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REVIEW

The quality of reporting of randomized controlled trials in solid organ transplantation

Liset H. M. Pengel, Leticia Barcena and Peter J. Morris

Clinical Effectiveness Unit, Centre for Evidence in Transplantation, Royal College of Surgeons of England and the London School of Hygiene and Tropical Medicine, University of London, London, UK

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Correspondence
Peter J. Morris, AC, FRS, FRCS, Centre for Evidence in Transplantation, Royal College of Surgeons of England, 35-43 Lincoln's Inn Fields, London WC2A 3PE, UK. Tel.: +44 20 7869 6627; fax: +44 20 7869 6644; e-mail: pmorris@rcseng.ac.uk

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Summary

Randomized controlled trials (RCTs) of interventions provide the highest level of evidence about efficacy but their value either alone or within a meta-analysis is dependent on its methodological quality. For this reason recent RCTs in organ transplantation were assessed for quality. RCTs published between 2004 and 2006 ($n = 332$) were assessed, after excluding duplicate and nonEnglish reports. Quality was evaluated using the Jadad score plus allocation concealment and intention to treat analysis. We noted journal type, journal author instructions, funding source, sample size and number and location of study centres. Around one-third of RCTs had a Jadad score of 3 or greater (indication of a methodologically good quality trial) and the other two parameters were satisfied in just over one third. Although the majority of trials were published in speciality journals the quality of those published in general journals was superior. Commercially sponsored trials were of better quality as were multicentre trials in contrast to single centre trials. Overall quality of reporting of RCTs in organ transplantation is poor and as RCTs provide the highest level of evidence in evaluations of interventions there needs to be a concerted effort within the transplant community to improve the standards of RCTs.

Introduction

Randomized controlled trials (RCTs) are widely considered the gold standard to examine the efficacy of new or existing interventions. Yet, the conclusions concerning outcomes of RCTs are weakened if the methodology of a trial is poor. To judge whether the methodology used was appropriate, full details of the methodology, such as randomization, blinding and concealment of allocation should be included in the trial report. Inadequate reporting of RCTs has previously been associated with poor methodology [1] and other studies have also found that poor quality trials significantly inflate the treatment effects [2–4].

Guidelines have been developed to assist authors when reporting their research to the medical community. One initiative is the 'International Committee of Medical Journal Editors' (ICMJE) 'Uniform requirements for manuscripts submitted to biomedical journals' (http://www.icmje.org/). These uniform requirements were produced by a group of editors of general medicine journals who produced the first version of the uniform requirements in 1979 with the aim to 'help authors and editors in their mutual task of creating and distributing accurate, clear, easily accessible reports of biomedical studies'. Another initiative is the Consolidated Standards for Reporting of Trials (CONSORT statement, http://www.consort-statement.org/), which was developed specifically to improve the quality of reports of RCTs. The CONSORT statement consists of a checklist of standardized details that should be included in a trial report and strongly recommends the use of a flow chart to describe the flow of study participants throughout the study.

Kane *et al.* evaluated whether the introduction of the CONSORT statement improved the reporting of RCTs in two leading general medicine journals before and

after the publication of the CONSORT statement [5]. One of the two journals added the CONSORT statement to their author instructions while the other journal did not refer to the CONSORT statement. The authors concluded that the overall quality of RCT reporting improved over a period of time when comparing the period before the introduction of the CONSORT statement with the period after the introduction of the CONSORT statement. But, notably, the improvement in reporting was most consistent and significant in the journal that adopted the CONSORT statement in their author instructions.

We have previously summarized the methodological quality and the quality of reporting of RCTs in solid organ transplantation that were published in 2004 and concluded that both were unsatisfactory [6]. The objective of this study was to examine the quality of reporting of RCTs in solid organ transplantation that were published over a 3-year period between 2004 and 2006. We also examined author instructions in transplantation speciality and general medicine journals for mention of the CONSORT statement and ICMJE's uniform requirements. Finally, the associations between the methodological quality and other study characteristics such as funding sources, sample size, the number of centres and country/countries of study were explored.

