Assessment of the methodological and ethical quality of clinical trials published in family medicine journals

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Abstract

Objective: To evaluate some methodological and ethical quality variables of clinical trials (CTs) published in 10 family medicine journals. **Methods:** Quality descriptive study of 10 family medicine journals including CTs in humans published since 2010 to 2013. We obtained 141 CT and 2447 were excluded. **Results:** CTs parallels controlled in 92.9% (95% confidence interval [95% CI]: 92.0-93.9). Masked randomization in 72.3% (95% CI: 71.7-73.1), decentralized in 51.8% (95% CI: 51.4-52.4) and using as control an active treatment in 82.2% (95% CI: 81.5-83.1). Wrote informed consent in 48.9% (95% CI: 48.5-49.5) and it was not withdrawn in 56.0% of cases (95% CI: 55.5-56.7). Approval by clinical research ethics committee (CREC) in 134, and there was no conflict of interest in 117 CTs. Average κ was 0.96 (95% CI: 0.93-0.99). **Conclusions:** We observe an increase in some quality variables like masked randomization (19.6%) and approval by CREC (75%) post CONSORT, in CTs published in 10 family medicine journals (2010-2013).

KEY WORDS: Checklist. Clinical trials as topic. Family practice. Statistical analysis. Random allocation. Research ethics committee.

Introduction

In current research, randomized clinical trial is the reference method to assess new therapies or strategies in medicine¹. Low quality in its design or publication² might lead to risk underestimation or even misrepresentation when using treatments that might be less beneficial or even harmful³, with possible consequences in daily clinical practice.

There are diverse methods for clinical trials publications quality assessment⁴. Dechartres et al.⁵ identified 26 scales or checklists derived from the Consolidated Standards of Reporting Trials (CONSORT). They found an increase in information about methodological aspects, but only 29% of adequate concealed allocation, showing that quality

assessment still has important problems. Current systematic reviews suggest that randomized clinical trials quality improvement is associated with the use of CONSORT guidelines^{6,7}.

Cluster-type trials (randomization by groups), as compared with other individual trials with the same number of subjects, are poorly efficient and have less statistical power⁸.

To date, we haven't found any study that uses a checklist similar to that of CONSORT in journals of the family medicine specialty⁹, and hence we have developed a new, more accurate tool to try to delve into different aspects of methodological and ethical quality of clinical trials that are published in these journals.

The purpose is to quantitatively and qualitatively analyze some variables that represent part of the

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methodological and ethical quality of clinical trials published between 2010 and 2013 in the 10 journals of the family medicine specialty with the highest impact-factor that publish clinical trials.

Methods

A descriptive study was carried out on the quality of articles published in the 10 journals of the family medicine specialty with the highest impact that publish clinical trials.

A manual search was carried out in the following journals: *Annals of Family Medicine*, *Atención Primaria*, *Australian Family Physician*, *BioMed Central Family Practice*, *British Journal of General Practice*, *Canadian Family Physician*, *European Journal of General Practice*, *Family Practice*, *Journal of American Board of Family Medicine* and *Scandinavian Journal of Primary Health Care*.

In this cross-sectional review, the Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) statement¹⁰ was taken as a basis, but only in the referred journals, as they are specific to the family medicine specialty, they publish clinical trials and have the highest impact-factor (Journal Citation Report). The search strategy in PubMed was carried out with the terms “(((“family practice”) OR “general practice” OR “primary care” OR “family medicine”) AND “clinical trial” AND “quality”), clinical trial, humans”. We found 1096 articles, and reviewed those selected in *Related citations* of all articles up to two levels. In Web of Knowledge, we used the following search criterion: “Topic=(“family practice”) OR Topic=(“general practice”) OR Topic=(“primary care”) OR Topic=(“family medicine”) AND Topic=(“clinical trial”) AND Topic=(“quality”), with the limits being adjusted to “Document Types=(CLINICAL TRIAL) AND Research Domains=(SCIENCE TECHNOLOGY) AND Research Areas=(HEALTH CARE SCIENCES SERVICES OR GENERAL INTERNAL MEDICINE)”. We found 5749 studies. In the Google scholar search engine, the following search criterion was used: “(((“family practice”) OR “general practice” OR “primary care” OR “family medicine”) AND “clinical trial” AND “quality”), with 20.600 articles being found. Finally, 1925 articles were retrieved in Scopus with the search criterion “(TITLE-ABS-KEY(“family practice”) OR TITLE-ABS-KEY(“general practice”) OR TITLE-ABS-KEY(“primary care”) OR TITLE-ABS-KEY(“family medicine”) AND TITLE-ABS-KEY(“clinical trial”) AND TITLE-ABS-KEY(“quality”)) AND DOCTYPE (ar) AND

(LIMIT-TO (SUBJAREA,“MEDI”))”. Pooling the three bibliographic sources, a total of 2588 original articles were obtained in the 10 journals selected for assessment.

