una muestra limitada que pudo no ser representativa de todas las agencias en Europa. Asimismo, la encuesta incluyó preguntas sobre proyectos de investigación financiados en 2005, lo que pudo comprometer los resultados obtenidos por un posible sesgo de recuerdo. Se espera haber superado estas deficiencias al incluir la contribución de todo el Consorcio OPEN y de las diferentes partes interesadas durante la elaboración de las recomendaciones propuestas.

Con respecto al estudio de identificación de revistas, se pudieron excluir revistas que no estaban indexadas o incluidas en ninguna de las fuentes consultadas. Para solventar esta limitación, se contó con la participación de colaboradores de la Red Cochrane Iberoamericana en cada país, que revisaron bibliotecas y otros repositorios locales. Además, es razonable suponer que si tales revistas existen, su circulación es muy limitada y la posibilidad de que publiquen ECAs es muy baja. Por otra parte, la información sobre las principales características de las publicaciones encontradas en bases de datos y repositorios como LILACS, Periódica o Latindex fue a veces obsoleta, especialmente en cuanto a si las revistas estaban actualmente activas y el tipo de investigación que publicaban.

En referencia al estudio de identificación de ECAs publicados en revistas de Fisioterapia, la búsqueda manual se llevó a cabo de manera individual, lo que pudo resultar en ECAs potencialmente elegibles que no se hayan identificado. Asimismo, los resultados de este estudio no proveen una descripción completa de la investigación en Fisioterapia llevada a cabo en España, dado que en los ECAs identificados no se incluyen aquellos llevados a cabo en España pero publicados en revistas internacionales o en otros idiomas.

Finalmente, BADERI puede requerir una evaluación más profunda por parte de otros profesionales involucrados en búsquedas de la literatura científica, especialmente de instituciones no relacionadas con la Colaboración Cochrane. Del mismo modo, el acceso a BADERI se concede por parte de un administrador local o general, lo que puede ser una barrera para su adopción. Sin embargo, BADERI está disponible para cualquier entidad interesada en utilizarla para sus necesidades específicas. Finalmente, la evaluación y descripción de los ECAs incluidos en BADERI no refleja la totalidad de los proyectos de búsqueda manual llevados a cabo hasta la fecha, dado que aún se continúa con el proceso de incorporación de referencias a BADERI.

6.4. Implicaciones para la práctica

Los resultados del proyecto OPEN proporcionan una imagen más clara del problema del sesgo de diseminación y del grado conciencia y sensibilidad que existe acerca de este tema por parte de los diferentes actores implicados en la diseminación de resultados de ECAs. Es de esperar que las recomendaciones que fueron presentadas en este documento y en otras publicaciones del Consorcio OPEN faciliten la implementación efectiva de estrategias que contribuyan a prevenir y controlar el sesgo de diseminación, aún tan prevalente.

También se hace necesario que las revistas biomédicas de España y Latinoamérica se adhieran de manera explícita a diferentes iniciativas para reducir el sesgo de diseminación y para garantizar la exhaustividad y calidad en el reporte de resultados de los ECAs. Esto incluye requerir el registro prospectivo de ECAs, la disponibilidad del protocolo del ECA para comparar las variables pre-especificadas con las finalmente publicadas y el uso de la herramienta CONSORT o alguna de sus extensiones para el reporte de resultados. Estas estrategias pueden tener un impacto favorable en reducir el sesgo de diseminación y en incrementar la calidad de los ECAs publicados.

Las revistas y los ECAs identificados a través de los proyectos de búsqueda manual presentados en esta tesis están disponibles para su consulta y posible inclusión en el desarrollo de revisiones sistemáticas. BADERI continuará facilitando la inclusión de ECAs identificados a través de proyectos de búsqueda manual presentes y futuros en CENTRAL.

Por último, el acceso a BADERI continuará siendo libre de costo para motivar su implementación por parte de equipos de búsqueda manual en diferentes países e instituciones. Además, BADERI puede adaptarse fácilmente para satisfacer las necesidades de gestión de proyectos de búsqueda manual de otras entidades. Actualmente se está impartiendo formación a varios equipos de búsqueda manual de España y Latinoamérica sobre cómo informar de los resultados de su trabajo a través de BADERI. Asimismo, BADERI puede fomentar nuevos proyectos os de búsqueda manual en *Cochrane Exchange* y *Cochrane Crowd*, dos iniciativas de la Colaboración Cochrane para promover proyectos colaborativos a nivel global (130).

6.5. Implicaciones para la investigación

Se hace necesario evaluar el efecto de las recomendaciones propuestas para prevenir y controlar el sesgo de diseminación de los ECAs. Los organismos de financiación y demás actores involucrados en la diseminación de ECAs pueden jugar un papel fundamental en prevenir y controlar el sesgo de diseminación.

Por otra parte, la lista de revistas biomédicas que se compiló como parte de este proyecto de tesis es un recurso útil para llevar a cabo actividades de búsqueda manual de ECAs para su eventual inclusión en revisiones sistemáticas. En el caso específico de ECAs identificados en el campo de la Fisioterapia, se hace necesario completar la búsqueda de ECAs publicados en revistas de España con los publicados en revistas Latinoamericanas, un proyecto que se encuentra en curso. Asimismo, y con el objetivo de obtener una mejor descripción de la investigación en Fisioterapia llevada a cabo en España y Latinoamérica, se hace necesario la identificación y el análisis de ECAs publicados en revistas internacionales indexadas por parte de autores con afiliaciones en estos países. Estos proyectos también están en marcha.

Es de vital importancia impulsar proyectos futuros de búsqueda manual de ECAs en especialidades médicas aun no incluidas en los proyectos llevados a cabo hasta la fecha. Desde el Centro Cochrane Iberoamericano se coordinan en la actualidad búsquedas manuales en Geriatría y Gerontología, Neurología, Oncología y Anestesiología. También se están impulsando proyectos de búsqueda manual a nivel de los países, específicamente en Cuba, Ecuador y Venezuela. De manera complementaria, se está llevando a cabo un seguimiento prospectivo de las revistas en las que se han identificado ECAs hasta la actualidad, con el objetivo de que envíen al Centro Cochrane Iberoamericano, de manera regular, los nuevos ECAs que publiquen.

Se busca que los proyectos actuales y futuros de búsqueda manual incluyan una evaluación crítica de los resultados y la calidad de los ECAs identificados. Sin embargo, este proceso se debe

aún llevar a cabo para los ECAs incluidos en BADERI que no se han incluido en algunas de los estudios de búsqueda manual publicados hasta la fecha.

7. Conclusiones

7. Conclusiones

1. Aunque existe conciencia sobre el problema que supone el sesgo de diseminación, así como buenas intenciones para reducirlo y controlarlo, la mayoría de las agencias que financian investigación biomédica en Europa no implementan estrategias rigurosas para verificar la diseminación de los ensayos clínicos aleatorios que fueron financiados.
2. Hay un número significativo de revistas biomédicas que publican investigación original en España y Latinoamérica. Sin embargo, la mayoría no tienen factor de impacto o no están indexadas en bases de datos de la literatura, lo que puede desalentar a los investigadores locales a la hora de publicar su trabajo en estas revistas.
3. El número de ECAs publicados en revistas españolas de Fisioterapia es limitado. Estos ECAs presentan una baja calidad metodológica. Dado que ninguna de las revistas españolas de Fisioterapia están indexadas en las principales bases de datos de la literatura, la identificación de estos ECAs y su posterior inclusión en CENTRAL, la base de datos mundial de ECAs de la Colaboración Cochrane, contribuye a reducir el sesgo de publicación en el desarrollo y la actualización de futuras revisiones sistemáticas.
4. La base de datos BADERI se ha convertido en una herramienta invaluable para gestionar la identificación manual de ECAs y para facilitar su envío a CENTRAL para su posible inclusión en revisiones sistemáticas y otros documentos de síntesis.

8. Abreviaturas

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CENTRAL: Central Register of Controlled Trials

CONSORT: Consolidated Standards of Reporting Trials

ECA: Ensayo clínico con distribución aleatoria

EMA: European Medicines Agency

FDA: Food and Drug Administration

GRADE: Grading of Recommendations Assessment, Development and Evaluation

ICMJE: International Committee of Medical Journal Editors

ICTRP: International Clinical Trials Registry Platform

MECIR: Methodological Expectations of Cochrane Intervention Reviews

OMS: Organización Mundial de la Salud

9. Anexos

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Esta tesis se presenta como compendio de publicaciones originales. Los resultados corresponden a los resultados reportados en cada una de las publicaciones de esta tesis, que son:

1. *X. Bonfill, G. Urrutia, M. Roque, M.J. Martinez, H. Pardo-Hernandez, D. Osorio, J. Pardo, P. Serón, M. Tzanova, I. Solà,* **Iberoamerican Cochrane Network. Cochrane develops widely in Latin America and strengthens ties with LatinCLEN.** J Clin Epidemiol. 2016.
2. *R.B. Gutarra-Vilchez, H. Pardo-Hernandez, I. Arevalo-Rodriguez, D. Buitrago, X. Bonfill***. Identification and description of controlled clinical trials published in Spanish Gynaecology and Obstetrics journals and risk of bias assessment of trials on assisted reproductive techniques.** Eur J Obstet Gynecol Reprod Biol. 2016;203:5-11.
3. *G. Sanclemente, H. Pardo, S. Sanchez, X. Bonfill.* **Identifying randomized clinical trials in Spanish-language dermatology journals.** Actas Dermosifiliogr. 2015;106(5):415-22.
4. *G. Sanclemente, H. Pardo, S. Sanchez, X. Bonfill.* **Analysis of the Quality of Clinical Trials Published in Spanish-Language** Dermatology Journals Between 1997 and 2012. Actas Dermosifiliogr. 2016;107(1):44-54.

9.1. Anexo 1

Iberoamerican Cochrane Network. Cochrane develops widely in Latin America and strengthens ties with LatinCLEN. J Clin Epidemiol. 2016.

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INVITED PAPER

Cochrane develops widely in Latin America and strengthens ties with LatinCLEN

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1. Introduction

The Cochrane Collaboration was founded in 1993. Since then, it has expanded across many countries, reaching almost every health-related professional discipline while attracting the interest of a large audience of patients and the general public [1,2]. INCLEN, on the other hand, was founded in 1982 as an international network whose goal was to strengthen the research capacity of medical schools in the developing world and to promote sound collaborative research efforts [3,4].

Given the direct conceptual and personal links between clinical epidemiology promoters around the world, the evidence-based medicine movement and the Cochrane Collaboration in particular, a large variety of interrelations was to be expected [5]. This article reviews the activities of Cochrane in Latin America and its relationship with LatinCLEN, the Latin American branch of INCLEN.

2. First steps of the Cochrane Collaboration in Latin America and ties with LatinCLEN

The first formal presence of Cochrane in Latin America dates back to August 1996 when the Escola Paulista de Medicina registered as the Brazilian Cochrane Centre, though it was already a LatinCLEN node since the 1980s. The Brazilian Cochrane Centre was one of several new centers that Cochrane established in non−English-speaking countries (Table 1). Each of these centers became the referent for an important number of countries, sometimes located in diverse geographical, linguistic, and cultural areas. Such was the case of the Brazilian Cochrane Centre, which assumed the responsibilities for all the Spanish-speaking Latin American countries.

In light of this situation, in the year 2000, the Cochrane Collaboration Steering Group (board of directors) transferred responsibility for these countries to the Iberoamerican Cochrane Centre (IbCC), located in Barcelona, Spain.

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Conflict of interest: H.P.-H. is a doctoral candidate at the Pediatrics, Obstetrics and Gynecology and Preventive Medicine Department, Universitat Autònoma de Barcelona, Barcelona, Spain. Authors have no other conflict of interest but being part of the IbCC.