Materials and methods

Selection of papers

We evaluated all English reports of RCTs that were included in the *Registries of randomized controlled trials* [7]. The registries were a 6-monthly feature of the journal *Transplantation* and provided an overview of RCTs of organ transplantation that were published between 2004 and 2006. To identify trials, we searched MEDLINE (Ovid and PubMed), the Cochrane Central Register of Controlled Trials and EMBASE to identify RCTs published between 2004 and 2006. Search terms in MEDLINE and Cochrane included all MeSH terms for solid organ transplantation and other generic transplantation MeSH terms. In addition, MeSH terms were also combined with the qualifier 'transplantation'. Specific terms for free-text search included all terms for organs combined with 'transplant*', 'allograft*', 'graft*'. The Cochrane highly sensitive search strategy was used to identify RCTs in MEDLINE. Search terms in EMBASE included all relevant EMTREE terms for organ transplantation and similar free-text search terms. A search strategy developed by the Cochrane Renal group was used to identify RCTs in EMBASE. If there were multiple reports of the same trial, only the major trial report was included.

Evaluation of methodological quality

There are over 35 different scales to assess the methodological quality of RCTs [8]. After evaluation of the different scales and consultation with experts, it was decided to assess the methodological quality of trials that were to be included in the registry using the Jadad scale plus allocation concealment and intention to treat [9]. The Jadad scale was developed to rate the methodological quality of reports of RCTs. The scale consists of items relating to randomization, blinding and description of withdrawals and follow up (Table 1). Scores range from 0 to 5 with trials scoring 3 or greater considered good quality trials. Allocation concealment was considered adequate if patients and investigators who enrolled patients could not foresee treatment assignment. Adequate means of allocation concealment included central randomization, pharmacy control, numbered or

Table 1. Description of the different items of the Jadad scale including scores.

Randomization		
Was the study described as randomized?	Described = 1	Not described = 0
Was the method used to generate the sequence of randomization described and appropriate, e.g. table of random numbers, computer-generated?	Described and appropriate = 1	Not described = 0
Was the method used to generate the sequence of randomization described but inappropriate, e.g. allocation according to date of birth?	Described but inappropriate = −1	Not described = 0
Blinding		
Was the study described as double-blind?	Described = 1	Not described = 0
Was the method of double-blinding-described and appropriate, e.g. identical placebo, active placebo, dummy?	Described and appropriate = 1	Not described = 0
Was the method of double-blinding-described but inappropriate, e.g. tablet versus injection?	Described but inappropriate = −1	Not described = 0
Withdrawals and dropouts		
Were the number of withdrawals and drop-outs described together with the reasons in each of the comparison groups.	Described = 1	Not described = 0

coded drug packs or sealed, opaque envelopes. The quality was independently assessed by two reviewers. Disagreements were resolved by discussion or through consultation with a third reviewer. Corresponding authors of all reports were contacted by e-mail to verify our quality assessment. They were invited to provide additional information regarding the study if not all the information regarding the quality items was included in the report. Additional information that was provided by authors was accepted in any form, for example a copy of the original trial protocol or an e-mail with additional information. Conflicting information was resolved by further e-mail contact. Three hundred and thirty-two authors were contacted and asked to reply whether they disagreed with our evaluation. One hundred and twenty-eight authors replied and 99 scores on individual quality items were changed following consultation.

