**1.2 Articles investigated** In the EKAT 2009, duplicate publications are likely to appear in the same structured abstract, since articles reporting the same RCT are collected in the same abstract. Therefore, we focused on 53 structured abstracts that refer to multiple articles, whereas the remaining 267 structured abstracts refer to only one article. In the 53 structured abstracts, 118 articles are reported and these articles can be categorized into six types (Table 2).

**Table 2 Classification of types of 118 articles referred to by 53 structured abstracts in the EKAT 2009**

| Types of structured abstracts | Number of articles |
|---|---|
| Original papers* | 37 (in 24 structured abstracts) |
| Quasi-original papers** | 13 (in 6 structured abstracts) |
| Conference papers, abstracts, and posters | 30 |
| Secondary publications | 28 |
| Advertisements | 7 |
| Reports | 3 |
| Total | 118 |

*: Abstracts follow the IMRAD (introduction, materials and methods, results, and discussion) format; **: abstrats do not follow the IMRAD format. EKAT: Evidence Reports of Kampo Treatment.

According to the URM[1], original papers that follow preliminary reports displayed at professional meetings, such as abstracts and posters, are not regarded as duplicate publications. So we checked 37 original papers and 13 quasi-original papers (totally 50) to detect duplication. We excluded articles other than original and quasi-original papers from this research.

Quasi-original papers are papers based on original research but not described according to the IMRAD (introduction, materials and methods, results, and discussion) format, which is generally regarded as a standard format for scientific papers.

**1.3 Identification of duplicate publications** The URM[1] stipulates that an article that overlaps with any article that is already published should inform readers on the title page that it has been published in whole or in part and should include cross-references to related articles. Taking into account the description in the URM, we considered what criteria to use to identify an article as duplicate publication: hypothesis and results are the same; authors are in common; no description as secondary publication; no cross-reference to related articles.

## 2 Results

First, we screened 50 original and quasi-original papers according to the criteria established (Table 3), and we suspected 20 articles of being duplicate publication. Second, we checked the 20 articles and excluded 9 articles from the duplicate publication group for the following reasons: references to the related articles were described although they were not stated clearly; results were similar but not judged as being the same. Finally, we identified 11 articles in 8 structured abstracts appeared in the EKAT 2009 as duplicate publication (Figure 1).

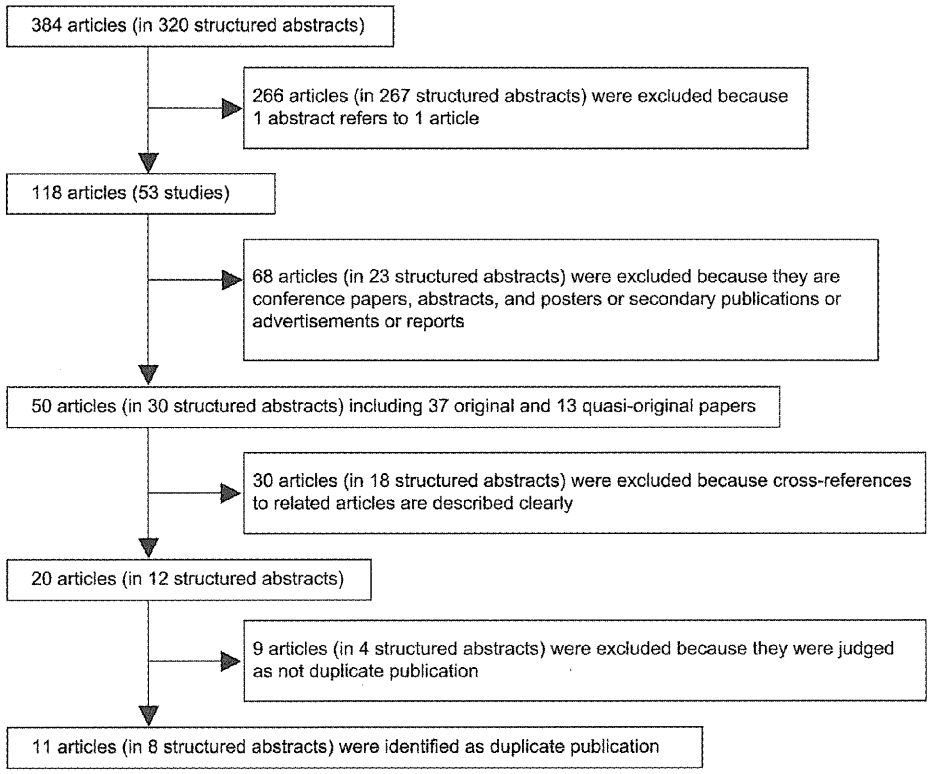


**Figure 1 Research process and results**

To analyze the practice of duplicate publication, we defined five patterns of duplication by using the classification proposed by Von Elm *et al*[8] (Table 3).

We discovered five patterns among 11 duplicate articles (Table 4): reproducing an already published article with the same sample data and results (Pattern 1, $n=3$); adding new sample data with the same results (Pattern 2, $n=1$); reporting part of the preliminary sample with the same results (Pattern 3, $n=1$); translating an original article into another language (Pattens 4A and 4B, $n=6$).

**Table 3 Duplicate publication patterns**

| Pattern No. | Definitions |
|---|---|
| 1 | Same sample and same results |
| 2 | Increased sample and same results |
| 3 | Decreased sample and same results |
| 4A | Translation from Japanese original to English |
| 4B | Translation from English original to Japanese |

**Table 4 Duplicate publications in the EKAT 2009**

| Study | Main/Duplicate | Article type | Publication year | Language | Indexed in MEDLINE | Indexed in Web of Science | First author | Duplicate pattern* |
|---|---|---|---|---|---|---|---|---|
| A | Main | Original | 1990 | Japanese | — | — | | |
| | Duplicate | Original | 1992 | English | — | — | Changed | 4A |
| B | Main | Original | 1993 | Japanese | — | — | | |
| | Duplicate | Original | 1993 | Japanese | — | — | Same | 2 |
| C | Main | Original | 2004 | English | √ | √ | | |
| | Duplicate 1 | Original | 2004 | English | — | — | Same | 1 |
| | Duplicate 2 | Review | 2007 | Japanese | — | — | Same | 4B |
| | Duplicate | Review | 2007 | English | — | — | Same | 1 |
| D | Main | Quasi-original | 2003 | Japanese | — | — | | |
| | Duplicate | Original | 2006 | English | √ | √ | Same | 4A |
| E | Main | Original | 1998 | English | — | — | | |
| | Duplicate 1 | Original | 1998 | Japanese | — | — | Changed | 4B |
| | Duplicate 2 | Review | 1999 | Japanese | — | — | Changed | 3 |
| F | Main | Original | 1998 | Japanese | — | — | | |
| | Duplicate | Original | 2003 | English | √ | √ | Same | 4A |
| G | Main | Original | 2002 | Japanese | — | — | | |
| | Duplicate | Quasi-original | 2002 | Japanese | — | — | Same | 1 |
| H | Main | Original | 2002 | Japanese | — | — | | |
| | Duplicate | Original | 2003 | English | √ | √ | Changed | 4A |

*: Duplicate patterns are shown in Table 3. EKAT: Evidence Reports of Kampo Treatment.

Study E (Table 4) authors in the main article were divided into two groups, each group wrote Duplicate 1 and Duplicate 2, respectively. Although the duplicate article of Study G (Table 4) cited the main article, we identified it as duplicate, because it cited the main article when it was in press. The authors seemed to submit the same results simultaneously to two journals.

Three review articles are in the list of duplicate publications (Table 4). Publishing overlapping information in review articles is regarded as appropriate; however, these 3 articles do not have a cross-reference to related articles.

## 3 Discussion

To our knowledge, this is the first comprehensive research to analyze the practice of duplicate publication performed in the field of Kampo in Japan. The existence of duplicate publications was revealed during the compiling process of the EKAT 2009. The EKAT 2009 lists related RCT articles in each structured abstract, which assists in finding articles that report the same results.

Eleven duplicate publications were found in the EKAT 2009 showing five patterns (Table 4) that seem to reflect the relation between publishing behavior of Japanese Kampo researchers and the practice of duplicate publication: whereby the authors complete a previous article and submit it to a more prestigious journal, especially a journal written in English (Patterns 1 and 4A); members of the same project publish articles separately (Pattern 3); translate an original English article for Japanese physicians without referring to the original (Patterns 1 and 4B).

Many Japanese researchers seem not to be aware of the problematic aspects of duplicate publication and submit overlapping manuscripts to increase the number of papers. Or some graduate students take their university's in-house journal as a way of publishing their manuscript to obtain their degree. After obtaining the degree, they write a complete paper and submit to a prestigious journal without citing the previously published paper.

In the field of Kampo, during the process of disseminating drug information to clinicians, original papers are sometimes rewritten in a plain and easy-to-understand way, or pharmaceutical

companies include already reported experimental data in articles in their publications. Attention should be paid to duplicate publication in such cases.

It is important to take account of the tendency that the distinction between clinical research and clinical practice is vague among Japanese physicians[9]. Articles dealing with clinical trials are sometimes regarded as reports on clinical practice, not as research papers. Some physicians would not care about publication ethics when writing and reading such articles and quote them without cross-references. This would be partly because that the widely used Japanese word "chiken" (治验) has two different meanings, that is, "clinical trials", which are conducted to obtain data for drug registration, and "clinical experiences".