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Table 1. Registration dates of existing Cochrane Centres worldwide

Date of registration	Center
October 1992	''The Cochrane Centre'' is established in Oxford, UK
March 1993	First Cochrane Centre renamed ''The UK Cochrane Centre''
August 1993	Canadian Cochrane Centre registered, based in Ottawa.
October 1993	Nordic Cochrane Centre registered, based in Copenhagen.
October 1993	Baltimore Cochrane Center registered (changed to New England Cochrane Center in Providence, RI and subsequently to United States Cochrane Center in December 2002)
February 1994	Australasian Cochrane Centre registered, based in Adelaide. Moved to Melbourne later on.
June 1994	Centro Cochrane Italiano (Italian Cochrane Centre) registered, based in Milano. Moved to Modena later on.
October 1994	Dutch Cochrane Centre registered, based in Amsterdam.
November 1994	San Francisco Cochrane Center registered (changed to United States Cochrane Center, San Francisco Branch in December 2002)
April 1995	San Antonio Cochrane Center registered. Closed in 2000
February 1996	Centre Cochrane Français (French Cochrane Centre) based in Lyon registered. Closed in 2002.
May 1996	New England Cochrane Center registered, based in Boston.
August 1996	Centro Cochrane do Brasil (Brazilian Cochrane Centre) registered, based in Sao Paulo.
October 1996	South African Cochrane Centre registered, based in Cape Town.
October 1997	Centro Cochrane Español (Spanish Cochrane Centre) registered, based in Sabadell (Barcelona), (changed to Iberoamerican Cochrane Centre in Barcelona in July 2000)
October 1997	Deutsches Cochrane Zentrum (German Cochrane Centre) registered, based in Freiburg.
March 1999	Chinese Cochrane Centre registered, based in Chengdu.
July 2008	South Asian Cochrane Centre registered, based in Vellore.
June 2010	French Cochrane Centre registered, based in Paris.

The IbCC had been initially registered in 1997 as the Centro Cochrane Español, to be the referent only for Spain and Portugal [6]. In the year 2000, this center was moved to the Hospital de la Santa Creu i Sant Pau in Barcelona, where it could benefit from a much stronger strategic and academic support than it had before [7].

To prevent the potential centralism of a single Cochrane Centre, the IbCC built up the Iberoamerican Cochrane Network (IbCN), a grid of Collaborative Centres that progressively took over responsibilities and integrated in a network structure (Table 2). People such as Zulma Ortiz, Agustín Ciapponi, and Guillermo Carroli in Argentina; Rodrigo Salinas in Chile; and Juan Manuel Lozano in Colombia were key figures in its beginnings. Concomitantly, members of Clinical Epidemiology departments at the Pontifical Xaverian University and the National University, both in Colombia, who had been active members of LatinCLEN since its foundation, started cooperating in different projects with the IbCC. Furthermore, Clinical Epidemiology master degree programs offered by LatinCLEN's CEUs incorporated material on the development of systematic reviews. A sizable proportion of the Cochrane Collaboration activity in the region has been led by graduates of these academic programs.

Several LatinCLEN units have also become Collaborative Centres of the IbCN (Table 3). The methodological expertise of their members and the common goals of both networks certainly favored a spontaneous and natural approach. In 2002, the IbCC applied for admission and was officially accepted as a LatinCLEN Unit.

3. The Iberoamerican Cochrane Network: organization, activities, and synergy with LatinCLEN

At an institutional level, agreements have been signed between the IbCC and several entities expressing interest in becoming Collaborating Centres; and taking over the responsibilities associated with being active nodes in their region. The ultimate aim of formalizing these agreements is to engage an explicit and adequate support for Cochrane contributors working in these centers; providing them with methodological support and funding to attend national and international meetings. Additionally, the Collaborating Centre benefits from the impact of reviews published by its members in The Cochrane Database of Systematic Reviews [8].

The IbCC also fosters partnerships between Collaborating Centres and Associated Groups, which are entities that assume dissemination activities of Cochrane activities in their regions. Currently, the IbCN has 39 Collaborative Centres and 39 Associated Groups across 17 countries. Its structure is described in Table 2 with further information available at http://es.cochrane.org/es/red-cochrane-iberoamericana.

At an individual level, the IbCN offers general or tailored training in Spain and almost every Latin American country to professionals who want to become systematic review authors or contribute otherwise. Furthermore, over 150 people, most of them from Latin America, have completed individual internships at the IbCC in Barcelona. Training has also been developed through online courses in which thousands of students have participated, as well as through webinars in collaboration with the Pan American Health Organization [9]. These efforts, together with LatinCLEN's training programs, have allowed almost 800 Iberoamerican individuals to become authors or coauthors of Cochrane reviews, with 330 reviews and 142 protocols currently published in The Cochrane Database of Systematic Reviews. In addition, Table 3 illustrates how large the influence of LatinCLEN's CEUs has been on the

Table 2. The Iberoamerican Cochrane Network (February 2016)

Branch	Country	Coordinating centers	Associated groups	Organization of Iberoamerican meetings
Iberoamerican Cochrane Centre	Spain	Centro Cochrane Iberoamericano. Hospital de la Santa Creu i Sant Pau, Barcelona Instituto Ramón y Cajal de Investigación Sanitaria y la Universidad Rey Juan Carlos, Madrid Departamento de Salud Gobierno de Navarra Universidad del País Vasco		2nd (Barcelona, 2003), 6th (Barcelona, 2007) and 10th (Madrid, 2011) Ib Cochrane Annual Meetings + 10th (Barcelona, 2007) and 12th (Madrid, 2011) LatinCLEN Congress + 2003 (Barcelona) and 2011 (Madrid) World Cochrane Annual Colloquia
Portuguese	Portugal	Faculdade de Medicina na Universidade de Lisboa (FMUL)		2017 International Cochrane Mid-term Meeting
Central American and Spanish Caribbean	Costa Rica	Fundación Instituto Centroamericano de Salud Internacional, San José	Escuela de Enfermería de la Universidad de Costa Rica	7th (San José, 2008) Ib Cochrane Annual Meeting
	Guatemala	Fundación Oxlajuj N'oj. Fraijanes		
	Panamá	Instituto para el Desarrollo de la Salud Humana y de la Efectividad Clínica de Panamá (IDECPA), Ciudad de Panamá		13th (Panamá City, 2014) Ib Cochrane Annual Meeting + International Cochrane Mid-term Meeting
	El Salvador		Fundación IHCAI	
	Cuba	Ministerio de Salud Pública: Dirección de Ciencia y Técnica, Instituto de Medicina Tropical ''Pedro Kourí'' INFOMED, Instituto Nacional de Higiene, Epidemiología y Microbiología (INHEM), Instituto Nacional de Endocrinología (INEN), Hospital ''Hermanos Amejeiras (HHA), Centro Nacional de Ensayos Clínicos (CENCEC), Centro de Registro de Medicamentos (CEDMEC), Escuela Nacional de Salud Pública (ENSAP)		
	Nicaragua		Centro de Investigaciones y Estudios de la Salud. Universidad Nacional Autónoma de Nicaragua (CIES-UNAN)	
Mexican	México	Instituto Tecnológico y de Estudios Superiores de Monterrey (ITESM)	Comisión Nacional de Arbitraje Médico. CONAMED Instituto Mexicano del Seguro Social (IMSS) Hospital Civil Dr. Juan I. Menchaca Instituto Nacional de Salud Pública	4th (Cuernavaca, 2005) and 12th (Monterrey, 2013) Ib Cochrane Annual Meetings
		Hospital Infantil de México Federico Gómez, México, D.F.	Centro Dermatológico ''Dr. Ladislao de la Pascua'' Instituto Nacional de Psiquiatría ''Ramón de la Fuente Muñiz'' Hospital General Dr. Manuel Gea González	
		Instituto Nacional de Pediatría (INP), México, D.F.	Instituto Nacional de Perinatología Isidro Espinosa de los Reyes Hospital Regional de Alta Especialidad Ixtapaluca Centro Nacional de Excelencia Tecnológica en Salud	

(*Continued*)

Table 2. Continued

Branch	Country	Coordinating centers	Associated groups	Organization of Iberoamerican meetings
		Hospital Pediátrico de Sinaloa ''Rigoberto Aguilar Pico,'' Culiacán, Sinaloa	Universidad Merista de Mérida	
		Hospital General de México ''Dr. Eduardo Liceaga,'' México, D.F.		
Andean	Colombia	Universidad Nacional de Colombia, Bogotá	Universidad Tecnológica de Pereira Universidad del Valle Universidad del Cauca	1st (Cartagena, 2002) and 8th (Bogotá, 2009) Ib Cochrane Annual Meetings + 11th (Bogotá, 2009) LatinCLEN Congress
		Pontificia Universidad Javeriana de Bogotá		
		Fundación Universitaria de Ciencias de la Salud (FUCS), Bogotá	Universidad Surcolombiana	
		Universidad de Antioquia		
	Ecuador	Universidad Tecnológica Equinoccial. Fundación Educación, Salud y Sociedad (FESS), Quito	Pontificia Universidad Católica del Ecuador	5th (Quito, 2006) Ib Cochrane Annual Meeting
	Peru	Universidad Peruana Cayetano Heredia, Lima	Universidad Católica Santo Toribio de Mogrovejo-Chiclayo (USAT) Universidad Nacional Mayor de San Marcos del Perú Facultad de Ciencias de la Salud de la Universidad Peruana de Ciencias Aplicadas (UPC)	11th (Lima, 2012) Ib Cochrane Annual Meeting + 13th (Lima, 2012) LatinCLEN Congress
		Instituto Nacional de Salud (INS), Lima		
	Venezuela	Asociación Cardiovascular Centroccidental (ASCARDIO), Barquisimeto	Escuela de Medicina Luis Razetti	
Southern American	Argentina	Instituto de Efectividad Clínica y Sanitaria (IECS), Buenos Aires	Asociación Odontológica Argentina Hospital de Niños ''Dr. Ricardo Gutiérrez'' Hospital de Pediatría ''Prof. Dr. Juan P. Garrahan'' Asociación GEDIC-GESICA Hospital Alemán	3rd (Buenos Aires, 2004) Ib Cochrane Annual Meeting
		Centro Rosarino de Estudios Perinatales (CREP), Rosario	Hospital de Emergencias Dr. Clemente Álvarez (HECA)	
		Instituto Universitario Hospital Italiano de Buenos Aires (IUHI)		
	Bolivia	Universidad Mayor de San Andrés —IINSAD, La Paz		
	Chile	Pontificia Universidad Católica de Chile, Santiago	Fundación Oftalmológica 2020 Grupo de Kinesiología Basada en la Evidencia, Universidad de las Américas Unidad de Odontología Basada en la Evidencia (OBE), Universidad de Chile Clínica Alemana de Santiago	9th (Santiago, 2010) Ib Cochrane Annual Meeting. 2019 World Cochrane Annual Colloquium
		Universidad Católica de la Santísima Concepción, Concepción	Centro de Rehabilitación Oral Avanzada e Implantología, Universidad de Concepción	
		Universidad de La Frontera (UFRO), Temuco		
		Facultad de Odontología de la Universidad de Chile		

(*Continued*)

Table 2. Continued

Branch	Country	Coordinating centers	Associated groups	Organization of Iberoamerican meetings
	Uruguay	Fondo Nacional de Recursos, Montevideo	Ministerio de Salud Pública Unidad de Investigación Clínica y Epidemiológica Montevideo (UNICEM) Universidad de la República —Instituto de Higiene	
	Paraguay		Sociedad Científica del Paraguay Facultad de Medicina de la Universidad María Auxiliadora	

production of Cochrane systematic reviews: globally, 39.7% (131 of 330) have authors that have pertained to one of such units. Table 4 summarizes the information disaggregated by countries.

