Pediatr Nephrol (2010) 25:2383–2392
DOI 10.1007/s00467-010-1595-x

EDITORIAL REVIEW

Systematic review of randomized controlled trial quality in pediatric kidney transplantation

Robert J. Brooks · Gail Y. Higgins · Angela C. Webster

Received: 9 February 2010 / Revised: 17 May 2010 / Accepted: 7 June 2010 / Published online: 6 August 2010

Abstract Limited pediatric-specific research can lead to sub-standard evidence for clinical decision making in children. We sought to systematically evaluate the methodological quality and the reporting standards of randomized controlled trials (RCTs) of transplantation trials in children. We included RCTs of kidney transplant recipients that had enrolled at least one child (aged 17 years or less) and that were reported in English language, peer reviewed journals from 2000 onward in the Cochrane Renal Group's specialized register. Trial reports were assessed against the 22 item checklist of the CONsolidated Standards Of Reporting Trials (CONSORT) statement. Twenty-seven RCTs were included. The reporting of the essential components of the methods, results and discussion domains was unsatisfactory. Mean CONSORT criteria score for the pediatric trials was 67% and 66% for trials including both adults and children (p value for the difference = 1.00). Trial reporting quality in pediatric transplantation trials is not different from trials involving adults. It is evident that the reporting standards of RCTs in both adult and pediatric transplantation require major improvements. This work bench-marks current standards for future quality improvement.

Keywords CONSORT · Kidney transplantation · Randomized trials · Reporting quality · Pediatrics

R. J. Brooks · A. C. Webster
Sydney Medical School,
University of Sydney,
Sydney, NSW, Australia

G. Y. Higgins · A. C. Webster
Cochrane Renal Group,
Centre for Kidney Research
at the Children's Hospital at Westmead,
Sydney, NSW, Australia

A. C. Webster
Centre for Transplant and Renal Research,
Westmead Millennium Institute, Westmead Hospital,
Sydney, NSW, Australia

A. C. Webster (✉)
School of Public Health, University of Sydney,
Room 304a, Edward Ford Building A27,
Sydney, NSW 2006, Australia
e-mail: angela.webster@sydney.edu.au

Introduction

End-stage kidney disease (ESKD) is a chronic, devastating illness in children with an incident rate of approximately 8 cases per million of the population in Australia [1]. Kidney transplantation is the first-line treatment for ESKD in children [2, 3]. Treatment guidelines for children receiving kidney transplants rely heavily on empirical evidence derived from studies in adults as a result of the under-representation of children in randomized controlled trials (RCT) throughout the medical literature [4, 5]. The paucity of pediatric-specific research is multifactorial, but translates into sub-par evidence for clinical decision-making in the treatment of children with ESKD. It is therefore of the utmost importance that pediatric research that has been done or will be undertaken has both the best design and transparent reporting as these elements are fundamental to clinical research.

Although there is a correlation between poorly designed RCTs and poor trial reporting, it has been widely recognized that poor reporting quality alone can lead to exaggeration of treatment efficacy, and that deficiencies in reporting trials are unfortunately very common even in well-designed clinical trials in prominent medical journals [6, 7]. In response to the substantial gap in the optimal reporting of RCTs, the CONSORT (CONsolidated Standards Of Reporting Trials) statement was developed by two international, multi-disciplinary work groups to re-establish robust reporting standards as the foundation for reliable, evidenced-based research [8]. Verification of improvement in the quality of

reporting with implementation of the CONSORT statement was followed by its widespread endorsement by leading medical journals and the completion of internal audits in several medical disciplines [9, 10].

Measurement of the reporting quality of pediatric trials to date has been limited to a few studies completed in psychology, dentistry, complementary medicine, and cerebral palsy physiotherapy [11–14]. Although no studies have examined the quality of reporting in pediatric renal transplantation, trials in adults investigating immunosuppressive interventions for kidney transplant recipients have demonstrated failings in trial reporting, with clinicians expressing that poor reporting quality contributed to difficulty in establishing best practice despite a substantial body of literature in this field [15, 16].

