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Twenty-two years' experience registering trials in a low-middle income country: The Peruvian Clinical Trial Registry

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Abstract

Aim: This study analyzes the quantitative and qualitative evolution of the Peruvian Clinical Trial Registry during the last 22 years.

Methods: Following a cross-sectional design, we reviewed all clinical trials registered at the Peruvian Clinical Trial Registry during 1995-2017. We downloaded and extracted all registries on 31 March 2018. We summarized qualitative variables and quantitative variables. Also, we performed trends analysis of the records by year, clinical phase, institutional review board, and children's participation.

Results: The Peruvian Clinical Trial Registry recorded 1748 clinical trials during 1995-2017. Considering World Health Organization 20-standard descriptors as the standard, the registry suitably recorded four of them in 1995 and 19 since 2013. There was a meaningful change in the trend of the registries, showing a significant upward registry trend until 2008 and a significant downward registry trend since then. This trend could be influenced by new regulation in clinical trials registry. Several trials had incomplete entries for different studied variables. Most of the clinical trials (82%) included male and female participants, and only 14% included children. Oncological disorders were the diseases most frequently investigated (20%). Most of clinical trials were registered by pharmaceutical companies. A few institutional review boards evaluated most of the clinical trials.

Conclusion: The registration of clinical trials in Peru has improved quantitatively and qualitatively since it started, but its quantitative grow stopped in 2008. Since then, the number of registries has declined steadily. There is an influence of pharmaceutical companies in clinical trial registration.

KEYWORDS

biomedical research, clinical trial as topic, Peru, registries

1 | INTRODUCTION

Randomized clinical trials (RCTs) represent one of the best sources of scientific evidence for informed health decision-making.[1] However, more than half of all RCTs remain unpublished[2] and RCTs with selective positive outcomes have a high likelihood of resulting in publication bias.[3] Both situations cause waste of resources while leading to wrong clinical decision-making due to biased evidence.[4] Registration of RCTs has been proposed as an alternative to solve the problems mentioned above.[5]

In 2005, The *International Committee of Medical Journal Editor* recommended the registration of each RCT before its publication.[6] Later on, in 2013, the World Medical Association Declaration of Helsinki listed as one of its principles that researchers must register every research

Abbreviations: RCTs, randomized clinical trials; ICTRP, International Clinical Trial Registry Platform; IQR, interquartile range; OGITT, in Spanish, General Office for Research and Technological Transference; REPEC, in Spanish, The Peruvian Clinical Trials Registry; WHO, World Health Organization.

study involving human subjects in a publicly accessible database before enrolling its first study subject.[7] The World Health Organization (WHO) adopted such recommendation and launched in 2009 the International Clinical Trial Registry Platform (ICTRP).[8] Therefore, the current recommendation is that each country has its registry and that such registry meets the ICTRP standards, so the WHO can oversee those registries. These standards include rules categorized into six main areas: content, quality and validity, accessibility, unambiguous identification, technical capacity and administration, and governance.[9]

Peru registers RCTs since the year 1995 and allows online registration since the year 2011. Such registry, named the Peruvian Clinical Trial Registry (REPEC, in Spanish), meets WHO standards and joined the ICTRP in 2016.[10] The REPEC is managed and regulated by the Peruvian National Institute of Health, which is responsible for evaluating and authorizing RCTs in Peru through the General Office for Research and Technological Transference (OGITT, in Spanish).[11] In 2012, the OGITT reported a decline of RCTs since 2008 presumably due to a sound media scandal that affected the public perception about RCTs carried on in the country.[12] In 2015, the Peruvian Ministry of Health suspended the authorizations of RCTs carried on children and native communities due to significant concerns about RCT carried on with these populations.[13] As a consequence, they committed a new regulation for RCTs, which was in revision for 2 years and was recently approved in June 2017.[14]

The realization of RCTs in low- and middle-income countries is positive because it allows developing new therapies, attracting investment, and improving research standards and the population's health.[15] However, each country establishes their regulations, primarily considering international ethical rules and their public health priorities. On the other hand, excessive regulatory bureaucracy may have adverse effects on RCTs approvals rates and sustainability.[16] In this study, we aimed to characterize the RCTs carried on in Peru during 1995-2017 to explore how the changes in the registration regulations may have influenced the RCTs, their approvals rates, and success to comply with WHO regulations.