Further data extraction

In February 2008, we examined the author instructions of the 10 most cited speciality journals in transplantation and all general medicine journals that published RCTs in transplantation for mention of the CONSORT statement (http://www.consort-statement.org/) and ICMJE's 'Uniform requirements for manuscripts submitted to biomedical journals'. For each report, we also recorded if a flow diagram or a satisfactory description of participant flow at each stage of the study was included as is required by the CONSORT statement. Additionally, we noted whether funding sources were included and the sources of funding were then classified as commercial, nonprofit, mixed (commercial & nonprofit), or no funding received. If no information regarding sponsorship was included but one or more authors were employees of a commercial, mostly pharmaceutical, company these trials were considered commercially sponsored. If there was a statement that study drugs were provided by a commercial company, then these trials were also considered commercially sponsored. In addition, we extracted the number of participants in each trial, the country or countries where the trial was conducted and whether the trial was a single or multicentre trial.

Statistical analysis

To explore the data, we calculated descriptive statistics using SPSS 16.0 for Windows. The Mann–Whitney *U*-test was used to examine the association between sample size and Jadad score (low quality versus high quality), allocation concealment and whether the analysis was on the basis of intention. *P*-values were two-tailed and *P*-values <0.05 were considered statistically significant.

Results

Included trials

There were 424 reports of RCTs that were published between 2004 and 2006 and included in the *Registries of randomized controlled trials*. We excluded 80 reports that were duplicate reports of the same trial and 12 reports that were not written in the English language. Therefore the total number of RCTs analysed was 332. Most trials evaluated immunosuppressive interventions in kidney transplantation (Fig. 1).

Methodological quality assessment

Approximately one-third of the trials was considered to be of good quality according to the Jadad score (Table 2). The median Jadad score was 2. Analysis of the individual items of the Jadad score showed that most reports (66%) did not include a statement on how the randomization sequence was generated. An adequate method to generate the randomization sequence was described in only 105 reports (32%) and in eight reports (2%) an inappropriate method to generate the randomization sequence was described such as alternation. Sixty-four reports (19%) described a double-blinded study of which 45 described an appropriate method of double-blinding. An appropriate statement or a flow diagram describing withdrawals and dropouts was included in 235 reports (71%).

One-third of trial reports (34%) adequately described concealed allocation. Nearly half of trial reports (45%) analysed the data on the basis of intention to treat, confirmed by the flow charts and description of exclusions, withdrawals and drop-outs. The quality scores on the Jadad scale, allocation concealment and intention to treat were similar for the different years (Table 2).

Speciality versus general medicine journals

Most of the RCTs (97%) were published in a total of 78 different transplantation speciality journals. All nine trials, except for one (89%), that were published in general medicine journals were of good quality according to the Jadad score versus only 35% of trials published in speciality journals (Table 3).

CONSORT statement

Only three out of 10 speciality journals mentioned the CONSORT statement together with a link to the CONSORT statement website in their author instructions (Table 4). Six out of 10 speciality journals referred to ICMJE's uniform requirements for manuscripts in their author instructions but two journals referred to dated