In this review, we aimed to evaluate the quality of reporting of transplantation trials in children published in contemporary biomedical literature. By measuring and describing the standard of reporting, we aimed to highlight what has been reported well, and what has been under-reported, to provide a bench-mark against which future improvement in reporting standards can be measured. Furthermore, we aimed to explore any potential differences in reporting standards among trials involving only children and trials involving a mixed population of adults and children.

Materials and methods

Review design

All RCTs and quasi-randomized trials (where allocation was not truly random, but based on day of week or patient record number or similar) in kidney transplant recipients that had enrolled at least one child (defined as age 17 or less), and that were reported from 2000 onwards were eligible for inclusion in the review. These trials could involve either children alone (referred to in this paper as pediatric trials), or mixed populations of adults and children (referred to in this paper as mixed population trials). Trials enrolling only adult participants (18 years and over) were excluded, as were trials in which recipients had received another solid organ in addition to kidney transplantation. We included only reports of trials published in peer-reviewed biomedical literature, and excluded trials reported only as abstracts from conference proceedings or in non-peer-reviewed journals. Non-English language publications were excluded because of a lack of feasibility as there were no resources available for translation. There were no other exclusions.

Identification of cohort of trials for inclusion

Relevant trials were obtained from the Cochrane Renal Group's specialized register of RCTs (2000 to 30 April 2008). The search was designed to retrieve contemporary reports of RCTs published since CONSORT reporting standards became widely accepted, and so did not include reports prior to this century. The search strategy was developed in collaboration with the Cochrane Renal Group's trial search coordinators, and included trials assigned the keyword "Child", OR trials assigned any or all of the medical subject heading (MeSH) terms "adolescence", "adolescent", "child", or "infant". Transplantation trials were further separated from trials investigating general renal medical conditions, chronic kidney disease, peritoneal dialysis or hemodialysis by a subset search strategy using text words (transplant*), (donor*), (graft*), or (recipient*). Where necessary, we reviewed the full citations to clarify all trial reports meeting the inclusion criteria. A second reviewer (AW) independently reviewed the search results and discrepancies were resolved by discussion. In the event of identification of multiple reports from the same trial, only the earliest publication reporting fullest clinical results was selected, and subsequent reports were discarded. In doing this, we reasoned that the first report of any trial to enter the public domain might be expected to report methods clearly and unambiguously.

Assessment tool

The revised CONSORT statement was used as a basis for assessing reporting quality. CONSORT is a validated, evidence-based guideline demonstrated to improve the quality of reporting of RCTs, which has been endorsed by the International Committee of Medical Journal Editors, and by over 343 medical journals including the *New England Journal of Medicine* and *The Lancet*, as well as the leading nephrology and transplantation journals (such as the *Journal of the American Society of Nephrology*, the *American Journal of Transplantation* and *Transplantation*) (Fig. 1) [8, 9, 17].

Data abstraction and analysis

Data abstraction was completed by a single reviewer (RB) not blinded to trial authors or journal, with any uncertainties discussed with a second reviewer (AW) using a standardized data form to document trial characteristics and the presence or absence of CONSORT checklist items. The reporting quality of included trials was assessed using the 22-item CONSORT checklist (Fig. 1), with the successful reporting of a CONSORT criteria item only awarded if all of the required components detailed in the CONSORT statement were completely satisfied [8]. Characteristics of each included trial were summarized descriptively, and quantitative frequencies for each individual item and overall trial CONSORT scores were tabulated. Comparisons of the reporting quality of CONSORT items were analyzed as binary variables (did not meet CONSORT requirement/did

Fig. 1 The 2001 revised CONSORT statement checklist of essential items that should be included in reports of randomized controlled trials (RCTs). This checklist was used to score reports of transplantation trials including children in this review