Using a checklist, clinical trials published in the 10 journals of the family medicine specialty with the highest impact factor and that publish clinical trials were assessed. *Annals of Family Medicine* is the one with the highest impact-factor (4.613)¹¹. These journals follow the CONSORT guidelines^{4,12} and International Committee of Medical Journal Editors (ICMJE) recommendations¹³. The CONSORT⁴ and Helsinki¹⁴ declarations, which provide checklists¹³ with higher quality for the publication of clinical trials¹⁵, were followed.

Clinical trials conducted in human subjects, both patients and healthy volunteers, published between January 2010 and December 2013, were included. Since the CONSORT guidelines were first published in 2001, this study was subsequently carried out in order to increase quality^{7,16}.

A CONSORT18-based checklist¹⁷ with 80 items (8 sections), which were increased to 133 (11 sections), was updated. Following the Helsinki Declaration¹⁹ and the Pragmatic-Explanatory Continuum Indicator Summary (PRECIS)²⁰ graph, items were created or modified to adapt them to the family medicine specialty. More explicit variables that helped to more specifically identify the use of placebo in treatment comparisons were created. The Agency for Healthcare Research and Quality (AHRQ)²¹ criteria, i.e. the Jadad scale, were introduced. An assessment was made for the existence of data and safety monitoring board (DSMB), stopping rules (Haybitt-le-Peto, Pocock, O'Brien-Fleming)²², futility analysis²³, sequential and optimized-type trials, and clinical research ethics committee (CREC); also whether participating subjects' race or language were indicated. Granted incentives, authors' specific bioethics training, types of conflicts of interests and the influence of sponsors on the clinical trials were investigated.

Two authors (FGG and ACG) independently reviewed the 141 selected articles with the checklist. They used detailed instructions for the fulfillment of variables (items) and discrepancies were solved by consensus. Frequency, percentage and Clopper-Pearson 95% confidence interval (CI)²⁴ were calculated²⁴. The mean, median, mode, minimum, maximum, standard deviation and its 95% CI were also obtained for quantitative variables. Mean κ and its 95% CI was obtained²⁵. The SPSS 20.0 statistical package was used.

Results

A total of 141 clinical trials meeting the inclusion criteria were found (Fig. 1), since most studies were observational. *The Journal of Family Practice* did not publish any clinical trial during the study period.

The main methodological variables analyzed in this study are presented in table 1. The results are presented as percentages or absolute numbers, as adequate, to highlight the data in question.

When completing table 1, in the “Country of authors” section within the “Other Europeans” group, the most commonly found was the Netherlands (22 clinical trials), and in the group of “Others”, it was Canada (14 clinical trials). As for “Continent of study”, the most common country in Europe was the Netherlands (22), followed by the United Kingdom (11), Sweden (9), Spain (8) and Denmark (6); in the “Others” group, New Zealand stands out (3 clinical trials).

In the “Rationale and objectives” section of our checklist, the “clinical trial” denomination was observed to appear in the title or subtitle in 107, and it was considered to be uncertain (not specifically named) in 33; related clinical trials appeared in 135 and it was uncertain in 2; at least one systematic review was cited in 128 clinical trials and it was uncertain in 3; reference to previous publication of the same clinical trial appeared in 44, and priori hypothesis appears in all.

About the “Type of clinical trial”, 54.6% (95% CI: 54.1-55.2) were carried out in more than 5 centers, 19.1% (95% CI: 19.0-19.4) in 5 or less centers, and 17.7% (95% CI: 17.6-18.0) were single-center trials. In 71.6% (95% CI: 71.0-72.4) some author was an epidemiologist or statistician, and acted as a collaborator in 14.9% (95% CI: 14.8-15.1).

As for “Clinical trial design”, 92.9% (95% CI: 92.0-93.9) were parallel-group controlled clinical trials, and 6 were factorial controlled trials. According to AHRQ criteria, there was higher tendency towards pragmatic rather than explicative clinical trials.

In 132 clinical trials, a baseline comparison was performed in a table, and the *P*-value appeared in 57.4% (95% CI: 56.9-58.1). No non-controlled clinical trials were found. Only the trial by Licciardone et al.²⁶ was sequential and used the stopping rule (O'Brien Fleming). In no study did the PRECIS graph appear²⁰, and neither were there optimized clinical trials. Concealment efficacy was only observed in 7 clinical trials. Withdrawals due to adverse effects were found in 11 clinical trials and were uncertain in 26 studies.

Figure 1. Cross-section review simplified flow diagram.