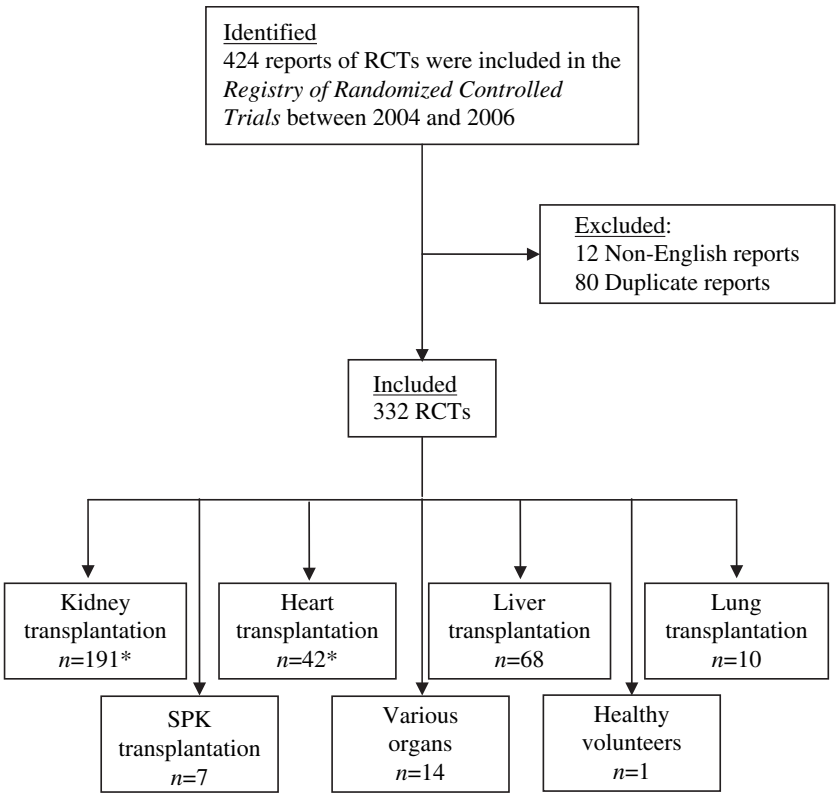

Figure 1 The number of trials that were identified and subsequently included or excluded. *Wabbijn *et al.* (18) reported on two RCTs in one report: one RCT on kidney transplantation and one RCT on heart transplantation. SPK, simultaneous pancreas and kidney.

Table 2. Quality assessment of trials published between 2004 and 2006 for the total number of trials and separately for each year.

	Jadad 0	Jadad 1	Jadad 2	Jadad 3	Jadad 4	Jadad 5	Jadad score ≥3	Allocation concealment	Intention-to-treat
Total (*n* = 331)*	4 (1)	70 (21)	134 (40)	84 (25)	18 (5)	21 (6)	123/331 (37)	113/331 (34)	149/331 (45)
2004 (*n* = 95)	1 (1)	20 (21)	38 (40)	20 (21)	9 (9)	7 (7)	36/95 (38)	29/95 (31)	44/95 (46)
2005 (*n* = 131)	2 (2)	27 (21)	52 (40)	35 (27)	5 (4)	10 (8)	50/131 (38)	47/131 (36)	63/131 (48)
2006 (*n* = 105)*	1 (1)	23 (22)	44 (42)	29 (28)	4 (4)	4 (4)	37/105 (35)	37/105 (35)	42/105 (40)

Values given in parentheses are percentages.
*This excludes a paper for which a quality rating was not relevant [17].

publications and did not include a web link. All of the general medicine journals included both the CONSORT statement and ICMJE's uniform requirements for manuscripts in their author instructions. A flow chart to present the flow of study participants through the different stages of the trial is strongly recommended by the CONSORT statement but only 50 trial reports (15%) included such a flow chart. However, 64% of reports that did not include a flowchart did provide an adequate description of drop-outs and withdrawals.

Multicentre versus single centre trials

Of the 332 trials, 217 trials were single-centre trials conducted in 30 different countries. A quarter of single-centre trials were conducted in the USA (Table 5). The 115 multicentre trials were conducted in 21 different countries or group of countries. The percentage of good quality trials according to the Jadad score was higher among multicentre trials than single centre trials (54% vs. 28%). In addition, more multicentre trials compared to single-centre trials used concealed allocation (50% vs. 26%) and based their analysis on intention-to-treat (74% vs. 30%).

Sponsorship and methodological quality

Funding sources were declared in 66% of the reports. Over one-third of all trials (39%) were sponsored by commercial companies, 18% of trials were sponsored by nonprofit institutions and 8% of trials received mixed

Table 3. Number of trials published for the 10 speciality journals with the most publications out of a total of 78 speciality journals and all general medicine journals together with scores on the quality features of the published trials for each journal.

