Title: Execution time determines the outcome of the multicenter randomized controlled trials

Yongjun Jiang^{1#}, Qijin Zhai^{1,2#}, Zheng Dai¹, Xiaomeng Xu¹, Xiaohui Xu¹, Zhuoyu Wen¹ and Xinfeng Liu^{1*}

1, Department of Neurology, Jinling Hospital, Medical School of Nanjing University, 305 Zhongshan East Road, Nanjing 210002, China

2, Department of Neurology, Huai'an Hospital affiliated of Xuzhou Medical College and The Second People's Hospital of Huai'an, 62 Huaihai Road South, Huai'an 223002, China

# These authors contributed equally to this manuscript

*To be addressed: Xinfeng Liu, Department of Neurology, Jinling Hospital, Medical School of Nanjing University, 305 Zhongshan East Road, Nanjing 210002, China

Tel. +86 25 8086 0124

Fax: +86 25 8466 4563

E-mail: xfliu2@vip.163.com

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Abstract

Objectives Multicenter randomized controlled trials are the core of evidence-based medicine. Our study aimed to investigate the key factor which determined the outcome of the multicenter randomized controlled trials.

Methods We searched publications in PubMed for multicenter randomized controlled trials reporting primary data on treating and preventing cardiovascular diseases circulation area. The data were extracted from the including trials and used for analysis.

Results A total of 1075 trials for treating and preventing cardiovascular diseases were included, of which 979 were involved in the heart diseases and 96 involved in stroke. The execution time significantly contributed to the outcome of trials with shorter time related to significant outcome. However, the numbers of participated centers and their locations and participants had no effect on the outcome of trials. Moreover, the number of centers showed no significant relationship with execution time.

Conclusions Execution time but not centers or participants contributed to the outcome of multicenter randomized controlled trials.

Keywords: clinical trials; multicenter; randomized; circulation; coronary artery disease; stroke

1. Introduction

Evidence-based medicine has been regarded as the gold standard of clinical practice[1]. The quality of evidence-based medicine relies heavily on the quality of the evidence on which its findings are based. Multicenter, randomized, controlled trials (RCTs) represent the top level of evidence according to the U.S. Preventive Services Task Force (USPSTF)[2]. The guidelines might be amended quickly after the publication of RCTs. Therefore, thousands of multicenter RCTs have been performed during the last two decades[3].

Multicenter RCTs have become more and more expensive in recent years, even costing as much as billions of US dollars[4]. RCTs are also time-consuming and usually require approximately 10 years to complete[5]. Hence, how to prepare, organize and handle multicenter RCTs properly has been a focus of researchers' investigations. In addition to the interventions tested in the trials, many other issues have significantly contributed to trials' final outcomes. Among them, the following two essential and fundamental issues often raise concerns among both investigators and sponsors: how many centers should participate in an RCT, and how long should the RCT last?

The number of participating centers may vary from 2[6] to more than 1000[4] based on the numbers of centers included in previous multicenter RCTs. The actual number depends primarily on the subjective judgment of the sponsors, as well as the relationship between either the sponsors or the principal investigators with other investigators, as well as the trial's budget. Theoretically, more centers mean more participants, faster recruitment rates and more solid data; however, some investigators

believe that more centers may cause trial failure due to the enormous differences in both ethical and routine clinical practices among different centers [7]. Therefore, journals and readers prefer the inclusion of more centers, whereas investigators may choose fewer centers. Whether the number of participating centers contributes to the outcomes of trials remains unknown.

Some investigators have noticed that execution time plays a fundamental role in the outcomes of multicenter RCTs[8, 9]. Recently, multicenter RCTs regarding the use of stent-based retrievers in the management of acute stroke have experienced a dramatic change from failure to success. Irrespective of other issues, the execution times of the successful trials (MR CLEAN and ESCAPE [8, 9]) were shorter than those of the trials that failed (IMS III[10] and MR RESCUE[11]). However, this finding was based on personal observations as opposed to data.

In the present study, we searched previous publications in cardiology and analyzed the issues determining the outcomes of the multicenter RCTs.

2. Results

2.1 The basic characteristics of the included clinical trials

A total of 1075 multicenter RCTs were included in the analysis. The basic characteristics are presented in Table 1. Briefly, 603 multicenter RCTs ended with a significant outcome. A total of 978 trials pertained to cardiology, and 97 pertained to stroke. Given the tremendous advancements in intravascular interventions, a total of 383 multicenter RCTs investigated the therapeutic effects of different non-drug

therapies; most focused on endovascular interventions. The earliest multicenter RCT was published in 1988, and the annual ratio of significant outcomes is presented in Fig. 1B. The trial with the largest number of centers included 1393 centers. One multicenter RCT completed subject recruitment in 2 months, whereas another trial required 135 months for subject recruitment. The largest RCT enrolled 68808 participants.