2 | METHODS

We assessed the REPEC and reviewed each of its registries, which documented every RCT carried on in Peru since 1995 up to 2017. We extracted all the data in two steps. First, we printed all the registries on 31 March 2018. Second, four authors (CAAR, JSRR, PH, and ARGB) extracted the data independently using structured spreadsheets and a standardized quality control protocol.

2.1 | About the registry

The REPEC is a public database that can be accessed online through a Web platform for free (http://www.ensayosclinicos-repec.ins.gob.pe/). It contains a detailed registry of each RCT carried on in Peru. Currently, the list of descriptors includes each of the 20 ones recommended by the ICTRP plus the ones required by the OGITT, totaling 87 descriptors. These descriptors belong to six different domains, including: (a) applicant organization/institution; (b) RCT general information; (c) research site, principal investigator, and institutional review board; (d) RCT contact person information; (e) authorization status; and (f) approved procedures.

2.2 | Data extraction

We evaluated each of the 1748 RCTs registered at the REPEC up to 31 March 2018. We focus to collect two types of variables. First, we extracted those variables that described the general characteristics of each RCT, which includes the following: applicant institution, main research institution, number of research institutions, main institutional review board, authorization status, medical specialty, and trial's phase. Moreover, second, we extracted the variables that describe the study design and interventions, which included the following: the use a control arm, randomization, blinding, assignment, enrollment status, participants' gender, sample size, and whether the participants include adults, elders (>64 years old) and/or children participants (<18 years old).

2.3 | WHO standard

We assessed the compliance of the REPEC with WHO standard by tabulating which and since what year the REPEC started to include each of the 20 ICTRP descriptors. Additionally, we assessed the compliance of REPEC with other international registries such as ClinicalTrials.gov, The Brazilian Clinical Trials Registry, The Cuban Public Registry of Clinical Trials, The European Union Clinical Trials Register and The Australian New Zealand Clinical Trial Registry. Moreover, we also revised the last RCTs of each of the mentioned registries to assess their compliance with the ICTRP 20-standard descriptors.

2.4 | Data entry and quality control

Before starting the data entry, we created and piloted a database using the totality of the registries from 2016. JSRR, CAAR, PL, and AGB extracted each of the variables of interest. Then, they discussed their suggestions to modify the database to facilitate the data entry process. These suggestions included adding or dropping new categories to the qualitative variables, and extending or reducing the range of possible values for the quantitative variables. All authors were required to achieve a consensus before starting the study data entry process. For quality control purposes, two groups of independent research (JSRR and CAAR, PL, and AGB) extracted and recorded the data independently in two datasets, using previously consensuses categories and ranges of values. Then, both datasets were contrasted for possible disagreements, which were resolved by an independent reviewer (AMQ) using the original registries as the data source.

2.5 | Statistical analysis

We summarized each categorical variable with its absolute and relative frequencies and the numerical variables with its mean and standard

TABLE 1 REPEC and other trials registries and their compliance with WHO criteria

	REPEC's modification				CT.gov	EU-CTR	ANZCTR	ReBec	RPCEC
Items proposed by WHO	1995	2011	2013	2016	2017	2017	2017	2017	2017
1. Primary registry and trial identifying number	●	●	●	●	●	●	●	●	○
2. Date of registration in the primary registry	○	●	●	●	●	●	●	●	●
3. Secondary identifying numbers	○	●	●	●	●	●	●	●	●
4. Sources(s) of monetary or material support	○	●	●	●	●	●	●	●	●
5. Primary sponsor	●	●	●	●	●	●	●	●	●
6. Secondary sponsor	○	●	●	●	●	○	●	○	●
7. Contact for public queries	●	●	●	●	●	○	●	●	●
8. Contact for scientific queries	○	●	●	●	●	○	●	●	●
9. Public title	●	●	●	●	●	●	●	●	●
10. Scientific title	○	●	●	●	●	○	●	●	●
11. Countries of recruitment	○	●	●	●	●	●	●	●	●
12. Health condition(s) or problem(s) studied	○	●	●	●	●	●	●	●	●
13. Interventions	○	○	●	●	●	●	●	●	●
14. Key inclusion and exclusion criteria	○	●	●	●	●	●	●	●	●
15. Study type	○	○	○	○	●	●	●	●	●
16. Date of first enrollment	○	●	●	●	●	○	●	●	●
17. Target sample size	○	●	●	●	●	●	●	●	●
18. Recruitment status	○	●	●	●	●	○	●	●	●
19. Primary outcome(s)	○	●	●	●	●	●	●	●	●
20. Key secondary outcome(s)	○	●	●	●	●	●	●	●	●