Journal	*n*	Jadad score ≥ 3	Allocation concealment	Intention-to-treat
Speciality journals (*n* = 323)				
Transplantation	66	30 (45)	29 (44)	29 (44)
Transplantation Proceedings	51	5 (10)	7 (14)	10 (20)
American Journal of Transplantation	38	19 (50)	21 (55)	29 (76)
Liver Transplantation	19	8 (42)	6 (32)	11 58)
Clinical Transplantation	19	5 (26)	2 (11)	8 (42)
Journal of Heart and Lung Transplantation	17	7 (41)	3 (18)	6 (35)
Transplant International	10	1 (10)	3 (30)	4 (40)
Nephrology Dialysis Transplantation	10	5 (50)	4 (40)	4 (40)
Journal of the American Society of Nephrology	7	4 (57)	4 (57)	4 (57)
Kidney International	7	3 (43)	3 (43)	3 (43)
General Medicine journals (*n* = 9)				
New England Journal of Medicine	5	4 (80)	2 (40)	5 (100)
Lancet	2	2 (100)	2 (100)	2 (100)
BMJ	1	1 (100)	1 (100)	1 (100)
Annals of Internal Medicine	1	1 (100)	1 (100)	1 (100)

Values given in parentheses are percentages.

Table 4. Information regarding the CONSORT statement and ICMJE '*Uniform requirements for manuscripts submitted to biomedical journals*' included in author instructions of the 10 most cited speciality journals and all general medicine journals that published RCTs in solid organ transplantation between 2004 and 2006.

Journal	CONSORT	ICMJE Guidelines
Speciality journals (n = 323)		
Transplantation (n = 66)	Yes (web address)	Yes regarding financial support and competing interests (web address)
Transplantation Proceedings (n = 51)	No	No
American Journal of Transplantation (n = 38)*	No	Yes (referral to the 1997 version of the guideline)
Liver Transplantation (n = 19)	No	No
Clinical Transplantation (n = 19)	No	Yes (web address)
Journal of Heart and Lung Transplantation (n = 17)	No	No
Transplant International (n = 10)	No	Yes (web address)
Nephrology Dialysis Transplantation (n = 10)	No	Yes (referral to the 1982 publication of the guideline)
Journal of the American Society of Nephrology (n = 7)	Yes (web address)	Yes but only regarding authors and contributors (web address)
Kidney International (n = 7)	Yes (web address)	No
General Medicine Journals (n = 9)		
New England Journal of Medicine (n = 5)	Yes (web address)	Yes (web address)
Lancet (n = 2)	Yes (web address)	Yes (web address)
British Medical Journal (n = 1)	Yes (web address)	Yes (web address)
Annals of Internal Medicine (n = 1)	Yes (web address)	Yes (web address)

ICMJ = International Committee of Medical Journal Editors.
*Author instructions were updated in April 2007.

funding from both commercial companies and nonprofit institutions (Table 6). Trials funded by commercial companies or that received mixed funding were of better quality than trials funded by nonprofit organizations. For example, 52% of trials funded by commercial companies and 63% of trials that received mixed funding were considered good quality trials according to the Jadad score versus only 27% of nonprofit-sponsored trials.

When comparing sponsorship between single- and multicentre trials, commercial companies more often sponsor multicentre trials ($n = 85$) compared with single-centre trials ($n = 47$) (Fig. 2). Of the trials that did not

Table 5. The five countries or group of countries where most studies were conducted for single centre and multicentre trials including the scores on the quality features of the trials for each country and for the total number of single centre and multicentre trials.

Country/countries	Number of trials	Jadad ≥3	Allocation concealment	ITT
Single-centre trials				
USA	56	19 (34)	12 (21)	25 (45)
Germany	19	2 (11)	3 (16)	3 (16)
Italy	18	6 (33)	6 (33)	4 (22)
UK	15	7 (47)	8 (53)	5 (33)
Spain	11	2 (18)	2 (18)	3 (27)
Total	217	61 (28)	57 (26)	66 (30)
Multicentre trials				
International*	32	20 (63)	15 (47)	27 (84)
Europe	21	13 (62)	10 (48)	17 (81)
USA	20	9 (45)	9 (45)	12 (60)
France	8	3 (38)	2 (25)	7 (88)
Netherlands	6	1 (17)	2 (33)	5 (83)
Total	114†	62 (54)	57 (50)	84 (74)

Values given in parentheses are percentages.
*Multicentre international trials include trials that were conducted on more than one continent.
†This excludes a paper for which a quality rating was not relevant [17].