Topic	Item	Descriptor
TITLE & ABSTRACT	1	How participants were allocated to interventions.
INTRODUCTION		
Background	2	Scientific background and explanation of rationale.
METHODS		
Participants	3	Eligibility criteria for participants and the settings and locations where the data were collected.
Interventions	4	Precise details of the interventions intended for each group and how/when they were administered.
Objectives	5	Specific objectives and hypotheses.
Outcomes	6	Clearly defined primary and secondary outcome measures.
Sample size	7	How sample size was determined and explanation of any interim analyses and stopping rules.
Sequence generation	8	Method used to generate the random allocation sequence; including details of any restrictions.
Allocation concealment	9	Method used to implement the random allocation sequence.
Implementation	10	Who generated the allocation sequence, enrolled participants, and assigned participants to their groups.
Blinding (masking)	11	Whether participants, study personnel, and data analysts were blinded to group assignment.
Statistical methods	12	Statistical methods used to compare groups for primary outcome(s); methods for additional analyses.
RESULTS		
Participant flow	13	Flow of participants through each stage including the numbers of participants randomly assigned, receiving intended treatment, completing the protocol, and analyzed for the primary outcome.
Recruitment	14	Dates defining the periods of recruitment and follow-up.
Baseline data	15	Baseline demographic and clinical characteristics of each group.
Numbers analyzed	16	Number of participants in each group included in each analysis and whether the analysis was by "intention-to-treat". State the results in absolute numbers when feasible.
Outcomes & estimation	17	For each outcome, a summary of results for each group, the estimated effect size and its precision.
Ancillary analyses	18	Address multiplicity by reporting other analyses performed; indicating those pre-specified/exploratory.
Adverse events	19	All important adverse events or side effects in each intervention group.
DISCUSSION		
Interpretation	20	Interpretation of the results; including study hypotheses, sources of potential bias or imprecision.
Generalizability	21	Generalizability (external validity) of the trial findings.
Overall evidence	22	General interpretation of the results in the context of current evidence.

meet CONSORT requirement) using a two-tailed Fisher's exact test. Overall CONSORT score in pediatric trials versus mixed population trials was analyzed using the two-tailed non-parametric Mann–Whitney *U* test. A value of $P<0.05$ was considered significant.

Results

A total of 1,775 abstracts were identified by the initial search strategy. A full paper review was undertaken for 161 trials that could not be excluded on title and abstract

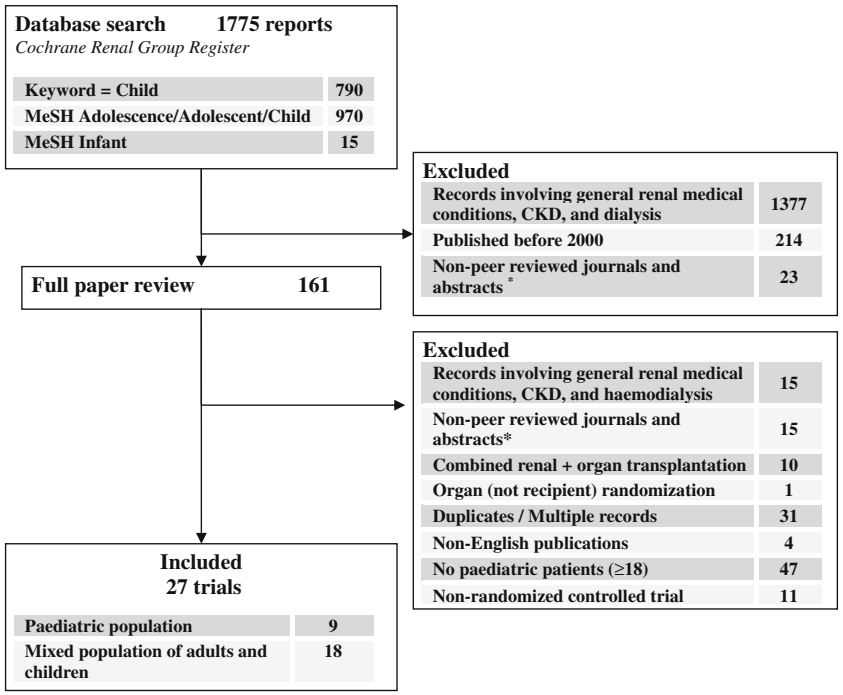

Fig. 2 Identification of reports of randomized controlled trials for inclusion in the systematic review of the quality of reporting of transplantation trials in children. Criteria for inclusion: all randomized controlled trials of kidney transplant recipients, reported in peer reviewed journals, from 2000 onwards, in the English language, conducted either exclusively in children, or including children within a mixed population of child and adult participants