2.2 Execution time determined the outcomes of the multicenter RCTs

To determine the factors affecting the outcomes of the multicenter RCTs, we used logistic-regression analyses. As demonstrated in Table 2, execution time contributed significantly to the outcomes of the multicenter RCTs. A shorter time was indicative of a greater chance of a significant outcome ($P<0.05$, OR 0.979, 95% CI 0.971-0.988). There was a significant difference between the number of participants included in the studies with significant and non-significant outcomes ($P=0.01$); the OR was 1.000 (95% CI, 1.000-1.000). However, the number of participants per month contributed significantly to the outcomes of the multicenter RCTs ($P<0.05$, OR 0.998, 95% CI 0.996-1.000).

Another important factor was the numbers of participating centers. However, the numbers of centers were not significantly related to the outcomes of the multicenter RCTs (Fig. 1A, $P>0.05$). The number of participants per center also had no effect on the outcomes of the multicenter RCTs ($P>0.05$, OR 0.998, 95% CI 0.996-1.0). Furthermore, we observed that the recruitment rate (participants per center per month) had no

significant effect on the outcomes of the multicenter RCTs ($P>0.05$, OR 1.028, 95% CI 0.989-1.070).

3. Discussion

In the present study, we investigated the issues that may have influenced the outcomes of the multicenter RCTs pertaining to cardiology. Our data demonstrated that execution time as opposed to either participants or included centers contributed to the outcomes of the multicenter RCTs. This was the first evidence regarding the role played by execution time in the outcomes of multicenter RCTs.

We selected the multicenter RCTs involved in management of cardiovascular disease based on the following considerations: first, cardiovascular disease is the leading cause of mortality and morbidity worldwide[12]. Therefore, many therapeutic tools have been developed, and multicenter RCTs, undertaken to evaluate both their efficiency and their safety. Unlike other areas such as neuroprotection, the clinical trials of which all failed[13], the multicenter RCTs pertaining to cardiology have exhibited both significant and non-significant outcomes. Therefore, these studies are an opportunity to analyze various issues. Finally, according to <https://www.clinicaltrials.gov>, many multicenter RCTs are ongoing, and many others are being prepared. These RCTs require guidelines to avoid unnecessary waste.

Our data demonstrated that execution time is associated with the outcomes of multicenter RCTs, which are more likely to have a successful outcome if they are completed quickly. This finding was consistent with those of previous studies. As

mentioned above, the investigators conducted the trials to test the efficiency of bridge treatments for acute stroke in similar cohorts within the same time interval. In the MR CLEAN trial, it took only 40 months to recruit participants[8], whereas the IMS III investigators required 68 months to complete recruitment[10]. The MR CLEAN trial was successful, whereas the IMS III trial failed. Our findings are indicative of the need to shorten the execution time as much as possible.

Another important finding was that the number of participating centers did not influence the outcomes of the multicenter RCTs. This finding was inconsistent with traditional opinions. The investigators involved in previous studies may have intentionally included fewer centers to achieve a significant outcome. In our analysis, some of the studies included only two centers[14]. Such decisions may have been sources of bias; therefore, the results of these trials should be interpreted with caution.

In the present analysis, we observed no relationship between the numbers of participating centers on the outcome of the multicenter RCTs, which may alleviate the concerns of other investigators. Moreover, we also observed that the numbers of participating centers had no effect on execution time. This finding resolved the misunderstanding that the inclusion of more centers may decrease execution time.

Investigators cannot simply increase the number of centers to accelerate the RCTs.

The locations of the centers also raised concerns, as different countries have different policies and clinical practices. However, we observed that the completion of trials involving either a single country or multiple countries did not influence the outcomes of the multicenter RCTs in question. If possible, the inclusion of more centers from

different countries is encouraged for future multicenter RCTs.

There were several limitations to this analysis that should be addressed when interpreting its results. We included only publications in cardiology. However, there have been several multicenter RCTs pertaining to other areas of medicine and scientific research. Furthermore, we included only published studies. There were several studies that were not published. If the results of these studies were combined with our data, it may provide us with new insights into multicenter RCTs. However, the unpublished studies lacked the information necessary for inclusion in our analysis, particularly the older studies. In recent years, registered systems such as clinicaltrials.gov have provided researchers with an opportunity to investigate these unpublished studies. However, many registered trials do not recruit subjects. If we added these planned trials to our analysis, it may result in bias. Therefore, we urge the investigators involved in these trials to update said trials' information to determine if they may be published and included in future analyses.

4. Conclusion

In conclusion, execution time contributed significantly to the outcomes of the multicenter RCTs pertaining to cardiology.

5. Methods

5.1 Search strategy

The search was conducted using PubMed, and the final search was performed on March 15, 2015. The search terms were (("Stroke"[title/abstract]) OR ("Heart") OR ("Coronary artery")) AND ("Multicenter Study" AND "Randomized Controlled Trial") AND "humans" AND "English."

