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ARTICLE

Publication and associated factors of clinical trials registered in Peru

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Abstract

Objective: We aim to determine the percentage of publication and its associated factors of clinical trials (CTs) registered in Peru.

Methods: Using a cross-sectional study design, we assessed CTs registered at the CT's Peruvian Registry (REPEC) during the 2011-2016 period, and evaluated its percentage of publication and associated factors. We used a bibliographic search algorithm to determine if the CTs were published and assessed the associated factors by using a Cox regression to estimate the adjusted hazard ratios (aHR) as the magnitude of association of interest.

Results: We analyzed 228 CTs, of which 63% were published. The regression analysis identified the year of registration (aHR 2012 = 1.15 [0.58-2.27]; aHR 2013 = 0.45 [0.21-0.95]; aHR 2014 = 0.89 [0.43-1.82]; aHR 2015-2016 = 0.16 [0.05-0.58]), total number of participants (aHR = 1.12; 1.05-1.18), and phase III-IV (aHR = 2.15; 0.1.16-4.03) as factors associated with the publication of the CTs.

Conclusions: The percentage of publication of CTs executed in Peru is insufficient, and it increases the older the year of its registration in the REPEC, mayor of the number of participating countries, and if it is a phase III or IV study.

KEYWORDS
biomedical research, clinical trials, Peru, publishing, registries

1 | INTRODUCTION

Randomized controlled clinical trials (CTs) are the gold standard study designs to assess health interventions and technologies.[1] Conducting a CT implies a prime responsibility and ethical obligation to report its results, even if they are not significant. Failure to publish a CT negative results causes publication bias[2] and a direct violation of the "ethical principles for medical research in human beings" embodied in the Helsinki Declaration.[3] However, a study showed that only around a third of CTs reported results in ClinicalTrials.gov.[4] Likewise, approximately half of the finished CTs got published as original articles in scientific journals.[5,6]

In general, several factors influence the CTs' publishing likelihood. Among them, one of the more important ones is getting favorable results for the intervention.[7] CTs with positive results are about four times more likely to be published than CTs with negative results.[8] This publication bias may distort the conclusions of systematic reviews and meta-analysis.[9] Other associated factors are time to publish, financing, and number of participants.[10]

Each country regulates and registers the CTs that runs in its territory. Lack of funding, human resources training, and regulatory and

ethical barriers are obstacles to the execution of CTs, especially in the middle- and low-income countries.[11] In Peru, all CTs must be previously approved by an institutional ethics committee and registered in the Peruvian Registry of Clinical Trials (REPEC, in Spanish), managed by the Peruvian National Institute of Health.[12] A CT must be registered at REPEC before it starts.[13] This compulsory rule differs from other international registries like ClinicalTrials.gov, the Australian New Zealand Clinical Trials Registry, the Brazilian Clinical Trials Registry, or the European Union Clinical Trials Register, which registration is optional and can be done retrospectively.[14–17]

Previous studies analyzed the REPEC and they reported that over 60% of the registered CTs were completed,[18] and since 2013, the number of registered CTs decreased steadily.[19] Most studies on this topic assessed retrospectively the registry of already published CTs,[20] or the publication of CTs registered only at ClinicalTrials.gov.[4,21] However, the proportion of publication in scientific journals out of all completed and registered CTs, in the middle- and low-income countries, is unknown. Hence, this study aims to estimate the percentage of publication of the CTs registered in a developing country like Peru and analyze its associated factors.

2 | METHODS

2.1 | Study design

We performed a cross-sectional study to estimate the percentage of publication of completed CTs recorded in the REPEC, during the period 2011-2016 and analyzed its associated factors. For this purpose, we used a bibliographic search algorithm to determine whether they were published. Then, we carried an evaluation to identify their characteristics as potential associated factors with the nonpublication/publication of the CTs.

2.2 | Study procedures

Briefly, the REPEC is a public access online platform developed by the Peruvian National Institute of Health. This public institution supervises the mandatory registration of all CTs carried out in Peru and their constant updating status. The REPEC got the certification from the World Health Organization in 2016, and since then, it has been an active member of the International Clinical Trial Registry Platform.[22] In March 2018, we performed a search in the REPEC database. However, there was not any CT registered in 2017 or 2018 as "completed." Therefore, we focused on the CTs registered during the 2011-2016 period.