* Reports of trials excluded if reported only as abstracts from conference proceedings, or if reported in non-peer reviewed journals such as Transplantation Proceedings

alone, and 27 were identified as meeting the inclusion criteria (Fig. 2). The 27 trials included comprised a total of 6,082 randomized participants; 928 participants in pediatric trials and 5,154 participants in mixed population trials containing both adults and children. For the mixed population trials it was not always clear exactly how many children were included, of the total randomized participants. The 27 trials included were reported in 12 different journals. The characteristics of the trials included are summarized in Table 1.

CONSORT items: title, abstract, and introduction

Only 4 out of 9 (44%) pediatric trials and 10 out of 18 (56%) mixed population trials described the trial as randomized in the title of the publication, but all the trials included appropriately described the fact that participants were randomly allocated to interventions in the trial abstracts (Table 2).

CONSORT items: methods

With the exception of the excellent reporting of specific objectives and hypotheses (27 out of 27) and the statistical methods for planned analyses (26 out of 27), the essential components of a well-reported methods section were absent from many of the trials (Table 2). Clearly defined trial eligibility criteria and sufficient information on data collection settings were not reported in one-third of the papers. Precise details of the interventions intended for each group and how and when they were received was reported in 78% of the trials included (7 out of 9 pediatric trials, 14 out of 18 mixed population trials). Sample size calculation was poorly reported with only 4 pediatric trials (44%) and 9 mixed population trials (50%) mentioning this information. Randomization reporting was unsatisfactory as many trials failed to include detailed descriptions of the methods used to generate the random allocation sequence (10 out of 27), to implement allocation concealment (9 out of 27), and to separate creation of the allocation sequence from assignment to the study groups (8 out of 27). Pediatric trials reported these randomization details marginally better than mixed population trials (44%, 56%, and 44% respectively compared with 33%, 22%, and 22% respectively), but the difference was not statistically significant. Blinding of participants, intervention administrators, and outcome assessors was under-reported. In particular, understanding who was blinded to treatment intervention was frequently unclear. Thirteen trials (48%) were clearly identified as open-label studies. For the remaining trials, only 2 mixed population trials (7%) provided complete details on blinding. Five trials (19%) reported partial information whereby at least one of the participants, administrators, or assessors was specifically reported as blinded. Three trials (11%) gave no other information beyond stating that the trial was either "double-blinded" or "blinded." There was no statistical difference ($P>0.05$) in the quality of reporting for any methodological items between pediatric and mixed population trials.

Table 1 Characteristics of trial reports included in review, stratified into those conducted exclusively in children, and those in mixed populations of both adults and children[a]