Duplicate publication has a negative influence on science and publishing communities regarding issues concerning copyright, cost-effective use of resources, and ethical conduct. Some journal editors publish the retraction of a published article if it turns out to be duplicated. Bibliographic databases, such as PubMed (MEDLINE) and Ichushi-Web (Japan Medical Abstract Society), prepare tags that indicate citations as "retracted" or "duplicate publication." The URM also comments on issuing a notice of duplicate publication.

Editor and publisher associations also have prepared guidelines for duplicate publication. The Committee on Publication Ethics (COPE), which was founded by medical journal editors in 1997 and has been concerned with the integrity of peer-reviewed publications in biomedicine, collects case reports of duplicate publication on its website and provides flowcharts for editors to follow when they suspect duplicate publication. COPE also requires editors to take action against authors of duplicate articles. Some medical editor or writer associations, such as the World Association of Medical Editors (WAME), host open forums or meetings for exchanging ideas on duplicate publication.

In the Asian-Pacific region, the Asia Pacific Association of Medical Journal Editors (APAME) was established in May 2008 with the support of the Korean Association of Medical Journal Editors (KAMJE). In the first meeting of the APAME, KAMJE's educational activities for publication ethics including duplicate publication were reported[10].

According to the COPE flow charts and other standard rules for publication ethics, we might have to tell the editors about the existence of duplicate publications in their journals. But considering the lack of awareness of duplicate publication among Japanese researchers, we also have to provide opportunities for researchers to develop awareness of publication ethics. The Japanese Association of Medical Journal Editors (JAMJE) was inaugurated in August 2008. In the second meeting of JAMJE, duplicate publication cases were reported. Such presentations are required to raise the awareness of duplicate publication among medical researchers.

In this study, we analyzed the practice of duplicate publication among Japanese researchers in the field of Kampo. Cases in other fields and countries have already been investigated, and measures to detect duplicate publications were considered[11, 12]. Our next challenge is to extend our results to a more comprehensive and generalized understanding by comparing related research and increasing the sample size.

## 4 Acknowledgments

We wish to thank Dr. Tetsuro Okabe (Chair, Task Force of Evidence Reports of The Special Committee of EBM, JSOM) and Task Force members for their advice and cooperation. We are also grateful to the reviewers of the *Journal of Chinese Integrative Medicine* for their helpful comments on earlier manuscripts of this paper.

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# 日本传统汉方医学文献的重复发表案例

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**目的**:文献的重复发表对于科学及出版业都有不利的影响。在整理日本东洋医学会循证医学特别委员会出版的汉方治疗证据报告(Evidence Reports of Kampo Treatment,EKAT)2009 的过程中,我们发现了一些重复发表的文献案例。因此,我们检查了所有 EKAT 2009 中的文献并分析了重复发表文献是如何产生的。

**方法**:EKAT 2009 中共有 320 个随机对照试验研究的结构式摘要。我们检查了这 320 个摘要所参考的 384 篇文献,并根据如下标准定义重复发表文献:假说及结果雷同,作者一致,没有说明为二次出版文献,没有交叉引用相关文献。

**结果**:我们最终确认在 EKAT 2009 中共有 11 篇重复发表文献。这些重复发表文献可以分为以下四类:与已发表文献的样本数据及结果完全雷同($n$=3);添加了新的样本数据,但结果与已发表文献雷同($n$=1);报告前期已发表文献的一部分样本数据,但结果雷同($n$=1);将已发表文献翻译为另外一种语言再次发表($n$=6)。

**结论**:EKAT 2009 中的 11 篇重复发表文献有四种不同形式,这四种形式反映了日本汉方医学研究领域的研究者发表重复文献的主要行为模式,即完善之前已发表的文献投稿至更好的杂志或是将原来英文发表的文献翻译为日文再次发表。为了提高研究者们对于重复发表的认识程度,应该对其进行更多的出版道德普及。

**关键词**:医学,汉方;文献;科学上不正当行为

Sawata et al. Trials 2011, 12:96
http://www.trialsjournal.com/content/12/1/96

TRIALS

RESEARCH Open Access

# Limited accessibility to designs and results of Japanese large-scale clinical trials for cardiovascular diseases

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**Abstract**

**Background:** Clinical evidence is important for improving the treatment of patients by health care providers. In the study of cardiovascular diseases, large-scale clinical trials involving thousands of participants are required to evaluate the risks of cardiac events and/or death. The problems encountered in conducting the Japanese Acute Myocardial Infarction Prospective (JAMP) study highlighted the difficulties involved in obtaining the financial and infrastructural resources necessary for conducting large-scale clinical trials. The objectives of the current study were: 1) to clarify the current funding and infrastructural environment surrounding large-scale clinical trials in cardiovascular and metabolic diseases in Japan, and 2) to find ways to improve the environment surrounding clinical trials in Japan more generally.

**Methods:** We examined clinical trials examining cardiovascular diseases that evaluated true endpoints and involved 300 or more participants using Pub-Med, Ichushi (by the Japan Medical Abstracts Society, a non-profit organization), websites of related medical societies, the University Hospital Medical Information Network (UMIN) Clinical Trials Registry, and clinicaltrials.gov at three points in time: 30 November, 2004, 25 February, 2007 and 25 July, 2009.

**Results:** We found a total of 152 trials that met our criteria for 'large-scale clinical trials' examining cardiovascular diseases in Japan. Of these, 72.4% were randomized controlled trials (RCTs). Of 152 trials, 9.2% of the trials examined more than 10,000 participants, and 42.8% examined between 1,000 and 10,000 participants. The number of large-scale clinical trials markedly increased from 2001 to 2004, but suddenly decreased in 2007, then began to increase again. Ischemic heart disease (39.5%) was the most common target disease. Most of the larger-scale trials were funded by private organizations such as pharmaceutical companies. The designs and results of 13 trials were not disclosed.

**Conclusions:** To improve the quality of clinical trials, all sponsors should register trials and disclose the funding sources before the enrolment of participants, and publish their results after the completion of each study.

## Background

Large numbers of clinical and non-clinical investigations are required to obtain evidence to improve the treatment of patients. This evidence can benefit the medical practice of health care providers by informing treatment guidelines and providing the rationale on which to make treatment decisions.

Clinical trials are necessary for producing appropriate clinical evidence. In clinical trials examining cardiovascular diseases, large-scale clinical trials with thousands of participants are often required to evaluate the risks of cardiac events and/or death, because it is necessary to evaluate the incidence of cardiovascular events that are relatively uncommon. Such clinical trials provide evidence about the most appropriate treatment regimen for preventing cardiovascular and metabolic diseases.

In the 1970s, researchers began to conduct clinical trials in Western countries, with the incidence of cardiovascular events as an endpoint [1,2]. Although the large-

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scale clinical trials in Japan were occurred approximately 10 years ago, the number of large-scale clinical trials has increased. Recently, a large number of clinical trials evaluating the incidence of cardiac events and/or death using hard endpoints have been conducted in the field of cardiovascular and metabolic medicine.

The Japanese Acute Myocardial Infarction Prospective (JAMP) study was the first non-pharmaceutical company-supported multicenter trial of a medication in Japan, and the results have already been reported [3]. Briefly, this randomized parallel-group study was carried out across 48 institutions from 1993 to 2000. The primary endpoint of the study was a composite of cardiac events involving at least one of the following: cardiac or non-cardiac death, recurrent non-fatal myocardial infarction, coronary revascularization, and hospitalization because of worsening angina or congestive heart failure. In total, 888 of 1,163 participants with acute myocardial infarction (AMI) were eligible for the full analysis set (FAS). Patients were randomly assigned to two groups; 422 received angiotensin-converting enzyme (ACE) inhibitors and 466 did not receive ACE inhibitors. The mean follow-up period was 5.8 years. The JAMP study group concluded that no significant improvement in outcome was associated with ACE inhibitor administration in subjects who survived AMI in a Japanese study population.

Following the JAMP study, we conducted a review to highlight important issues regarding large-scale clinical trials. The major issues revealed by our review were the funding sources and infrastructure surrounding clinical trials. Financial and infrastructural resources must be maintained for clinical trials to be conducted appropriately. However, a high investigation cost is required for this, and obtaining adequate funding is critical for conducting clinical trials. The infrastructural environment necessary for clinical trials is currently inadequate, although the situation is improving, with efforts being made by government, medical institutions and other organizations. At present, Japanese clinical trials are typically funded by various sources, including public agencies, private companies and foundations. However, some researchers have suggested that industry-funded studies are likely to be affected by biases in their results and interpretations [4-10]. For example, Ridker, et al. reported that cardiovascular trials funded by for-profit organizations reported between 2000 and 2005, were more likely to report positive findings than those funded by not-for-profit organizations [4]. Given the current research situation in the medical and pharmaceutical industries, it is not possible to completely avoid conflicts of interests among researchers. Recently, the International Committee of Medical Journal Editors (ICMJE) requested that sponsors disclose certain information regarding trial management, including funding sources [11]. However, there are currently no comprehensive regulations for managing conflicts of interest.

The current study had two main objectives:

1) To clarify the current funding and infrastructural environment surrounding large-scale clinical trials in cardiovascular and metabolic diseases in Japan

2) To find more general ways to improve the environment surrounding clinical trials in Japan.