Another important milestone has been the establishment of *La Biblioteca Cochrane Plus*, an electronic array of medical databases where reviews originally published in English in The Cochrane Library are translated into Spanish. Since 2003, *La Biblioteca Cochrane Plus* has provided universal free access for residents in Spain. In Latin American countries, the access has been mainly through the *Biblioteca Virtual de Salud* (Virtual Health Library). The use of *La Biblioteca Cochrane Plus* has progressively increased until reaching over 6 million annual visits [10].

Further documents translated into Spanish include the *Cochrane Handbook for Systematic Reviews of Interventions* [11] and the *Methodological Expectations of Cochrane Intervention Reviews* [12], among other training material [13] (available at www.cochrane.es). Moreover, several members of the IbCN keep an active role in Cochrane Editorial and Working Groups.

Additional achievements include the hand searching of controlled clinical trials initiative. Thanks to a broad volunteer effort, this project has allowed the retrieval of over 5,000 clinical trials references in Spanish from 553 biomedical journals in 16 different countries. These references are incorporated into CENTRAL (Cochrane Central Register of Controlled Trials) for their inclusion in systematic reviews.

Table 3. Influence of LatinCLEN units in the publication of Cochrane systematic reviews (SRs) in Latin America

Country	Clinical epidemiology units (CEUs)	LatinCLEN incorporation	Iberoamerican Cochrane Network Incorporation	Cochrane SRs per country[a]	Cochrane SRs with participation of a LatinCLEN unit[b]
Argentina	Universidad Nacional de Tucuman	1998–2000	—	47	2 (4.25)
	Instituto de Efectividad Clínica y Sanitaria	2000s	2004		15 (31.91)
Bolivia	Universidad Mayor San Andrés de La Paz	1998–2000	2010	1	0
Colombia	Universidad del Cauca	1998–2000	2009	51	2 3.92
	Universidad Nacional de Colombia	1998–2000	2000		10 (19.61)
	Universidad Industrial de Santander	1998–2000	—		0 0
	Universidad de Antioquia	1998–2000	2009		8 15.69
	Universidad del Rosario	2010s	—		1 (1.96)
	Pontificia Universidad Javeriana	1980s	2010		13 (25.49)
Chile	Universidad de La Frontera	1980s	2005	30	5 (16.67)
	Universidad de Chile	1980s	—		6 (20.00)
Mexico	Instituto Nacional de Nutrición y Ciencias Médicas	1980s	—	24	5 (20.83)
	Instituto Mexicano de Seguridad Social	1980s	2013		1 (4.17)
Peru	Universidad Peruana Cayetano Heredia	1998–2000	2005	9	6 (66.67)
Spain	Iberoamerican Cochrane Centre	2000s	2000	138	64 46.38
Rest of the countries				65	0
Total CEU[c]				330	131 (39.70)

[a] Determined by the country of authors.

[b] Measured as the number of published Cochrane Systematic Reviews with any author affiliated to a LatinCLEN unit (percentage over the reviews published at the respective country).

[c] Total number of unique documents.

Table 4. Registered protocols and systematic reviews production in the Cochrane Library by Iberoamerican authors

Country	Protocols (P)	Reviews (R)	Total
Bolivia	0	1	1
Uruguay	0	8	8
Cuba	2	7	9
Costa Rica	1	9	10
Peru	4	9	13
Ecuador	5	9	14
Mexico	16	24	40
Venezuela	11	31	42
Portugal	10	37	47
Chile	33	30	63
Argentina	22	47	69
Colombia	20	51	71
Spain	64	138	202
Total Iberoamerica[a]	142	330	472

Data updated February 2016. The production by country has been considered counting the presence of an author in the registered protocols and systematic reviews.

[a] Total number of unique documents.

They also allow a critical analysis of the clinical trials conducted in each country [14–22] and across the region.

The IbCN also took over the organization of the 2003, 2011, and 2019 World Cochrane Colloquia, in Barcelona, Madrid, and Santiago de Chile, respectively, as well as the 2014 and 2017 yearly Cochrane Mid-term Meetings, in Panama City and Lisbon, respectively. Additionally, the first joint meeting between Cochrane in LatinCLEN was held in 2007 in Barcelona, an initiative that has been later repeated on several occasions (Table 2).

In summary, the IbCN and LatinCLEN have had a remarkable impact providing training and support to foster the development of professionals with expertise in Clinical Epidemiology and the development of systematic reviews. This has translated into the development, assessment, and uptake of new evidence that can and has been used in health care, as well as into the design and implementation of key public health measures across the region.

4. Future prospects and challenges

Although the satisfaction with the achievements of the IbCN is fair and legitimate, it is even more important to define present and future challenges in the frame of the Cochrane Strategy to 2020 [23] which consists of four key points:

(1) To publish high-quality systematic reviews that regularly synthesize and update the best existing evidence, applied to a wide range of health issues. The IbCN is committed to increasing the number of Latin American authors involved in the development of Cochrane systematic reviews

(2) To encourage the dissemination of Cochrane contents. Cochrane is currently working on adopting open-access policies, as well as on simultaneously publishing Cochrane reviews in the six WHO official languages.

(3) To keep an efficient and transparent structure and management system. The IbCN and the Cochrane Collaboration as a whole are assessing different approaches to combine the participative and open nature of the organization with an improved capacity to make and implement collective decisions.

(4) To achieve economic sustainability. Increasing the Cochrane Collaboration's presence worldwide will facilitate sharing the inherent economic burden among more organizations. The close cooperation with LatinCLEN achieved in Latin America can be considered a very valid referent. Nevertheless, the future of this partnership will very much depend on the capacity of LatinCLEN—as an independent network—to keep its goals of promoting primary research in Latin America.

5. Conclusions

Over its first 20 years, the Cochrane Collaboration has made important contributions such as published systematic reviews, methodological developments and advances, training programs, technological innovations, and enhancement of research ethical values. Cochrane has proven that global cooperation between different people and entities is not only necessary but also possible. In Latin America, the IbCN and has made significant contributions. The alliance established with LatinCLEN has been key to these achievements.

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9.2. Anexo 2

Identification and description of controlled clinical trials published in Spanish Gynaecology and Obstetrics journals and risk of bias assessment of trials on assisted reproductive techniques. Eur J Obstet Gynecol Reprod Biol. 2016;203:5-11.

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Review

Identification and description of controlled clinical trials published in Spanish Gynaecology and Obstetrics journals and risk of bias assessment of trials on assisted reproductive techniques

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ABSTRACT

Objectives: To identify and describe controlled clinical trials (CCTs) published in Spanish Gynaecology and Obstetrics journals. In addition, to assess the quality of the CCTs on Assisted Reproduction Techniques (ART) identified in this project.
Study design: In order to identify eligible CCTs, all Spanish Gynaecology and Obstetrics journals were handsearched. Handsearching was conducted following the guidelines provided by the Cochrane Collaboration, which state that each journal article must be carefully reviewed, including original articles and other types of studies, letters to the editor, abstracts, and conference presentations. The results of the handsearching process were compared with an electronic search conducted in MEDLINE (PubMed). A descriptive analysis of the main characteristics of the identified CCTs was performed, as well as a methodological assessment of CCTs on ART.
Results: Sixteen Gynaecology and Obstetrics journals were identified, four of which have been indexed in MEDLINE at some point, although not currently. The journal with the most CCTs was "Progresos de Obstetricia y Ginecología". A total of 235 CCTs were published in these journals, of which 29 were on ART. Most CCTs (216, 91.9%) were carried out in a hospital setting; 201 (89.4%) were unicentric. Obstetrics was the most studied subspecialty (46.4%). Among CCTs on ART, the risk of bias was predominantly high.
Conclusions: The number of CCTs published in Spanish Gynaecology and Obstetrics journals is limited. CCTs on ART present deficiencies in the report of results and low methodological quality. It is advised that authors and journals adhere to the CONSORT statement and to the Cochrane Collaboration recommendations to reduce risk of bias when designing and disseminating research projects.

Contents

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Introduction

Well-designed and properly executed controlled clinical trials (CCTs) provide the best evidence on the impact of health interventions. Nevertheless, these might result in exaggerated estimates of this effect, if carried out using an inappropriate methodology [1–3]. Therefore, CCTs ought to be properly evaluated before being used in clinical practice. Evidence-Based Medicine (EBM) is defined as "conscientious, explicit, and judicious use of current best evidence in making decisions about the care of individual patients" [4]. EBM depends largely on the methodological quality of the CCTs and its exhaustive identification. These features are equally indispensable for conducting systematic reviews (SR) [4,5] and Clinical Practice Guidelines (CPG) [6,7]. Given these prerequisites, identifying the highest number of CCTs is critical to have SR and CPGs with no publication bias.

It is known that the best strategy to identify clinical trials is to combine electronic and manual (handsearch) search strategies [8,9]. Electronic search strategies, widely used and based on filters and keywords applied to databases, are limited for different reasons [10–12]. First, because only since 2004 the World Health Organization (WHO) recorded CCTs of different languages, which means that many CCTs published in previous years may not have be included in this platform [12]. Second, because even though there are other bibliographic databases accessible online that allow identifying CCTs through electronic searching, the sensitivity of these searches is limited due to issues with classification (indexing) of the CCTs. In addition, the term "controlled clinical trial" was only indexed as such in 1990, and introduced in MEDLINE and EMBASE in 1991 and 1994, respectively. For this reason, it is considerably more difficult to identify older CCTs publications using algorithms and search filters [10,1].

Given this problem, the Cochrane Collaboration proposed to complement electronic search strategies with a handsearching strategy. Handsearching involves the progressive review of all articles (conference proceedings, theses, letters, editorials, etc.) published in a journal [8–13]. It requires a rigorous inspection, which allows the identification of CCTs that are not included in electronic databases, as well as CCTs that have not been properly indexed or that simply cannot be retrieved through an electronic search. Handsearching allows identifying 92% to 100% of CCTs available, whereas electronic searches of the main databases, MEDLINE and EMBASE, contribute only 55% and 49% of these, respectively [13]. This difference is due to the fact that the handsearching allows the identification of CCTs published before 1991, those published as abstracts or letters, and those published in languages other than English [8,13].

Several CCTs identification studies that combine electronic and handsearching strategies conducted in Pharmacology journals [14], General and Internal Medicine [15], Ophthalmology [16] and patient safety [17], confirm the limitations of electronic search strategies. Through these projects, it has been found that the sensitivity of electronic searches is about 77%, whereas the accuracy or specificity hoovers around 50%, with cases in which it does not exceed 5% [15,17].

During recent years, there is a marked increase in scientific production published on Gynaecology and Obstetrics in Spanish language. To our knowledge, no handsearching project has been conducted so far in order to identify these CCTs. In reference to Assisted Reproduction Techniques (ART), and the importance of gathering all available evidence on this field, it is essential to evaluate the quality of work carried out [18,19], considering that since 1978, when the first baby conceived through Fertilization In vitro was born, ART techniques have evolved considerably without this being reflected in higher pregnancy rates [20–23].

This study was conducted in order to identify and describe the main features of CCTs published in Spanish Gynaecology and Obstetrics journals. Additionally, in order to obtain a clearer picture of the strengths and challenges of research in ART, a description of the methodological aspects and potential risk of bias of CCTs identified in this area was made. The studies identified in this article will be incorporated into CRS, the global CCTs registry of the Cochrane Collaboration.

Materials and methods

Identification of eligible journals and handsearching of clinical trials

The first step of this study consisted of determining which journals should be handsearched, considering eligible those that publish original research in the field of Gynaecology and Obstetrics. Eligible journals were identified through the Spanish Medical Index (SMI), the National Catalogue of Spanish Publications in Health Sciences Libraries C-17, Latindex, Periodic, LILACS, Scielo, and MEDLINE (PubMed). This search was carried out by a trained investigator who followed a protocol that established the order in which the sources had to be consulted. All relevant information for each journal was collected and their full texts were identified on the Internet, libraries, publishers, corporations, and other sources.