2.3 | Publication assessment

In March 2018, we carried out a systematic review to determine whether the REPEC CTs were published. We used an ad hoc methodology based on previous papers about CTs' publication.[23–25] Briefly, we reviewed Medline/PubMed, Scopus, and Google Scholar using a combination of the following entry terms: "Responsible author last name," "Intervention," "NCT number," and "Applicant institution." We performed a double-check using matching criteria between identified reference and CT. For this process, we took in account the study aim, design, type of intervention, sample size, and the number of sites. We included a reference if its study aim, design, and interventions matched with registered CT, at the minimum. Another inclusion criterion was: studies final results, preliminary results, or secondary analysis published as an original article in a peer-reviewed and indexed scientific journal. Exclusion criteria were: study protocols or study methods.

2.4 | Data extraction

We extracted the data using a standard procedure described in a previous publication.[19] Briefly, we printed every record from the REPEC in PDF format to facilitate data quality control. Then, we extracted the data of interest from every file using double data entry (PH and CAAR), a specific range of values, and coded categories to minimize information bias. During this process, the principal investigator solved every divergence detected by contrasting the records with the original files. From every record, we extracted the following variables of interest: year of registration, type of study (phases I-IV), industry registration (yes or no), type of blinding (simple, double, triple or open-label), type of allocation (single-arm, parallel, factorial, crossover, and others), randomization, gender and age of participants, number of participants, number of Peruvian participants, number of participating countries, treatment time, follow-up time, and study duration. For published CTs, we also included additional information, regarding the year of publication, scientific journal, Scopus or PubMed indexed (yes or no), type of publication (original or conference abstract), time of publication (months since REPEC registration to the publication date), open access (yes or no), Peruvian authors (yes or no), author affiliated with a pharmaceutical company (yes or no), and corresponding author's country of affiliation.

2.5 | Data analysis

The descriptive analysis summarized qualitative variables by using their relative and absolute frequencies, and the quantitative variables by using their mean ± standard deviation or median ± interquartile range (IQR), depending on the normality of their distribution. For bivariate analysis, we used chi-square (or exact Fisher), *t*-Student (or U Man-Whitney) test for bivariate analysis. To assess the associated factors with the "publication" as an event, we used cox regression models to estimate the crude (cHR) and adjusted (aHR) hazard ratios as the magnitude of association of interest. During this process, we considered the following variables as potential publication associated factors. We added to the multivariate model: year of registration, type of study (dichotomized as phases I-II or III-IV), type of blinding (dichotomized as blinded [simple, double, and triple] or nonblinded [open label]), type of allocation (dichotomized as parallel vs nonparallel