## Methods

Our search covered all large-scale clinical trials whose primary endpoints were true endpoints in clinical trials examining cardiovascular and metabolic diseases. A true endpoint was defined as an endpoint consisting of cardiovascular events, such as myocardial infarction, chronic heart failure, ischemic heart attack, and/or death. We defined 'large-scale clinical trials' as trials where the target number of participants or enrolled number of participants was 300 or more. If a trial was discontinued before enrolling 300 participants, but the planned number of participants was 300 or more, this trial was also regarded as 'large-scale clinical trial'. We searched for clinical trials using PubMed, Ichushi (Japana Centra Revuo Medicina by the Japan Medical Abstracts Society, a non-profit organization), URL: http://login.jamas.or.jp/), websites of related medical societies, University Hospital Medical Information Network (UMIN) Clinical Trials Registry (URL: http://www.umin.ac.jp/ctr/index-j.htm), and clinicaltrials.gov (URL: http://www.clinicaltrials.gov/).

We conducted searches at three different times. The first search was carried out in 2004, with a cut-off date of 30 November, 2004. The second and third searches were conducted in 2007 and 2009, with cut-off dates on 25 February, 2007 and on 25 July, 2009, respectively. The second search was conducted to evaluate the changes in the environment surrounding clinical trials in Japan after improving the awareness of conflicts of interest in 2005-2006. The third search was conducted to evaluate the impacts of some scandals regarding clinical researches that were reported by the media in Japan in 2007-2008.

For all clinical trials that met the criteria described above, we recorded the 1) sponsor, 2) objectives of trial, 3) design (randomized clinical trial or non-randomized clinical trial), 4) interventions, 5) chief investigator, 6) contact address, 7) starting year of the trial, 8) duration of the trial/ending year of the trial, 9) number of enrolled participants or target number of participants, 10) results of trial, 11) publications of results or methods of trial, 12) funding agencies, and 13) others. Here, we defined a 'sponsor' as 'an individual, company, institution or organization that took responsibility for the initiation, management and/or financing of a clinical trial' [12-14].

## Results

### 1) Screening of large-scale clinical trials in cardiovascular diseases

We found a total 152 trials conducted in Japan that met our criteria for 'large-scale clinical trials' examining cardiovascular diseases. Sixty-four trials were found in the search conducted on 30 November, 2004, 53 additional trials were found on 25 February, 2007, and 35 additional trials were found on 25 July, 2009.

### 2) Trial design (RCT/non-RCT) and number of participants

We categorized the trials as randomized controlled trials (RCTs) or non-randomized controlled trials (non-RCTs) according to their design, as shown in Table 1. 72.4% (110/152) of the trials were RCTs, and 27.6% (42/152) were non-RCTs. Examining the numbers of participants revealed that 9.2% (14/152) of the trials examined more than 10,000 participants, 42.8% (65/152) examined between 1,000 and 10,000 participants, and 42.8% (65/152) examined less than 1,000 participants. 28.6% (4/14) of the trials with 10,000 participants or more were RCTs, 70.8% (46/65) of the trials with 1,000 to 10,000 participants, and 81.5% (53/65) of the trials with less than 1,000 participants were RCTs. This result indicated that the proportion of RCTs tended to be higher in trials with a lower number of participants.

### 3) Number of trials by starting year

We counted the number of trials according to the starting year and trial design (Figure 1). From 1992, several large-scale clinical trials were started each year. After 2001, the number of large-scale clinical trials markedly increased to more than 10 per year. In 2004, the number of large-scale clinical trials peaked, with 16 trials started within a year. In 2007, the number suddenly decreased to only seven, then increased again after 2007.

### 4) Number of trials by target disease

We categorized the numbers of trials by target disease (Table 2). Large-scale clinical trials examining ischemic heart disease (39.5%) were conducted most frequently, followed by studies of hypertension (22.4%), cerebrovascular disorders (18.4%), and heart failure (11.2%). No clear trend was observed between target disease and trial design.

### 5) Number of trials by funding sources

We analyzed the relationships among starting year of the trials, their numbers of participants and the types of funding agencies (Figure 2). 'Public' funding agencies include governmental organizations such as the Ministry of Health, Labour and Welfare, and 'Private' agencies include non-governmental or civilian organizations such as pharmaceutical companies.

Most of the larger-scale studies were funded by private organizations. The number of public funded studies increased from the latter half of the 1990s. Trials with combined funding sources were conducted until 2005, but no combined funding trials were conducted after 2006. We consistently found that the majority of large-scale clinical trials were privately funded. In particular, most large studies (10,000 or more participants) were privately funded.

Summary statistics of the numbers of participants by funding source are shown in Table 3. The median number of participants in publicly funded trials was 762, that in privately funded trials was 1,000, and that in trials with combined funding sources or other sources was 2,100.

### 6) Number of trials by presence or absence of publication

We searched for publications arising from each trial in medical journals (including abstracts of medical or scientific congresses). Overall, 60.5% (92/152) of the trials were published (Table 4). Of the published trials, 70 of 92 were RCTs and 22 were non-RCTs. 39.5% (60/152) of the trials were not published. Of these 60 trials, 39 trials were RCTs and 21 were non-RCTs. However, trial designs and/or results in 33 out of 39 RCTs and 14 out of 21 non-RCTs were found in clinical trial registries, such as clinicaltrials.gov and the UMIN Clinical Trials Registry. Six RCTs and seven non-RCTs were not disclosed anywhere.

**Table 1 Numbers of trials by number of participants and trial design (RCT or non-RCT)**

| Number of participants | Number of trials | | | | Proportion of RCT (RCT/Total) |
|---|---|---|---|---|---|
| | RCT* | Non-RCT* | Total | | |
| ≥10,000 | 4 | 10 | 14 | (9.2%) | 0.286 |
| 1,000-10,000 | 46 | 19 | 65 | (42.8%) | 0.708 |
| <1,000 | 53 | 12 | 65 | (42.8%) | 0.815 |
| Unknown† | 7 | 1 | 8 | (5.3%) | - |
| Total | 110 | 42 | 152 | (100%) | 0.724 |

* RCT: randomized controlled trial, Non-RCT: non-randomized controlled trial

† Eight multi-national trials where the number of Japanese participants was not known were categorized as 'unknown'.

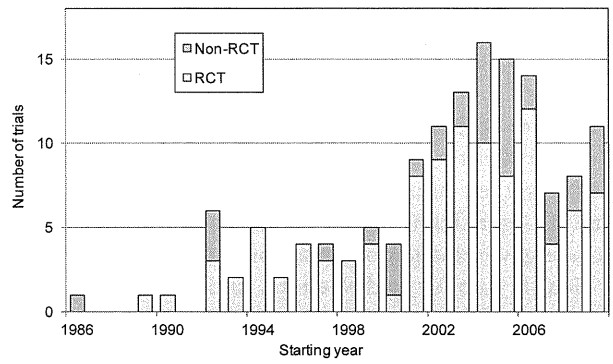


**Figure 1 Number of trials by starting year and trial design (RCT or non-RCT).** RCT: randomized controlled trial, Non-RCT: non-randomized controlled trial. Ten clinical trials (six RCTs and four non-RCTs) whose starting years were unknown were not counted.

## Discussion

We found a total of 152 trials that met our criteria for 'large-scale clinical trials' examining cardiovascular diseases in Japan. Sixty-four trials were found on 30 November, 2004, 53 trials were additionally found on 25 February, 2007, and 35 additional trials were found on 25 July, 2009.

72.4% (110/152) of the trials were RCTs, and 27.6% (42/152) were non-RCTs. Only 14 (9.2%) trials were large-scale cardiovascular clinical trials involving 10,000 or more participants, while there were 65 trials (42.8%) with less than 1,000 participants. Thus, larger clinical trials in Japan were found to be relatively rare. We propose two possible causes for this finding: first, it may be perceived that conducting such large clinical trials is not necessary for events that are considered to have a high incidence of mortality and morbidity. Second, limited funding and human resources may limit the feasibility of large-scale clinical trials.

In trials with larger sample sizes, the proportion of non-RCTs was higher than among trials with smaller sample sizes. This finding is in accord with our proposal that large-scale clinical trials may be restricted because of limited funding and human resources.

**Table 2 Numbers of trials by target disease and trial design (RCT or non-RCT)**

| Target disease | Number of trials | | | |
|---|---|---|---|---|
| | Total | | RCT* | Non-RCT* |
| Ischemic heart disease | 60 | (39.5%) | 39 | 21 |
| Hypertension | 34 | (22.4%) | 21 | 13 |
| Cerebrovascular disorder | 28 | (18.4%) | 23 | 5 |
| Heart failure | 17 | (11.2%) | 12 | 5 |
| Hyperlipidemia | 13 | (8.6%) | 9 | 4 |
| Diabetes mellitus | 10 | (6.6%) | 9 | 1 |
| Chronic kidney disease | 7 | (4.6%) | 5 | 2 |
| Arrhythmia | 5 | (3.3%) | 5 | 0 |
| Total | 152 | (100%) | 108 | 46 |

* RCT: randomized controlled trial, Non-RCT: non-randomized controlled trial

We compared trial designs and the number of participants by search date (Table 5). This analysis revealed that the proportion of trials of cardiovascular diseases in Japan with smaller sample sizes increased over time. Furthermore, the ratio of RCTs to non-RCTs was greater among the small-scale trials than among the large-scale trials.

After 2001, the number of large-scale clinical trials markedly increased to more than 10. In 2004, the number of large-scale clinical trials peaked, with 16 trials started within a year. In 2007, the number suddenly decreased to seven per year, then increased again after 2007. This pattern may be related to changes in the climate of public opinion regarding financial disclosures revealing relationships between study sponsors and funding agencies. Some reports in the mass media in Japan regarding private industry funding to academic sponsors without advance disclosures in 2007 and 2008 might have affected this tendency.