The handsearching of each journal was systematic and performed according to the guidelines of the Cochrane Collaboration, which establish that each journal must be carefully reviewed, not only original articles but also letters to the editor, abstracts and conference presentations. Handsearching consists of four stages: first, reading table of contents; second, location of keywords in the title of each article (randomized, random, fortuitous, blind, etc.); third, reading of the summary (abstract) of each article; and fourth, reading of the materials and methods section. The process must be completed retrospectively, i.e. backwards from the last year of publication. If no CCTs are found in a period of five years, handsearching for the corresponding journal must be stopped.

The process of handsearching involved 12 reviewers. Following the recommendations of the Cochrane Collaboration, each reviewer conducted a pilot test which involved handsearching of a volume journal that had been previously reviewed by personnel with expertise in this field.

Electronic identification of clinical trials

Additionally, an electronic search was conducted on MEDLINE (PubMed access) in order to identify CCTs amongst the eligible journals for this study and compare results with those of the handsearch. The search strategy used can be found in Annex 1.

Subsequently, we calculated the sensitivity and specificity of this search with the following definitions:

- Sensitivity: Proportion of all studies identified by the electronic search over those identified by handsearching.
- Specificity: Proportion of truly eligible studies among all those recovered by the electronic search strategy.

Inclusion criteria

To be considered a CCT, a study had to fulfil the eligibility criteria of clinical trials proposed by the Cochrane Collaboration:

(a) The study compares treatments in humans.
(b) The study is prospective (interventions are planned before the study takes place, and assignment of subjects to intervention is decided by the researchers).
(c) Two or more treatments or interventions are compared (one can be a control with no treatment or placebo group). Interventions can be of any type: drugs, surgery, diagnostic, educational, rehabilitative, organizational, etc.
(d) The allocation to treatments should be randomized or quasi-randomized.
   - Random: the authors explained that the compared groups were formed by random assignment, usually describing the allocation method.
   - Quasi-randomized: it attempts to produce similar groups to assign each participant intervention. The methods used include allocation according to date of birth of the subject, day or month of the year, even and odd numbers, or medical record number.

The review of journals was conducted individually. Two authors (RG and IA or DB) verified the eligibility of each possible CCT identified. Discrepancies were resolved by consensus or consultation with a third author (HP, XB).

Data extraction

Once the CCTs are identified and classified according to the previous criteria, in order to make a descriptive analysis of trials, the variables collected were evaluated in a data sheet specifically designed for this study.

Also, an assessment of risk of bias (high/medium/low) of the identified CCTs in ART was conducted using the Cochrane Collaboration tool recommended for this objective [9]. This tool value several aspects of the methodology of CCTs, including method of generating the allocation sequence, concealing of this sequence, blinding of patients or investigators, intention-to-treat analysis, reasons for missing data (where applicable) and other likely sources of bias.

Analysis

A descriptive analysis of the variables of interest was performed using SPSS version 17 (SPSS, Inc., Chicago, IL, USA). Central measures and dispersion measures were calculated and the features of quantitative variables were described. In addition, the absolute and relative frequencies of qualitative variables were calculated.

Results

Sixteen Gynaecology and Obstetrics journals were identified, of which 11 published CCTs. A total of 235 CTTs on different subspecialties were retrieved from these publications. The most active journal was *Progresos de Obstetricia y Ginecología* with 54 CCTs (23%), followed by *Clínica e Investigación en Ginecología y Obstetricia* with 46 CCTs (19.6%) and *Acta Ginecológica* with 35 CCTs (14.9%) (Table 1). Of all the CCTs, 29 (12.3%) were of ART.

The first CCT was published in 1967 in *Acta Ginecológica* (Víctor Ruiz Velasco y Gonzalo Río de la Rosa. *La pentazocina en la analgesia obstétrica*. Acta Gin. 1967;18(6):368–372), while the first CCT on RMA was published in 1987 in the same journal (J. Balash, et al. *Endometriosis y esterilidad: Tratamiento con acetato de medroxiprogesterona y danazol*. Acta Gin. 1987;44(2):39–72). The year with the highest number of CCTs was 1982 with a total of 14 (6%), followed by 1990 with 12 (5.1%). The decade with the most identified CCTs was the 90s (Fig. 1).

A total of 187 (79.6%) of the CCTs identified were classified as randomized clinical trials (RCTs), whereas 48 (20.4%) were quasi-randomized. The most studied subspecialty was Obstetrics with 109 CCTs (46.4%), followed by Gynaecology with 72 (30.6%). The main researched topics were pregnancy and any associated conditions, including premature rupture of membranes, intrauterine growth restriction, preterm labour, gestational diabetes,

Table 1
Spanish Gynaecology and Obstetrics Journals.

Journal	Posted period	Publication years	No. CCT	% CCT
1. Progresos de Obstetricia y Ginecología	1958–2013	36	54	23%
2. Clínica e Investigación en Ginecología y Obstetricia	1971–2013	42	46	19.6
3. Acta Ginecológica	1950–2010	48	35	14.9%
4. Revista Española de Obstetricia y Ginecología	1962–2011	43	27	11.5%
5. Revista Iberoamericana de Fertilidad y Reproducción Humana	1990–2013	23	26	11.1%
6. Toko Ginecología Práctica	1971–2013[a]	42	14	6.0%
7. Actualidad Obstétrico Ginecológica	1989–2000	9	12	5.1%
8. Ciencia Ginecológika	1996–2008	12	7	3.0%
9. Acta Obstétrica y Ginecológica Hispano-Lusitana	1968–2013	32	7	3.0%
10. Ginecología Catalana	1998–2002	5	4	1.7%
11. Avances en Obstetricia y Ginecología	1976–1983	7	3	1.3%
12. Clínica Ginecológica	1988–2000	1	0	0%
13. Revista de Senología y Patología Mamaria	1987–2013	5	0	0%
14. Folia Clínica en Obstetricia y Ginecología	1997–2010	5	0	0%
15. Progresos de Diagnóstico Prenatal	1978–2013	5	0	0%
16. Ginecología Clínica y Quirúrgica[b]	2000–2001	2	0	0%
Ginecología y Obstetricia Clínica[b]	2000–2002	2	0	0%
Ginedips[b]	1970–1999	5	0	0%
Total	1950–1984		235	100%

[a] 1970–1936 failed to obtain the full text copies of these years for this journal.
[b] Ginecología Clínica Y Quirúrgica, Ginecología Y Obstetricia Clínica, and Ginedips: They are the same journal.

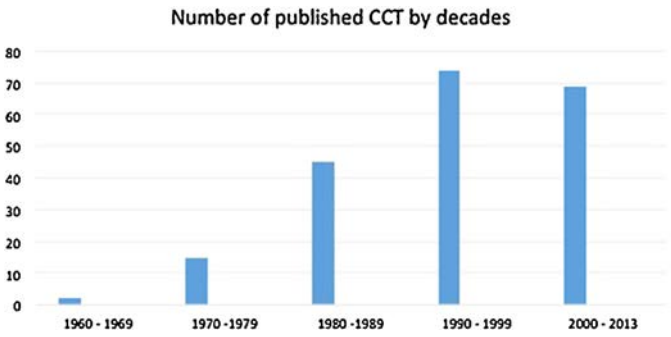

Fig. 1. Number of published CCT by decade.

anaemia, and others (24.7%). Infertility treated with RMA was studied in 12.1% of the studies (Fig. 2).

The average age of participants in the identified CCTs was 34.04 years (DS 9.318), with a minimum age of 20 and a maximum of 60. However, age was reported only in 126 CCTs, representing 54.2% of the identified studies. Most studies were conducted among subjects with pathology, and the most common comparison was treatment versus treatment (156, 66.4%). Most CCTs were conducted in hospitals (216, 91.9%), followed by primary care centres (9, 3.8%). A total of 210 (89.4%) of the CCTs were single centre, compared to 9 (3.8%) multicentre (Table 2).

In 224 (95.3%) of the cases, the authors did not specify the sponsor(s) of the study, while nine (3.8%) reported receiving private funds and two (0.9%) public funds. 234 CCTs (99.6%) did not report whether there was a conflict of interest, compared to one (0.4%) that did report it (Table 2).

29 ART studies were identified in six of the elegible journals (Revista Iberoamericana de Fertilidad y Reproducción Humana, Revista Española Obstétrica Ginecológica, Acta Ginecológica, Progresos de Obstetricia y Ginecología, Tokoginecología Práctica and Actualidad Obstétrica Ginecológica). Regarding their methodological quality, we found that risk of bias was high in 20 CCTs (69%). In most (18, 62.1%), randomization sequence generation features were unidentified, while in nine (31%) randomization was performed properly. Only one CCT (3.4%) implemented a proper strategy to conceal allocation of patients to treatments or interventions. Double-blind assessment of results was adopted in five CCTs (17.2%). Intention-to-treat analysis was implemented

Table 2
Characteristics of the identified CCTs..

Features	*n*	%
Speciality		
Gynaecology	72	30.6%
Obstetrics	109	46.4%
Assisted Reproduction Techniques	29	12.3%
Gynaecologic Oncology	7	3.0%
Mastology	3	1.3%
Endocrinology	15	6.4%
Centre		
One centre	210	89.4%
Multicentre	9	3.8%
Not reported	16	6.8%
Area		
Hospital care	216	91.9%
Primary Care	9	3.8%
Others	5	2.1%
Not reported	5	2.1%
Intervention		
Drug vs. drug	156	66.4%
Drug vs. placebo or no treatment	32	13.6%
Others	47	20.0%
Design		
Randomized CCTs	187	79.6%
Quasi-randomized CCTs	48	20.4%
Type of funding		
Public	2	0.9%
Private	9	3.8%
Not reported	224	95.3%
Conflict of interest		
Reported	1	0.4%
Not reported	234	99.6%

in 21 studies (72.2%); in 24 (82.8%) all relevant data was reported, and groups were comparable at baseline in 22 (75.9%) studies (Table 3).

The electronic search conducted in MEDLINE allowed identifying five potential CCTs with no summaries (abstracts) available. These articles were identified in four journals: *Acta Obstétrica Ginecológica Hispana Lusitana, Acta Ginecológica, Toko Ginecología Práctica*, and *Revista Española de Obstetricia y Ginecología.* These journals are indexed in MEDLINE in different periods of time, although not currently. The full-text of the potential CCTs was

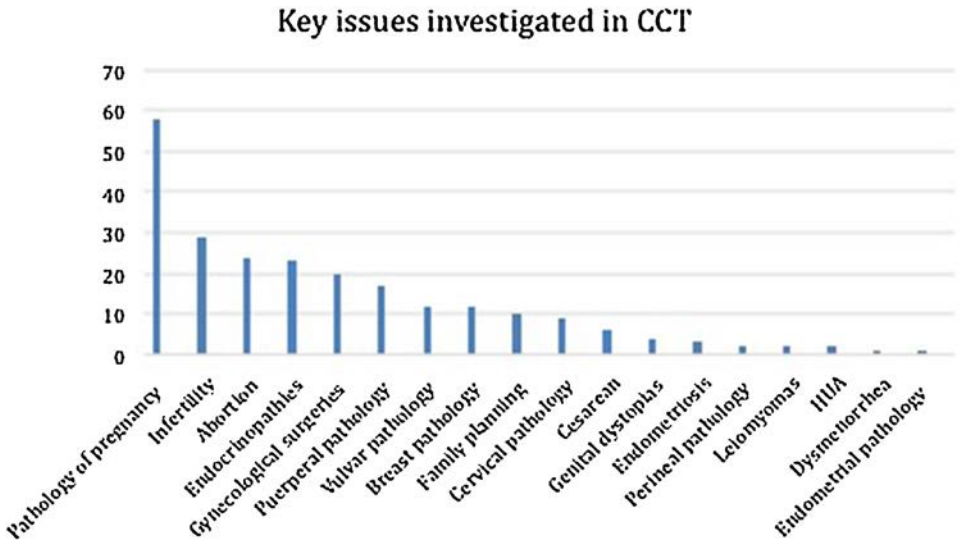

Fig. 2. Key issues investigated in CCT.