As for “Subject selection”, Caucasian subjects were included in 27.0% (95% CI: 26.8-27.4), African Americans in 18.4% (95% CI: 18.3-18.7), Hispanics in 14.2% (95% CI: 14.1-14.4) and Asians in 11.3% (95% CI: 11.2-11.5) in 16 studies. Ethnicity was not indicated in 71.6% (95% CI: 71.0-72.4), it was not specified in 25 clinical trials (17.7%; 95% CI: 17.6-18.0) and, in 9, subjects were ethnic minorities, such as Native Americans and Vietnamese. Inclusion of immigrant or low income population has increased over the past 3 years (20 clinical trials), and “vulnerable” people were observed²⁷.

In “Sample size”, the methodological quantitative variables are indicated in table 2. Their descriptive statistics and standard deviation 95% CI²⁸ are shown in table 3.

The alpha error was 87.9% (95% CI: 87.1-88.8), beta error was 83.7% (95% CI: 82.9-84.6), the magnitude of the least difference to be found was 80.9% (95% CI: 80.2-81.8) and flow diagram was observed in 86.5% (95% CI: 85.7-87.4).

As regards “Treatment description”, with an efficacious standard treatment, placebo or no intervention was used as control in 79.4% (95% CI: 78.7-79.3). A sound and convincing methodological reason for using placebo or no intervention was given in 11 clinical trials, and the determination of efficacy and safety in 13. No study was found where the use of placebo

Table 1. Description of the sample and methodological variables: frequencies, percentages and 95% confidence intervals

Variable	Value	Frequency	%	95% CI
Authors' country	USA	36	25.5	25.3-25.8
	United Kingdom	11	7.8	7.8-7.9
	Spain	10	7.1	7.1-7.2
	Scandinavia	18	12.8	12.7-13.0
	Other Europeans	31	22.0	21.8-22.3
	Other	35	24.8	24.6-25.1
Continent where the study is carried out	North America	50	35.5	35.2-35.9
	Latin America	2	1.4	1.4-1.5
	Asia	4	2.8	2.8-2.9
	Australia	8	5.7	5.7-5.8
	Europe	71	50.4	50.0-51.0
	Other	6	4.3	4.3-4.4
Type of funding	Non-profit: public	78	55.3	54.8-55.9
	Non-profit: private*	71	50.4	50.0-51.0
	Pharmaceutical industry*	17	11.9	11.8-12.1
	Not indicated	8	5.7	5.7-5.8
	None	3	2.1	2.1-2.2
Randomization system	Simple randomization	49	34.8	34.5-35.2
	Block randomization	39	27.7	27.5-28.1
	Stratified	23	16.3	16.2-16.5
	Paired	5	3.6	3.6-3.7
	Minimization*	5	3.6	3.6-3.7
	Cluster*	46	32.5	32.3-32.9
	Other*	2	1.4	1.4-1.5
	Non-randomized: simple	4	2.8	2.8-2.9
Was there a concealed randomization method followed?	Yes	102	72.3	71.7-73.1
	No	23	16.3	16.2-16.5
	Uncertain	11	7.8	7.8-7.9
	No randomization	5	3.6	3.6-3.7
Is the concealed randomization method specified?	De-centralized	73	51.8	51.4-52.4
	Nontransparent envelopes with sequential opening*	21	14.9	14.8-15.1
	Other*	18	12.8	12.7-13.0
	Not mentioned	10	7.1	7.1-7.2
	Inexistent	29	20.6	20.5-20.9
Type of control	Placebo	13	9.2	9.1-9.4
	Active treatment*	116	82.2	81.5-83.1
	No treatment*	12	8.5	8.5-8.6
	Not indicated	1	0.7	0.7-0.7
	Other	1	0.7	0.7-0.7
Is the degree of assessment concealment indicated?	Open or non-blinded	17	11.9	11.8-12.1
	Single-blind	18	12.8	12.7-13.0
	Double-blind	10	7.1	7.1-7.2
	Blinded assessment by third parties	26	18.4	18.3-18.7
	Triple-blind	6	4.3	4.3-4.4
	Not indicated	64	45.4	45.0-45.9
Is it explained why the trial is not blind?	Yes	14	9.9	9.8-10.1
	No	58	41.1	40.8-41.6
	Uncertain	10	7.1	7.1-7.2
	There is blinding	59	41.8	41.5-42.3
Is the blinding method indicated?	Yes	31	22.0	21.8-22.3
	No	22	15.6	15.5-15.8
	Uncertain	8	5.7	5.7-5.8
	There is no blinding	80	56.7	56.2-57.4

(Contd...)