Ischemic heart disease (39.5%) was the most common target disease for large-scale clinical trials in Japan, followed by hypertension (22.4%), cerebrovascular disorders (18.4%), and heart failure (11.2%). Large-scale clinical trials were conducted for not only lifestyle-related chronic diseases but also for acute diseases such as myocardial infarction.

Our evaluation of changes in target diseases is shown in Table 6. The number of trials targeting ischemic heart disease gradually decreased over the study period, although it remained the major target disease in 2009. The numbers of trials targeting hypertension and cerebrovascular disorders decreased over the study period. On the other hand, the number of trials focusing on chronic kidney disease markedly increased after 2007. This was not a target disease in any trials before 2007, but seven trials on chronic kidney disease were started after 2007. This may reflect a heightened awareness of chronic kidney disease as a major risk factor for cardiovascular events [15].

We analyzed the relationship among the starting year of trials, the number of participants and the types of funding agencies. 'Public' funding agencies included governmental organizations such as the Ministry of Health, Labour and Welfare, and 'Private' funding agencies included non-governmental or civilian organizations such as pharmaceutical companies.

Most of the larger-scale trials were funded by private organizations, such as pharmaceutical companies. Several publicly funded trials were started in 1998, but few publicly funded trials were conducted after 2005. Trials with combined funding sources were conducted until 2005, but no such trials were started after 2006. The

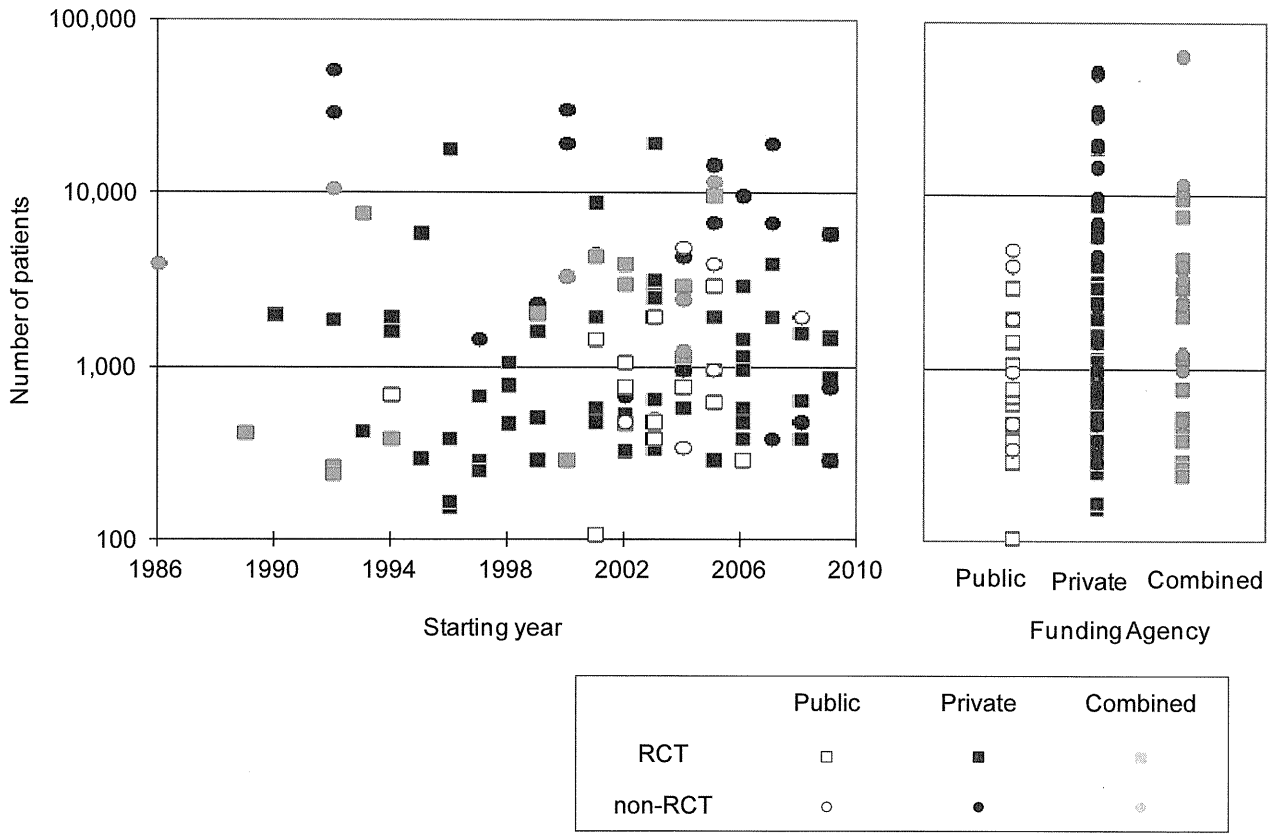


**Figure 2 Dot plot of starting year, funding agency, and number of participants.**

majority of large-scale clinical trials were consistently privately-funded. In particular, most studies with 10,000 or more participants were privately funded.

The median number of participants in public funded trials was 762, that in private funded trials was 1,000, and that in trials with combined funding sources or other sources was 2,100. This result suggests that it is possible to conduct larger scale clinical trials with private funding, but that it may be difficult to conduct studies of this size with funding from public sources. This trend was similar to the global trends for 2000-2005, where the median sample sizes of clinical trials funded by not-for-profit organizations and by for-profit organizations were 421 and 1486, respectively [4].

Thirteen trials (six RCTs and seven non-RCTs) did not disclose their designs or results at all. When we examined the changes in numbers of 'unpublished trials' in Table 7, the number did not decline between 2004 and 2009, resembling the global situation in which 54% of the trials were unpublished [16]. Among 12 completed trials with more than 10,000 participants, of which five were industry funded, 10 trials (83.3%) had been published. On the other hand, 37 (72.5%) of 51 completed trials with less than 1,000 participants had been published. When we counted the numbers of 'unpublished' trials by the type of funder, seven trials

**Table 3 Summary statistics about numbers of participants by funding source**

| Parameter | Number of trials | | | |
|---|---|---|---|---|
| | Public | Private | Combined | Total |
| Number of trials (N) * | 20 | 95 | 29 | 144 |
| Mean | 1,257 | 3,948 | 5,062 | 3,799 |
| Standard deviation | 1,340 | 7,959 | 12,064 | 8,463 |
| Median | 762 | 1,000 | 2,100 | 1,007 |
| Max | 5,000 | 53,000 | 65,434 | 65,434 |

* Eight multi-national trials where the numbers of Japanese participants was not known were excluded.

**Table 4 Number of trials by presence or absence of publication in medical journals**

| Publication status | Number of trials (N = 152) | | |
|---|---|---|---|
| | RCT* | Non-RCT* | Total |
| Published trials | 70 | 22 | 92 (60.5%) |
| Unpublished trials | 39 | 21 | 60 (39.5%) |
| Completed but unpublished trials | 14 | 8 | 22 |
| Ongoing unpublished trials | 25 | 13 | 38 |

* RCT: randomized controlled trial, Non-RCT: non-randomized controlled trial

**Table 5 Numbers of trials by number of participants and trial design (RCT or Non-RCT) by registration date**

| Number of participants | Number of trials | | | | | |
|---|---|---|---|---|---|---|
| | Until 30 November, 2004 (N = 63) | | From 1 December to 25 February, 2007 (N = 53) | | From 26 February to 25 July, 2009 (N = 152) | |
| | Total n (%) | Number of RCT* n (% vs Total) | Total n (%) | Number of RCT* n (% vs Total) | Total n (%) | Number of RCT* n (% vs Total) |
| ≥10,000 | 6 (9.5%) | 1 (16.7%) | 8 (15.1%) | 3 (37.5%) | 0 | NA |
| 1,000-10,000 | 29 (46.0%) | 23 (79.3%) | 26 (49.1%) | 14 (53.8%) | 9 (33.3%) | 9 (100%) |
| <1,000 | 28 (44.4%) | 24 (85.7%) | 19 (35.8%) | 19 (100%) | 18 (66.7%) | 10 (55.6%) |

* RCT: randomized controlled trial

were self-funded and six were industry-funded. This means we may require different approaches to improve the current problems. For example, improving the awareness of the importance of publishing results would be effective for the sponsors of self-funded trials, while issuing guidelines to force disclosure would be appropriate for the industry-funded trials. Japan established a clinical trial registry system in 2005 [17]. Three systems, i.e. UMIN Clinical Trials Registry; Japan Pharmaceutical Information Center (JAPIC); and Japan Medical Association, Center for Clinical Trials (JMACCT) were incorporated into the Japan Primary Registries Network in 2008. As mentioned by the ICMJE in 2004 [18], the Declaration of Helsinki revised in 2008 [19] and the CONSORT declaration in 2010 [20], the disclosure of trial protocol summaries and results is important to avoid publication bias. Therefore, the situation in Japan is currently problematic.

