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Scientometric measures of prospectively registered clinical trials over time: A comparison of IRCT and ClinicalTrials.gov

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Abstract

Background: Iranian Registry of Clinical Trials (IRCT) started as a primary registry in 2008. We examined the characteristics and scientometric measures of prospectively registered clinical trials in IRCT over time and compared them with that of ClinicalTrials.gov.

Methods: We selected eligible trial records between 2008 and 2016 from the IRCT database. We assessed their characteristics and the journal metrics of ensuing outputs over the study period and compared our findings with the corresponding information from ClinicalTrials.gov reported by Magdalena Zwierzyna et al. and a random sample of trials registered with this registry. We used the chi-square test for comparison of proportions and Mann-Whitney U test for comparison of medians. P-value <0.05 was considered statistically significant. Statistical analyses were performed using IBM SPSS Statistics V.22.

Results: 1751 prospectively registered clinical trials were eligible for analysis, of which 1526 (87%) had parallel-group design, 1541 (88%) reported to be randomized, 753 (43%) used double-blinding design, 485 (%27.7) had sample size more than 100, 1313 (75%) completed within a year, 1539 (87.9%) were single centered and 1529 (87.3%) exclusively used public money. Comparison with ClinicalTrials.gov showed that they are less likely to have multiple centers, funded by private sectors, continue beyond one year; and more likely to be randomized, double-blind and get published as a paper. The sample sizes were similar. Journal scientometric measures remained constant over the study period for both databases but were higher in ClinicalTrials.gov (median SJR=1.67, IQR=1.1-3.23) compared with IRCT (median SJR=0.58, IQR=0.34-0.91).

Conclusion: Our findings suggest that clinical trials registered in IRCT are predominantly investigator-initiated studies with acceptable methodological features and high publication rate albeit in journals with substantially lower scientometric measures compared with that of ClinicalTrials.gov. Journal metric indices remained constant despite an increase in the number of registrations in IRCT.

Keywords: Scientometric measures, Clinical trials, IRCT, Characteristics

Conflicts of Interest: *None declared*
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Introduction

Randomized clinical trials are the gold standard to assess preventive, therapeutic, diagnostic, or rehabilitative inter-

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↑What is "already known" in this topic:
Journal's scientometric indices represent the quality of papers it publishes. The number of registered trial studies in IRCT has risen steadily, however, it is not known if their quality is comparable to the trials conducted within the rest of the world.

→What this article adds:
Our findings suggest that clinical trials registered in IRCT are predominantly investigator initiated studies with acceptable methodological features and high publication rate albeit in journals with substantially lower scientometric measures compared with that of ClinicalTrials.gov. Journal metric indices remained constant despite increase in the number of registrations in IRCT.

ventions and constitute a foundation for evidence-based medicine (1). They play a critical role in evidence-based policy decision making, provided that they are high quality, transparent and discoverable and their results have been fully disclosed (2, 3). The design, conduct, and reporting of clinical trials have been under focus worldwide and some initiatives such as protocol registration have tried to increase transparency and availability of clinical trials' results (4).

The objective of clinical trial registration is to make key information of all clinical trials accessible to the public before they start recruiting, although retrospective registration is still allowed in most WHO primary registries (5, 6). It increases transparency in clinical trial conduct and reduces the chance of publication bias and selective reporting (7, 8). Clinical trial registration is now widely considered as an ethical and scientific responsibility (9) and has been included in the World Medical Association's 3rd Helsinki declaration since 2008 (10).

Iranian Registry of Clinical Trials (IRCT) was established as a primary registry in 2008. Its number of annual registrations has increased steadily since then to more than 3500 per year in 2018 and currently contains over 20000 trial records. However, it is not certain whether or not the quality of conducted trials has reciprocated this rapid quantitative growth, and the characteristics of registered trial protocols are comparable to that of global standards. Or, has this considerable increase in quantity come at the price of decline in quality? To examine this, we assessed the characteristics of the registered records and the journal metrics of resulted outputs over the study period and compared our findings with the corresponding information from ClinicalTrials.gov reported by Magdalena Zwierzyna et al. and a random sample of trials registered with this registry.

Methods

Data source

We used trial protocols registered in the Iranian Registry of Clinical Trials and ClinicalTrials.gov. IRCT is a primary registry in the WHO registry network developed and maintained by the Ministry of Health and Medical Education of Iran. It registers all trial protocols according to International Clinical Trial Registry Platform (ICTRP) guidelines. ClinicalTrials.gov is a Web-based resource maintained by the National Library of Medicine (NLM) at the National Institutes of Health (NIH) currently holding registrations from 320,080 research studies from 209 countries all over the world.