Table 6. Different types of sponsorship for RCTs and quality scores for each type of sponsorship.

Sponsorship	*n*	Jadad ≥3	Allocation concealment	ITT
Commercial	130	67 (52)	53 (41)	87 (67)
Nonprofit	60	16 (27)	20 (33)	16 (27)
Mixed funding	27	17 (63)	11 (41)	14 (52)
No funding received	1	1	1	1
Not described	113	22 (19)	29 (26)	32 (28)

Values in parentheses are percentages.

include any information regarding sponsorship most were single-centre reports ($n = 101$) compared to multicentre reports ($n = 12$).

Sample size and methodological quality

The number of patients per study ranged from 10 to 2858 with the median being 70 participants per trial. When trials were divided into high quality (Jadad score 3–5) and low quality trials (Jadad score 0–2), the sample size was larger for high quality studies than low quality trials (median sample size 100 vs. 63; $P = 0.004$) (Table 7). The sample size was also larger for trials that employed concealed allocation (median sample size 100 vs. 62; $P = 0.001$) or that based the analysis on intention-to-treat (median sample size 108 vs. 52; $P = 0.000$).

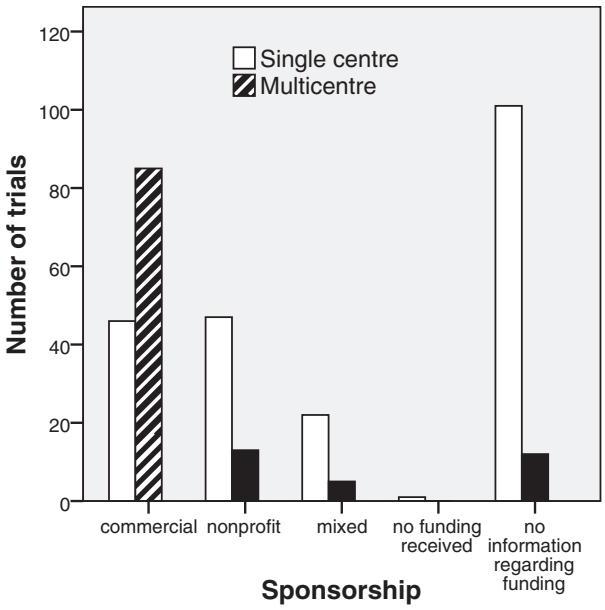

Figure 2 Sponsorship and multicentre ($n = 115$) versus single centre ($n = 217$) trials.

Table 7. Comparison of the number of participants per trial in terms of the Jadad score, and whether the trial described adequate concealed allocation and analysis based on intention-to-treat.

Quality criteria	Trials (*n*)	Sample size median (interquartile range)	Mann–Whitney *U*-test
Jadad score			
≥3 (high quality)	123	100 (42–185)	$P = 0.004$
<2 (low quality)	208	63 (34–118)	
Allocation concealment			
Yes	114	100 (45–204)	$P = 0.001$
No	217	62 (32–115)	
Intention-to-treat			
Yes	150	108 (56–224)	$P \leq 0.001$
No	181	52 (30–98)	

Power calculations were given in too few reports to allow evaluation on this basis.