**Table 6 Numbers of trials by target disease and registration date**

| Target disease | Number of trials | | |
|---|---|---|---|
| | Until 30 November, 2004 (N = 64) | From 1 December to 25 February, 2007 (N = 53) | From 26 February to 25 July, 2009 (N = 35) |
| Ischemic heart disease | 30 (46.9%) | 20 (37.7%) | 10 (28.6%) |
| Hypertension | 19 (29.7%) | 13 (24.5%) | 2 (5.7%) |
| Cerebrovascular disorder | 12 (18.8%) | 14 (26.4%) | 2 (5.7%) |
| Heart failure | 8 (12.5%) | 5 (9.4%) | 4 (11.4%) |
| Hyperlipidemia | 6 (9.4%) | 2 (3.8%) | 5 (14.3%) |
| Diabetes mellitus | 4 (6.3%) | 1 (1.9%) | 5 (14.3%) |
| Chronic kidney disease | 0 | 0 | 7 (20.0%) |
| Arrhythmia | 3 (4.7%) | 1 (1.9%) | 1 (2.9%) |

**Table 7 Number of trials by presence or absence of publication in medical journals by search date**

| | Number of trials | | |
|---|---|---|---|
| | As of 30 November, 2004 (N = 64) | As of 25 February, 2007 (N = 117) | As of 25 July, 2009 (N = 152) |
| Published trials | 45 (70.3%) | 67 (57.3%) | 92 (60.5%) |
| Unpublished trials | 19 (29.7%) | 50 (42.7%) | 60 (39.5%) |
| Completed but unpublished trials | 9 | 17 | 22 |
| Ongoing unpublished trials | 10 | 33 | 38 |

## Conclusions

To minimize the bias caused by funding sources, entirely publicly funded trials should be conducted by 'neutral' investigators. However, this is difficult because of limitations in the financial resources necessary for conducting large-scale clinical trials in Japan. This appears to be why most of the trials revealed by our search were funded by private industry.

Some sponsors required more than one funding source. This finding indicates that some sponsors were concerned with obtaining sufficient funding for large-scale clinical trials. However, in some large-scale trials, the relationships between sponsor and funding agencies were not clear. Some sponsors did not disclose information about trials, although this publication policy may have changed. We propose that all sponsors of clinical trials should register trials and disclose their funding sources before the enrolment of participants, and publish their results after the completion of each study to improve the quality of clinical trials. For this purpose, improving the sponsors' awareness of the importance of publications and issuing guidelines to mandate the disclosure of funding sources can offer the solutions to these problems.

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**Authors' contributions**

HS and KU searched the clinical trials for the study, participated in analyzing the research and drafted the manuscript. KT searched the clinical trials for the study and helped to draft the manuscript. All authors read and approved the final manuscript.

**Competing interests**

HS is an employee of Novartis Pharma K.K. The Department of Drug Policy and Management, Graduate School of Pharmaceutical Sciences, The University of Tokyo, is a department endowed by Towa Pharmaceutical Co., Ltd., one of the leading manufacturers of generic drugs in Japan.

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RESEARCH ARTICLE Open Access

# How Can the Evidence from Global Large-scale Clinical Trials for Cardiovascular Diseases be Improved?

Hiroshi Sawata* and Kiichiro Tsutani

## Abstract

**Background:** Clinical investigations are important for obtaining evidence to improve medical treatment. Large-scale clinical trials with thousands of participants are particularly important for this purpose in cardiovascular diseases. Conducting large-scale clinical trials entails high research costs. This study sought to investigate global trends in large-scale clinical trials in cardiovascular diseases.

**Findings:** We searched for trials using clinicaltrials.gov (URL: http://www.clinicaltrials.gov/) using the key words 'cardio' and 'event' in all fields on 10 April, 2010. We then selected trials with 300 or more participants examining cardiovascular diseases. The search revealed 344 trials that met our criteria. Of 344 trials, 71% were randomized controlled trials, 15% involved more than 10,000 participants, and 59% were funded by industry. In RCTs whose results were disclosed, 55% of industry-funded trials and 25% of non-industry funded trials reported statistically significant superiority over control ($p = 0.012$, 2-sided Fisher's exact test).

**Conclusions:** Our findings highlighted concerns regarding potential bias related to funding sources, and that researchers should be aware of the importance of trial information disclosures and conflicts of interest. We should keep considering management and training regarding information disclosures and conflicts of interest for researchers. This could lead to better clinical evidence and further improvements in the development of medical treatment worldwide.

## Background

The evidence from a large number of clinical trials can be beneficial for the medical practice of many health care providers, informing clinical practice guidelines by providing a rationale for determining the most appropriate treatment. Accordingly, this evidence can be also beneficial for patients by receiving the most appropriate treatment.

Clinical trials are critical for obtaining new clinical evidence. In cardiovascular diseases, large-scale clinical trials involving thousands of participants are particularly important for evaluating the risk reductions of cardiac events and/or death, because of the requirement for the evaluation of cardiovascular events with relatively small differences in incidences between groups. These clinical trials can provide important evidence about the most appropriate treatment regimen for preventing cardiovascular and metabolic diseases. In the 1970s, researchers began to conduct large-scale clinical trials in Western countries with the incidence of cardiovascular events as endpoints [1,2]. The number of large-scale clinical trials has markedly increased since then. Recently, a large number of clinical trials for evaluating the incidence of cardiac events and/or death using hard endpoints have been conducted in cardiovascular and metabolic medicine.

We reviewed important issues surrounding large-scale clinical trials in Japan from 2007 [3,4]. The major issues revealed by the review were the funding sources and infrastructure surrounding of clinical trials. The review indicated that financial and infrastructural resources must be maintained to conduct clinical trials appropriately. However, high research costs are involved in clinical trials. Currently, clinical trials receive funding

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from various sources, including public agencies, private companies, foundations, etc. It has been proposed that industry-funded trials may be more likely to produce biased results, interpretations and conclusions [5-11]. Ridker, et al. reported that cardiovascular trials reported between 2000 and 2005 funded by for-profit organizations were more likely to report positive findings than those funded by not-for-profit organizations [5].

Considering this situation, it is important to clarify the problems and solutions surrounding current large-scale clinical trials. Thus, in this study we sought to elucidate the current situation and important global trends in large-scale clinical trials examining cardiovascular diseases.

## Methods

We searched for trials using clinicaltrials.gov (URL: http://www.clinicaltrials.gov/) with the words 'cardio' or 'event' in all fields on 10 April 2010. We then selected all large-scale clinical trials examining cardiovascular diseases. We defined 'large-scale clinical trials' as trials involving 300 participants or more. If the trial was ongoing and the planned number of participants was 300 or more, this trial was regarded as a 'large-scale clinical trial'. We defined 'trials examining cardiovascular diseases' as trials where the primary endpoint was the incidence of cardiovascular events, e.g. myocardial infarction, chronic heart failure, ischemic heart attack, and/or mortality including death.

For the target trials, we recorded 11 items: 1) primary objective of trial, 2) trial design, 3) interventions, 4) sponsor(s), 5) starting year and month, 6) ending year and month, 7) number of enrolled participants or target number of participants, 8) countries of trial sites, 9) results of trial, 10) publications linked from clinicaltrials.gov, 11) funding sources.

We categorized the trials by each criterion, and calculated summary statistics. The relationship between funding sources (industry or non-industry) and the results of a primary analysis (positive or negative) were tested using 2-sided Fisher's exact tests. A result was regarded as positive if a trial met the primary objective of statistically significant superiority or non-inferiority over control conditions or behavioral interventions.

## Results

### Screening of large-scale clinical trials in cardiovascular diseases

We showed the number of trials during screening of the trials in Figure 1. We found 2,058 trials registered in clinicaltrials.gov with the words 'cardio' or 'event' in all fields as of 10 April, 2010. Of 2,058 trials, 787 met the criterion of involving 300 participants or more. Of these 787 trials, 344 met the criteria that the primary endpoint of the trial was the incidence of cardiovascular events and the trial population was patients with cardiovascular diseases.

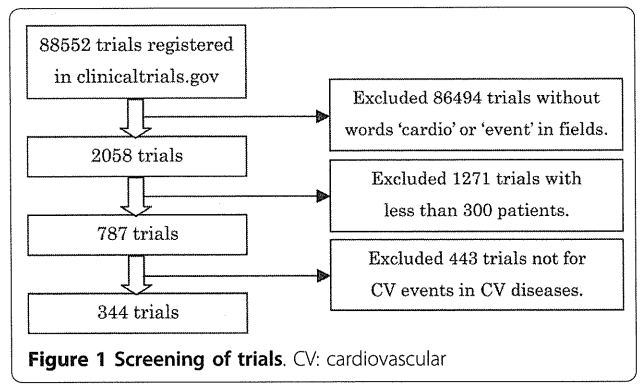


**Figure 1 Screening of trials**. CV: cardiovascular

None of these 344 trials were excluded from our analysis because of insufficient information.

### Trial design (RCT/non-RCTs) and number of participants

We categorized all 344 trials according to the trial design and the number of participants (Table 1). Of these trials, 71% (243/344) were randomized controlled trials (RCTs), and 29% (101/344) were not RCTs (non-RCTs). Examining the number of participants revealed that 0.6% (2/344) of the trials involved 100,000 participants or more, 2% (6/344) of trials involved between 30,000 and 99,999 participants, 12% (42/344) involved between 10,000 and 29,999 participants, and 35% (121/344) of trials involved less than 1,000 participants. The results revealed a trend towards an association between smaller proportion of trials and larger numbers of participants. The statistical significance of this trend was not tested because of small sample sizes.