Reference	Setting		Participants				Intervention rationale	Main outcome	Declaration of pharmaceutical sponsorship
	Site	Country/Region[b]	*N*	Population	Age[a] Mean (SD)	Range			
[18]	Multi	AR	27	Children	8.9 (0.6)	≤16	Steroid formulation	Bone metabolism	Yes
[19]	Multi	CA, US	68	Children	ns	≤16	Hormone therapy	Growth	No
[20]	Single	US	23	Children	ns	≤16	Hormone therapy	Bone metabolism	Yes
[21]	Multi	EU	204	Children	ns	≤18	Immunosuppression	Acute rejection	Yes
[22]	Single	ns	60	Children	13.2 (4.3)	≤17	Calcium replacement	Bone metabolism	No
[23]	Multi	US	287	Children	ns	ns	Immunosuppression	Graft survival	No
[24]	Multi	EU	192	Children	ns	≤18	Immunosuppression	Acute rejection	Yes
[25]	Single	US	23	Children	14.6 (3.7)	ns	Self-care technique	Gingival over-growth	Yes
[26]	Multi	NL	44	Children	11.9 (ns)	ns	Immunosuppression	Graft function	No
[27]	Multi	CA, US	223	Mixed	46.5 (12.4)	12+	Immunosuppression	Composite efficacy	Yes
[28]	Multi	US	719	Mixed	44.9 (13.6)	13+	Immunosuppression	Acute rejection	Yes
[29]	Multi	EU, US	616	Mixed	40.3 (ns)	15–76	Anti-viral therapy	Economic analysis	Yes
[30]	Single	ns	82	Mixed	31.2 (ns)	4–56	Biopsy technique	Biopsy adequacy	No
[31]	Single	US	104	Mixed	49 (ns)	16–76	Immunosuppression	Acute rejection	Yes
[32]	Multi	AU, CA, EU	525	Mixed	48.8 (ns)	16–73	Immunosuppression	Graft survival	Yes
[33]	Multi	CA, EU, US	103	Mixed	43.6 (10.7)	16–65	Immunosuppression	Acute rejection	Yes
[34]	Multi	AU, CA, EU, US	576	Mixed	45.6 (12.7)	15–71	Immunosuppression	Acute rejection	Yes
[35]	Multi	ns	354	Mixed	ns	16–70	Immunosuppression	Graft survival	Yes
[36]	Single	IT	11	Mixed	15.9 (3.4)	11–22	Diet supplementation	Nutrition biomarkers	No
[37]	Multi	CN	114	Mixed	42.2 (10.6)	14–72	Pharmacokinetics	Economic analysis	Yes
[38]	Multi	ns	150	Mixed	44 (16)	14–78	Immunosuppression	Acute rejection	Yes
[39]	Single	EG	70	Mixed	28 (12)	16–45	Pharmacokinetics	Economic analysis	No
[40]	Single	BR	70	Mixed	34.8 (10.6)	13+	Immunosuppression	Acute rejection	Yes
[41]	Multi	ns	111	Mixed	45.9 (11.9)	16–65	Immunosuppression	Composite efficacy	No
[42]	Multi	AR, BR, CA, US	583	Mixed	43.3 (ns)	16–71	Immunosuppression	Composite efficacy	Yes
[43]	Single	ns	75	Mixed	34.7 (11.9)	7–67	Surgical technique	Graft function	No
[44]	Multi	BR, CA, US	668	Mixed	47.8 (13)	17–74	Immunosuppression	Composite efficacy	Yes

ns = items not reported in the original publication documented as "not stated"

[a] There may be other important descriptive data reported at trial level that we have not included in this table, including different measures of the age of trial participants, and we direct readers to the citations for further clarification

[b] Country or region where research was conducted as reported according to the International Organization for Standardization (ISO) two-letter region code: AR = Argentina, AU = Australia, BR = Brazil, CA = Canada, CN = China, EG = Egypt, EU = multiple countries of the European Union, IT = Italy, NL = The Netherlands, US = United States of America

CONSORT items: results

Although the flow of participants through each stage of the study was reported in 8 of the pediatric trials (89%) and 12 of the mixed population trials (67%), only 6 trials (22%) in total made adequate use of the recommended CONSORT flow diagrams, with fewer mixed population trials (11%) than pediatric trials (44%) using these visual flow diagrams (difference not significant $P>0.05$, Table 3). When describing the participant analysis set, we found appropriately reported intention-to-treat (ITT) analysis in only 13 trials (48%). Furthermore, 5 trials (28%) mislabeled their analyses as ITT when they were in fact not examined using a full analysis set. Outcome reporting was extremely poor, with only 9 trials (33%) reporting complete details for all trial arms of the intervention summary results, estimated effect size, and precision. Ancillary analyses including exploratory and sub-group analyses were common with one third of trials in total completing analyses not pre-specified in the methods section. There was no statistical difference ($P>0.05$) in the quality of reporting for any CONSORT results items between pediatric and mixed population trials.

