Title: Trial registration and declaration of registration by authors of randomized controlled trials

Authors: Richard G McGee[1, 2], Michael Su[2], Patrick J Kelly[2], Gail Y Higgins[1], Jonathan C Craig[1, 2], Angela C Webster[1-3]

[1]Centre for Kidney Research & Cochrane Renal Group, The Children's Hospital at Westmead, Locked Bag 4001, Westmead, NSW 2145, Australia

[2]Sydney School of Public Health, University of Sydney, NSW 2006, Australia

[3]Centre for Transplant and Renal Research, Westmead Hospital, Westmead, NSW 2145, Australia

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Address for Correspondence: Richard McGee

Centre for Kidney Research, Westmead Children's Hospital, Westmead, NSW, 2145 Australia

Phone: +61 2 9845 1466 Fax: +61 2 9351 5049 Email: richard.mcgee@sydney.edu.au

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Authors: Richard G McGee[1, 2], Michael Su[2], Patrick J Kelly[2], Gail Y Higgins[1], Jonathan C Craig[1, 2], Angela C Webster[1-3]

[1]Centre for Kidney Research & Cochrane Renal Group, The Children's Hospital at Westmead, Locked Bag 4001, Westmead, NSW 2145, Australia

[2]Sydney School of Public Health, University of Sydney, NSW 2006, Australia

[3]Centre for Transplant and Renal Research, Westmead Hospital, Westmead, NSW 2145, Australia

Corresponding author: Richard McGee. Centre for Kidney Research, The Children's Hospital at Westmead, Locked Bag 4001, Westmead, NSW 2145, Australia.

Abbreviations

95% confidence intervals (CI)

International Committee of Medical Journal Editors (ICMJE)

International Clinical Trials Registry Platform (ICTRP)

Odds ratios (OR)

World Health Organisation (WHO)

Abstract

Background

Trial registration was introduced to reduce research bias by promoting trial transparency and accountability. We aimed to evaluate the frequency of, and factors associated with, trial registration and declaration of trial registration.

Methods

We selected all randomised controlled trials in kidney transplantation, published between October 2005 and December 2010 and determined if a trial was registered and if a trial declared their registration in subsequent trial reports.

Results

Of 307 eligible trials identified, 24% (74/307) were registered and of those 59% (44/74) contained trial registration details within at least one trial report. Trial registration was more likely for trials published more than once, in later years or reported in journals that followed the International Committee of Medical Journal Editors (ICMJE) guidelines. Trial registration was less likely for trials that did not declare their funding sources. Registered trials were more likely to declare registration details in related reports if published in later years, or in a journal that followed ICMJE guidelines. Trials that did not declare their funding sources were less likely to declare registration details.

Conclusions

Although still suboptimal, the situation is improving over time, with both trial registration and declaration of registration details more likely in later years.

Introduction

Trial registration is designed to reduce research bias by promoting research transparency and accountability (1, 2). The importance of trial registration has been highlighted since 1986 (3), and in 2000 the US National Library of Medicine established the Web-based registry ClinicalTrials.gov to facilitate the registration of clinical trials (4). When the results of clinical trials are altered, suppressed or not published there is the potential for scientific misconduct, wasted resources and harmful outcomes for patients (5, 6). After decades of debate (7), in September 2004 the International Committee of Medical Journal Editors (ICMJE) announced that prospective trial registration would be a mandatory requirement for publication in a member journal for any trial beginning recruitment after July 2005 (8). For unregistered trials that began before July 2005, retrospective registration was allowed until September 2005 (8). Since then, the importance of trial registration has been further promoted by the World Health Organisation (WHO) (9), the Declaration of Helsinki (10), guidelines groups (11) and other editorial groups for example the World Association of Medical Editors (12) and Surgery Journal Editors Group (13).

The WHO has defined a minimum amount of information that must appear in a register in order for a given trial to be considered fully registered (14). This includes information on the study intervention, inclusion and exclusion criteria as well as the predefined primary and secondary outcomes. This information allows users to compare important methodological features defined a-priori with those subsequently presented when trial results are published. While previous studies have evaluated the frequency of trial registration (15-17), none have evaluated the frequency with which trials declare their registration details in associated reports. Unless a trial's registration details are available to users of research and

appear on all reports and documents associated with a trial, transparency of research practice is not maintained and it becomes very difficult to trace the life-cycle of a trial from design through to conduct and publication to ensure consistency. Therefore, while trial registration is a vital first step in promoting transparency and accountability, for it to be effectively translated into practice, declaration of trial registration is equally important.