In trials involving between 3,000 and 9,999 participants, and those involving between 10,000 and 29,999 participants, the proportions of RCTs were 82% and 88%, respectively. In trials involving less than 1,000

**Table 1 Numbers of trials by number of participants and trial design (RCT or Non-RCT)**

| Number of participants | Number of trials | | | | Proportion of RCT (%) |
|---|---|---|---|---|---|
| | RCT | Non-RCT | Total | | |
| ≥100,000 | 0 | 2 | 2 | (0.6%) | 0 |
| 30,000-99,999 | 2 | 4 | 6 | (1.7%) | 33.3 |
| 10,000-29,999 | 37 | 5 | 42 | (12.2%) | 88.1 |
| 3,000-9,999 | 56 | 12 | 68 | (19.8%) | 82.4 |
| 1,000-2,999 | 72 | 33 | 105 | (30.5%) | 68.6 |
| < 999 | 76 | 45 | 121 | (35.1%) | 62.8 |
| Total | 243 | 101 | 344 | (100%) | 70.6 |

RCT: randomized controlled trial; Non-RCT: non-randomized controlled trial

participants, and those involving between 1,000 and 2,999 participants, the proportion that were RCTs was 63% and 69%, respectively. These proportions were substantially lower for trials involving between 3,000 and 29,999 participants.

### Number of trials by starting year

We categorized the numbers of trials according to the starting year (Figure 2). The number of large-scale clinical trials increased gradually from the latter 1990s, and showed a 2.4-fold increase in 2003 relative to 2002. Fifty-nine trials were registered with clinicaltrials.gov in 2009. This was the highest number of all the years we examined. It should be noted that the number of trials reported for 2010 includes trials registered before 10 April, 2010.

A larger proportion of trials were RCTs before 2000, relative to after 2000. Conversely, the number of non-RCTs increased after 2000. From 2005, the trend of the increasing number of non-RCTs became more obvious, although number of RCTs has not changed noticeably during this period.

### Number of trials by funding sources

We categorized trials according to the category of funding sources; industry, academic, government, foundation, and other. We found that 204 trials (59%) were funded by industry (e.g. pharmaceutical companies or medical device providers), 122 trials (35%) were funded by academic organizations, e.g. universities and research centers, 55 trials (16%) were funded by governmental organizations, 32 trials (9%) were funded by foundations, 48 trials (14%) were funded by other organizations (e.g. hospitals and individuals), 97 trials (28%) were funded by multiple funding organizations, and 17 trials (5%) were funded by both governmental organizations plus industries or foundations (Table 2).

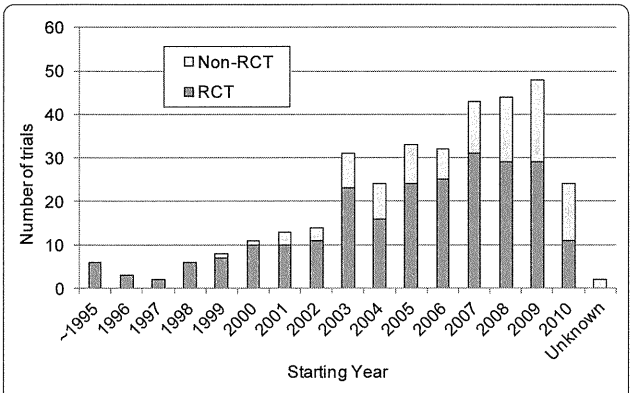


**Figure 2 Trends in the number of trials by starting year and trial design (RCT or non-RCT).**

**Table 2 Numbers of trials by funding source and trial design (RCT or non-RCT)**

| Funding source | Number of trials | | | Proportion of RCT (%) |
|---|---|---|---|---|
| | RCT | Non-RCT | Total | |
| Industry | 142 | 62 | 204 (59.3%) | 69.6 |
| Academic | 79 | 43 | 122 (35.5%) | 64.8 |
| Government | 44 | 11 | 55 (16.0%) | 80.0 |
| Foundation | 28 | 4 | 32 (9.3%) | 87.5 |
| Other | 37 | 11 | 48 (14.0%) | 77.1 |
| Total | 243 | 101 | 344 (100%) | 70.6 |

We analyzed the relationship between starting years of trials, types of funding sources, and the numbers of participants (Figure 3). 'Public' funding sources included governmental organizations, and 'Private' sources included industry, academic institutions, foundations, and others.

Trials with larger numbers of participants were mainly conducted with funding from private sources.

Summary statistics of the numbers of participants according to funding sources are shown in Table 3. The median of number of participants in publicly funded trials was 2,331, and that in trials with combined funding sources was 2,450. The median number of participants in privately funded trials was 1,400, substantially lower than publicly funded trials and trials with combined funding sources.

### Number of trials by region or country

We calculated the number of trials with multiple participating countries according to the starting year of trials (Table 4). The results showed that 227 trials (68%) were conducted in a single country, while 106 trials (32%) were conducted in multiple countries. The number of trials conducted in single country showed a 7.1-fold increase between 2006 and 2010 compared with those conducted before 2000, although those conducted in multiple countries showed a 3.1-fold increase by the 2006-2010 period compared with those conducted before 2000. The number of trials involving more than 20 countries from 2001-2005 and from 2006-2010 was 16 and 17, respectively, and one trial involving more than 20 countries was conducted before 2000.

We investigated the regions involved and starting year in each trial. 171 trials (51%) were in Western Europe, which was the most frequently involved region. 161 trials (48%) were conducted in North America, 95 trials (28%) were in East Asia. Only 32 trials (10%) were in Africa and 33 (10%) were in Southeast Asia. Until 2000, North America and Western Europe were the only major regions involved in large-scale clinical trials.

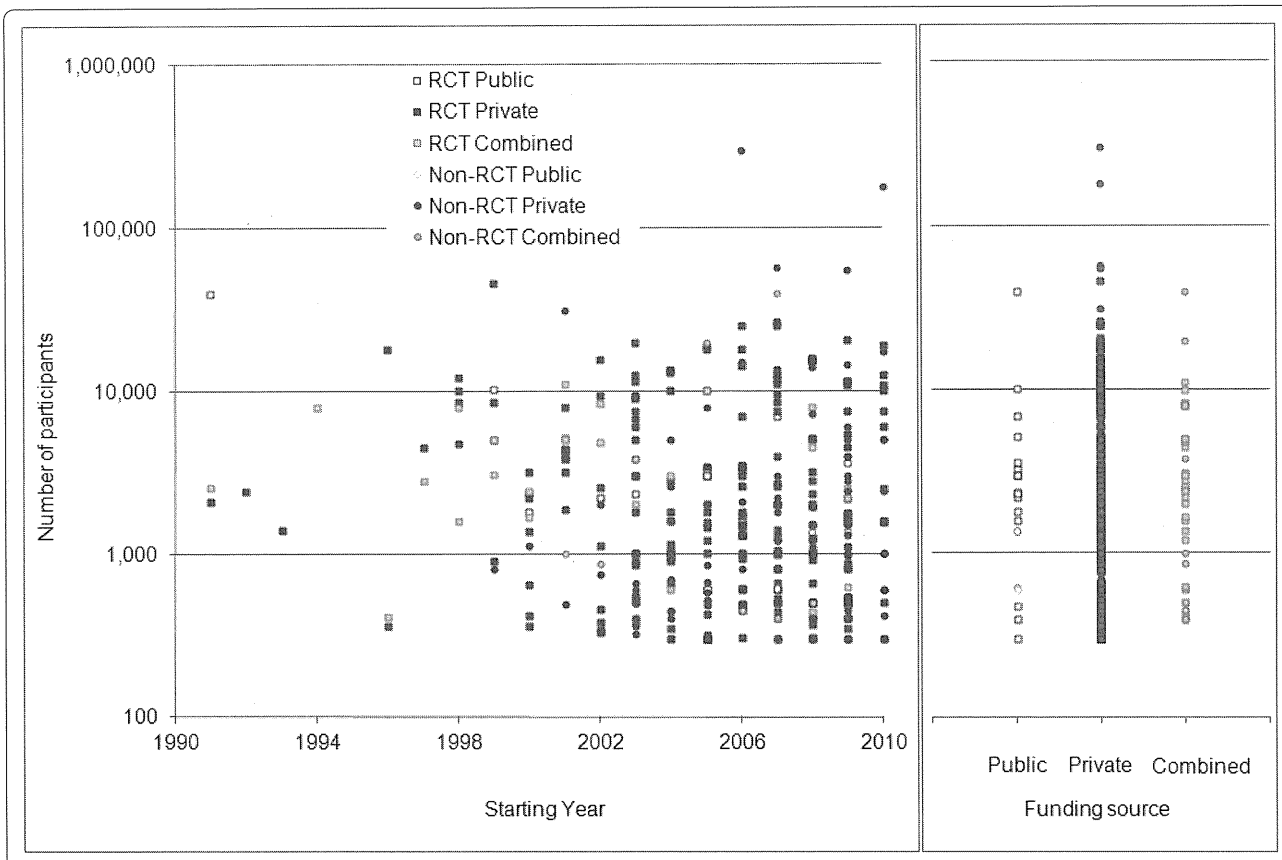


**Figure 3 Dot plot by starting year, funding source, and number of participants.**

Between 2006 and 2010, however, East Asia became a major region of involvement.

### Relationship between results and funding sources

In 83 (24%) RCTs whose results were disclosed, we counted the number of trials according to the primary result and funding source. Trial results with parallel group comparisons were grouped into two categories, positive and negative, according to the statistical superiority or non-inferiority relative to control, revealed by primary analysis.