Table 3
Risk of bias assessment of CCTs on ART.

	Number	Percentage
Risk of bias		
• Low	1	3.4%
• Moderate	8	27.6%
• High	20	69.0%
1. Selection bias		
Sequence generation		
• Adequate	9	31.0%
• Unclear	18	62.1%
• Inadequate	2	6.9%
Allocation concealment		
• Adequate	1	3.4%
• Unclear	26	89.7%
• Inadequate	2	6.9%
2. Performance bias		
Double blind		
• Adequate	5	17.2%
• Unclear	0	0%
• Inadequate	24	82.8%
3. Detection bias		
Blinding of outcome assessors		
• Yes	0	0%
• No	5	17.2%
• Not reported/Unclear	24	82.8%
4. Attrition bias (incomplete outcome data)		
Analysis by intention to treat		
• Yes	21	72.4%
• No	2	6.9%
• Not reported/Unclear	6	20.7%
5. Selective reporting of results		
• Clinical	24	82.8%
• Intermediate	2	6.9%
• Not reported/Unclear	3	10.3%
6. Other sources of bias		
Comparable at baseline groups		
• Yes	22	75.9%
• No	1	3.4%
• Not reported/Unclear	6	20.7%

retrieved; it was then determined that none were CCTs. Therefore, the sensitivity and specificity of the electronic search was 0% (Table 4).

Comments

The main objective of this study was to identify and describe the CCTs published in Spanish Gynaecology and Obstetrics journals until December 31, 2013. The number of CCTs identified in these publications is low, specifically 224 published between 1967 and 2013, an average of 4.82 CCTs per year. The journal that published the most CCTs was *Progresos de Obstetricia y Ginecología*, with 24.1% of CCTs.

The most researched health problems were conditions associated with pregnancies, including premature rupture of membranes, intrauterine growth restriction, preterm labour, gestational diabetes, and anaemia, among others. However, it was expected that the most studied problem would be ART, since Spain is one of the countries in the European Union with the lowest fertility rates (1.48 per female), along with Greece, Italy and Germany [24].

Most CCTs were single-centre (210, 89.4%) and were developed in hospital care (216, 91.9%), which is consistent with the fact that these studies were conducted mainly among patients with pathologies. The average age of participants was 34.04 years (DS9.318), but this variable was not reported in 104 CCTs, which represents 45.8% of the identified studies. These deficiencies coincide with similar studies in other specialties, with slight deviations [14,15]. It was detected that only 11 CCTs (4.9%) reported who was the promoter of the study, compared with 224 (95.8%) who did not. In the same line, 99.6% of CCTs did not report whether there were conflicts of interest, which is consistent with the results of other similar studies [15,17].

A total of 29 studies were on ART, equivalent to less than one per year. The leading journal in publishing on this subject was *Revista Iberoamericana de Fertilidad y Reproducción Humana*, with 85.2% of the total. In relation to the methodological quality of these studies, the majority present a high risk of bias. Randomization sequence generation characteristics are unknown in 62.1% of the cases, and frequently the sequence of allocation was not concealed. Furthermore, only 17.2% reported a method for blinding the interventions. These biases may overstate results of the corresponding studies [24]. On the other hand, over 70% of the CCTs completed an intention-to-treat analysis, 82.8% reported all clinical variables, and 75% had groups comparable at baseline groups. These data is encouraging because it contributes to reduce reporting and attrition biases [9].

This study emphasizes that the CCTs identified through handsearching would not have been identified via an electronic search in MEDLINE (PubMed). This is proof of the limitations of exclusively electronic searches and the invaluable role of handsearch in identifying CCTs, especially those reported as abstracts or letters to the editor, or reported in languages other than English [15–17]. Moreover, it is worth-mentioning the large number of publications reviewed: a total of 15 journals. Handsearching, in accordance with the criteria of the Cochrane Collaboration, was systematic and exhaustive for all volumes and supplements.

A possible limitation of this study is that the electronic and handsearching strategies were limited to Spanish journals. This may have left out CCTs published in foreign journals, or in journals that are not specifically on Gynaecology and Obstetrics. In addition, this paper focuses exclusively on studies in Spain: a study on journals from Latin American countries is being carried out at present. Another limitation is that the handsearching of journals were conducted individually, which could have left out some eligible CCTs. However, the possibility of false positives was minimized since the 235 CCTs identified were verified by at least two of the authors. Likewise, the possibilities of false negatives were minimized since each researcher conducted a pilot test to standardize the handsearching process.

In conclusion, the number of CCTs published in Spanish Gynaecology and Obstetrics journals is low. The CCTs identified in this study would not have been retrieved through an electronic search, which highlights the importance of handsearching of journals. Regarding CCTs on ART, the number of articles published is similarly low; they carry a high risk of bias in their methodology. Authors are advised to carefully consider the design and completion of CCTs, in order to minimize potential bias and ensure their methodological quality. They are advised to adhere to the Consolidated Standards of Reporting Trials (CONSORT) statement [25] when publishing the results of their studies.

Table 4
Items identified by both searches.

Items identified	Identified		Confirmed	
	No.	%	No.	%
Identified by handsearching	257	98.09%	235	100%
Identified by electronic search	5	3.91%	0	0%
Total	262	100	236	100

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Conflicts of interest

The authors have no conflicts of interest to declare.

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Annex I. Strategy search in PubMed

((“ActaSuomlaakDuodecim” [Journal] OR “acta” [All Fields] OR “ActaSuomLaakDuodecim” [Journal] OR “acta” [All Fields]) AND ginecol. [All Fields]) AND (Clinical Trial [ptyp] OR Clinical Trial, Phase I [ptyp] OR Clinical Trial, Phase II [ptyp] OR Randomized Controlled Trial [ptyp] OR Clinical Trial, Phase III [ptyp] OR Clinical Trial, Phase IV [ptyp]).

(“TokoginecolPract” [Journal] OR (“tokoginecol” [All Fields] AND “pract” [All Fields]) OR “tokoginecolpract” [All Fields]) AND (Clinical Trial [ptyp] OR Clinical Trial, Phase I [ptyp] OR Clinical Trial, Phase II [ptyp] OR Randomized Controlled Trial [ptyp] OR Clinical Trial, Phase III [ptyp] OR Clinical Trial, Phase IV [ptyp]).

(“Rev EspObstetGinecol” [Journal] OR (“rev” [All Fields] AND “esp” [All Fields] AND “obstet” [All Fields] AND “ginecol” [All Fields]) OR “rev espobstetginecol” [All Fields]) AND (Clinical Trial [ptyp] OR Clinical Trial, Phase I [ptyp] OR Clinical Trial, Phase II [ptyp] OR Randomized Controlled Trial [ptyp] OR Clinical Trial, Phase III [ptyp] OR Clinical Trial, Phase IV [ptyp]).

(Rev. [All Fields] AND senol. [All Fields] AND patol. [All Fields] AND mamar. [All Fields]) AND (Clinical Trial [ptyp] OR Clinical Trial, Phase I [ptyp] OR Clinical Trial, Phase II [ptyp] OR Randomized Controlled Trial [ptyp] OR Clinical Trial, Phase III [ptyp] OR Clinical Trial, Phase IV [ptyp]).

(“ClinGinecol” [Journal] OR (“clin” [All Fields] AND “ginecol” [All Fields]) OR “clinginecol” [All Fields]) AND (Clinical Trial [ptyp] OR Clinical Trial, Phase I [ptyp] OR Clinical Trial, Phase II [ptyp] OR Randomized Controlled Trial [ptyp] OR Clinical Trial, Phase III [ptyp] OR Clinical Trial, Phase IV [ptyp]).

(Actual. [All Fields] AND obstet. [All Fields] AND ginecol. [All Fields]) AND Madr [All Fields] AND (Clinical Trial [ptyp] OR Clinical Trial, Phase I [ptyp] OR Clinical Trial, Phase II [ptyp] OR Randomized Controlled Trial [ptyp] OR Clinical Trial, Phase III [ptyp] OR Clinical Trial, Phase IV [ptyp]).

(Av [All Fields] AND obstet [All Fields] AND ginecol [All Fields]) AND (Clinical Trial [ptyp] OR Clinical Trial, Phase I [ptyp] OR Clinical Trial, Phase II [ptyp] OR Randomized Controlled Trial [ptyp] OR Clinical Trial, Phase III [ptyp] OR Clinical Trial, Phase IV [ptyp]).

(Cienc. [All Fields] AND ginecol. [All Fields]) AND (Clinical Trial [ptyp] OR Clinical Trial, Phase I [ptyp] OR Clinical Trial, Phase II [ptyp] OR Randomized Controlled Trial [ptyp] OR Clinical Trial, Phase III [ptyp] OR Clinical Trial, Phase IV [ptyp]).

(Folia [All Fields] AND Clin. [All Fields] AND Obstet. [All Fields] AND Ginecol. [All Fields]) AND (Clinical Trial [ptyp] OR Clinical Trial, Phase I [ptyp] OR Clinical Trial, Phase II [ptyp] OR Randomized Controlled Trial [ptyp] OR Clinical Trial, Phase III [ptyp] OR Clinical Trial, Phase IV [ptyp]).

(ginecol. [All Fields] AND catalano [All Fields]) AND (Clinical Trial [ptyp] OR Clinical Trial, Phase I [ptyp] OR Clinical Trial, Phase II [ptyp] OR Randomized Controlled Trial [ptyp] OR Clinical Trial, Phase III [ptyp] OR Clinical Trial, Phase IV [ptyp]).

(Ginecol. [All Fields] AND obstet. [All Fields] AND clin. [All Fields]) AND (Clinical Trial [ptyp] OR Clinical Trial, Phase I [ptyp] OR Clinical Trial, Phase II [ptyp] OR Randomized Controlled Trial [ptyp] OR Clinical Trial, Phase III [ptyp] OR Clinical Trial, Phase IV [ptyp]).

(Gine [All Fields] AND (“3,5-diisopropylsalicylic acid” [Supplementary Concept] OR “3,5-diisopropylsalicylic acid” [All Fields] OR “dips” [All Fields])) AND (Clinical Trial [ptyp] OR Clinical Trial, Phase I [ptyp] OR Clinical Trial, Phase II [ptyp] OR Randomized Controlled Trial [ptyp] OR Clinical Trial, Phase III [ptyp] OR Clinical Trial, Phase IV [ptyp]).

(Prog. [All Fields] AND diagn. [All Fields] AND trat. [All Fields] AND prenat. [All Fields]) AND (Clinical Trial [ptyp] OR Clinical Trial, Phase I [ptyp] OR Clinical Trial, Phase II [ptyp] OR Randomized Controlled Trial [ptyp] OR Clinical Trial, Phase III [ptyp] OR Clinical Trial, Phase IV [ptyp]).

(Prog [All Fields] AND Obstet [All Fields] AND Ginecol. [All Fields]) AND (Clinical Trial [ptyp] OR Clinical Trial, Phase I [ptyp] OR Clinical Trial, Phase II [ptyp] OR Randomized Controlled Trial [ptyp] OR Clinical Trial, Phase III [ptyp] OR Clinical Trial, Phase IV [ptyp]).

(Rev. [All Fields] AND iberoam. [All Fields] AND fertil. [All Fields] AND reprod. [All Fields] AND hum. [All Fields]) AND (Clinical Trial [ptyp] OR Clinical Trial, Phase I [ptyp] OR Clinical Trial, Phase II [ptyp] OR Randomized Controlled Trial [ptyp] OR Clinical Trial, Phase III [ptyp] OR Clinical Trial, Phase IV [ptyp]).