Search strategy

We selected prospectively registered trial protocols (date of registration approval on or before the date of recruitment) between 29th of October 2008 and 31st of December 2016 (Diagram 1) conducted in Iran, which had valid and complete registration dates. We extracted the characteristics of clinical trial protocols including registration date, expected recruitment start and end dates, gender of participants, purpose, funding source, health conditions studied, use of randomization or blinding methods, use of placebo, type of intervention, study design, study phase, number of recruitment centers and sample size. We categorized the condition studied using the ICD-10 coding system. If several ICD-10 codes were listed in this part, we only considered the first code.

We systematically assessed the publication status of the records by comprehensive searching of electronic databases, including PubMed, EMBASE, Google Scholar, Cochrane, Scopus and general Google search, up until 15th of February 2018. Our search terms included the IRCT registration number, the name of the corresponding author for scientific inquiries and the scientific title of the study. The corresponding authors for scientific inquiries of the study were also contacted via email to determine if the clinical trial has already been published. An independent search of electronic databases by a second investigator was conducted on a 10% random sample of the trial protocols to check if all resultant published papers have been retrieved.

We used the published results of the study conducted by Magdalena Zwierzyna et al. (11) that covered the period between 2005 and 2017 to compare the characteristics of registered clinical trials in IRCT with those of ClinicalTrials.gov. We reclassified funding data in Zwierzyna's paper into three major groups: industry (small and big pharma), public (NIH) and others. Furthermore, we selected and downloaded a random sample of 250 trial protocols registered in ClinicalTrials.gov. Our criteria for inclusion in the selection pool were completed interventional studies with cited results and a start date later than October 2008 and a completion date before 2017.

Scientometric Indicators

Journal metrics for the resultant published papers from both IRCT and ClinicalTrials.gov samples, including CiteScore, Source Normalized Impact per Paper (SNIP) and Scimago Journal Rank (SJR), were extracted over the study period from 2017 published Scopus journal metrics. CiteScore measures average citations received per document published in the serial in the past three years. SNIP and SJR measure weighted citations on subject field and prestige of the citing serial, respectively.

Data Analysis

We used descriptive statistics to summarize the general characteristics of prospectively registered clinical trials in IRCT. Categorical variables were reported as frequencies and percentages; continuous variables as medians and interquartile range (IQR). Three-year moving average was used to depict the trends of scientometric measures over the study period. We used the chi-square test for comparison of proportions and Mann-Whitney U test for comparison of medians. P-value <0.05 was considered statistically significant. Statistical analyses were performed using IBM SPSS Statistics V.22.

Results

A total number of 1751 prospectively registered clinical trials were eligible for analysis (Diagram 1), of which 87% had parallel-group design, 88% reported to be ran-