Table 1. Description of the sample and methodological variables: frequencies, percentages and 95% confidence intervals (Continued)

Variable	Value	Frequency	%	95% CI
Type of treatment	Already marketed drug	10	7.1	7.1-7.2
	Medical device	5	3.6	3.6-3.7
	Medical intervention method*	73	51.8	51.4-52.4
	Other: water aerobics, yoga...*	53	37.6	37.3-38.1
Trial result	Treatment significantly better			
	Difference by author (s), but not significant	50	35.5	35.2-35.9
	Trend towards treatment	22	15.6	15.5-15.8
	Uncertain	12	8.5	8.5-8.6
	No difference	1	0.7	0.7-0.7
	Trend towards control	44	31.2	31.0-31.6
	Control significantly better	1	0.7	0.7-0.7
	Other: significant improvement in a primary variable	3	2.1	2.1-2.2
Response assessment (endpoint)	Death	8	5.7	5.7-5.8
	Laboratory diagnosis	3	2.1	2.1-2.2
	Symptomatic diagnosis*	21	14.9	14.8-15.1
	Other: sphygmomanometer, medical records...*	5	3.6	3.6-3.7
		55	39.0	38.7-39.5
	Inexistent	1	0.7	0.7-0.7
	Questionnaire*	16	11.2	11.1-11.4
	Measuring scale*			

* Sum of the same result in several identical variables.

or no intervention produced additional risk of serious and irreversible harm. The clinical trial was reproducible in all cases but in two, and in one it was uncertain. In 48 studies there were concomitant treatments (allowed or not), and in 68 the intervention was innocuous. In 31.2% (95% CI: 31.0-31.6), serious adverse events were observed in general (even deaths) and were uncertain in 21 studies. Intent-to-treat analysis was carried out in 64 clinical trials, it was not indicated (it was performed, but not mentioned) in 7 and it was uncertain (it was mentioned but not adequately performed) in 6. According to Jadad score, 70 trials had good quality (3 or 4) 54, low quality (1 or 2) and 11, excellent (5).

When the "Trial development and response assessment" section was analyzed, the primary outcome variable (endpoint) was not described in 3 clinical trials and it was uncertain in 9.2% (95% CI: 9.1-9.4). In 139 clinical trials, statistical methods to assess the results were specified. Multivariate analysis was applied in 61.7% (95% CI: 61.2-62.4), and the number needed to treat only in 4. A DSMB was found in 5.7% (95% CI: 5.7-5.8). Changes to the protocol during the clinical trial were made in 9, with the CREC additionally being informed about it in 3. Finally, 29.1% (95% CI: 28.9-29.5) were observed to follow the CONSORT guidelines.

The most important ethical variables are shown in table 4. In 7 studies, only the Helsinki Declaration was

taken into account (lower quality than approval by a CREC), and one study was published not indicating to have followed it (very low ethical quality). In 9 clinical trials, individuals who were candidates to be included were observed to have received partial information on the objectives, funding, etc. of the clinical trial, and in 8 clinical trials, it was not clearly verified that this information was understood¹⁹.

Participating subjects that were minors of age were found in 14 clinical trials. Parents or legal guardians granted informed consent in 4 clinical trials, with this not being clearly established in 10. In 2.8% (95% CI: 2.8-2.9), minors participated as a necessary characteristic of the study, and it was uncertain in 7.1% (95% CI: 7.1-7.2).

Participating subjects' personal information confidentiality was observed to be protected in 44.7% (95% CI: 44.3-45.2), and in no study was the possibility of keeping these data for future use included in the informed consent. Harm to participating subjects was shown by 4.3% (95% CI: 4.3-4.4) of studies, but there was no indication of any compensation. In one clinical trial, the protocol referred to the repair of potentially sustained harm in order for not being left with sequels, and in 2 clinical trials, there were arrangements in order for potential harm to ultimately equate to the potential beneficial result in all participating subjects. In addition, in 32.6% (95% CI: 32.4-33.0) no study protocol was mentioned. Five clinical trials provided the most

Table 2. Quality of information for quantitative variables: frequencies, percentages and 95% confidence intervals