The search returned 3910 publications. Both the title and abstract were subsequently checked by two independent researchers (Xm. X. and Xx. X.) to determine whether the publication pertained to cardiovascular disease management. The full texts and supplementary materials attached to the publications were also checked to collect all necessary information pertaining to the articles in question. If these items were missing, related materials, including the publications of both study design and rationale, the registered information from <https://www.clinicaltrials.gov>, <http://www.isrctn.com> and additional materials such as editorial comments and responses, were also reviewed. If the publications did not provide accurate information, the item was listed as missing. If any disagreements between the two researchers occurred, a third researcher (Y. J.) participated in the review process and made a judgment.

If a study used the same cohort but was used to publish separate publications, it was recognized as a single study in the analysis. Studies without any interventions were excluded from the analysis. The subgroup analysis, the pool analysis and the long-term follow up analysis were also excluded.

5.2 The definitions of the terms in the analysis

We extracted the information from the included publications regarding the subject area

(stroke or cardiology), the intervention type (drug or non-drug), the outcome (significant or non-significant), the numbers of participating centers, the numbers of participants, the time of publication, and whether the study in question was a multinational study.

The subject area to which the publication belonged was defined according to the participants' diseases. When a publication focused on the risk factors for a particular disease, the subject area was based on the study's primary outcome.

All interventions listed in the included RCT were grouped as either drug or non-drug interventions. Drug treatment included both chemical and biological agents such as stem cells administered orally, intravenously, or via other means. Non-drug treatment included all other forms of treatment except drug treatment.

An outcome was considered significant if there was a significant difference in the primary outcome between the intervention group and the control group. The non-inferiority design was determined according to the primary outcome. When the primary outcome was safety, the non-inferiority was defined as significant; when the primary outcome was efficiency, the non-inferiority was defined as a non-significant outcome. If there were more than two groups included in the trial, all groups except the control group were recognized as the intervention group. If the two groups were both intervention groups, the group that used the earlier form of intervention was recognized as the control group.

Participating centers were defined as those enrolling study subjects whose data were used in the final analysis. The number of participants was recorded as the number of

subjects included in the statistical analysis. The publication time was the formal date, other than the online date of publication. As for recent publications without a formal date, the online date was defined as the publication time.

The execution time was defined as follows: when the publication provided definitive dates, the duration was calculated as the final date minus the start date. If the rest days were more than 15 (including 15), the execution time was another month; if the rest days were less than 15, it was ignored. When the publication provided only the month, the duration was calculated as the final month minus the start month plus one. When the trial was stopped early, the stop date was defined as the final date.

5.3 Statistical analysis

Parameter data were expressed as means $\pm$ standard deviations and were analyzed using the unpaired *t*-test. Differences between proportions were assessed via either the χ^2 test or the Fisher exact test. The number of participating centers, the execution time, whether the study was multinational, the numbers of participants per center, the numbers of participants per month, the numbers of participants per center per month and the publication year were evaluated via logistic-regression analyses. $P < 0.05$ was considered statistically significant. All analyses were completed using SPSS 13.0 software.

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No.

7. Author contributions

Y. Jiang design the study and prepared the draft; Q. Zhai did the statistical analysis and prepared part of the draft; XX. Xu, Z. Wen and XH. Xu collected the data; X. Liu revised and approved the manuscript.

8. Competing financial interest

No conflict of interest.

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Table 1 Basic characteristic of included studies

	Outcome		<i>P</i>
	Significant	Non-significant	
Area			>0.1
Cardiology	557	421	
Stroke	56	41	
Intervention			>0.1
Drug	387	314	
Non drug	206	158	
Participant centers (Mean, range)	89.4 (2-1315)	130.6 (2-1393)	<0.1
Execution time (Mean, range, months)	28.5 (2-123)	36.9 (2-135)	<0.1
Year	1988-2015	1989-2015	
Countries*			>0.1
Single	222	168	
Multi	344	287	
Participants	2231.3±5587.0	3005.2±5391.9	<0.05
Participants per center	53.9±136.7	65.7±152.4	0.058
Participants per month	97.6±176.2	116.1±221.5	<0.05
Participants per center per month	2.8±7.48	2.4±7.0	>0.1

* Some publications missed this information

Table 2 Logistic regression analysis

	B	SE	Wald	Odds ratio (95% CI)	<i>P</i>
Participant centers	-0.001	0.001	3.395	0.999 (0.998-1.000)	0.065
Execution time	-0.021	0.004	22.688	0.979 (0.971-0.988)	<0.05*
Year	-	-	55.599		<0.05*
Multi Countries	0.102	0.164	0.388	1.107 (0.804-1.525)	>0.05
Participants	0.000	0.000	6.556	1.000 (1.000-1.000)	0.01
Participants per center	-0.002	0.001	3.024	0.998 (0.996-1.000)	>0.05
Participants per month	-0.002	0.001	5.877	0.998 (0.996-1.000)	<0.05*
Participants per center per month	0.028	0.020	1.933	1.028 (0.989-1.070)	>0.05

Figure legend

Figure 1 (A) No significant relationship between execution time and center numbers.

(B) The ratio of multicenter RCTs with significant outcome from 1988 to 2015.