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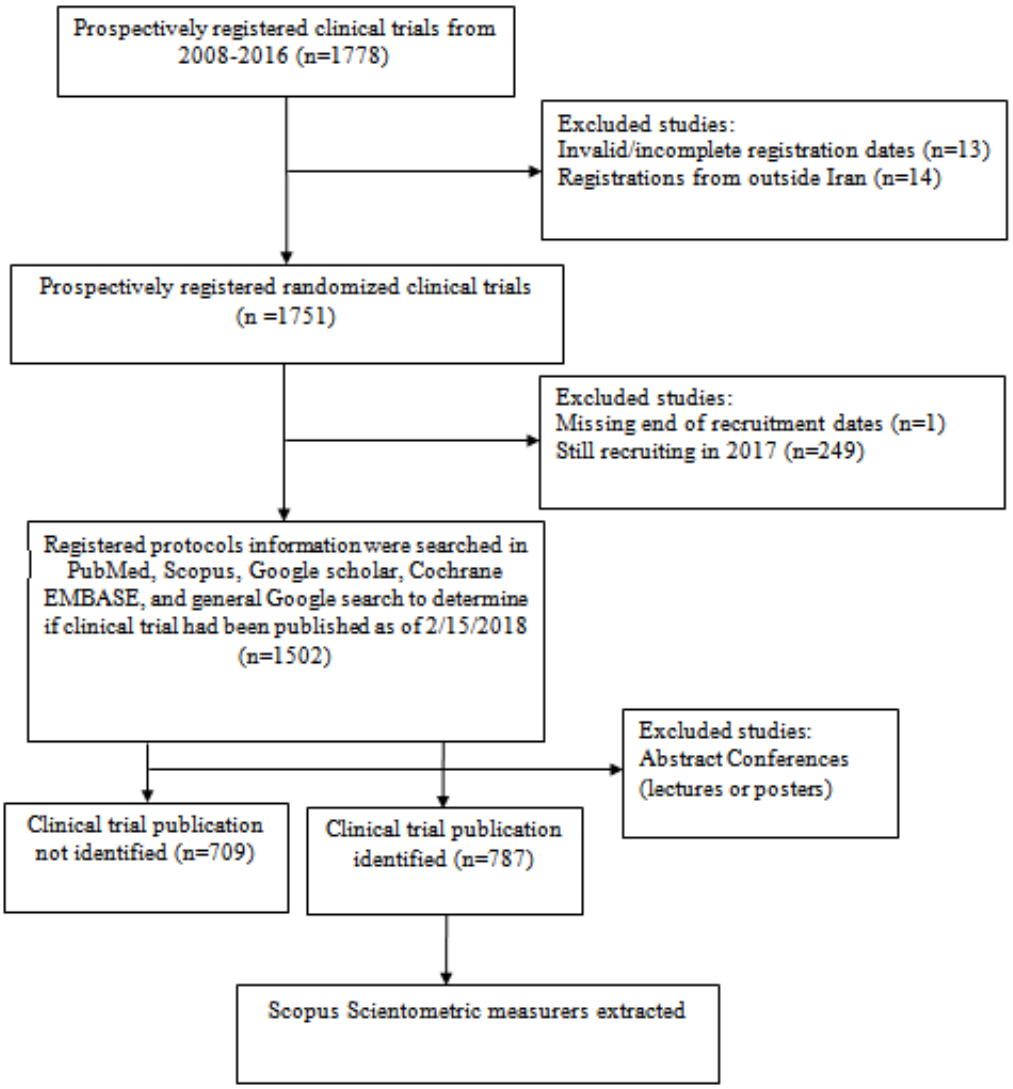

Diagram 1. Clinical trial inclusion flow chart

domized, 43% used double-blinding design, %27.7 had sample size more than 100, 75% completed within a year, 87.9% were single centered and 87.3% exclusively used public money (Tables 1 and 2).

Of the 119840 registered clinical trials in ClinicalTrials.gov, 62% was reported to be randomized, 37.6% used double-blinding design, %37.6 had sample size more than 100, 62.6% were single centered and 52.2% exclusively used industry funders. Comparison with ClinicalTrials.gov showed that trials registered in IRCT are less likely to have multiple centers, funded by private sectors, and take more than one year to complete, and more likely to be randomized, double-blind and get published as a paper. Median sample sizes were similar (Table 1).

The more frequently studied medical conditions in IRCT were mental and behavioral disorders with 12.3% trials, followed by diseases of the genitourinary system and endocrine, nutritional and metabolic diseases, whereas oncology was the most represented discipline in ClinicalTrials.gov with 29.1% of the trials, followed by infectious and cardiovascular diseases.

Of the phase II-IV clinical trials registered in IRCT, %47.7 were published in scientific journals while this figure for ClinicalTrials.gov has been reported to be about %30. The median CiteScore for IRCT was 1.44, IQR=0.88-2.22 that was half of the corresponding scientometric measure in ClinicalTrials.gov of 3.01, IQR=2.28-4.46. This was also true for both SNIP (median SNIP =0.83, IQR=0.59-1.01 versus 1.32, IQR=0.98-2) and SJR (median SJR=0.58, IQR=0.34-0.91 versus 1.67, IQR=1.1-3.23) in IRCT and ClinicalTrials.gov respectively (Table 1).

Trends of the three years moving average of median CiteScore, SNIP and SJR over the period of 2009 to 2015 in the published papers resulted from the registered trial protocols in IRCT and ClinicalTrials.gov showed that the

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Table 1. Comparison of characteristics of registered protocols in ClinicalTrials.gov [a] and IRCT