Variable: quality of information	Frequency	%	95% CI
Assessed subjects			
Mentioned in article	114	80.9	80.2-81.8
Calculated or implicitly understood by the reader	8	5.7	5.7-5.8
Omitted and incalculable	17	11.9	11.8-12.1
Eligible subjects not shown	2	1.4	1.4-1.5
Assessed subjects (cluster)			
Mentioned in article	35	24.8	24.6-25.1
Calculated or implicitly understood by the reader	5	3.6	3.6-3.7
Omitted and incalculable	4	2.8	2.8-2.9
Not a cluster-type clinical trial	97	68.8	68.2-69.6
Subjects refusing to participate			
Mentioned in article	48	34.1	33.8-34.6
Calculated or implicitly understood by the reader	72	51.1	50.7-51.7
Omitted and incalculable	19	13.5	13.4-13.7
Not shown	2	1.4	1.4-1.5
Subjects refusing to participate (cluster)			
Mentioned in article	16	11.3	11.2-11.5
Calculated or implicitly understood by the reader	24	17.0	16.9-17.2
Omitted and incalculable	4	2.8	2.8-2.9
Not a cluster-type clinical trial	97	68.8	68.2-69.6
Randomized patients			
Mentioned in article	116	82.3	81.6-83.2
Calculated or implicitly understood by the reader	19	13.5	13.4-13.7
Omitted and incalculable	3	2.1	2.1-2.2
Not shown	3	2.1	2.1-2.2
Randomized subjects (cluster)			
Mentioned in article	33	23.4	23.2-23.7
Calculated or implicitly understood by the reader	10	7.1	7.1-7.2
Omitted and incalculable	1	0.7	0.7-0.7
Not a cluster-type clinical trial	97	68.8	68.2-69.6
Received assigned treatment			
Mentioned in article	71	50.4	50.0-51.0
Calculated or implicitly understood by the reader	64	45.4	45.0-45.9
Omitted and incalculable	6	4.3	4.3-4.4
Received assigned treatment (cluster)			
Mentioned in article	20	14.2	14.1-14.4
Calculated or implicitly understood by the reader	23	16.3	16.2-16.5
Omitted and incalculable	1	0.7	0.7-0.7
Not a cluster-type clinical trial	97	68.8	68.2-69.6
Withdrew informed consent			
Mentioned in article	22	15.6	15.5-15.8
Calculated or implicitly understood by the reader	78	55.3	54.8-55.9
Omitted and incalculable	16	11.3	11.2-11.5
There is no informed consent	25	17.7	17.6-18.0
Withdrew informed consent (cluster)			
Mentioned in article	6	4.3	4.3-4.4
Calculated or implicitly understood by the reader	25	17.7	17.6-18.0
Omitted and incalculable	4	2.8	2.8-2.9
There is no informed consent or not a cluster-type clinical trial	106	75.2	74.5-76.0
Losses to follow-up			
Mentioned in article	24	17.0	16.9-17.2
Calculated or implicitly understood by the reader	92	65.2	64.6-65.9
Omitted and incalculable	25	17.7	17.6-18.0

(Contd...)

Table 2. Quality of information for quantitative variables: frequencies, percentages and 95% confidence intervals (Continued)

Variable: quality of information	Frequency	%	95% CI
Losses to follow-up (cluster)			
Mentioned in article	13	9.2	9.1-9.4
Calculated or implicitly understood by the reader	24	17.0	16.9-17.2
Omitted and incalculable	6	4.3	4.3-4.4
Not shown or not a cluster-type clinical trial	98	69.5	68.9-70.3
Main analysis over one total			
Mentioned in article	62	44.0	43.6-44.5
Calculated or implicitly understood by the reader	75	53.2	52.8-53.8
Omitted and incalculable	4	2.8	2.8-2.9
Main analysis over one total (cluster)			
Mentioned in article	12	8.5	8.5-8.6
Calculated or implicitly understood by the reader	28	19.9	19.8-20.2
Omitted and incalculable	3	2.1	2.1-2.2
Not shown or not a cluster-type clinical trial	98	69.5	68.9-70.3
Cases with endpoints desired to be avoided			
Mentioned in article	8	5.7	5.7-5.8
Calculated or implicitly understood by the reader	40	28.4	28.2-28.8
Omitted and incalculable	92	65.2	64.6-65.9
There is no endpoint	1	0.7	0.7-0.7
Cases with endpoints desired to be avoided (cluster)	5	3.6	3.6-3.7
Mentioned in article	37	26.2	26.0-26.5
Calculated or implicitly understood by the reader	99	70.2	69.6-71.0
Omitted and incalculable			

Table 3. Qualitative variables most representative statistics

	Mean	Median	Mode	Minimum	Maximum	Standard deviation (95% CI)
Assessed subjects	9098.15	641.00	91 (several)	32	572546	53871.94 (48233.54-61015.48)
Assessed subjects (cluster)	108.68	69.50	40	9	373	95.02 (85.07-107.62)
Subjects refusing to participate	363.08	3.00	0	0	18882	1936.66 (1733.96-2193.46)
Subjects refusing to participate (cluster)	25.34	0.00	0	0	203	53.44 (47.85-60.53)
Randomized subjects	1150.84	280.00	125 (several)	11	38147	3936.06 (3524.10-4457.99)
Randomized subjects (cluster)	107.58	51.00	45 (several)	9	1361	211.22 (189.11-239.23)
Received assigned treatment	1161.22	289.00	237	11	38147	4057.90 (3633.19-4595.99)
Received assigned treatment (cluster)	101.35	51.00	41	9	1361	208.97 (187.10-236.68)
Withdrew informed consent	4.22	0.00	0	0	97	14.20 (12.71-16.08)
Withdrew consent (cluster)	0.74	0.00	0	0	16	3.10 (2.77-3.51)
Losses to follow-up	74.78	13.00	0	0	1612	233.09 (208.69-264.00)
Losses to follow-up (cluster)	4.11	0.00	0	0	54	9.92 (8.88-11.23)
Main analysis over one total	1062.51	234.00	164	11	36092	3864.55 (3460.07-4377.00)
Main analysis on one total (cluster)	100.95	47.00	40	9	1361	216.22 (193.59-244.89)
Cases with endpoints desired to be avoided	181.46	73.00	0	7	1912	348.60 (312.11-394.82)
Cases with endpoints desired to be avoided (cluster)	3.20	0.00	0	0	16	7.15 (6.40-8.10)