For our study, we chose to study trial registration and the declaration of registration details in a medical specialty field, to reflect the perspective of users of clinical research, who use trial evidence to inform their decision-making in clinical practice. We chose the field of kidney transplantation, because it is a rapidly developing and technologically innovative field, and because trial results are typically published in both general medical and speciality journals. If the global efforts to encourage trial registration have been effective, we hypothesised that trials reported more recently were more likely to be registered and to declare their registration details in subsequent reports, compared with older trials.

Results

Characteristics of included trials

Figure 1 illustrates the process of identification of trials and trial reports for this study. We identified 523 reports of 307 trials. The number of published reports per trial varied from one to 33. Ninety-eight percent (515/523) of trial reports identified were published articles available from 53 journals, the remainder were conference abstracts related to published trials. **Table 1** displays the characteristics of the included trials and their related reports.

Twenty-four percent of trials (74/307) were registered in a trial registry, and these trials were reported in 212 reports. Fifty-nine percent (44/74) of registered trials declared their trial registration details within at least one trial report. Seventy-four percent of (156/212) the reports for registered trials did not contain any indication of the relevant trial registration details. **Table A** in the **supplementary material file** details the performance of specific journals in relation to the publication of registered and unregistered trials and the declaration of trial registration identifiers.

Factors associated with trial registration

Table 2 displays the unadjusted OR and CI for factors associated with trial registration, while **Figure 2** displays the adjusted OR and CI. Trials published more than once were more likely to be registered (2 reports- OR 3.1, CI 1.1 to 8.4. >2 reports- OR 14.6, CI 4.8 to 44.9; P<0.001), as were those that were reported in journals that followed ICMJE guidelines (OR 7.4, CI 3.2 to 17.3; P<0.001) and published in later years (2007- OR 2.8, CI 1.0 to 7.7. 2008- OR 7.0, CI 2.2 to 21.7. 2009- OR 10.1, CI 2.4 to 43.1. 2010- OR 37.4, CI 8.0 to 175.6; P<0.001). Trial registration differed according the region in which the trial was conducted, P=0.01.

Trials conducted in the USA were significantly more likely to be registered than European trials (OR 6.4, CI 1.9 to 21.8). Trials conducted in other regions and globally were also more likely to be registered but not significantly so (Other regions – OR 1.8, CI 0.6 to 5.7. Global – OR 3.7, CI 0.9 to 14.6). Trial registration differed according to funding source, P<0.006. Trials which did not declare their funding source, were significantly less likely to have been registered (OR 0.2, CI 0.1 to 0.5), as were those that were commercially funded but not significantly so (OR 0.4, CI 0.1 to 1.1.). No interaction term proved significant on analysis. The model adequately fitted the data (Hosmer–Lemeshow goodness of fit test P=0.53).

Factors associated with declaration of trial registration

Table 2 displays the unadjusted OR and CI for factors associated with declaration of trial registration details within reports of registered trials, while **Figure 3** displays the adjusted OR and CI. Trials that were registered were more likely to declare registration details in related reports if published in later years (2007- OR 6.3, CI 1.3 to 29.8. 2008- OR 4.6, CI 1.3 to 16.0. 2009- OR 9.5, CI 1.8 to 50.1. 2010- OR 30.5, CI 5.9 to 158.7; P=0.002), or if published in a journal that followed ICMJE guidelines (OR 3.9, CI 1.6 to 9.6; P=0.003). Compared to European trials, trials conducted globally were significantly less likely to declare their registration details (OR – 0.3, CI 0.08 to 0.9). Trials conducted in the USA or other regions were no more or less likely to declare their registration details than European trials (USA- OR 0.7, CI 0.2 to 2.4. Other- OR 1.0, CI 0.3 to 3.3) Declaration of trial registration differed according to funding source, P=0.007. Trials which did not declare their funding source, were significantly less likely to declare their registration details (OR 0.1, CI 0.02 to 0.4), as were those that were commercially funded but not significantly so (OR 0.4, CI 0.2 to 1.1). No interaction term proved significant on analysis. The model adequately fitted the data

(Hosmer–Lemeshow goodness of fit test P=0.78). Exclusion of abstracts on sensitivity analyses did not results in qualitatively altered outcomes (data not shown).