● Present item ○ Absent item.
Abbreviations: ANZCTR, Australian New Zealand Clinical Trials Registry; CT.gov, ClinicalTrials.gov; EU-CTR, Europe Union Clinical Trials Register; ReBec, Brazilian Clinical Trials Registry; REPEC, Peruvian Clinical Trials Registry; RPCEC, Cuban Public Registry of Clinical Trials; WHO, World Organization Health.

deviation, or median and interquartile range (IQR) depending on the presence of outliers. We evaluated the presence of outliers using the Shapiro Wilk normality test. We assessed the trends of the REPEC's annually registration graphically and statistically, by clinical phase, children participation, and the main institutional review board. The trends were assessed statistically using the Pearson X^2 test. All the study analysis was conducted with STATA™ MP version 14.0 (Stata Corp., College Station, TX) using a .05 significant level.

3 | RESULTS

There were 1748 records from 1995 to 2017. All records indicated their public title, protocol code, and status. Applicant institution, main research institution, number of research institutions, main institutional review board, status, and clinical phase were descriptors registered at REPEC since 1995. The rest of the descriptors, which are included in the present study, were registered at REPEC since 2011. REPEC recorded 1216 RCTs (70%) from 1995 to 2010. Only variable "status" was a satisfactorily completed descriptor in the total of registered records.

REPEC collected four of WHO 20-standard items in 1995. Then, it collected 8/20 items in 2011 and finally since 2013, 19/20 items. REPEC missing item was "Study type" specifically "Type of study (interventional or observational)." We compared REPEC with national registries from other countries. Only ClinicalTrials.gov and the Australian New Zealand Clinical Trial Registry have complete compliance of their items (Table 1).

3.1 | Global characteristics of RCTs and quality of registration

One-thousand one-hundred eighty-one (68%) RCTs were completed; 232 (13%) were active; 179 (10%) were suspended; 118 (7%) were unauthorized; 35 (2%) were finalized with anticipation; and 3 (0.2%) were cancelled. One-thousand seven-hundred forty-seven (99.9%) and 1651 (94%) RCT records were completed with a specific entry of their applicant institution descriptor and the main research institution descriptor, respectively. Two international pharmaceutical companies registered almost one-fourth of all RCTs. Two-hundred seventy-one (16%) RCTs were registered by Merck Sharp & Dohme; and 125 (7%) RCTs, by Novartis Biosciences. Additionally, research institutions from the Peruvian Ministry of Health: Instituto Nacional de Enfermedades Neoplásicas and Hospital Nacional Cayetano Heredia executed 155 (9%) and 85 (5%) RCTs, respectively. Otherwise, 105 (6%) RCTs were executed in a private research institution: Clínica Ricardo Palma; and 81 (5%) and 79 (5%) were executed in Social Security research institutions: Hospital Nacional Edgardo Rebagliati Martins and Hospital

Nacional Guillermo Almenara Irigoyen, respectively. Finally, the median Peruvian research institutions executing a RCT was 3 [IQR: 1-5].

Out of the 1748 registries analyzed, 1462 (84%) described which Peruvian main institutional review boards approved the studies, and three Peruvian institutional review boards approved half of them. One-thousand seven-hundred sixteen RCTs (98%) reported their clinical phase. One-thousand one-hundred and four RCTs (64%) were in phase III; 358 (21%) were in phase II; 176 (10%) were in phase IV; and 75 (4%) were in phase I.

3.2 | Interventions characteristics of RCTs and quality of registration

We included 532 RCTs (30%) registered from 2011 to 2017 in this part of the analysis. REPEC started to add more descriptors during this period.

RCTs total duration, subjects' treatment time, and subjects' follow-up time were present in 532 (100%), 517 (97%), and 501 (94%) RCTs, respectively. The median RCTs' total duration was 36 months [IQR: 24-60]. Median subjects' treatment time was 12 months [IQR: 4.2-24]. Median subjects' follow-up time was 4 months [IQR: 1-18]. There were 339 RCTs (64%) that registered their Peru enrolment status. One-hundred forty-two RCTs (42%) were without enrolment, 116 (34%) were in a closed enrolment, 78 (23%) were in enrolment, and three (0.9%) were in a stopped enrolment. Furthermore, 532 RCTs (100%) reported their medical specialty. Oncology was the most studied medical specialty with 130 RCTs (24%). Finally, 86 (16%) and 82 (15%) RCTs were in infectology and rheumatology fields, respectively.