Table 2 Identification of CONSORT criteria items (1 through 12) presented in the title, abstract, introduction, and methods of the kidney transplantation trials included in the study

Item	CONSORT criteria		Child[b] (%) n=9	Mixed[b] (%) n=18	Total[c] (%) n=27	P value*
1	Title and abstract		9 (100)	18 (100)	27 (100)	1.000
		Title	4 (44)	10 (56)	14 (52)	0.695
		Abstract	9 (100)	18 (100)	27 (100)	1.000
2	Introduction		9 (100)	17 (94)	26 (96)	1.000
		Scientific background	9 (100)	17 (94)	26 (96)	1.000
		Explanation of rationale	9 (100)	17 (94)	26 (96)	1.000
3	Participants		6 (67)	12 (67)	18 (67)	1.000
4	Interventions		7 (78)	14 (78)	21 (78)	1.000
5	Objectives		9 (100)	18 (100)	27 (100)	1.000
6	Outcomes		7 (78)	11 (61)	18 (67)	0.667
7	Sample size		4 (44)	9 (50)	13 (48)	1.000
8	Randomization sequence generation		4 (44)	6 (33)	10 (37)	0.683
9	Randomization allocation concealment		5 (56)	4 (22)	9 (33)	0.108
10	Randomization implementation		4 (44)	4 (22)	8 (30)	0.375
11	Blinding	Complete reporting	0 (0)	2 (11)	2 (7)	0.538
		Partial reporting	2 (22)	3 (17)	5 (19)	1.000
		"Double blind"; "blinded"[a]	1 (11)	2 (11)	3 (11)	1.000
		Insufficient reporting	3 (33)	1 (6)	4 (15)	0.093
		Open label study	3 (33)	10 (56)	13 (48)	0.420
12	Statistical methods		9 (100)	17 (94)	26 (96)	1.000

*P value for difference between child and mixed population trials, calculated using Fisher's exact test

[a] No elaboration of blinding provided; trial was described only as either "double blind" or "blinded"

[b] Pediatric trials including only children; all participants ≤17 years old. Mixed population of adults and children; at least one participant aged ≤17 years

[c] Total number of trials including both pediatric and mixed population trials

CONSORT items: discussion

Reporting of result interpretation was poor with only 10 trials (37%) in total clearly discussing both the summary of key findings and the trial limitations (Table 3). Failure to report these items was largely a result of deficiencies in reporting any trial limitations, with only 2 pediatric trials (22%) and 8 mixed population trials (44%) describing this CONSORT item as recommended. All included trials interpreted their results in the context of other current evidence, but 0 pediatric trials and only 3 mixed population trials (17%) incorporated a systematic review of current evidence into the discussion section. There was no statistical difference (P>0.05) in the quality of reporting for any of the required CONSORT discussion item components between pediatric and mixed population trials.

Overall CONSORT score

As demonstrated in Fig. 3, neither pediatric nor mixed population trials scored well overall when compared against the 22 item CONSORT checklist. In fact, one trial scored as low as 8 out of 22 of the CONSORT criteria (36%) [39]. The difference between the mean CONSORT scores for pediatric trials (14.78) and mixed population trials (14.50) was not statistically significant (P=0.56, Mann–Whitney U test).

Discussion

Summary of main findings

This systematic review of trial reporting quality in pediatric transplantation trials indicates that it is generally not optimal, and has room for further improvement when evaluated against the established reporting criteria endorsed by the majority of journals that published these reports. None of the trials included completely satisfied the requirements of the CONSORT statement despite all but one of these trials being published in journals that endorse CONSORT (as of May 2009) [39]. Moreover, the trials on average reported absolutely no information for one third of the recommended 22-item CONSORT checklist. In general, while the CONSORT statement requirements for

Table 3 Identification of CONSORT criteria items (13 through 22) presented in the results and discussion sections of the kidney transplantation trials included in the study