Thirty of 55 (55%) industry-funded trials and seven of 28 (25%) non-industry funded trials showed statistical superiority or non-inferiority to control. Forty-six (55%) trials failed to meet the primary objective. The relationship between trial results and funding sources was statistically significant (p = 0.012, 2-sided Fisher's exact test).

**Table 3 Summary statistics regarding numbers of participants by funding source**

| Parameter | Public | Private | Combined | Total |
|---|---|---|---|---|
| Number of trials (N) | 19 | 289 | 36 | 344 |
| Number of participants | | | | |
| ≥100,000 | 0 | 2 | 0 | 2 |
| 30,000-99,999 | 1 | 4 | 1 | 6 |
| 10,000-29,999 | 1 | 38 | 3 | 42 |
| 3,000-9,999 | 6 | 51 | 11 | 68 |
| 1,000-2,999 | 6 | 88 | 11 | 105 |
| < 999 | 5 | 106 | 10 | 121 |
| Mean | 4,696 | 5,944 | 4,703 | 5,745 |
| Standard deviation | 8,877 | 21,485 | 7,299 | 19,934 |
| Median | 2,331 | 1,400 | 2,450 | 1,555 |
| Max | 39,876 | 300,000 | 40,000 | 300,000 |

**Table 4 Number of participating countries by starting year of trials**

| Number of countries | Number of trials (N = 333*) | | | | |
|---|---|---|---|---|---|
| | -2000 | 2001-2005 | 2006-2010 | Total | |
| Single country | 19 | 73 | 135 | 227 | (68.2%) |
| Multiple countries | 16 | 40 | 50 | 106 | (31.8%) |
| 2-5 countries | 8 | 14 | 13 | 35 | (10.5%) |
| 6-20 countries | 7 | 10 | 20 | 37 | (11.1%) |
| > 20 countries | 1 | 16 | 17 | 34 | (10.2%) |

* 11 trials whose starting years or countries were unknown were excluded.

## Discussion

We found 344 trials involving 300 or more participants that were registered with clinicaltrials.gov, using the search terms 'cardio' and 'event' in any field. All of the selected trials were conducted to evaluate the incidence of cardiovascular events and/or death in cardiovascular diseases.

Of 344 trials, more than 70% were RCTs, and 15% of trials enrolled more than 10,000 participants. In trials involving between 3,000 and 9,999 participants, and those involving between 10,000 and 29,999 participants, the proportion of trials that were RCTs was greater than 0.8, substantially higher than the proportion of RCTs among trials involving less than 3,000 participants.

We categorized the number of trials by starting year. The number of large-scale clinical trials increased gradually from the latter 1990s, and showed 2.4-fold increase in 2003 compared with 2002. From 2003, number of non-RCTs increased obviously. This increase was considered to be related to the International Committee of Medical Journal Editors' (ICMJE) request for the registration of trials that began enrolling participants any time before July 1, 2005, if investigators wished to submit the results of their trial to journals that follow ICMJE policy [12,13]. This requirement might have increased investigators' awareness of the importance of trial registration. Fifty-nine trials registered with clinicaltrials.gov started in 2009. It should be noted that the number of trials reported for 2010 includes those registered before 10 April, 2010. The number of trials registered with clinicaltrials.gov has thus steadily increased.

Regarding funding sources, about 60% of trials were funded by private industry, e.g. pharmaceutical companies or medical device providers, 28% were funded by multiple funding organizations, and 5% were funded by a combination of governmental organizations and industries or foundations. These results revealed that various organizations funded large-scale clinical trials, and sponsors sometimes required multiple funding sources to conduct large-scale clinical trials. When we examined the 50 trials with 10,000 participants or more, 40 trials (80%) were found to be funded by industry (or industry plus other organizations), while six trials (12%) were funded at least partially by governmental organizations, and only two trials (4%), both started in the 1990s in the United States, were solely funded by governmental organizations such as the National Heart, Lung, and Blood Institute (NHLBI).

Our examination of the relationship between the types of funding sources and participant numbers revealed that the median number of participants involved in privately funded trials was lower than that involved in publicly funded trials and trials with combined funding. On the other hand, the mean and maximum of numbers of privately funded trials were higher than for publicly funded trials and trials with combined funding sources. Trials with larger numbers of participants were mainly conducted with funding from private sources, although there were also a large number of smaller trials funded by private sources. These findings indicate that it is relatively difficult to conduct large-scale clinical trials funded solely by governmental organizations.

According to the records in clinicaltrials.gov, 26 of 344 trials (8%) did not disclose their planned ending years. Of 308 trials whose ending years were disclosed, 127 trials have been completed by the end of 2009. However, in September 2010, the results of only 77 trials (61%) commenced before 2009 were accessible, and the results of 50 trials (39%) were not disclosed. In other words, we could not access to the ending years or results of 76 trials (22%). This result indicates that some sponsors did not update the registered information in clinicaltrials.gov.

In 83 RCTs where publications were disclosed, 55% of industry-funded trials and only 25% of non-industry funded trials reported statistically significant superiority of the target intervention relative to control. This difference was statistically significant ($p = 0.012$, 2-sided Fisher's exact test), indicating that industry-funded trials were significantly more likely to report statistically significant differences favoring target interventions compared with references. This result is consistent with the findings of previous reports [5-11], showing that industry-funded trials tended to produce results in favor of target interventions compared with references.

It should be noted that more than half of the trials failed to meet the primary objective. This means not only sacrifices in terms of the voluntary cooperation of participants, but also represents the wasting of limited resources. This finding suggests that sponsors should discuss the rationale of their study design and sample size in detail before trials begin. Conducting small pilot trials may provide an appropriate solution for avoiding unsuccessful trials. The involvement of independent data monitoring committees, including third party biostatisticians, may be another worthwhile solution. In addition, sponsors should stop or modify the trial when blinded interim analysis indicates that there is a strong possibility the primary objective will not be achieved. A greater number of worthwhile trials will be possible if the waste of resources by failed trials is reduced.

The current study suffers from the limitation that all data were obtained from clinicaltrials.gov, which is run by NIH in United States. As such, clinical trials in which the United States was not involved may have been omitted.

## Conclusions

Our research revealed that number of large-scale clinical trials in cardiovascular diseases increased steadily over time, and that clinical trials are becoming increasingly globalized. This indicates that the quality and quantity of evidence is improving. However, sponsors should aware that the timely update of the registered trial information in clinicaltrials.gov is important.

Our findings highlight a concern about the potential bias related to funding sources. More than 80% of the trials we found were conducted by private funding sources, especially clinical trials with larger numbers of participants. Therefore, sponsors as well as researchers at each site should be aware of the importance of conflicts of interest. The ICMJE requests that sponsors disclose certain information regarding the trial management, including funding sources. We should keep considering management and training regarding conflicts of interest. Sponsors should also be aware that minimizing the waste of resources by careful consideration of their study designs is also one of their responsibilities as sponsor.

Addressing these issues may facilitate the improvement of the quality of clinical evidence, and the development of better medical treatment worldwide.

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**Authors' contributions**
HS examined the study and drafted the manuscript. KT helped to draft the manuscript. All authors read and approved the final manuscript.

**Competing interests**
HS is an employee of Novartis Pharma K.K.. The Department of Drug Policy and Management, Graduate School of Pharmaceutical Sciences, The University of Tokyo, is endowed department by Towa Pharmaceutical Co., Ltd., one of the leading companies of generic drugs in Japan.

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# Funding and infrastructure among large-scale clinical trials examining cardiovascular diseases in Japan: evidence from a questionnaire survey

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## Abstract

**Background:** Large-scale clinical trials with thousands of participants are often needed to evaluate the risk reductions of cardiac events and/or death. Many recent clinical trials have evaluated the incidences of cardiac events using hard endpoints, especially in cardiovascular and metabolic medicine. A high investigation cost is involved in conducting a large-scale clinical trial, and obtaining sufficient funding is essential. The infrastructural environment of clinical trials is currently inadequate in Japan. We conducted a questionnaire-based survey to address this issue. The present study sought to clarify the current situation surrounding large-scale clinical trials in terms of funding and infrastructure, and to inform discussion about improving the financial and infrastructural situation for clinical trials.

**Methods:** We sent questionnaires to 119 sponsors of large-scale clinical trials between August 2007 and December 2007, and between July 2009 and August 2009. Answers to each question were summarized and data were statistically analyzed.

**Results:** We received responses from the sponsors of 63 (52.9%) out of 119 trials to which questionnaires were sent. The results revealed that 25 trials (39.7%) were funded by foundations, and 21 trials (33.3%) were funded by public agencies. All of the foundations involved in conducting clinical trials, where funding sources were specified, were funded by private organizations such as pharmaceutical companies. All of the clinical trials with a cost of JPY 300 million (USD 3.27 million) or more were funded by private organizations, and none were funded solely by public agencies. The sponsors of 23 trials (36.5%) responded that the trial was 'not registered' to clinical trial registry.

**Conclusions:** The questionnaire responses revealed that there were still many trials whose funding sources were unclear and many sponsors were unaware of their responsibilities in managing and/or financing the costs of clinical trials. These findings indicate that further discussion is required to establish appropriate frameworks and/or rules regarding funding, while considering conflicts of interest. This discussion should take place as soon as possible to facilitate appropriate clinical trials.

## Background

In the 1970s, researchers began to conduct large-scale clinical trials in Western countries, with the incidence of cardiovascular events as endpoints [1,2]. Although large-scale clinical trials in Japan began approximately 10 years later than in Western countries, the number of large-scale clinical trials has since increased. Recently, a large number of clinical trials seeking to evaluate the incidence of cardiac events and/or death using hard endpoints have been conducted in cardiovascular and metabolic medicine in Japan.