Table 4. Ethical variables: frequencies, percentages and 95% confidence intervals

Variable	Value	Frequency	%	95% CI
Is it mentioned if informed consent was obtained?	Yes	111	78.7	78.0-79.6
	No	30	21.3	21.2-21.6
Was informed consent voluntarily obtained?	Yes	10	7.1	7.1-7.2
	Uncertain	101	71.6	71.0-72.4
	No informed consent was obtained	30	21.3	21.2-21.6
Is the type of informed consent specified, and whether it is witnessed and documented?	Verbal (no witness mentioned)	1	0.7	0.7-0.7
	Written	69	48.9	48.5-49.5
	Not mentioned (if written or verbal)	41	29.1	28.9-29.5
	No informed consent was obtained	30	21.3	21.2-21.6
Did the patient receive information when obtaining the informed consent?	Yes	43	30.5	30.3-30.9
	No	68	48.2	47.8-48.8
	No informed consent was obtained	30	21.3	21.2-21.6
Was informed consent obtained under a dependence relationship or under pressure?	Dependence relationship	44	31.2	31.0-31.6
	No	14	9.9	9.8-10.1
	Uncertain	53	37.6	37.3-38.1
	No informed consent was obtained	30	21.3	21.2-21.6
Was an unrelated qualified person appointed to obtain informed consent?	Yes	2	1.4	1.4-1.5
	No	35	24.8	24.6-25.1
	Uncertain	60	42.6	42.3-43.1
	No informed consent or not under pressure or dependence	44	31.2	31.0-31.6
Was informed consent of the participating subject withdrawn anytime during the clinical trial?	Yes	21	14.9	14.8-15.1
	No	79	56.0	55.5-56.7
	Uncertain	11	7.8	7.8-7.9
	No informed consent was obtained	30	21.3	21.2-21.6
Any incentive for investigators, participating centers or subjects?	No	96	68.1	67.5-68.9
	To investigators	26	18.4	18.3-18.7
	To participating centers	4	2.8	2.8-2.9
	To participating subjects*	16	11.2	11.1-11.4
	To investigator assistants*	6	4.3	4.3-4.4
	To participating physicians (cluster)*	7	5.0	5.0-5.1
If the answer is affirmative, specify type and amount	Bonus to investigators	7	5.0	5.0-5.1
	Subsidy or grant to investigators*	23	16.3	16.2-16.5
	Bonus to participating centers	4	2.8	2.8-2.9
	Bonus to subjects for participating*	16	11.2	11.1-11.4
	Bonus to assistants*	6	4.3	4.3-4.4
	Bonus to physicians (cluster) for participating*	7	5.0	5.0-5.1
	No incentives were given	96	68.1	67.5-68.9
Has the given incentive been proportionate?	Yes	41	29.1	28.9-29.5
	No	4	2.8	2.8-2.9
	No incentives were given	96	68.1	67.5-68.9
Provided information with regard to conflicts of interests	There is no conflict of interests	117	83.0	82.2-83.9
	Remuneration or grant from company	12	8.5	8.5-8.6
	Any author works for company*	14	9.9	9.8-10.1
	Other: author was consultant or owner*	7	5.0	5.0-5.1
	Any author is stockholder of the company	1	0.7	0.7-0.7

* Sum of the same result in several identical variables.

beneficial intervention to the rest of participating subjects after their conclusion, but only in one case was that possibility specified in the informed consent. Study general results were shown to all participants at its conclusion in 1.4% (95% CI: 1.4-1.5) of studies.

No study referred specific bioethics training of the authors. All clinical trials informed about potential conflicts of interests. Sponsor influence was not described in 57.4% (95% CI: 56.9-58.1). Analyzed studies were registered (in ClinicalTrials.gov or similar, according

to the country of study) in 55.3% (95% CI: 54.8-55.9).

Among 112 comparable variables, a κ mean of 0.96 (95% CI: 0.93-0.99) was obtained.

Discussion

It is possible claiming that the type of clinical trial most commonly published in the 10 reviewed journals is multi-center, publicly funded, controlled, parallel, of simple randomized design, with de-centralized concealed randomization, using an active treatment as control, with a 12-month duration, in Caucasian patients and with a medical intervention method, with a positive result in 50% (measured by means of a questionnaire). In 45%, intent-to-treat analysis is carried out. Serious adverse effects and good quality are shown (Jadad 3). In addition, informed consent (verbal or not mentioned), lack of incentives and non-existence of conflicts of interests appear more often than in other referred publications.