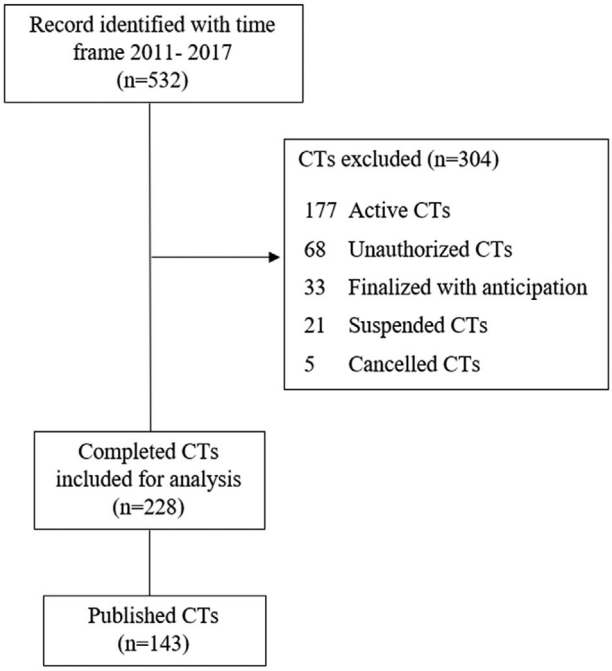

FIGURE 1 Selection of completed CTs registered in the REPEC 2011-2016

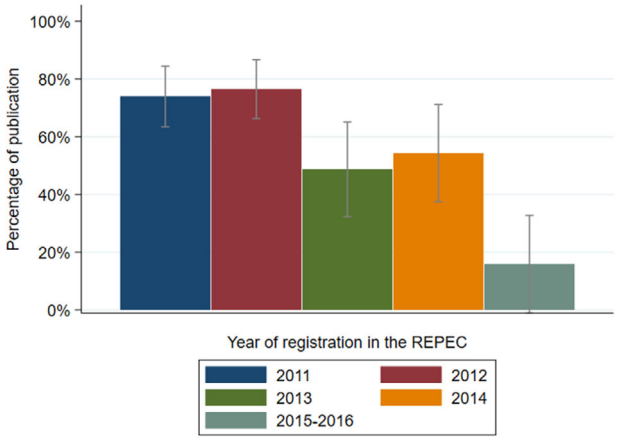

FIGURE 2 Completed CTs registered in the REPEC, distribution by year

[single arm, crossed, factorial or others]), randomization, industry registration, number of participants (every 500 participants), treatment time (years), and follow-up time (years). Additionally, we plotted the percentage of publication using Kaplan-Meier analysis. In all cases, we estimated 95% confidence intervals (95% CI) and used the STATA MP v16.0 statistical package (Stata Corp LP, College Station, TX, USA).

2.6 | Ethical issues

The present study analyses a public database, so all the data collected is available to the public through the REPEC website. The Institutional Ethics Committee of the Faculty of Human Medicine at Ricardo Palma University assessed and approved the research protocol (Code: 001–2018).

3 | RESULTS

3.1 | General characteristics of completed CTs registered at the REPEC

During the 2011-2016 period, the REPEC registered 532 CTs. We excluded 304 CTs because 177 were still active, 68 were unauthorized, 33 were finalized with anticipation, 21 were temporally suspended, and 5 were canceled. Finally, we included 228 completed CTs (Figure 1). We identified a significant descendant trend in the annual counts of completed CTs, decreasing from 69 CTs in 2011 to three in 2016. Most CTs were randomized (93%), with a parallel allocation (85%), double-blinded interventions (68%), and phase III studies (65%). The trials' median treatment and follow-up times were 6 months (IQR = 3-13 months) and 3 months (IQR = 1-12 months), respectively. Most studies' population were adults (88%) of both genders (85%), with a median sample size of 600 (IQR = 300-922 participants per study), a median number of Peruvian participants of 36 (IQR = 20-76 Peruvian participants per study), and a median number of participating countries of 14 (IQR = 6-23). Most of the CTs were directly registered by the industry (84%): PPD Peru SAC (15%), Merck Sharp & Dohme Peru SRL (11%), GlaxoSmithKline Peru SA (7%), Quintiles Peru SRL (6%), and Novartis Bioscience Peru SA (6%). Regarding the medical speciality, during the study period, the following corresponded to most CTs: oncology (20%), infectious disease (19%), pneumology (18%), rheumatology (12%), and endocrinology (7%).

3.2 | Percentage of publication of completed CTs

During the 2011-2016 period, the percentage of publication of CTs was 63% (95% CI 56% to 69%) ($n = 143$) for the completed CTs registered at the REPEC. In our trend analysis, we observed that during the study period the percentage of publication had a significantly negative trend ($P = .001$), decreasing from 74% (95% CI 63% to 84%) in the year 2011 to 16% (95% CI 2% to 34%) in the year 2016 (Figure 2). Additionally, the percentage of publications decreased according to the time of publication in months. We observed that the CTs' publication was most likely within the first 2 years of completion (Figure 3).

3.3 | Characteristics of published CTs registered at the REPEC

We observed that most CTs registered at the REPEC got published as original (93%) and open access (60%) articles. Scopus or Medline-indexed journals (95%) published most of these articles, with the New England Journal of Medicine being the most frequent (12%). The median time to publication was 17 months (IQR = 12-26). Corresponding authors affiliated with US institutions (58%) published most CTs