Five-hundred twenty-two RCTs (98%) reported the country enrolment. Median country that participated in a RCT was 15 [IQR: 7-24]. There were 532 (100%) and 531 (99.8%) RCTs that reported the total and Peruvian participants, respectively. The median of total and Peruvian participants in registered RCTs was 555 [IQR: 250-1041] and 30 [IQR: 16-70], respectively. Only 174 RCTs (33%) reported participants' gender. One-hundred forty-three RCTs (82%) included both genders, and 19 (11%) included only women. Finally, 523 (98%) RCTs reported participants' age. Four-hundred sixty-six (89%) and 414 (79%) RCTs included adults and older adults, respectively.

Most RCTs reported their randomization (n = 509). Four-hundred fifty-nine RCTs (86%) had a control group and 467 (92%) RCTs were randomized. Five-hundred twenty-three RCTs reported their type of masking. Three-hundred forty-four RCTs (66%) were doubl-blinded; 164 (31%) were open-label; 13 (3%) were single-blinded; and only two (0.4%) were triple-blinded. Four-hundred nineteen RCTs reported their intervention model. Most RCTs (345, 82%) had parallel assignment; 40 (10%) had singled-group assignment; 20 (5%) had other intervention model; nine (2%) had factorial assignment; and five (1%) had crossover assignment.

3.3 | Trends in RCTs

The RCTs registration showed a biphasic trend. First, the registries increase significantly from years 1995 to 2008 (Pearson $r = 94.5\%$; $P < .0001$) and, second, the significantly decreases from years 2009 to 2017 (Pearson $r = -97.8\%$; $P < .0001$). During the first phase, there were two sudden increases: one in 1998-2000 and another in 2007-2008. In the year 2008, REPEC registered 161 RCTs, and then, it started the second phase. During this second phase, the annual counts of registries also showed two sudden decreases: one in 2008-2010 and another one in 2012-2013. Distribution of registered RCTs, by year and the circumstances, is described in Figure 1.

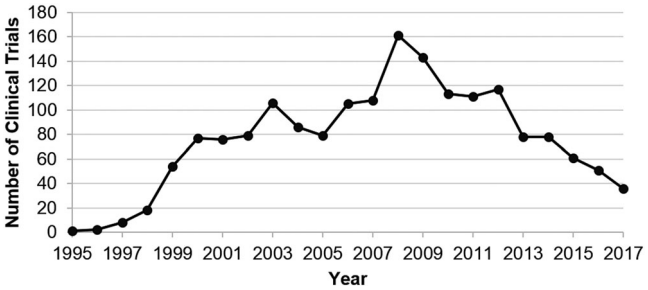

FIGURE 1 Distribution of registered clinical trials in the REPEC by year

Note: We divided the curve of year registration into four stages: (a) slow and constant increasing (1995 to 2000), (b) stationary with fluctuations (2001 to 2007), (c) peak (2008), and (d) steady decrease (2009 to 2017). 2003: National Health Institute receives clinical trials regulation responsibility. 2006: First clinical trials regulation and registration manual were approved. 2007: Modification of regulation with lesser restrictions to clinical trials registration. 2008-2012: There were isolated tries to make clinical trials registration more ethical. 2012: The second manual was approved, including more restrictions. 2015: Clinical trials on children and native communities were banned.

Phase I RCTs were the most prevalent only in 1997. Then, phase III RCTs have been the most frequent since 1999. Additionally, phase IV RCTs were one of the most widespread in 1998 and 2000. In the last years, phase I and IV RCTs barely represent a significant percentage of registered RCTs. In general, RCTs distribution by clinical phase shows a steady trend over last years (Figure 2).

Fourteen percent of all registered RCTs since 2011 included children. Registered RCTs including children as participants represented 25% of the total RCTs in 2011. This value decreased in the last 6 years.