On the other hand, the checklist used in this analysis has more items than the CONSORT list in order to consider specific aspects where CONSORT has not sufficient impact according to our opinion. In addition, by basing ourselves on the latest Declaration of Helsinki, we delved even more into different ethical aspects than the CONSORT guidelines, which, in our opinion, do not consider them sufficiently.

If we make a comparative analysis with the clinical trials of the study performed about the *New England Journal of Medicine*, *British Medical Journal*, *Journal of the American Medical Association* and *Lancet* journals¹⁷, we find that concealed randomization has progressively increased: from 33.1% in 1993-1995 to 56.7% in 2004¹⁷, and even more in our study. This might be explained by the fact that after CONSORT, it was much insisted that this type of assignment was essential to reduce selection bias. In contrast, double blinding is less common than in previous reviews (43.9% in 1993-1995 and 43.3% in 2004)¹⁷, and the use of placebo as control has also been decreasing (37.0% in 1993-1995 and 16.7% in 2004)¹⁷, and even less in our study, probably because, over the years, there are more standard treatments to compare and higher demands of regulatory authorities for considering new treatments launch into the market, with their efficacy having to be demonstrated with already standardized treatments.

With regard to ethical quality indicators, the number of clinical trials where reference to one CREC and

more appears has increased in recent years: 25.5% in 1993-1995 and 20% in 2004¹⁷. Clinical trials with children and disabled subjects are very rare, probably because these are articles about clinical trials published in primary care and internal medicine journals.

Sinha et al.²⁹ obtained a Jadad score ≥ 3 in 40% of 42 clinical trials²⁹, which is an inferior result to ours.

Agha et al.³⁰ concur with us with their sample of 57 clinical trials, on that the USA (with 15 studies) is the country where clinical trials are more commonly carried out.

Public funding was most common in 74 clinical trials assessed by Lai et al.³¹, just as in our study, probably because clinical trials are highly expensive. In addition, important adverse effects are more common (64.9%; 95% CI: 52.9-75.6) than in our study, probably because they did not study innocuous medical interventions, but more aggressive treatments. Methodological quality is also higher in our study since, in their review³¹, the primary variable only appears in 45.9% (95% CI: 34.3-57.9), sample size calculation in 39.2% (95% CI: 28.0-51.2), concealed randomization in 29.7% (95% CI: 19.7-41.5), blinding in 2.2% (95% CI: 4.5-19.8) and intent-to-treat analysis in 27% (95% CI: 16.7-37.4).

Comparing different methodological quality aspects of our study with others recently conducted in other specialties, we can highlight the following. In a review of 300 cluster-type clinical trials³², 55% wrote about sample size calculation (a lower figure than in our review). In another review³³ of 89 randomized clinical trials about endodontics, a lower percentage was found in comparison with our study, since only 45% generated a randomization sequence to reduce bias risk, 75% provided no information on the assignment method and 19.1% had a non-blinded design. Furthermore, only 55% had adequately carried out the sample size estimation, only 16% obtained confidence intervals and 25% did not report the p-value. Finally, 2.2% did not perform statistical tests. In the field of orthopedics, in a review of 222 studies³⁴, in none of them was the sample size adequately calculated, in 33.4% was there an adequate randomization sequence generated, only in 3.7% was randomization correctly performed and in 8.1% was there an adequate blinding (figures that are inferior to those in our review). Specifically, in the 8 articles chosen from the *Orthopaedics Traumatology Surgery & Research* journal, 12.5% were found not to mention having performed an adequate randomization sequence, in 50% was not a correct

randomization reported and in 25% was there an adequate blinding (figures that are inferior to ours as well). In the field of the respiratory system, in a review of 176 trials³⁵, 53% were found to mention adequate generation of a randomization sequence, in 38% was randomization correct, 45% were double-blinded, in 70% was sample size calculation adequate, in 50% was there an intent-to-treat analysis carried out and 69% included a flow diagram. Except for the double blinded percentage, the rest of the figures are quite inferior to those found in our review. In a review of 305 studies published in journals about diabetes³⁶, the authors found that 35.4% of trials showed an adequate randomization sequence generation, in 28.5% was randomization correct and in 23.8% was there an intent-to-treat analysis carried out (which are lower percentages to those found in our study). In a review of 321 articles on epidural anesthesia³⁷, the authors found a Jadad score mean value of 2 (lower than that observed in our review) and a general increase in methodological quality in those articles published after the CONSORT guidelines appearance, which is consistent with our review. In the field of transplantations, the authors of a review³⁸ of 290 studies found that 43% had good quality according to Jadad scale (a figure a bit lower than ours) and, in one third of these, randomization and data analysis were satisfactory (quite lower than that which was observed in our study). In addition, methodological quality and adherence to CONSORT guidelines were higher in trials of journals that were in compliance with CONSORT³⁸. In colorectal cancer treatment, the authors of a review³⁹ found quite inferior data to ours in 40 randomized clinical trials, since only 7.5% were identified as randomized clinical trials in the title, and also only 7.5% applied a randomization method to the sequences, only 5% mentioned the randomization type and only 2.5% applied a concealment method or calculated the sample size. Only 2.5% described the flow diagram and primary and secondary outcome variables with estimated sample effect. Finally, 32.5% showed baseline demographic and clinical characteristics, and 25% performed an intent-to-treat analysis. In a review⁴⁰ of 53 clinical trials on multiple sclerosis, the authors found that 79% were sponsored by a pharmaceutical company, 13% had mixed funding and only 6% were funded by non-profit institutions. This might compromise the validity of this trial, since funding is clearly biased, just the opposite of what we found in our review. Mean assessed patients were 297 (range: 30-2244); 83% of studies were placebo-controlled and did not show randomization systems. The