((“GinecolClin” [Journal] OR (“ginecol” [All Fields] AND “clin” [All Fields]) OR “ginecolclin” [All Fields]) AND quir. [All Fields]) AND (Clinical Trial [ptyp] OR Clinical Trial, Phase I [ptyp] OR Clinical Trial, Phase II [ptyp] OR Randomized Controlled Trial [ptyp] OR Clinical Trial, Phase III [ptyp] OR Clinical Trial, Phase IV [ptyp]).

(“Clin Invest GinecolObstet” [Journal] OR (“clin” [All Fields] AND “invest” [All Fields] AND “ginecol” [All Fields] AND “obstet” [All Fields]) OR “clin invest ginecolobstet” [All Fields]) AND (Clinical Trial [ptyp] OR Clinical Trial, Phase I [ptyp] OR Clinical Trial, Phase II [ptyp] OR Randomized Controlled Trial [ptyp] OR Clinical Trial, Phase III [ptyp] OR Clinical Trial, Phase IV [ptyp]).

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9.3. Anexo 3

Identifying randomized clinical trials in Spanish-language dermatology journals. Actas Dermosifiliogr. 2015;106(5):415-22.

Actas Dermosifiliogr. 2015;106(5):415–422

ACTAS Dermo-Sifiliográficas

Full English text available at www.actasdermo.org

ORIGINAL ARTICLE

Identifying Randomized Clinical Trials in Spanish-Language Dermatology Journals☆

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KEYWORDS
Randomized clinical trial;
Manual literature search;
Dermatology journals

Abstract
Background: The necessary foundation for good clinical practice lies in knowledge derived from clinical research. Evidence from randomized clinical trials (RCTs) is the pillar on which decisions about therapy are based.
Objective: To search exhaustively and rigorously to identify RCTs in dermatology journals published in Spanish.
Methods: We located dermatology journals through the following search engines and indexes: PubMed, LILACS, SciELO, Periódica, Latindex, Índice Médico Español, C-17, IBECS, EMBASE, and IMBIOMED. We also sought information through dermatology associations and dermatologists in countries where Spanish was the usual language of publication, and we searched the Internet (Google). Afterwards we searched the journals electronically and manually to identify RCTs in all available volumes and issues, checking from the year publication started through 2012.
Results: Of 28 journals identified, we included 21 in the search. We found a total of 144 RCTs published since 1969; 78 (54%) were in Latin American journals and 66 (46%) were in Spanish journals. The most frequent disease contexts for RCTs in Spanish journals were psoriasis, mycoses, and acne vulgaris. In Latin American journals, the most frequent disease contexts were common warts, mycoses, acne vulgaris, and skin ulcers on the lower limbs. Manual searches identified more RCTs than electronic searches.

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Conclusions: Manual searches found a larger number of RCTs. Relatively fewer RCTs are published in Spanish and Latin American journals than in English-language journals. Internet facilitated access to full texts published by many journals; however, free open access to these texts is still unavailable and a large number of journal issues are still not posted online.

PALABRAS CLAVE
Ensayo clínico aleatorizado;
Búsqueda manual;
Revistas dermatológicas

Identificación de ensayos clínicos en revistas dermatológicas publicadas en español

Resumen
Introducción: Para asegurar una práctica adecuada se hace necesario incorporar el conocimiento derivado de la investigación clínica, en la que los ensayos clínicos con asignación aleatoria (ECA) son el pilar fundamental para la decisión de una terapia.
Objetivo: Buscar e identificar de manera exhaustiva y rigurosa los ECA publicados en revistas dermatológicas en español.
Métodos: Se detectaron las revistas dermatológicas mediante búsquedas en PubMed, LILACS, SciELO, Periódica; Latindex; Índice Médico Español; el C-17; el IBECS, EMBASE e IMBIOMED; y/o por el contacto con las asociaciones de dermatología/especialistas de cada país y la búsqueda libre por Google. Posteriormente se realizó tanto una búsqueda manual como electrónica de los ECA en los volúmenes y números disponibles. La revisión de cada revista se realizó en cada volumen y número desde su publicación hasta el año 2012.
Resultados: De las 28 revistas encontradas se incluyeron 21. Desde 1969 se identificaron 144 ECA, 54% (78) en las revistas latinoamericanas y 46% (66) en las españolas. Entre las enfermedades estudiadas predomina la psoriasis, las micosis y el acné vulgar entre las revistas españolas, mientras que entre las latinoamericanas prevalecen las verrugas vulgares, las micosis, el acné vulgar y las úlceras de los miembros inferiores. La búsqueda manual identificó más ECA de los detectados por búsqueda electrónica.
Conclusiones: La búsqueda manual permitió una alta detección de ECA. El número de ECA identificados en revistas dermatológicas iberolatinoamericanas es bajo comparado con las revistas publicadas en inglés. Internet facilitó el acceso al texto completo de muchas revistas, pero se carece aún de un acceso libre al texto completo y de un volumen importante de números publicados por esta vía.

Introduction

An individual clinician's experience is an important source of knowledge in dermatology. However, when such knowledge becomes the sole basis for clinical decision-making, therapeutic effects are often overestimated. Compounding this problem is the physician's tendency to rely on knowledge acquired during residency training or to find it difficult to incorporate current evidence into routine practice, especially if new information calls beliefs and previous experience into question.[1–3] Clinical trials follow an experimental design in which a researcher manipulates exposure to 1 or more treatments in order to compare effects.[4,5] The main purpose of this type of study is to assess the efficacy and safety of an intervention that seeks to prevent or cure a health condition or to speed recovery.[4,5]

Given the importance of randomized clinical trials (RCTs), it might be supposed that they would be easily available to both treating physicians and researchers. Problems arise, however, when health care professionals seek to locate and use information from RCTs. Among the difficulties that have been reported are 1) the novelty of the terminology itself, 2) the underuse of descriptors when trials are indexed in databases, and 3) the high percentage of journals that do not post articles online.[6–8] Problems that further interfere with physicians' use of RCTs are lack of time for reading these articles and the lack of access to the publishing journals.[9,10]

To help identify RCTs published in the Spanish language in several medical specialties, the Cochrane Collaboration undertook a project to search for them manually. Searching in databases alone reportedly fails to find a significant number of RCTs in the specialties of ophthalmology, public health, anesthesiology and critical care, and general and internal medicine.[8,11–14] In addition, online MEDLINE searches can fail to return up to 25% of RCTs available, mainly when the authors have not included the search terms *randomized controlled trial* or *controlled clinical trial* in the titles.[15]

We present the results for dermatology journals included in the Cochrane Collaboration's project on hand searching for RCTs in Spanish, as these findings complement the important earlier work of González-Castro et al.[7,16] in identifying trials reported in *Actas Dermo-Sifiliográficas* between 1948 and 2000 and *Medicina Cutánea Ibero-Latino-Americana* between 1970 and 2000.

Aim of This Study

We sought to exhaustively and rigorously search for RCTs in dermatology journals published in the Spanish language.

Material and Methods

Identification of Journals

We identified journals within the framework of a project led by the Iberoamerican Cochrane Centre (IbCC) in Barcelona, Spain, to find biomedical journals in countries where Spanish is spoken. An IbCC-trained researcher, who was responsible for managing and coordinating the study, carried out the journal search and sent the results to the IbCC collaborators in each country. The collaborators were charged with confirming that the journal information was complete and accurate. Any other sources that might help us find these journals, such as national library catalogs and collections, were also searched.

Appropriate databases (IBECS [the Spanish health sciences index], EMBASE [Excerpta Médica dataBASE], and IMBIOMED) and the web pages of dermatology associations in Latin American countries where Spanish is spoken were included in the search. We also made direct contact with journals' editorial boards and specialists in dermatology, and as a last resort we searched for candidate journals in Google.

Journals were eligible if they published original research articles and made full texts available to researchers in print or online. Journals were excluded if they focused on pediatric dermatology, covered areas already included in the project under another specialty (for example, infectious diseases), or published only reviews or case reports in dermatology. If a journal's full texts could not be obtained by any means, it was likewise excluded.

Each journal was searched in reverse chronological order from 2012 to the first issue published (provided full texts were still available). If no RCTs were found for 5 consecutive years, the manual search was halted, unless we had ready access to issues, in which case we extended the search.

Additionally, we checked whether these journals instructed authors to follow the CONSORT (Consolidated Standards of Reporting Trials) guidelines and whether they were indexed in MEDLINE or EMBASE.

Hand Search Method

We asked 40 undergraduate and postgraduate students in the health sciences to carry out the systematic hand searches. Each student did a test search of a journal for a period the IbCC had already assessed. The searchers' training was based on the IbCC's hand RCT search protocol for Spanish articles (available from http://www.cochrane.es/~cochrane/?q=es/node/140). That protocol was based on the Cochrane Collaboration's *Training Manual for Handsearchers*.

Once training and the pilot search had been completed, the searcher was assigned volumes in which to find RCTs by 1) reading the tables of contents, 2) locating key terms for RCT-associated concepts in Spanish (*aleatorizado, prospectivo, comparación*, etc.) in titles and abstracts, and 3) reading the patients and methods sections of the full texts. Afterwards, the searcher filled in the form for recording the results of hand searches of journals or updates.

Electronic Search Method

So that we could compare electronic and hand-searching results, we conducted RCT searches in MEDLINE (through PubMED), EMBASE, LILACS (Latin American index of scientific and technical literature) and IBECS. Validated combinations of descriptors were used in multiterm combinations, along with free-text terms.[1,2] (See Appendix 1, online supplementary material.) These searches were updated in November 2014 to check for RCTs published between 2012 and 2014.

RCT Inclusion Criteria

We followed the Cochrane Collaboration criteria for defining RCTs. Thus, we included 1) trials comparing treatments in humans; 2) trials designed to gather data prospectively; 3) clinical comparisons of 2 or more interventions (1 of which could be a control treatment) of any type (medications, operations, diagnostic or educational procedures, rehabilitation therapies, management systems, or other); and 4) trials using random, or quasi-random, assignment of treatments, and/or use of double blinding. The randomization units could be individuals, clusters (hospitals, communities), or parts of the body (such as split faces or different limbs).

Classification of Information and Identification of RCTs

Each searcher recorded the number of RCTs found while reading the assigned issues. Later, 2 evaluators who had formal training in clinical epidemiology (G. S. and H. P.) read the full texts in order to confirm that each RCT met the selection criteria.

Planned Analysis

Descriptive statistics were compiled. Continuous variables were summarized in appropriate measures. Qualitative variables were reported as absolute and relative frequencies and percentages. Data were stored in a spreadsheet (Excel, version 2010, Microsoft Office, Redmond, WA, USA). SPSS software (IBM, version 19 (Armonk, NY, USA) was used to analyze the data.

Results

The only dermatology journal we found to be indexed in both MEDLINE and EMBASE at this time is *Actas Dermo-Sifiliográficas*. The journals indexed only in EMBASE are *Dermatología Revista Mexicana*, *Revista Argentina de Dermatología*, *Medicina Cutánea Ibero-Latino-Americana*, and *Piel*.