Characteristics	ClinicalTrials.gov (N=119,840)	IRCT (N=1751)	P-value
Randomization			<0.001 [b]
Non-randomized	41266 (34.4%)	44 (2.5%)	
Randomized	74313 (62.0%)	1541 (88%)	
N/A	0	166 (9.5%)	
Allocation missing	4261 (3.6%)	0	
Blinding			<0.001 [b]
Open label	64222 (53.6%)	578 (33%)	
Single blind	6383 (5.3%)	322 (18.4%)	
Double blind	45094 (37.6%)	753 (43%)	
Triple blind	0	98 (5.6%)	
Masking missing	4141 (3.5%)	0	
Study centers			<0.001 [b]
Multi-center	44775 (37.4%)	212 (12.1%)	
Single-center	75065 (62.6%)	1539 (87.9%)	
Median sample size (IQR) [f]	60 (26-157)	66 (45-100)	<0.001 [b]
<100	74780 (62.4%)	1247 (71.2%)	
≥100	45059 (37.6%)	485 (27.7%)	
Study duration (days) Median (IQR) [f]	701.0 (335-1,218)	177.5 (90-364)	-
Funding [f]			<0.001 [b]
Industry	62556 (52.2%)	37 (2.1%)	
Public	13541 (11.3%)	1529 (87.3%)	
Others	43741 (36.5%)	185 (10.6%)	
Purpose			<0.001 [b]
Treatment	94074 (78.5%)	1022 (58.4%)	
Prevention	10306 (8.6%)	360 (20.6%)	
Number of study groups			<0.001 [b]
Single group	42902 (35.8%)	146 (8.3%)	
Controlled group	76937 (64.2%)	1605 (91.7%)	
Phase II-IV trials published in scientific journal	8338 (29.9%) [d]	160 (47.7%) [e]	-
Scientometric measures			
CiteScore	3.01 (2.28-4.46)	1.44 (0.88-2.22)	<0.001 [c]
SNIP	1.32 (0.98-2)	0.83 (0.59-1.01)	<0.001 [c]
SJR	1.67 (1.1-3.23)	0.58 (0.34-0.91)	<0.001 [c]

[a] Data is reported by Magdalena Zwierzyna et al [b] P-values are calculated using chi squared test; [c] P-values are calculated using Mann-Whitney U test; [d] Of 27835 phase II-IV registered protocols in ClinicalTrials.gov; [e] Of 335 phase II-IV of registered protocols in IRCT; [f] missing values are less than 1.5% in IRCT

Journal scientometric measures remained constant over the study period for both databases (Fig. 1).

Table 2. Additional characteristics of prospectively registered clinical trials in IRCT between 2008 and 2017

Characteristics	All trials (N=1751)
	N (%)
Purpose	
Treatment	1022 (58.4%)
Prevention	360 (20.6%)
Supportive	229 (13.1%)
Basic sciences	13 (0.7%)
Diagnostic	24 (1.4%)
Health service research	49 (2.8%)
Screening	8 (0.5%)
Other	46 (2.6%)
Phase	
Phase 1 or 0	32 (1.8%)
Phase 2 or 1-2	280 (16%)
Phase 3 or 2-3	472 (27%)
Phase 4	15 (0.9%)
N/A	951 (54.3%)
Bioequivalence	1 (0.1%)
Placebo	
Not used	1061 (60.6%)
Used	690 (39.4%)
Trial design	
Single group	146 (8.3%)
Parallel group	1526 (87.2%)
Crossover	53 (3.0%)
Factorial	11 (0.6%)
Other	15 (0.9%)

Discussion

We found that prospectively registered clinical trials in IRCT within the period of 2008-2017 are usually single centered and investigator-initiated studies which are mostly completed in less than a year and sponsored by publicly

Table 2. Ctd

Characteristics	All trials (N=1751)
	N (%)
Number of study groups	
1.00	146 (8.3%)
≥ 2.00	1605 (91.7%)
Type of intervention	
Treatment - Drugs	1550 (41.5%)
Treatment - Other	255 (6.8%)
Treatment - Devices	46 (1.2%)
Treatment - Surgery	75 (2.0%)
Prevention	410 (11.0%)
Rehabilitation	145 (3.9%)
Placebo	418 (11.2%)
Lifestyle	114 (3.1%)
Early detection	16 (0.4%)
Diagnosis	34 (0.9%)
Behavior	128 (3.4%)
N/A	146 (3.9%)
Missing	8 (0.2 %)
Other	386 (10.4%)
Gender of the study population	
Female	440 (25.1%)
Male	86 (4.9%)
Both	1224 (69.9%)
Missing	1 (0.1%)

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Fig. 1. Trends of three year moving average of median CiteScore, SNIP and SJR over the period of 2009 to 2015 in journals publishing papers resulted from the trial protocols registered in IRCT and ClinicalTrials.gov

funded universities. In contrast, trials registered with ClinicalTrials.gov are more likely to have multiple centres, funded by private sectors and take more than a year to complete. The journal scientometric measures for the published papers in IRCT were generally much lower than the figures for ClinicalTrials.gov with CiteScore value being half and SJR third the corresponding figure in ClinicalTrials.gov. In both data sources, however, they remained constant over the study period.