Discussion

Despite mandatory trial registration being endorsed in 2005 by the ICMJE (8), the majority (76%) of randomised controlled trials in kidney transplantation reported from 2005 to 2010 were not prospectively registered, and even when registered frequently did not cite registration details in related reports (74%). After controlling for other factors, we found that trials where the funding source was not stated were less likely to be registered and when registered were less likely to declare their registration details in trial reports. Although still suboptimal, the situation is improving over time, with both trial registration and declaration of registration details more likely in later years.

Consistent with our findings, previous research has shown low rates of trial registration (15-17). Commercial funding is known to affect rates of publication and the size and direction of results presented (18-20). However, to our knowledge, no previous study has demonstrated a negative correlation between funding source and the uptake of trial registration or its subsequent declaration. This underutilisation of trial registration subverts the intention of bias minimisation and transparency in contemporary research. Additionally, the non-declaration of a trial's registration details when trial findings are published makes any potential manipulations less detectable to the reader.

Our study has several limitations. First, as our analyses were based on data from reports of published trials, we have not included unpublished trials. Unpublished trials may differ from published trials in their rate of trial registration, although probably in the direction of less registration. Second, as our study is a retrospective cohort study, it is prone to more bias, for example, selection and measurement bias, than a prospective study (21). We attempted

to overcome these limitations using predefined hypotheses, inclusion criteria, study factors and analyses. Finally, our study only included trials related to kidney transplantation. Because of this, the generalisability of our results may be limited. However, we deliberately designed our study with this approach, in order to reflect the clinical reality of the end-users of research working in a medical specialty.

If trial registration is going to increase transparency and scientific rigour, the evidence of trial registration needs to be available to users of research. This requires the co-operation of study investigators and journal editors. Our findings suggest that neither investigators nor editors implement best practice. To improve this situation, more journals need to make prospective trial registration a pre-requisite for publication and make trial registration details clearly visible in related reports. Currently, 910 journals unofficially 'follow' the ICMJE's uniform requirements for manuscripts submitted to biomedical journals (http://www.icmje.org/journals.html, accessed on the 01/01/2011). In the subset of trials included in our study, which were published in journals that followed ICMJE guidelines, only 45% of trials were registered and of those 49% declared this in their publication, so clearly these journals are not fully implementing ICMJE policy. The success of trial registration will depend on all journals consistently implementing these policies. Therefore, we suggest that the ICMJE and other editorial groups encourage their affiliated journals to enforce the implementation of their trial registration requirements.

Although we disagree, some argue that because of the lack of repercussions and policing, the effect of trial registers is negligible and that study protocol changes, omissions and suppressions are the rule (22). Trial registers may even have a deterrent effect on

commercial incentives to conduct trials as the increased transparency means the conduct of a trial becomes public knowledge and the investment necessary for the conduct of a trial will be scrutinised by market forces to assess the opportunity cost of such an investment, resulting in fewer trials being conducted due to the increased risk (23). If open access to trial protocols via trial registries is an inadequate method to detect subsequent reporting bias (24), then trial registration by itself may be inadequate to prevent research misconduct. Multiple complementary methods are probably required to combat publication bias. One complementary alternative is to supply open-access to the raw data from a trial, so that anyone may scrutinize the presented results. Spurred on by the Wakefield debacle and other cases, where only prolonged investigation fully revealed gross data manipulation, the proposal to allow access to the raw data from trials has gained momentum (25, 26). Clearly, any efforts to improve reporting transparency in the medical community are desirable. The EQUATOR network (http://www.equator-network.org/about-equator/), seeks to promote transparent and accurate reporting of all research studies and is therefore an important central repository for such efforts, for example the Standardized Protocol Items for Randomized Trials (SPIRIT) initiative and the GPP2 guidelines, which promote unbiased and ethical reporting respectively (27, 28).

The aim of trial registration is to increase trial transparency and accountability. Although the situation is improving over time, currently, the trial registration process is not being utilised wholly effectively, which means users of research are less able to identify protocol deviations. A concerted effort from all parties, to increase education, awareness, implementation and utilisation of trial registration and its principles is necessary to produce higher quality research. It remains to be seen whether other efforts such as the proposal to

allow access to trial data or the use of reporting guidelines, will improve trial transparency and accountability.