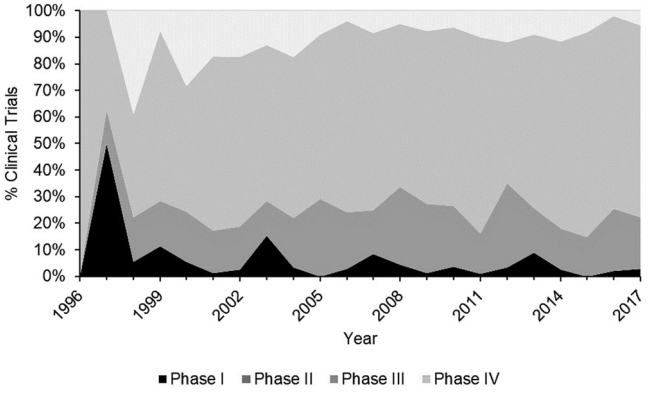

FIGURE 2 Distribution of registered clinical trials, by phase, during 1996-2017

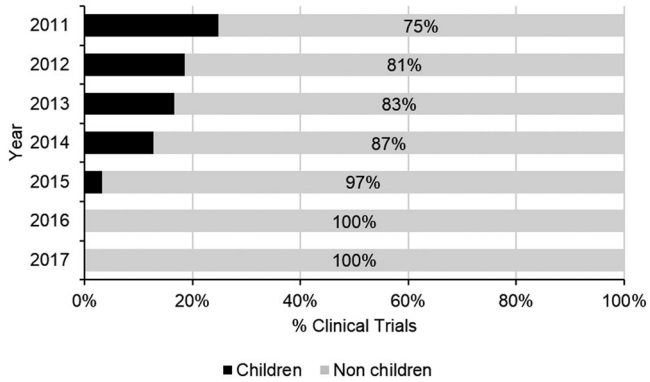

FIGURE 3 Distribution of registered clinical trials including children, by year, during 2011-2017

Finally, none of the RCTs registered in 2016 and 2017 included children (Figure 3).

Institutional review boards from the Universidad Peruana Cayetano Heredia and the Instituto Nacional de Enfermedades Neoplasicas evaluated most of RCTs during first years included in the analysis. The institutional review board from the Universidad San Martin de Porres was taking greater position during the years 2005-2008. It had a peak in 2009 (two-thirds of registered RCTs). Later, there was a decrease in RCTs evaluated by this institutional review board (no registered RCTs in 2016 and 2017). Institutional review board from the Asociación Benéfica Prisma and Vía Libre increased their evaluated RCTs in last years, reaching 65% and 35%, respectively, of total RCTs assessed (Figure 4).

4 | DISCUSSION

We described the 22-year RCT registration in Peru. To our knowledge, this is the first report of a RCT registry over such a long period. The quality and quantity of the registries of RCTs in Peru have improved greatly over the last years. Such improvement correlates strongly with the REPEC's efforts to join the WHO-ICTRP. However, the registry of RCTs had two clear trends during the 1995-2017 period, and showed an upward trend until 2008 and a constant decrease tendency since then. Regardless, 63% of theses RCTs were later published with a median time to publication of 17 months since the end of the study.[17] Our study represents the first analysis of the items collected in REPEC since following WHO recommendations and provides detailed information about its latest progress and registration tendency.

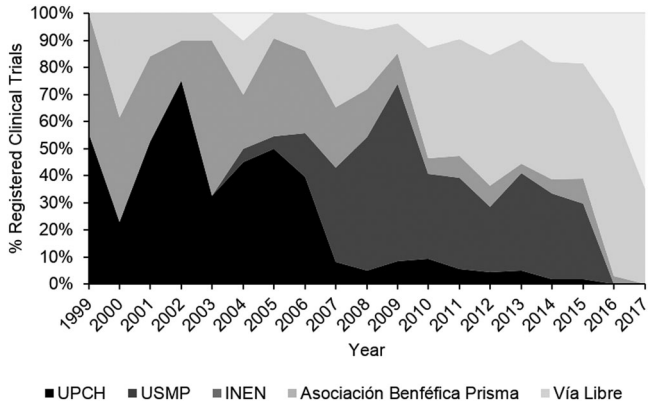

FIGURE 4 Distribution of registered clinical trials, by the five most prevalent main institutional review boards, during 1999-2017
Abbreviations: INEN, Instituto Nacional de Enfermedades Neoplásicas; UPCH, Universidad Peruana Cayetano Heredia; USMP, Universidad San Martin de Porres.