Item	CONSORT criteria		Child[a] (%) n=9	Mixed[a] (%) n=18	Total[b] (%) n=27	P value*
13	Participant flow		8 (89)	12 (67)	20 (74)	0.363
		Flow diagram	4 (44)	2 (11)	6 (22)	0.136
14	Recruitment		4 (44)	13 (72)	17 (63)	0.219
15	Baseline data		7 (78)	16 (89)	23 (85)	0.582
16	Numbers analyzed		8 (89)	15 (83)	23 (85)	1.000
		Intention-to-treat	3 (33)	10 (56)	13 (48)	0.420
		Pseudo-ITT	2 (22)	3 (17)	5 (19)	1.000
		ITT not reported	4 (44)	5 (28)	9 (33)	0.423
17	Outcomes		3 (33)	6 (33)	9 (33)	1.000
18	Ancillary analyses	Pre-specified	6 (67)	12 (67)	18 (67)	1.000
		Not pre-specified	3 (33)	6 (33)	9 (33)	1.000
19	Adverse events		6 (67)	15 (83)	21 (78)	0.367
20	Interpretation		2 (22)	8 (44)	10 (37)	0.406
		Summary of key findings	8 (89)	18 (100)	26 (96)	0.333
		Discussion of limitations	2 (22)	8 (44)	10 (37)	0.420
21	Generalizability		7 (78)	12 (67)	19 (70)	0.676
22	Overall evidence		9 (100)	18 (100)	27 (100)	1.000
		Systematic review	0 (0)	3 (17)	3 (11)	0.529

*P for the difference between child and mixed population trials, calculated using Fisher's exact test

[a] Pediatric trials including only children; all participants ≤17 years old. Mixed population of adults and children; at least one participant aged ≤17 years

[b] Total number of trials including both pediatric and mixed population trials

titles, abstracts, and introductions were well reported, the reporting of essential components of the methods, results and discussion domains was unsatisfactory.

This review identified no evidence of discrepancy between the quality of reporting of trials that included only children compared with trials in which children were a subset of patients in an otherwise adult study. Trials including children alone were no better or no worse than those that included both children and adults, with no statistical difference identified between the reporting quality in any of the 22 required CONSORT items, nor any significant difference (P=0.56) in the overall average CONSORT criteria scores. We acknowledge that the sample size of our trial cohort was small, but nevertheless, this suggests that sub-optimal reporting of trials might be a widespread problem, and that report standards of RCTs in both adult and pediatric transplantation require major improvement [16].

Findings in context

To our knowledge this is the first systematic review of the reporting quality of RCTs in the pediatric transplantation population, but is among a small but growing number of studies assessing reporting standards in the broader pediatric literature [11–14]. Other studies in reporting quality in pediatric research to date have been limited to other fields and specialist areas and findings from these studies have unfortunately been equally unimpressive, showing similar deficiencies in reporting standards. Despite our findings in the transplantation trials, the results of our study compare favorably with those of the other pediatric settings. We demonstrated that the reporting of pediatric transplantation trials met an average of 67% of the CONSORT criteria for trials including only children and 66% for trials including a mixed population of adults and children. In contrast, only 40% of the CONSORT criteria items in complementary medicine reports in children and 47% of the CONSORT criteria items in reports in cerebral palsy physiotherapy were well reported [13, 14]. Another study in pediatric psychology found that half of CONSORT items were reported less than 25% of the time [11]. Although this is not the first time that many of these reporting deficiencies have been identified in the broader literature, our findings provide a somber summary of the quality of the reports of trials available to inform treatment choices in pediatrics.