Materials and Methods

Study sample

We conducted a cohort study of all randomised controlled trials in kidney transplantation, published at least once in a journal, between October 2005 and December 2010. We identified these trials from the Cochrane Renal Group's specialised register. This register is updated daily and contains records of randomised trials in nephrology, identified from searches of MEDLINE, Embase and CENTRAL. In addition, records identified from hand searching of selected journals and the proceedings of major conferences are continuously added to the specialised register (29). We chose the lower limit of October 2005 for publication as according to ICMJE policy all trials (both those initiated before and after July 2005) should have been registered by September 2005 (8). We chose the upper limit of December 2010 for publication to reduce any selection bias that might arise due to potential differences among medical specialty journals due to a time lag from publication to indexing by the National Library of Medicine (last search May 2011). Once all eligible trials were identified, we retrieved any additional reports, including journal articles and conference abstracts that related to that trial. We excluded trials that were published only as conference abstracts. To create a cohort of comparable studies, we excluded trials reported only in a language other than English, trials of other solid organ transplants, and trials where the unit randomised was not a transplant recipient. We established the registration status of each trial by conducting investigator and title searches of the WHO International Clinical Trials Registry Platform (ICTRP: http://apps.who.int/trialsearch/) between 25/11/09 and 14/05/2011. Trials not found through the WHO ICTRP were considered unregistered. Subsequently, for trials that were registered, we examined all published reports that related to that trial for the presence of trial registry identifiers, to

determine if trial registration details had been declared. Data collection and analysis was conducted by one author and checked by another, without blinding to the trial names or authors.

Data analysis

As many trials are reported more than once, we first identified reports from the same trial using trial characteristics (such as sample size, study intervention, location of trial, study population, etc.) and then grouped them. To determine the factors associated with trial registration we conducted logistic regression analyses, with the trial as the unit of analysis. We considered the following study factors: number of reports per trial (1, 2, >2), sample size (<200, ≥200), earliest date of publication (<2007, 2007, 2008, 2009, 2010), funding source (investigator, commercial, not stated), whether the primary outcome favoured the intervention (p value <0.05, or not), region in which the trial was conducted (global or >2 continents, USA, Europe, other) and whether the trial had at least one report in a journal affiliated with the ICMJE (determined either by the journal being listed on ICMJE website on 06/01/2010 or as stated or implied from each journal's 'instructions to authors'). In attributing trial funding source, where trials were funded by both investigator and commercial sources we recorded the trial as commercially funded. Trial funding source was recorded from trial reports, trial declarations and conflict of interest statements. The primary outcome of a trial was identified as the outcome reported as such from the trial report or if this was unclear from the sample size calculation. The earliest year of trial publication entered and remained in the adjusted analyses regardless of statistical significance, as calendar year was central to our research question. To allow for potential effect modification among study factors, we pre-specified potential interaction terms. We

hypothesised that commercially funded trials were more likely to be larger and reported more than once; hence we considered potential for commercial funding source being associated with multiple reports, and commercial funding source being associated with larger sample size.

To determine the factors associated with declaration of trial registration details within trial reports we conducted logistic regression analyses using generalised estimating equations. The unit of analysis was the trial report and adjusted for any clustering effect that might be present due to multiplicity of reports within trials via a sandwich estimator (30). We considered the following study factors using the same categories and rules as with the first model: number of reports per trial, sample size, date of publication, funding source, whether the primary outcome reported favoured the intervention, region in which the trial was conducted and whether the trial report was published in a journal affiliated with the ICMJE. To allow for potential effect modification among study factors, we pre-specified potential interaction terms. In line with existing studies (16, 17, 29-31), we hypothesised that commercially funded trials were more likely to reach conclusions favouring the drug than non-commercially funded trials. Therefore, we considered potential for commercial funding source being associated with a statistically significant result.

For both models, associations between the covariates and outcomes were reported as odds ratios (OR) with 95% confidence intervals (CI). All factors were considered in adjusted analyses if the unadjusted association showed $P<0.25$, and were sequentially eliminated using backward selection if adjusted association showed $P>0.05$. All P-values were calculated from Wald $\chi 2$ test statistics. The final models were checked using a Hosmer and Lemeshow goodness-of-fit test. To investigate the robustness of our analyses we repeated

our analyses excluding abstract reports. Statistical analyses were carried out using STATA software (Stata11, StataCorp LP, Texas, USA).