The Japanese Acute Myocardial Infarction Prospective (JAMP) study [3] was the first non-pharmaceutical company-funded multicenter trial of a medication in Japan. The JAMP study group concluded that there was no significant improvement in outcomes associated with angiotensin-converting enzyme inhibitor administration in

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patients who had survived acute myocardial infarction in a Japanese study population.

After the JAMP study, we found a number of issues surrounding large-scale clinical trials [4]. In particular, the funding sources and infrastructure of clinical trials were found to be major issues. Our results indicated that financial and infrastructural resources must be maintained to adequately conduct clinical trials. However, a substantial cost is involved, and obtaining funding is thus essential for clinical trials. The infrastructural environment surrounding clinical trials is currently inadequate, although this situation is improving. At present, Japanese clinical trials are funded by various sources, including public agencies, private companies, foundations, etc. Several studies have reported that industry-funded trials potentially suffer from biased results, interpretations and conclusions [5-11]. Ridker, et al. found that cardiovascular trials reported between 2000 and 2005 that were funded by for-profit organizations were more likely to report positive findings than those funded by not-for-profit organizations [5]. Considering the current situation surrounding the medical and pharmaceutical industries, as well as the situation for researchers, it is unlikely that researchers can completely avoid conflicts of interest. As such, the International Committee of Medical Journal Editors (ICMJE) requested in 2004 that sponsors disclose information regarding trial management, including funding sources [12]. However, no comprehensive regulations are currently in place to manage conflicts of interest in Japan.

In the current study, we conducted a survey among trial sponsors, using questionnaires to elucidate the current funding and infrastructural environment surrounding large-scale clinical trials investigating cardiovascular diseases in Japan. In this article, we report the results of our survey regarding relevant issues surrounding large-scale clinical trials for cardiovascular diseases in Japan.

## Methods

We sent questionnaires to the sponsors of large-scale clinical trials. A 'sponsor' was defined as 'an individual, company, institution or organization that takes responsibility for the initiation, management and/or financing of a clinical trial' [13-15]. We targeted our questionnaires to the chairperson, or, when the sponsor was an institution or organization, to the individual with the most responsibility according to the official disclosure of the organization.

Between August 2007 and December 2007 we sent questionnaires to 90 large-scale clinical trial programs that commenced before February 2007. One-hundred and seventeen trials were found by 1) PubMed, 2) Ichushi (Japana Centra Revuo Medicina, URL: http://login.jamas.or.jp/), 3) websites of related medical societies, 4) University Hospital Medical Information Network (UMIN) Clinical Trials Registry (URL: http://www.umin.ac.jp/ctr/index-j.htm), and 5) clinicaltrials.gov (URL: http://www.clinicaltrials.gov/) on 25 February, 2007. Of 117 trials, we found addresses of sponsors for 90 trials, and we sent questionnaires to all sponsors whose addresses could be identified. In addition, 35 more trials were found using the same data sources as mentioned above on 25 July, 2009. We found addresses for sponsors of 29 of these 35 trials, and, sent questionnaires to all sponsors whose addresses could be identified between July 2009 and August 2009.

We defined 'large-scale clinical trials' as trials where the number of participants was 300 or more. If a trial was ongoing beyond the cut-off date and its planned number of participants was 300 or more, this trial was also regarded as a 'large-scale clinical trial'. We sought to include all large-scale clinical trials that examined cardiovascular and metabolism disease (i.e. cardiovascular, cerebrovascular events, and/or death) and used true endpoints as their primary endpoints. A true endpoint was an endpoint involving cardiovascular events, such as myocardial infarction, chronic heart failure, ischemic heart attack, and/or death. We sent questionnaires to the sponsors of all clinical trials that met the above criteria, except for sponsors that we did not have access to.

Our questionnaires consisted of categorical choices (Additional file 1 Figure S1). Sponsors were asked to return the questionnaires within 2 weeks, but all responses were included in our analyses, regardless of when they were returned. We analyzed all responses after checking the accuracy and appropriateness of the data, without specifying the trial or each sponsor.

We presented mean, standard deviation, median and IQR for the continuous variables, absolute numbers and percentages for binary and categorical variables. The statistical tests were used for the comparisons between the groups by funding source. P-values were calculated using Kruskal-Wallis test, and $p < 0.05$ was considered to be statistically significant. Data were statistically analyzed using software (R version 2.13.1).

We did not obtain an ethical approval for this study, because our study was not a medical research involving human subjects to understand the causes, development and effects of diseases and improve preventive, diagnostic and therapeutic interventions.

## Results

### Numbers of participants in large-scale clinical trials to which questionnaires were sent and those that answered

We sent questionnaires to sponsors of 119 large-scale clinical trials. We received responses from 63 trials (52.9%). Of the 90 trials to which questionnaires were sent in August 2007 - December 2007, we received responses from 53

(58.9%). Of the 29 trials to which questionnaires were sent in July 2009 - August 2009, we received responses from 10 (34.5%).

The number of participants is summarized in Table 1. Twenty-four of the 63 responding trials (38.1%) involved less than 1,000 participants, 19 (30.2%) involved 1,000 - 2,999 participants, 15 (23.8%) involved 3,000 - 9,999 participants, and three (4.8%) involved 10,000 participants or more. The results did not reveal clear differences in the numbers of participants between trials that responded relative to all target trials.

### Numbers of trials and participants by funding source

We calculated the numbers of large-scale clinical trials per funding source.

Twenty-five trials (39.7%) were funded by foundations, 21 trials (33.3%) were funded by public agencies such as the Ministry of Health, Labour, and Welfare (MHLW), 13 trials (20.6%) were funded by private organizations such as pharmaceutical companies, and 10 trials (15.9%) were self-funded. Sponsors of two trials (3.2%) reported that their trials were funded by "others", and the sponsor of one trial (1.6%) reported that the funding source was "unknown or unspecified". For this question, the sum of all frequencies did not equal 63 (100%), because multiple answers were allowed. Of the 25 trials that were funded by foundations, all trials except for those where funding was unknown or unspecified were found to be funded by private organizations (such as pharmaceutical companies) through foundations.

The number of participants by funding source is summarized in Table 2. In total, the mean number of participants was 2,582. The mean number of participants in private funding and combined funding trials were 3,202 and 3,361, respectively. In publicly funded trials the mean number was 1,348.

The number of large-scale clinical trials by total cost is shown in Table 2. Nineteen trials (30.2%) where the cost or estimated cost was JPY 100 - 300 million (i.e. USD 1.09 - 3.27 million, calculated based on the foreign exchange rate on 20 February, 2010). Most of the trials were categorized in this range. The second- and third-most common cost categories were JPY 30 - 100 million (USD 0.33 - 1.09 million) and JPY 300 million - 1 billion (USD 3.27 - 10.9 million), respectively, with 10 trials (15.9%) fitting into each of these categories. 58.1% of the trials (32 out of 55 answered trials) cost JPY 100 million (USD 1.09 million) or more.

Regarding the relationship between funding sources and the cost of the trials, none of the clinical trials with a cost of JPY 300 million (USD 3.27 million) or more were funded solely by public agencies. The total trial costs were significantly different between trials involving different types of funding sources ($p = 0.0003$).

Eight trials (12.7%) responded that the source was unknown or left the question unanswered.

In an additional question, we asked details of the cost to the sponsors. The sponsors of 29 trials responded. Of these, 18 trials were funded by private sources. Nine of the 29 sponsors answered this question. Of these 9 unanswered trials, 8 trials were funded by private sources. The major reasons given for not answering were that the details were 'unknown' because some of the responders were not involved in cost management for their trials.

### Party responsible for monitoring and data management activities, and involvement of third-party

Regarding the infrastructure required for conducting large-scale clinical trials, we investigated the situations surrounding the support of human resources and material resources in trials whose sponsors reported foundations or private organizations as funding sources. Of 63 trials, 37 trials were private-funded. Nineteen of 37 trials (51.4%) received human or material resources from other organizations. Sixteen trials (43.2%) were supported with human resources only, one trial (2.7%) was supported with material resources only, and one trial (2.7%) was supported with both human and material resources. Fifteen trials (37.0%) were not supported with human or materials resources, receiving only financial resources. Three trials (8.1%) either reported that their support was unknown or left the question unanswered.

**Table 1 Numbers of participants involved in large-scale clinical trials to which questionnaires were sent, and number of participants involved in trials that responded**

| Number of participants in clinical trial | Responded trial* n (%) | Not-responded trial* n (%) | Total † n (%) |
|---|---|---|---|
| < 999 | 24 (38.1%) | 28 (50.0%) | 52 (43.7%) |
| 1,000 - 2,999 | 19 (30.2%) | 14 (25.0%) | 33 (27.7%) |
| 3,000 - 9,999 | 15 (23.8%) | 7 (12.5%) | 22 (18.5%) |
| ≥ 10,000 - | 3 (4.8%) | 6 (10.7%) | 9 (7.6%) |
| Unknown or no target number | 2 (3.2%) | 1 (1.8%) | 3 (2.5%) |
| Total | 63 (100%) | 56 (100%) | 119 (100%) |

* Proportions (%) in all responding trials (63 trials) or all not-responded trials (56 trials) are shown.

† Proportions (%) in all trials (119 trials) are shown.