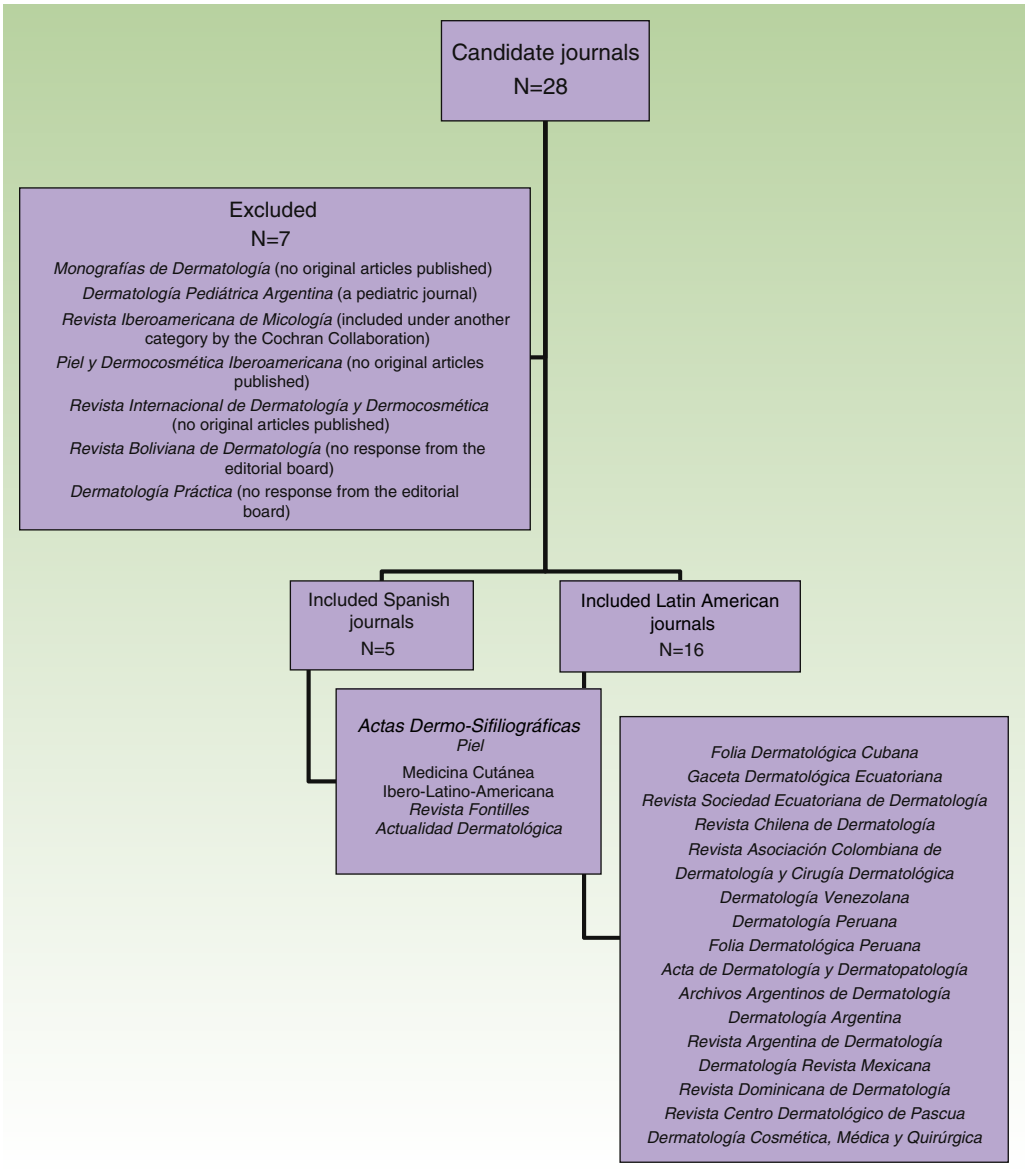

Figure 1 Flow chart of the dermatology journal search process and the selection of included and excluded journals.

Included and Excluded Journals

Of the 28 candidate journals, 21 were included. All 28 journals and the reasons for exclusions are shown in Fig. 1.

Actas Dermo-Sifiliográficas is the only journal included in this study that specifies and promotes the use of the CONSORT guidelines.[17]

RCTs Identified

A total of 144 RCTs published since 1969 were found in the 21 included journals (Table 1). Seventy-eight (54%) of the RCTs were published in the 16 Latin American journals searched, and 66 (46%) were found in the 5 Spanish journals (Table 1, which also shows the number of RCTs found in each journal). A large number of the RCTs found in *Actas Dermo-Sifiliográficas* and *Medicina Cutánea Ibero-Latino-Americana* were previously gathered and described in 2 earlier publications.[7,16]

Analysis by 5-year intervals shows that many of the RCTs (89 in total) were published in the last 20 years (from 1993 to 2012). The 25 preceding years (from 1992 to 1968) saw 55 RCTs published (Fig. 2).

The most frequently studied skin diseases in the Spanish trials were psoriasis (11 RCTs), mycoses (9), and acne vulgaris (8). The most frequent disease contexts in the Latin American trials were common warts (9 RCTs), mycoses (8), acne vulgaris (7), and lower-limb ulcers (6). Details of the RCTs found are listed in Appendix 2 of the online supplementary material.

The MEDLINE search identified 3997 entries, 669 of which were in *Actas Dermo-Sifiliográficas*. Two of these entries

Table 1 Included Dermatology Journals.

No.	Journal Name	Period Searched	First Year of Publication	Periods Not Searched[a]	No. of RCTs Found
	Latin America				
1	*Dermatología Revista Mexicana*	1981–2012	1956	1969–1980, 1984, 1987	21
2	*Dermatología Venezolana*	1984–2012	1957	1969–1983	13
3	*Dermatología Peruana*	1996–2012	1996	–	9
4	*Revista Asociación Colombiana de Dermatología*	1991–2012	1991	–	8
5	*Revista Chilena de Dermatología*	1985–2012	1985	–	8
6	*Dermatología Cosmética, Médica y Quirúrgica*	2003–2012	2003	–	4
7	*Revista del Centro Dermatológico Pascua*	1999–2012	1999	–	4
8	*Revista Argentina de Dermatología*	1981–2012	1908	1969–1980	4
9	*Folia Dermatológica Peruana*	1986–2012	1986	–	2
10	*Dermatología Argentina*	1995–2012	1995	–	2
11	*Folia Dermatológica Cubana*	2007–2012	2007	–	2
12	*Archivos Argentinos de Dermatología*	1983–2012	1951	1969–1982	1
13	*Actas de Dermatología y Dermatopatología*	2001–2009	2001 (publication ceased in 2009)	–	0
14	*Revista Dominicana de Dermatología*	2010–2012	1971	1971–2009	0
15	*Revista Sociedad Ecuatoriana de Dermatología*	2003–2010	1991	1991–2002, 2005, 2008, 2009, 2011, 2012	0
16	*Gaceta Dermatológica Ecuatoriana*	1998	1998	1997–2012	0
Total RCTs in Latin American journals					**78**
	Spain				
17	*Actas Dermo-Sifiliográficas*	1969–2012	1909	–	30
18	*Medicina Cutánea Ibero-Latino-Americana*	1969–2012	1966		25
19	*Piel*	1986–2012	1986	–	10
20	*Actualidad Dermatológica*	1974–2008	1962	1969–1973,	1
21	*Revista Fontilles*	2008–2012	1932	1969–2002	0
Total RCTs in Spanish journals					**66**

Abbreviation: RCT, randomized clinical trial.

[a] These years could not be searched because neither print nor digital content was available.

were initially considered candidates for inclusion, but were not in fact RCTs, and 4 were. These 4 articles included the word *randomized* in their indexed title. All these RCTs had also been found by hand searching (Fig. 3).

The EMBASE search initially yielded 9584 entries (Fig. 3); 16 of these were for RCTs. Of these, 6 had been previously identified by hand searching and 2 were newly identified ones from the *Dermatología Revista Mexicana*. These 2 articles had not been found during earlier hand searching because neither print nor digital versions of the table of contents could be found for issue 6 of volume 56 or issue 2 of volume 48 (Fig. 3).

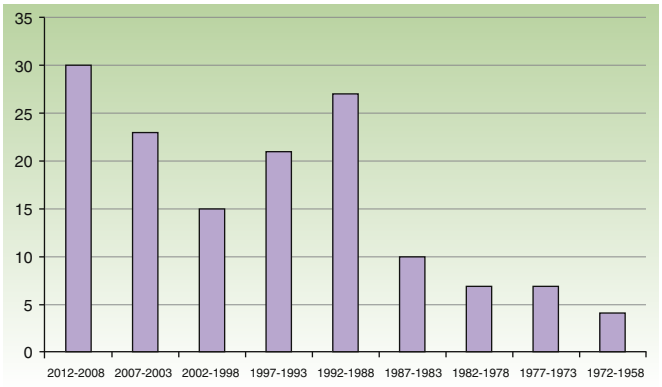

Figure 2 Number of randomized clinical trials published in 5-year periods.

The search of indexes on the Spanish language Virtual Health Library (BVS) initially returned 5140 entries (Fig. 3). After filtering for dermatology, 30 candidates were identified; 2 of these were not RCTs. Thus, the digital searches found only 28 (19.5%) of the 144 RCTs that had already been found by hand searching (Fig. 3).

We were unable to hand search all of the following journals because of missing volumes or issues: *Dermatología Revista Mexicana*, *Dermatología Venezolana*, *Revista Argentina de Dermatología*, *Archivos Argentinos de Dermatología*, the 2 Ecuadoran journals, the single journal published in the Dominican Republic, and *Revista Fontilles* (Table 1).

Discussion

RCTs are the principal units of analysis for systematic reviews, clinical practice guidelines, and other documents that synthesize knowledge. Regulatory agencies also require them before medicines can be approved for use in humans.

Hand searching identified about 80% more RCTs than database searching. This finding is consistent with previous reports for our own field, in which journals like *Archives of Dermatology*[18] and *Actas Dermo-Sifiliográficas*[7,19] were searched. It is also consistent with reports for other medical specialties.[8] These results underline the importance of manually checking dermatology journals, as many of the RCTs we found could not have been otherwise identified, possibly because MEDLINE and EMBASE are not sensitive to search terms in Spanish.[11,19–22] Alternatively, the reason may be that *Actas Dermo-Sifiliográficas* is the only Spanish language dermatology journal indexed in MEDLINE or that EMBASE does not index all of the other Spanish journals. Compounding the problem is the inherent difficulty of electronic searching in any language other than English. Searches in other languages have returned 37% fewer entries than searches in English.[15]

Dermatología Revista Mexicana and *Dermatología Venezolana* were the Latin American journals that published the largest number of RCTs. In Spain, *Actas Dermo-Sifilográficas* published the most. We offer no explanation for these observations, but we think it may be that more funding is available for conducting RCTs in the countries where these journals are published. It is also possible that these journals have less stringent policies governing the RCTs they publish than other Latin American journals do.

Our findings showed an increase in the number of RCTs published in Spanish in recent decades. The reason for the increase may lie in the importance currently placed on evidence-based medicine, an approach that obliges researchers to value this type of study above others because it provides more and stronger evidence.

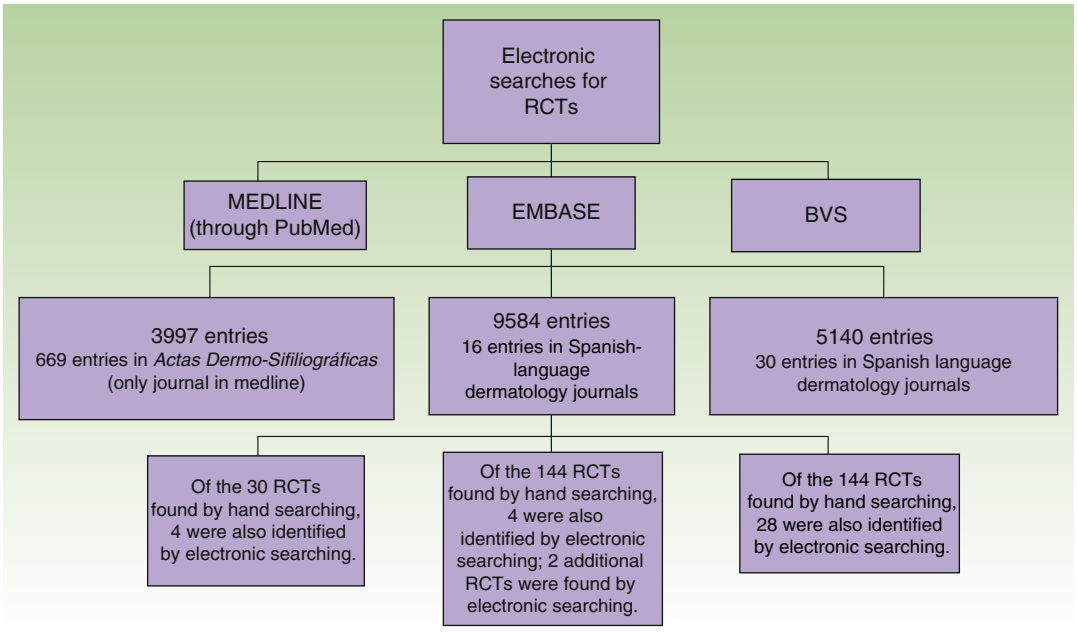

Figure 3 Flow chart of the digital search process for each database searched and the selection of randomized clinical trials (RCTs). BVS refers to the Biblioteca Virtual de la Salud (Virtual Health Library).