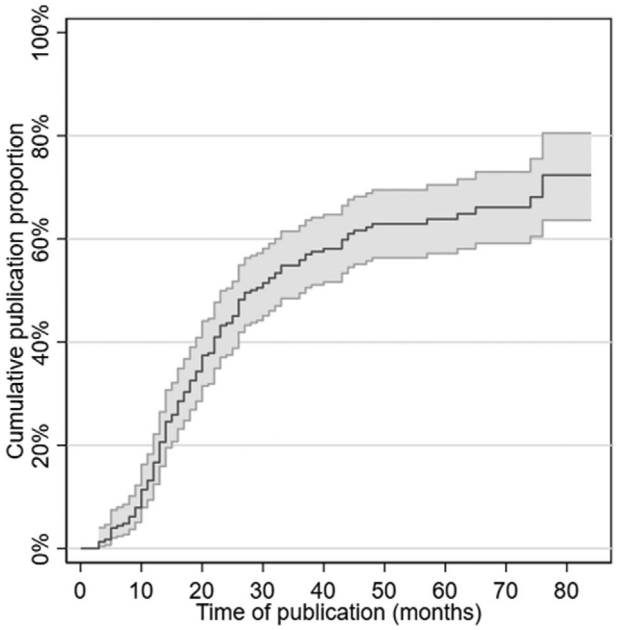

FIGURE 3 Time to publication of completed CTs registered in the REPEC 2011-2016 ($n = 228$)

registered at the REPEC, and nearly all included one author affiliated with a pharmaceutical company (92%). Only 19% of all articles had at least one coauthor with a Peruvian affiliation, and only 3% of all papers had a corresponding Peruvian author. Most published CTs were registered at the REPEC by pharmaceutical companies (84%), including PPD Peru SAC (15%), Merck Sharp & Dohme Peru SRL (10%), GlaxoSmithKline Peru SA (9%), Novartis Bioscience Peru SA (8%), and Covance Peru Services (7%). Most published CTs were related to the fields of oncology (22%), pneumology (21%), infectology (18%), rheumatology (11%), and endocrinology (8%).

3.4 | Associated factors with the publication of CTs

The bivariate analysis (Table 1), showed that the percentage of publication was significantly associated with the year of registration at REPEC ($P < .05$), the number of participants ($P < .001$), phase III-IV ($P < .05$), and parallel assignment ($P < .001$). In the multivariable regression analysis (Table 2), some of these findings were confirmed, the percentage of publication was significantly associated with the year of registration (2011 [Ref.]; aHR 2012 = 1.15 [95% CI: 0.58-2.27]; aHR 2013 = 0.45 [0.21-0.95]; aHR 2014 = 0.89 [0.43-1.82]; aHR 2015-2016 = 0.16 [0.05-0.58]), the total number of participants (aHR = 1.12; 1.05-1.18), and phase III-IV (aHR = 2.15; 0.16-4.03).

4 | DISCUSSION

4.1 | Summary of results

The present study found that during the period 2011-2016, the REPEC registered 228 completed CTs. Out of these, 63% were published, with the lowest percentage of publications in the subgroup of the CTs registered in 2016 (16%). Overall, most CTs were published during 2016 and 2017. Most of the corresponding authors have an affiliation with a US institution. A small fraction of these publications had at least an author with Peruvian affiliation, and out of them, only five published CTs had a corresponding Peruvian author. The median publication time was 17 months. The percentage of published CTs increased the older the year of its registration in the REPEC, mayor of the number of participants, and if it was a phase III or IV study.

4.2 | CTs registered in the REPEC

During 2011 and 2016, we observed a significant decreasing trend in the REPEC. These results add to a previous report published by our group,[19] which conveyed that this notorious decreasing trend started in the year 2009. The update of the Peruvian regulation could explain this. The new regulations prove to be more rigorous, expensive (it requires insurance coverage for every participant), bureaucratic and seem to be more challenging to comply with.[26,27]

Most CTs registered at the REPEC are trials sponsored by the pharmaceutical industry. This observation is consistent with previous reports[28] and with the analysis of ClinicalTrials.gov database,[24] which found that the pharmaceutical industry financed over 80% of the registered CTs. Such a link with the pharmaceutical industries' funding may negatively affect unique aspects of the interpretability of a CT, including publication bias, misconduct, predetermined conclusions, and authoring problems.[29]

Most CTs registered at the REPEC aimed to assess oncology interventions, which represents one of the leading causes of adult mortality but not the most prevalent in Peru and the Americas region.[30] This observation was consistent with observations from Spain, where the most studied interventions were those in the oncology field.[28] However, our results differ from a study in South Africa, where the most studied interventions were those designed to treat respiratory diseases and HIV/AIDS infections.[25] The variability in terms of morbidity in every region can explain these differences. Overall, acute respiratory diseases and cardiovascular diseases cause the highest mortality and disease burden in Peru.[9] In contrast, the CTs performed in Peru seem to neglect these pathologies.