The observed differences in the characteristics of registered trials in IRCT and ClinicalTrials.gov could be partly explained by their source of funding (11). Following the 1985 integration of medical education into the National Health Service of Iran, there was a rapid increase in the number of public universities and postgraduate students over the decade after, resulting in a surge in the number of investigator-initiated trials (12). The number of international pharmaceutical industry-sponsored trials, however, has been limited due to sanctions and the domestic pharmaceutical companies have only recently started contributing substantially to this area. Therefore, the bulk of trials registered in IRCT are investigator-initiated studies funded by the public sector.

On the other hand, the median sample size is similar in both IRCT and ClinicalTrials.gov registered trials, and the publication rate is even higher for IRCT registered trial protocols (47% versus 30%). We believe, therefore, that the scale of the study alone is unlikely to explain the low

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journal metrics.

Our data showed that the IRCT registered trials are more likely to be randomized (88% vs. 62%) and double-blind (43% vs. 37.6%) compared with ClinicalTrials.gov. This suggests, on the face of it, that IRCT registered trials are conducted by researchers that are familiar with trial methodologies. However, low scientometric measures in IRCT registered trials (Table 1) indicate that this hasn't been enough for high ranking journals to publish their results. Given that the novelty of the subject besides sound methodology plays an important role in the acceptance of a paper in a high ranking journal, we believe this to be an important contributing factor for low journal metrics of IRCT registered trials.

The authors believe that the reason behind selecting subject matters with a lower degree of novelty by academic staff at publicly funded universities of Iran is the policy of excessive pressure to increase research paper production. For example, asking master's degree postgraduate students to publish a paper as a condition for graduation (13), where the resources are inadequate, could negatively impact the quality of the research conducted. Review of the content of the registered trial protocols showed that, in some extreme cases, healthcare and clinical audit studies might be transformed into trial lookalikes by choosing a control group and comparing the outcomes in the two groups. Audit studies by themselves are valuable tools for improving the quality of clinical and healthcare services; however, they could be misused to create studies with questionable scientific value and ethical justifications and lack of equipoise.

We found that journal metric indices did not change over the study period. This could be interpreted in both ways. On one hand, this shows that no effective intervention has been implemented over the study period to improve the quality of the trials. On the other hand, this could be a positive sign showing that despite a substantial increase in the number of registrations in IRCT (14) the increase has not come at the price of further losing quality.

Our study had some limitations. CiteScore, the journal metrics index, of the resultant publication was used as an indication for the overall quality of the study. This might not always be true. Furthermore, this may vary across disciplines and citations are not of equal value everywhere. We used the Source Normalized Impact per Paper (SNIP) and Scimago Journal Ranking (SJR) to account for this. Some trials conducted in Iran might not be registered in IRCT; however, we believe the mainstream trials conducted in Iran are sufficiently represented particularly in the later study period where the registration coverage has greatly improved because of the complete integration IRCT registration in the country's medical research management system.

The number of missing values in IRCT was very low (less than 1.5%) for each of the variables used in the analysis partly because most of the collected variables are designated as "required" at the time of data entry. Furthermore, the entries are reviewed by IRCT officers upon submission and missing data are normally detected and affected records are returned to the registrant for completion.

Our findings suggest that the quality of the trials registered in IRCT is not acceptable compared with the global standard and therefore is in need of urgent attention. We believe clinical trials with no novelty in their subject matters should be discouraged, and in extreme cases, trial lookalikes should be detected and stopped. In the process of approving a trial subject, enough attention should be paid to the scientific values of the study. Thorough literature review and if necessary, systematic reviews should be conducted first before choosing a subject for a trial study. Institutional review boards and ethics committees should make sure that clinical equipoise has been demonstrated before allowing the research team to embark on the study. It is also necessary to review some of the policies that may contribute to the current situation. Implementing global standards (ICH GCP) (15) in design (SPIRIT) (16), conduct and reporting (CONSORT) (17) of trials could be another important step in improving the quality. However, this is not a task only for those governing researches such as research councils or ethics committees, but it is the responsibility of all members of the research community to increase the awareness about the problem and work towards improving the quality of conducted trials.

Conclusion

Our findings suggest that clinical trials registered in IRCT are predominantly investigator-initiated studies with acceptable methodological features and high publication rate albeit in journals with substantially lower scientometric measures compared with that of ClinicalTrials.gov. Journal metric indices remained constant despite an increase in the number of registrations in IRCT.

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Conflict of Interests

The authors declare that they have no competing interests.

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