Discussion

Randomized controlled trials have the most rigorous study design in that the allocation of participants to a particular intervention is random as will be the distribution of confounding factors. Meta-analyses of RCTs can therefore potentially provide the highest level of evidence. But if the quality of RCTs is not adequate then the conclusions either from a RCT or from meta-analyses are limited. Furthermore, this means that the development of guidelines for patient care is also limited by a lack of

definitive evidence. Our analysis of 332 RCTs published over a 3-year period shows that the quality of reporting of recently published trials in transplantation is mostly not satisfactory. This is not different from other disciplines, e.g. an evaluation of the methodological quality of trials in general surgery also found that only one-third of trials were of satisfactory quality according to the Jadad scale [10].

For this analysis reports published in languages other than English were excluded. It has been previously shown that trials reported in languages other than English are of lower methodological quality [11]. Our sample included 332 reports and 12 nonEnglish reports were excluded. This is less than 4% of the total sample. We do not believe given the small number of nonEnglish reports that excluding these reports had a severe impact on the overall estimate of quality. It is likely that if these nonEnglish reports were included in our sample, then the overall estimate of study quality would have been even lower.

Despite the development of widely accepted guidelines to improve the reports of RCTs, e.g. the CONSORT statement or ICMJE's guidelines, we found that only four out of the 10 most cited journals in transplantation included the CONSORT statement in their author instructions and six out of 10 referred to ICMJE's guideline including two journals that refer to out-of-date publications of the ICMJE's guideline. A recent study by Hopewell *et al.* [12] evaluated the top five journals (according to impact factor) from 33 medical specialities and they concluded that only 38% of journals mentioned the CONSORT statement in their author instructions and 42% referred to the ICMJE's guidelines. Furthermore, they assessed the journal editors' endorsement of the CONSORT statement and showed that while 88% of journals recommend authors to comply with the CONSORT statement only 41% incorporated the CONSORT statement in their peer review process and 47% incorporated the CONSORT statement in their editorial process. These findings clearly show that referring to the CONSORT statement is not sufficient to ensure that authors comply with the statement but also not sufficient for peer reviewers and journal editors to comply as well.

We found that trials that were funded by commercial companies or that received mixed funding from both commercial and nonprofit institutions were of better methodological quality than studies that were funded by nonprofit institutions. This was previously found by some but not all studies that examined this relationship. Lexchin *et al.* conducted a systematic review investigating whether drug studies funded by the pharmaceutical industry differ in methods from studies with other sources of funding [13]. They concluded that no studies reported that industry funding had poorer methodological quality and some studies concluded that industry sponsored studies were of better quality. However, Clifford *et al.* evaluated 100 RCTs that were published in high impact factor, general medical journals and found no relationship between Jadad quality scores and funding sources [14]. The majority of trials conducted in organ transplantation test the efficacy of (immunosuppressive) drugs and are therefore often sponsored by pharmaceutical companies. It could be suggested that because of the strict process for drug approval requirements by the European Medicines Agency and the US Food and Drug Administration, these studies are more likely to be of high quality.

In conclusion, the majority of trials that are conducted in solid organ transplantation are of insufficient methodological quality. Despite the development of guidelines to improve the reporting of RCTs and their support by medical journal editors, both authors and journals show insufficient compliance with these standardized guidelines. It would appear that there is a strong need to educate the transplant community about the importance of adequate methodology and reporting guidelines. For example if the CONSORT statement was consulted during the design of a trial there would be far less problem with adequate reporting of the trial at a later time. In this context, the Centre for Evidence in Transplantation and the European Society for Organ Transplantation have initiated a collaboration to help with the design and reporting of RCTs in Europe [15] (http://www.esot.org). The collaboration hopes to improve the quality of RCTs in organ transplantation in Europe by advising investigators in the early stages of trial design and planning. In this way a strong evidence base for the best possible patient care can be built. The Registry of published trials has now been replaced by the electronic transplant library that includes all RCTs published from 1970 and the prospective evaluation of the quality of trials, which began in 2004, is continuing [16]. It is hoped that a similar analysis to this in a few years time will show an improvement in the methodological quality and reporting of RCTs in organ transplantation.

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