4.3 | CTs published and registered in the REPEC

Over half (63%) of the CTs registered in the REPEC were published. This percentage of publication is higher compared with the CTs registered at ClinicalTrials.gov (46%) and those registered at the South African Registry of Clinical Trials (49%).[6,25] In contrast, CTs registered with the National Institute of Health from the United States and Norway have a higher proportion of CTs published (93% and 71%, respectively).[23,31] The percentage of published CTs is a good indicator of monitoring national or regional registries. In the Peruvian context, despite the proportion of publication of the Peruvian conferences'

TABLE 1 Characteristics of completed CTs registered in REPEC (2011-2016)

Characteristics	Not published CTs	Published CTs	Total
No. of sample[a] (median, IQR)	330 (190-738)	600 (349-1050)	544 (300-922)
No. of Peruvian sample[b] (median, IQR)	30 (18-60)	40 (20-90)	33 (20-77)
Participant countries[b] (median, IQR)	12 (3-20)	15 (7-24)	14 (6-23)
Treatment time, months (median, IQR)	6 (1-19)	7 (3.2-13)	6 (3-13)
Follow-up time, months (median, IQR)	4 (1-12)	3 (1-12)	3 (1-12)
Study duration, months (median, IQR)	36 (24-60)	34 (24-48)	36 (24-48)
Year registration in REPEC[a] (*N*, %)			
2011	18 (21.2)	51 (35.7)	69 (30.3)
2012	16 (18.8)	52 (36.4)	68 (29.8)
2013	19 (22.4)	18 (12.6)	37 (16.2)
2014	16 (18.8)	19 (13.3)	35 (15.4)
2015	14 (16.5)	2 (1.4)	16 (7.0)
2016	2 (2.4)	1 (0.7)	3 (1.3)
Industry-financed (*N*, %)	68 (80.0)	123 (86.6)	191 (84.1)
Phase III o IV (*N*, %)	57 (32.4)	112 (78.3)	169 (74.1)
Blinding (simple, double or triple) (*N*, %)	27 (31.8)	39 (27.3)	66 (29.0)
Parallel assignment[b] (*N*, %)	52 (61.2)	81 (56.6)	133 (58.3)
Randomization (*N*, %)	74 (87.1)	125 (87.4)	199 (87.3)
Controlled (*N*, %)	71 (83.5)	126 (88.1)	197 (86.4)
Both gender sample (*N*, %)	81 (95.3)	137 (95.8)	218 (95.6)
Included minors (*N*, %)	15 (17.7)	29 (20.3)	44 (19.3)

IQR: interquartile range.
[a] $P < .001$.
[b] $P < .05$.

TABLE 2 Associated factors to the publication of completed CTs registered in REPEC (2011-2016)

Factors	cHR (95% CI)	aHR (95% CI)
Year registration in REPEC		
2011	Ref.	Ref.
2012	1.05 (0.71-1.55)	1.15 (0.58-2.27)
2013	0.54 (0.31-0.93)[a]	0.45 (0.21-0.95)[a]
2014	0.83 (0.49-1.42)	0.89 (0.43-1.82)
2015 or 2016	0.21 (0.07-0.68)[a]	0.16 (0.05-0.58)[a]
No. sample (×500)	1.06 (1.02-1.09)[a]	1.12 (1.05-1.18)[b]
Follow-up time (years)	0.87 (0.74-1.02)	0.82 (0.63-1.08)
Treatment time (years)	0.98 (0.84-1.14)	1.23 (1.00-1.52)
Phase III or IV	1.62 (1.09-2.41)[a]	2.15 (1.16-4.03)[a]
Industry-financed	1.53 (0.94-2.48)	0.67 (0.29-1.51)
Blinding (simple, double or triple)	1.25 (0.86-1.81)	1.40 (0.67-2.96)
Parallel assignment	2.06 (1.03-4.10)[a]	1.78 (0.62-5.16)
Randomization	1.20 (0.61-2.37)	0.95 (0.25-3.69)

aHR: adjusted hazard ratio; cHR: Crude hazard ratio.
[a] $P < .05$.
[b] $P < .001$.

abstracts is lower than 30%,[32,33] this percentage of publication of registered and complete CTs is insufficient. So, we cannot rule out the possibility of publication bias.