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Table 1: Characteristics of trials and related trial reports included in analyses

	Trials [a] (%)	Reports of registered trials [b] (%)
Total	307 trials	212 trial reports
Registered		
Yes	74 (24)	212 (100)
No	233 (76)	-
Journal		
Transplantation	217 (71)	147 (69)
Nephrology	58 (19)	50 (24)
General medical	25 (8)	14 (7)
General surgical	7 (2)	1 (1)
Publication status		
Full text publication	307 (100)	204 (96)
Abstract/Conference proceeding	-	8 (4)
Intervention rationale		
Immunosuppression	214 (70)	187 (88)
Hypertension	21 (7)	7 (3)
Infection	17 (6)	6 (3)
Endocrine	16 (5)	9 (4)
Other	39 (13)	3 (1)
Year of publication		
<2007	128 (42)	68 (32)
2007	67 (22)	43 (20)
2008	58 (19)	54 (25)
2009	29 (9)	19 (9)
2010	25 (8)	28 (13)
Sample size		
<200	235 (77)	67 (32)
≥200	72 (23)	145 (68)
Number of reports per trial		
1	227 (74)	37 (17)
2	42 (14)	26 (12)
>2	38 (12)	149 (70)
Published following ICMJE guidelines		
No	170 (55)	128 (60)
Yes	137 (45)	84 (40)
Region in which the trial was conducted		
Europe	57 (19)	22 (10)
USA	56 (18)	62 (29)
Other	163 (53)	34 (16)
Global	31 (10)	94 (44)
Funding source		
Investigator	51 (17)	25 (12)
Commercial	122 (40)	171 (81)
Not stated	134 (44)	16 (8)
Result in favour of primary outcome		
Not significant	133 (43)	71 (33)
Significant	174 (57)	141 (67)

[a] Unit of analysis is the trial. [b] Unit of analysis is the trial report.

Table 2: Factors associated with trial registration and declaration of trial registration within reports of registered trials.

Trial characteristics	Trial registration [a] (Total trials 307)				Declaration of registration details in trial reports [b] (Total reports of registered trials 212)			
	Not registered (%)	Registered (%)	Unadjusted odds ratio (95% CI)	P value [c]	Did not declare (%)	Declared (%)	Unadjusted odds ratio (95% CI)	P value [c]
Total	233 (76)	74 (24)			156 (74)	56 (26)		
Year of publication								
<2007	103 (80)	25 (20)	1.0 (Referent)[d]	<0.007	65 (96)	3 (4)	1.0 (Referent)[d]	<0.001
2007	54 (81)	13 (19)	1.0 (0.5, 2.1)		32 (74)	11 (26)	7.4 (1.7, 32.3)	
2008	44 (76)	14 (24)	1.3 (0.6, 2.8)		39 (72)	15 (28)	8.3 (2.3, 29.9)	
2009	21 (72)	8 (28)	1.6 (0.6, 4.0)		11 (58)	8 (42)	15.8 (3.7, 66.8)	
2010	11 (44)	14 (56)	5.3 (2.1, 12.9)		9 (32)	19 (68)	45.7 (9.5, 219.2)	
Sample size								
<200	195 (83)	40 (17)	1.0 (Referent)[d]	<0.001	40 (60)	27 (40)	1.0 (Referent)[d]	0.015
≥200	38 (53)	34 (47)	4.4 (2.5, 7.7)		116 (88)	29 (12)	0.4 (0.2, 0.8)	
Number of reports per trial								
1	190 (84)	37 (16)	1.0 (Referent)[d]	<0.001	15 (41)	22 (59)	1.0 (Referent)[d]	<0.001
2	29 (69)	13 (31)	2.3 (1.1, 4.8)		17 (65)	9 (35)	0.4 (0.1, 1.1)	
>2	14 (37)	24 (63)	8.8 (4.2, 18.6)		124 (83)	25 (17)	0.1 (0.1, 0.3)	
Published following ICMJE guidelines								
No	158 (93)	12 (7)	1.0 (Referent)[d]	<0.001	113 (88)	15 (12)	1.0 (Referent)[d]	<0.001
Yes	75 (55)	62 (45)	10.9 (5.5, 21.4)		43 (51)	41 (49)	7.2 (3.2, 16.3)	
Region in which the trial was conducted								
Europe	41 (72)	16 (28)	1.0 (Referent)[d]	<0.001	9 (41)	13 (59)	1.0 (Referent)[d]	0.01
USA	32 (57)	24 (43)	1.9 (0.9, 4.2)		45 (73)	17 (27)	0.3 (0.09, 0.8)	
Other	143 (88)	20 (12)	0.4 (0.2, 0.8)		22 (65)	12 (35)	0.4 (0.1, 1.2)	
Global	17 (55)	14 (45)	2.1 (0.8, 5.3)		80 (85)	14 (15)	0.1 (0.03, 0.4)	
Funding source								
Investigator	35 (69)	16 (31)	1.0 (Referent)[d]	<0.001	11 (44)	14 (56)	1.0 (Referent)[d]	<0.003
Commercial	73 (60)	49 (40)	1.5 (0.7, 2.9)		131 (77)	40 (23)	0.2 (0.1, 0.6)	
Not stated	125 (93)	9 (7)	0.2 (0.06, 0.4)		14 (87.5)	2 (12.5)	0.1 (0.02, 0.6)	
Result in favour of the primary outcome								
Not significant	99 (74)	34 (26)	1.0 (Referent)[d]	0.6	41 (58)	30 (42)	1.0 (Referent)[d]	<0.006
Significant	134 (77)	40 (23)	0.9 (0.5, 1.5)		115 (82)	26 (18)	0.3 (0.1, 0.7)	