statistical method used to generate the randomized list was specified by 81.1%, with block randomization being most widely used (81.4%). Double blinding was used by 90.6%, and only one trial was not blinded. Among the trials with single blinding, 94.2% showed details about who had carried out the blinding and 59.6% about how it had been performed. All studies but two defined the primary outcome variable. Significantly positive trials were found to be 64.2%. Intent-to-treat analysis was used in 79.2%. No CONSORT flow diagram was shown by 20.8%. In 52 trials, the number of patients lost to follow-up was reported. All studies showed baseline characteristics in a table. Just as the above studies, data are less common, except for double blinding; the trials with positive significance and the sample of baseline characteristics are presented in a table. The authors of a review⁴¹ of 73 cluster-type clinical trials observed that 50% had been conducted in the USA or the United Kingdom (a percentage higher than that found by us). Sample size calculation was performed by 60%. Information on patients lost to individual follow-up appeared in 53 trials, whereas on groups only in 28. Blinded assessment by third parties appeared in 44% (a superior figure to that in our review). In 51 trials, a statistician appears as co-author (less than in our study), and this appearance, together to the publication period, has more influence on quality than the strength of the journal adherence to the CONSORT guidelines⁴¹. In a review⁴² about immunosuppression in kidney transplantation, the authors observed that, in 179 studies, all had a parallel design. No funding source was declared or there wasn't any in 35%, 57% were funded by the pharmaceutical industry, and 14% by a public entity (figures that are very different from those found in our review). Seventeen percent were multinational, with patients being recruited in more than one continent: 26% in North America, 44% in Europe, 7% in Asia and 11% in other zones (similar percentages to ours). In 67%, the studies were published in journals that adhered to the CONSORT guidelines (a lower percentage than that in our study). The number of participating subjects ranged from 15 to 1645. Two percent of studies showed $\leq$ 1-month follow-up and 7% $\leq$ 6-month follow-up results, with a range from 0.25 to 240 months (figures also lower to those found in our study).

Finally, if we compare our study with the one by Hopewell et al.⁷, we observe that, in the reviewed studies of 2006, the following appears: the primary outcome variable is defined in 53%, sample size

calculation in 45%, the concealed randomization method employed in 34%, the randomization method in 25%, blinding appears in 59%, flow diagram in 28%, patients lost to follow-up in 69%, intent-to-treat analysis in 31%, pharmaceutical industry funding in 17% and clinical trial registry in 9%.

As Baskerville et al.¹⁵, we only have been able to have access to clinical trials' published data and not to the original works, which could be different.

In our analysis there is important variability between studies regarding the measurement of the main variables, due to the many types that were found according to the study treatment.

As in the study by Hopewell⁷, we may have missed some articles in the search, since the indexation date in PubMed and other search engines has a certain delay with regard to the moment the article is published.

Furthermore, although we have performed an agreed pairwise evaluation with an optimal mean κ coefficient, there is always the possibility of error in data collection when indicating item answers in the checklist used.

The creation of a checklist with so many items had the purpose to analyze methodological and ethical, general and quality characteristics, rather than being a regular tool for the review of clinical trials.

Finally, owing to space limitations we don't include the checklist used or its instructions, which could be available for readers if they desire.

Conclusions

After the publication of the CONSORT guidelines, general quality of published clinical trials has considerably increased, but there are some aspects that could be improved. Concealed randomization has increased by 19.6%¹⁷, and approval by a CREC by 75%¹⁷, but double blinding has decreased by 36.2%¹⁶, as well as the use of placebo to compare a new treatment by 7.5%¹⁷ as methodological and ethical quality criteria, respectively, in clinical trials published in the 10 reviewed journals of the family medicine specialty (2010-2013).

Conflict of interests

The authors declare not having any conflicts of interests.

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