The 19% of the published CTs have Peruvian authorship, and of these, only 5 have a corresponding author affiliated to a Peruvian institution. This low participation of Peruvian authors may result due to the limited involvement of local researchers during CTs planning and grants application, and consequently in the manuscript's final draft.[34] Additionally, Peruvian health professionals lack research funding, technical support, and training for research and publication process.[33] A potential benefit of conducting multicenter CTs in medium and low-income countries is the research training for local human resources. However, our results may suggest that most of the Peruvian clinical researchers limit their role to participants recruiters into these CTs.

Public access to CT's protocols, data, and results should be guaranteed to allow further analysis and replications of results.[35] We report that almost 60% of registered CTs got published as open access. In a cohort study of ClinicalTrials.gov registry, only 49.0% of registered trials reported results before the deadline; and 63.8% reported results at any time.[36] Despite that, more than half of CTs registered in Peru are published, but it should be higher, mainly because pharmaceuticals sponsored most CTs. Furthermore, precisely because of this funding bias, most manuscripts should be published as open-access original articles and consequently, facilitate critical appraisal and evidence-based medicine.[37]

Almost all registered and published CTs had at least one author with institutional affiliation from a pharmaceutical company. This result is similar to a study that included published CTs registered in ClinicalTrials.gov, where 80% had an author with affiliation from the pharmaceutical industry.[34] This situation reflects a potential conflict of interest in the development, execution, and publication of CTs in Peru.

We report the median publication time is 17 months, which is consistent with previous studies. Additionally, we observe that most CTs are published within the first 2 years of completion; then, it is less likely to be published. Some reports observed that CTs took around 15 months to be published in high-impact journals.[38] Other authors, like those assessing the CTs registered in Clinicaltrial.gov, estimated that the time for publishing a CT into a Medline-indexed journal was 21 months.[10] However, waiting over 18 months to release and publish CTs results might be considered excessive. Welsh et al[38] recommend to the CTs' authors to draft certain parts of the manuscript, such as the introduction and methodology, before the data analysis, to save time during the writing process.

Additionally, other authors recommend choosing journals that have a postpublication peer review and an open access system. In these journals, the online publication of the manuscript takes a few days, and also the peer review is open access. The authors who published in these journals consider them for their open access, postpublication peer review, and short final acceptance time of approximately 6 months.[39]

The main factors associated with the scientific publication of a CT registered in the REPEC during the years 2011 and 2016 are the year of registration (inverse association) and the size of the total sample of the CT (direct association). A larger sample size increases the likelihood of the publication of the CTs. This observation concurs with previous studies, which reported that the larger the sample size, the higher the possibility of publication.[23,40]

4.4 | Study limitations

Among the significant limitations of our study, it is essential to highlight the following. First, there is a chance that the data we collected was incomplete because of the changes in the data structure of the REPEC. However, that is one reason we analyzed the 2011-2016 period because trough those years, the registry has the highest data quality since the new register launched. Second, there is a chance that we missed some publications. However, that is the reason why we used a standardized search strategy. Third, the study sample size may be insufficient to found statistically significant effects and to avoid overfitting. Nevertheless, we included all the study populations in the Peruvian context, so our results cannot be extrapolated. Finally, there is a possibility of follow-up bias, given that the most recent records have a lower chance of publication than older. As explained before, that is one reason why we selected the study period, so that we could analyze over 2 years of follow-up for every CT. Although the mentioned limitations, we believe that nonregistered CTs executed in Peru during the last years are unlikely, because of the mandatory registration for CTs in the country. So, the numbers reported in this paper represent the reality of CTs in Peru.

4.5 | Recommendations

We recommend the REPEC to include an additional domain in its CT database, showing if there is a publication of the results once they got the results. Likewise, we suggest reviewing the adequate report of the primary outcomes according to the protocols.[41] Additionally, we promote the participation of Peruvian institutions, especially universities, to develop, register, execute, and publish CTs in the country, following the leading local health priorities.

5 | CONCLUSIONS

The percentage of publication of CTs registered in the Peruvian National Registry of Clinical Trials during the period 2011-2016 is insufficient, mainly influenced by the year of the CT registry and its total sample size. Additionally, the leadership of Peruvian researchers is low, and the time until publication sometimes is extensive.

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CONFLICTS OF INTEREST

The authors declare no conflict of interest.

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