[a] Unit of analysis is the trial. [b] Unit of analysis is the trial report. [c] P values based on the Wald chi-squared test statistic.
[d] This is the group against which the other groups are compared.

Figures legends

Figure 1. Flow chart for identification of kidney transplantation randomised controlled trials published between October 2005 and December 2010.

Figure 2. Factors associated with trial registration, adjusted analysis (odds ratios and 95% confidence intervals).

Figure 3. Factors associated with declaration of trial registration in reports of registered trials, adjusted analysis (odds ratios and 95% confidence intervals).

Figures

Figure 1. Flow chart for identification of kidney transplantation randomised controlled trials published between October 2005 and December 2010.

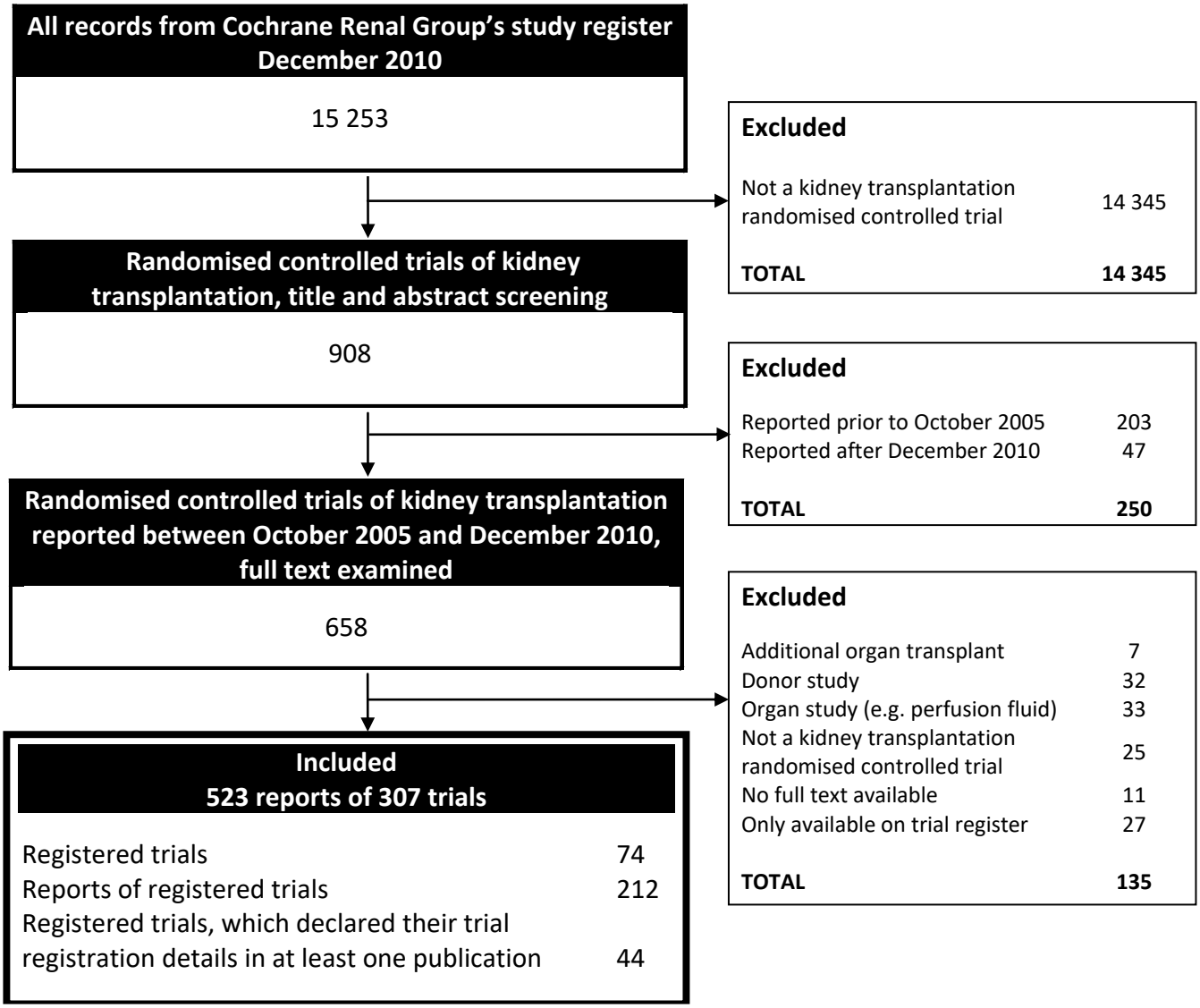
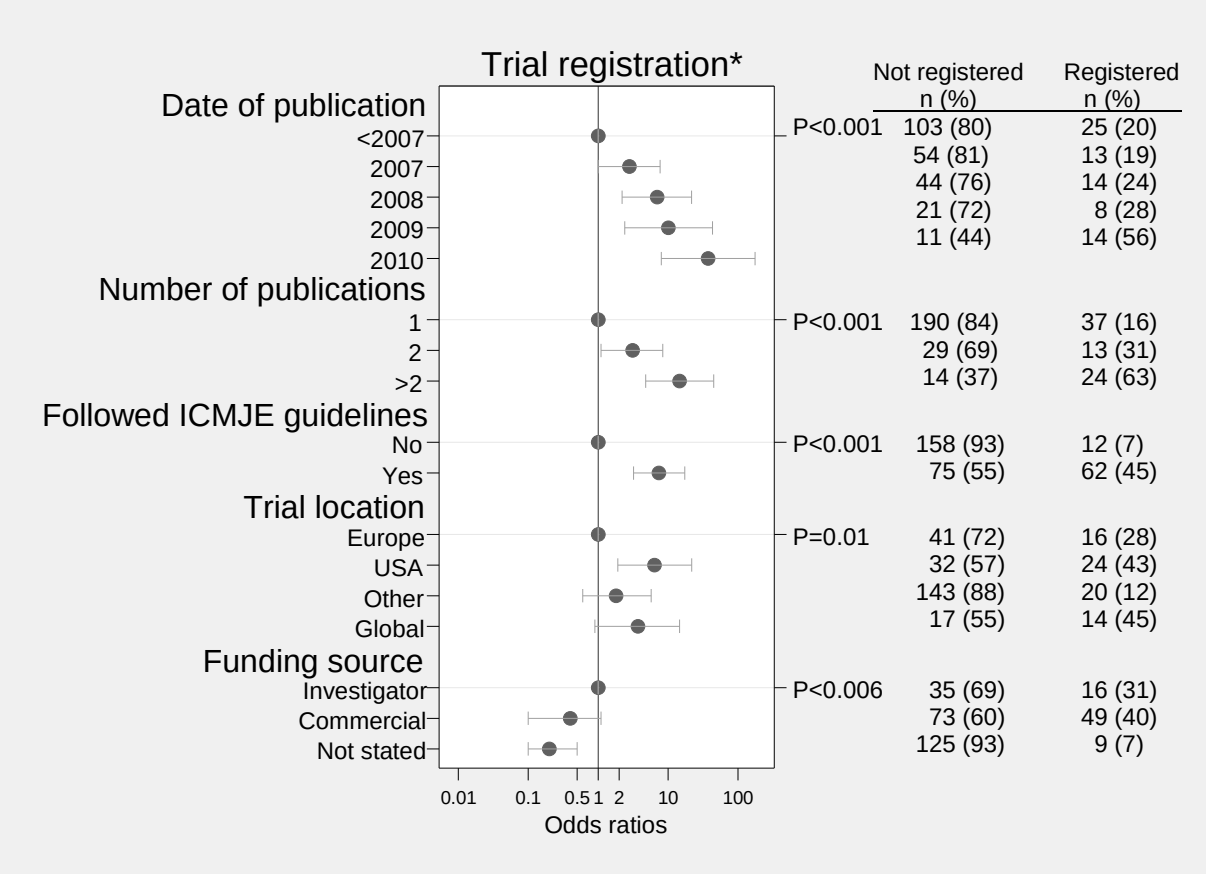