The Peruvian registry exists since 1995, and during the last two decades has improved quantitatively and qualitatively. We think that the main trigger of the latest evolution of the REPEC was the desire to be part of the ICTRP, and in consequence, follow the requirements of this international platform. Some countries of Latin America have been already part of ICTRP before Peru. Both Brazil and Cuba form part of ICTRP since 2012;[18] however, the time of existence of these registries is less than the Peruvian registry. Despite the progression of these registries, many Latin American countries host many RCTs without having a registry approved by the WHO.[19] We believe that Peru's experience registering RCTs may highlight not only the importance of high standards, but also the potential negative impact of strong regulations for the approval of RCTs.

The REPEC has improved qualitatively both in content as in detail. Prior 2008, the REPEC collected fewer items than similar registries from China, India, the Netherlands, and Sri Lanka,[20] but since 2017, it collects only one item less than Clinicaltrials.gov and the Australian - New Zealand registries. Furthermore, now the REPEC collects five more items than the European registry and the same number of items than the Cuban and Brazilian registries. Such improvement most likely is a direct consequence of Peru's desire to join the WHO ICTRP.

Upon the RCTs registration tendency, the steady decrease stage agrees with the trend reported by the OGITT in 2012.[12] A possible explanation for the peak and sustained decrease stage could be the modification of the "Regulation of Clinical Trials" and the "Manual of Clinical Trials Procedures".[11,21] Both include rules that produce, respectively, the reducing and increasing of restrictions for the performance of RCT. Compared with other registries influenced by new regulations, there were growth trends in Japan's registry between 2004 and 2010,[22] and also in Clinicaltrials.gov between 2005 and 2010.[23,24] However, there was a tendency to decrease in European countries due to the implementation of RCTs' regulation.[25]

Pharmaceutical industry organizations register one-fourth of all RCTs. We did not evaluate the funding of RCTs because of its variability; besides, we observed empirically that most of RCTs were funded by pharmaceutical industries. This was similarly observed in the previous report of REPEC.[12] Also, the financial support from the industry can influence publication bias, trial data, and authorship.[26] Otherwise, Ranakawa et al describe that most RCTs registered in Sri Lanka Clinical Trials Registry were funded by researchers.[27]

Additionally, the influence of pharmaceutical industry could affect the diseases that most study. Most RCTs registered in REPEC were from oncology, infectology, rheumatology, pneumology, and endocrinology specialty. Also, lower respiratory infection, low back and

neck pain, sense organ diseases, skin diseases, and ischemic heart diseases are the most important burden of diseases in Peru.[28] There was no correlation between RCTs specialty and main burden diseases, similar reported in Iran.[29] Then, we suggest encouraging Peruvian research institutions and hospitals to develop and implement financial support to RCTs execution, in order to attend the main diseases in the country.

Publicly dissemination of RCTs' information among clinicians, researchers, and patients is an international statement.[30] Viergever et al describe small but significant improvements in the reporting of contact information, interventions, and outcomes in RCTs registered in ICTRP.[31] At the same time, Reveiz et al reported lack of methodological information in RCTs of seven international registries,[32] and Kosa et al reported the disagreement in methodological information between publication and registry.[33] Also, Fleminger et al describe the inaccuracy on completion status between Clinicaltrials.gov and the European registry.[34] REPEC's registries do not report methodological and intervention characteristics before 2011. Probably, this information is not publicly available because the Peruvian National Institute of Health saved it in a physical format. Furthermore, the requirements to register RCTs change throughout the time in Peru.

4.1 | Strengths and limitations

It is the first time that a study reports the WHO-standard items collected in REPEC and contextualized the tendency through modification and appearing of new regulations. We do not try to cover the quality of the design or conduct of RCTs.

The amount of information collected in the datasheets varied every year, mainly between 1995 and 2010, with incomplete data. To overcome this, we carried out a pilot test to standardize the data collection and reported all missing data in each variable. Also, most intervention variables are reported since their registration in 2011, so their percentages are biased.

5 | CONCLUSION

The REPEC had a quantitative and qualitative improvement since its creation in 1995. Although the quality of registries has improved substantially, its quantitative grow has stopped in 2008 and the quantity of registered RCTs has continually decreased in time. There is an influence of pharmaceutical companies in RCT registration. The majority of RCTs corresponds to controlled, randomized, parallel, double blind, and phase III. A few institutional review boards approved the majority of RCTs.

We recommend that others studies are necessary, focusing on the effect of funding source on the report of items and the need of RCTs according to the national health research priorities.

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COMPETING OF INTEREST

None.

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