We found 78 Spanish-language RCTs in Latin American journals and 66 in Spanish ones published over the course of 44 years. On average, RCTs were published at a rate of 1 to 2 per year, a statistic that is in sharp contrast with the rate of RCT publication in English. Up to 11 RCTs per year are published by *Archives of Dermatology* alone, for example.[18]

The CONSORT reporting guidelines were established in 1996 to standardize the way clinical trials are reported in different journals.[17] These standards indirectly encourage greater methodological rigor by obliging the researcher to describe the design explicitly and fully. Only 1 journal in this study, namely *Actas Dermo-Sifilográficas*, requires authors to follow the CONSORT guidelines. There seems to be a need, therefore, not only to promote the design of RCTs but also to encourage journals to require CONSORT-guided reporting, just as the important English-language dermatology journals do.

That both Spanish and Latin American researchers showed interest in psoriasis, mycoses, and acne was noteworthy. The attention is probably attributable to the greater impact of these diseases among patients, given that clinical importance would drive an effort to identify effective therapies; alternatively, the pharmaceutical industry may be more interested in funding RCTs in these areas.[23,24]

This study identified Spanish-language dermatology journals. Their full texts proved impossible to find in only a few cases once we applied various means to locate them. This experience underlines the importance of posting full texts online because this strategy not only facilitates the identification of RCTs for systematic reviews but also contributes to making knowledge available worldwide and enhancing the visibility of Spanish-language publications.

One of the strengths of this study is the large number of journals, volumes, and issues we searched exhaustively and systematically. A total of 28 dermatology journals were initially identified. Electronic searching found nearly all the RCTs that had been identified manually. Two references were found by database searching but not by hand searching, since print copies of the issues in question were unavailable. A limitation of our study is our lack of access to all of the articles published from the start of publication (Table 1). However, those early issues probably did not contain RCTs, since this design was little used before the 1970s. Another limitation is that we excluded relevant RCTs that were published in journals that focus on other specialties or in dermatology journals published in other languages. Furthermore, we did not evaluate the quality of the RCTs for this report, although we have recently been working on that task and plan to publish the results shortly.

In conclusion, manual searches identified a large number of RCTs in dermatology journals in Spain and Latin America. However, these journals publish far fewer RCTs than English-language dermatology journals do. Finally, ready access to these RCTs and a large number of other articles of interest is still lacking.

Ethical Disclosures

Protection of human and animal subjects. The authors declare that no experiments were performed on humans or animals for this investigation.

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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Group of Investigative Dermatology (GRID), Medical Faculty, Universidad de Antioquía, Medellín, Colombia.

Conflicts of Interest

The authors declare that they have no conflicts of interest.

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Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.adengl.2015.04.010.

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9.4. Anexo 4

Analysis of the Quality of Clinical Trials Published in Spanish-Language Dermatology Journals Between 1997 and 2012. Actas Dermosifiliogr. 2016;107(1):44-54.

Actas Dermosifiliogr. 2016;107(1):44–54

ACTAS Dermo-Sifiliográficas

Full English text available at www.actasdermo.org

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;
Methodology;
Dermatology journals;
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.

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/Guidances/ucm073122.pdf and 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 DERMO-SIFILIOGRÁFICAS 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 DERMO-SIFILIOGRÁFICAS 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

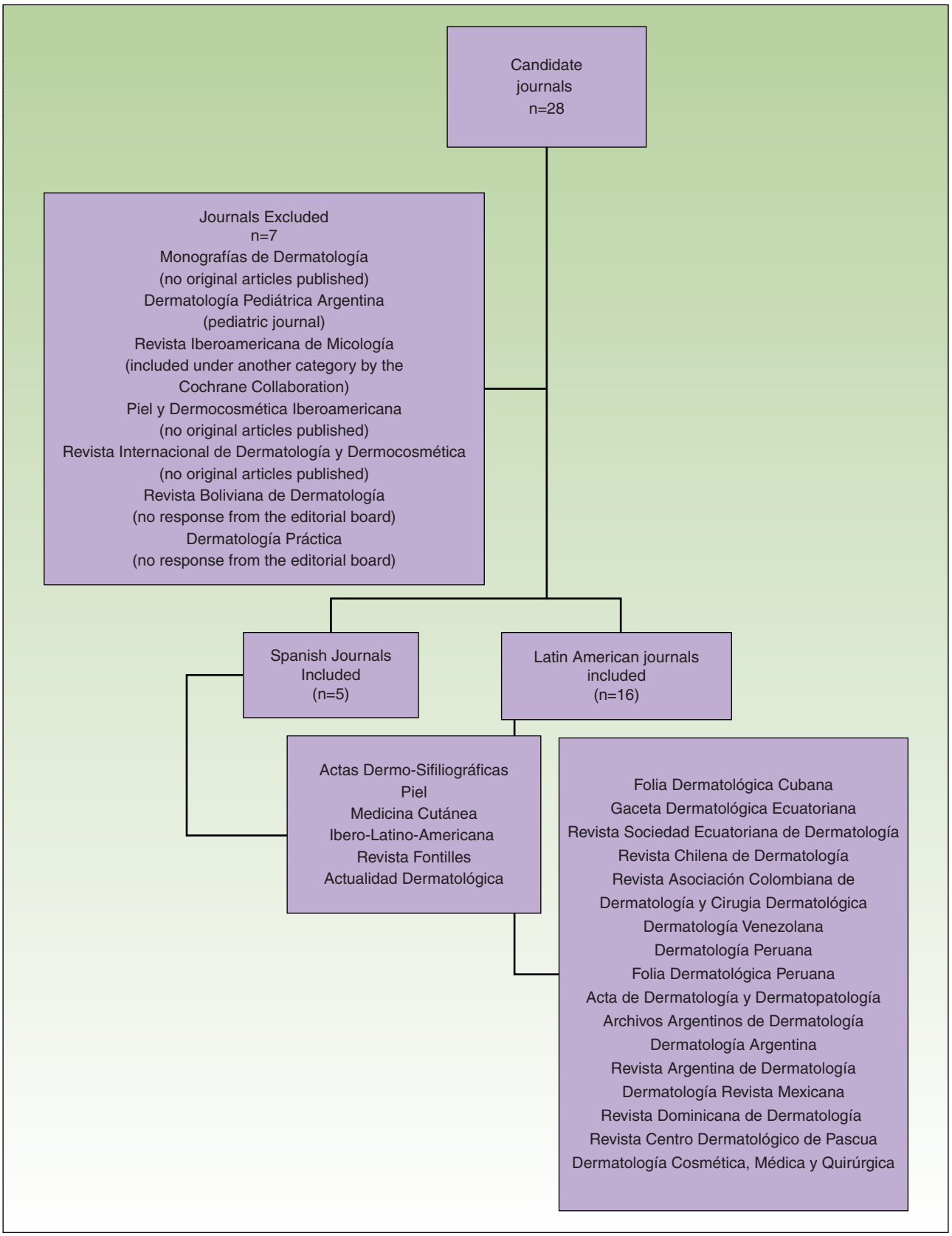

Figure 1 Flow chart showing the process used to select dermatology journals according to inclusion and exclusion criteria. Source: Sanclemente G, Pardo H, Sánchez S, Bonfill X. Identificación de ensayos clínicos en revistas dermatológicas publicadas en español. Actas Dermosifiliogr. 2015;106:415-422).

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	*Dermatología Revista Mexicana*	–	16
2	*Dermatología Peruana*	–	9
3	ACTAS DERMO-SIFILIOGRÁFICAS	–	8
4	*Piel*	–	8
5	*Revista Chilena de Dermatología*	–	5
6	*Dermatología Cosmética, Médica Y Quirúrgica*	–	4
7	*Revista del Centro Dermatológico Pascua*	–	4
8	*Revista Asociación Colombiana de Dermatología*	–	4
9	*Medicina Cutánea Ibero-Latino-Americana*	–	3
10	*Folia Dermatológica Peruana*	–	2
11	*Dermatología Argentina*	–	2
12	*Folia Dermatológica Cubana*	–	2
13	*Dermatología Venezolana*	–	2
14	*Revista Argentina de Dermatología*	–	1
15	*Archivos Argentinos de Dermatología*	–	0
16	*Actas de Dermatología y Dermatopatología*	–	0
17	*Revista Dominicana de Dermatología*	1997-2009	0
18	*Revista Sociedad Ecuatoriana de Dermatología*	1997-2002, 2005, 2008, 2009, 2011, 2012	0
19	*Gaceta Dermatológica Ecuatoriana*	1999-2012	0
20	*Actualidad Dermatológica*	–	0
21	*Revista Fontilles*	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-SIFILIOGRÁFICAS,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

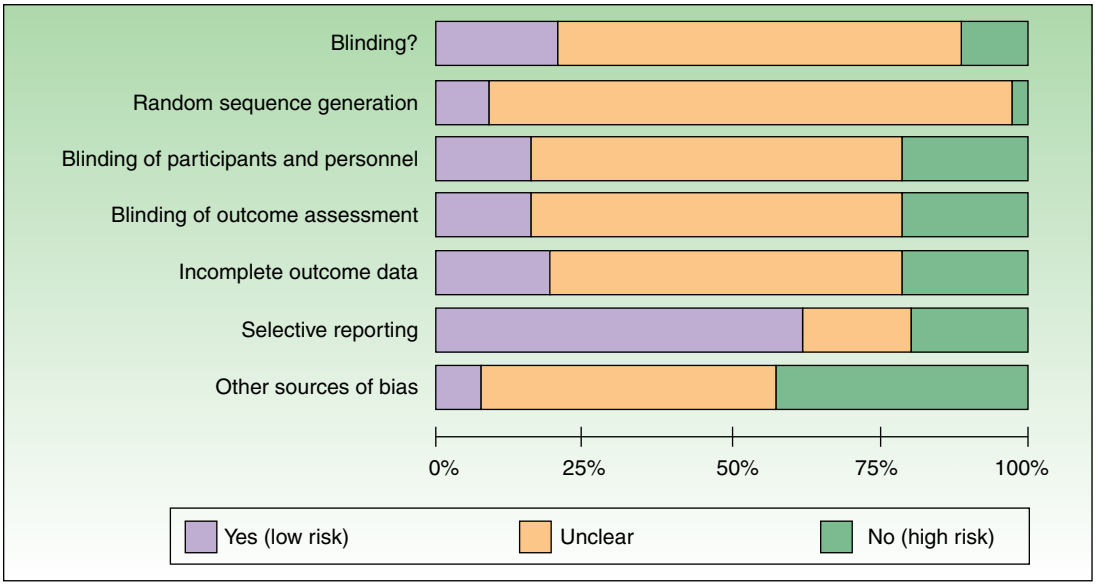

Figure 2 Risk of bias of the RCTs analyzed (graphic designed using Review Manager, version 5.2, Copenhagen, The Nordic Cochrane Centre, The Cochrane Collaboration, 2012).

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

Methodological Aspect	No. (%)	95% CI
Allocation concealment		
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 DERMO-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 RCTs[7] 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 EMBASE[7] (*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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Dr. Gloria Sanclemente is a PhD candidate in the department of pediatrics, obstetrics, gynecology, and preventive medicine of the Universitat Autónoma 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.

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