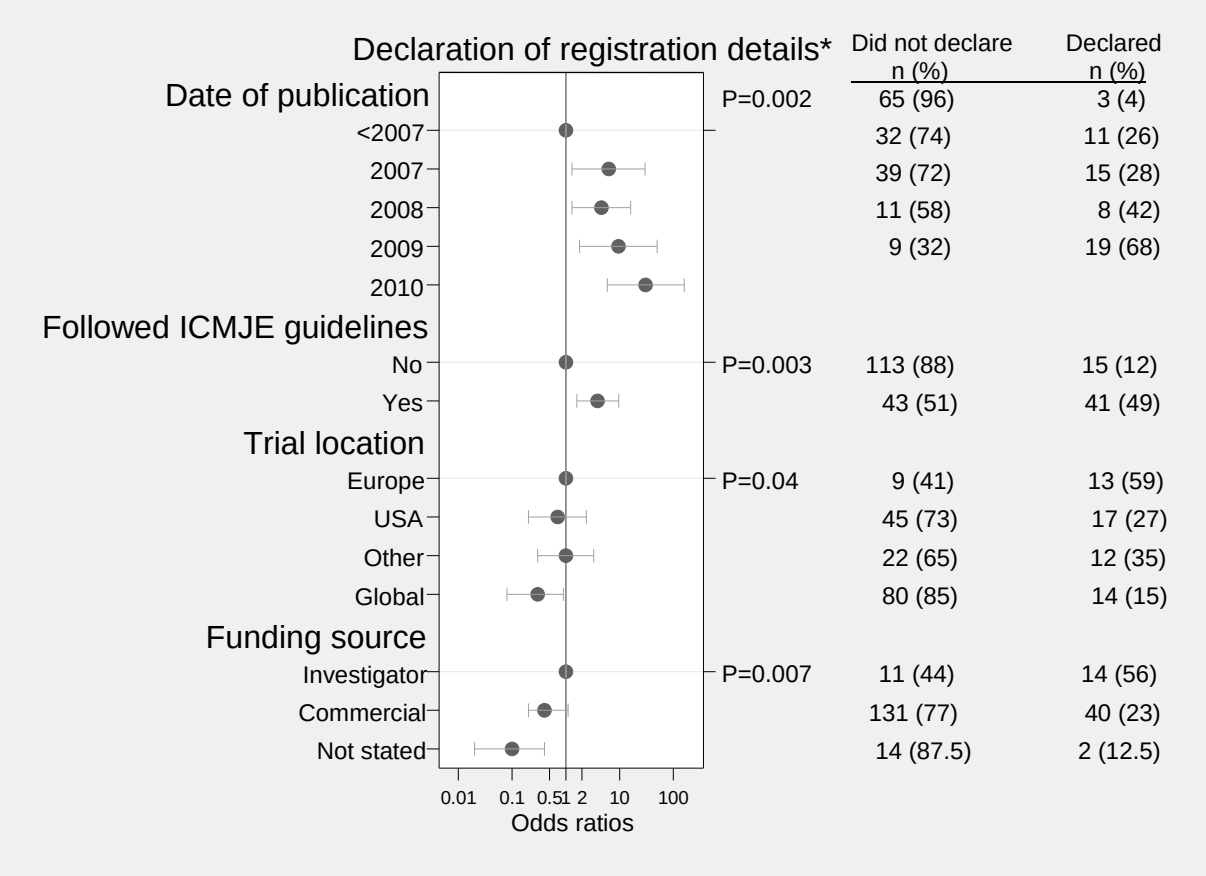


Figure 2. Factors associated with trial registration, adjusted analysis (odds ratios and 95% confidence intervals).



Note: * P values based on the Wald chi-squared test statistic.

Figure 3. Factors associated with declaration of trial registration in reports of registered trials, adjusted analysis (odds ratios and 95% confidence intervals).



Note: * P values based on the Wald chi-squared test statistic.