Strengths and weaknesses

Our systematic review identified and summarized all available trials from the Cochrane Renal Group's spe-

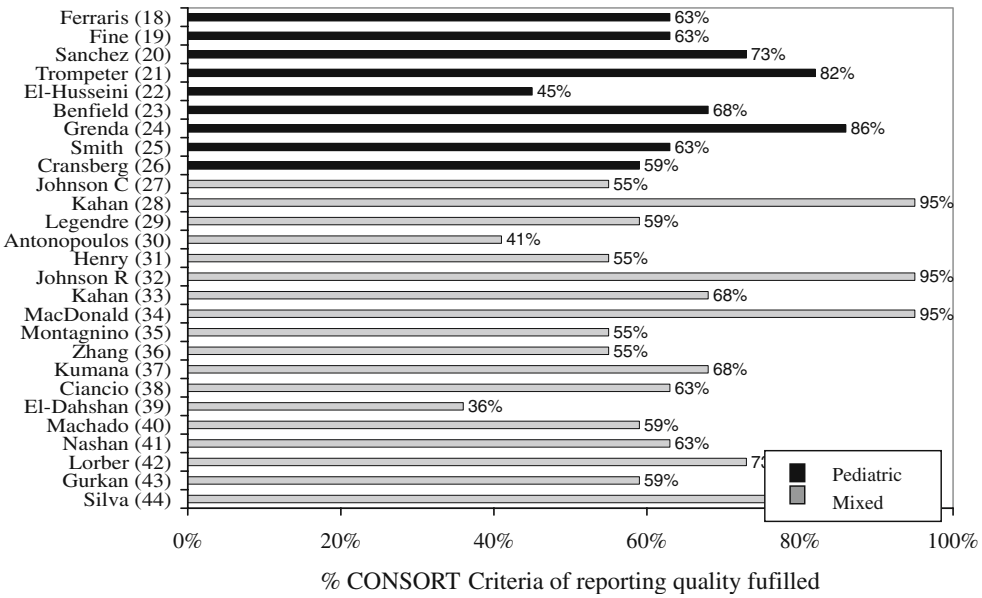

Fig. 3 Quality of reporting of included kidney transplantation trials: the percentage of CONSORT criteria that were completely reported for each pediatric (*black*) trial and mixed population (*gray*) trial. Pediatric trials comprised solely children 17 years or younger, and mixed population trials consisted of a mixed population of adults and children in which there must be at least one child aged 17 years or younger. Mean CONSORT criteria score for the pediatric trials was 14.78 (±2.68; 67%) and 14.50 (±3.94; 66%) for the mixed population trials (P=0.56, Mann–Whitney U test)

cialized register of RCTs that met our inclusion criteria in an effort to capture the totality of RCT evidence available on kidney transplantation in children. In an effort to maintain a robust methodology, two different reviewers worked independently to identify trials, and in data abstraction agreement was sought with a second reviewer for any data that were in any way ambiguous. However, although there is the intention to be meticulous, this type of research is time-consuming and open to human error, which is not helped by an absence of structured rational reporting in many of the trial reports, and differences in the formatting of manuscripts among different journals [14].

The exclusion of non-English publications has been demonstrated to introduce bias into meta-analyses of interventions. A limitation of our work was to exclude non-English language literature, due to difficulty in obtaining translations of these reports, and it is possible that in this way we have introduced some bias to our findings [45].

In limiting this review to only transplantation trials, we included a relatively small number of trials, and as a result we may have had inadequate power to detect differences in reporting quality between pediatric and mixed populations trials that do exist. In fact, only one third of trials assessed in this review involved transplantation in an exclusively pediatric population. This may also explain why the findings were more comparable to the results of a systematic review of renal transplantation immunosuppression in an adult population (adequate reporting of 69.1% of the CONSORT criteria) rather than those of other pediatric systematic reviews that had lower overall reporting adequacy [16]. Thus, a larger work examining the totality of RCTs related to pediatric nephrology might be more informative.

Implications for clinical practice and conclusion

Consistent with the literature in other medical disciplines, there is much room for improvement in the reporting of RCTs in children requiring kidney transplantation. Although a multitude of factors contribute to the underrepresentation of children in randomized trials compared with adult-centered research, our findings are the first to suggest that the quality of reporting in pediatric transplantation trials is no worse than that of the adult literature. However, it does suggest that even when children with kidney transplants do take part in an RCT, the results of these trials are not reported as adequately and as transparently as they could be, which is a general failing warranting action.

The evidence supports initiatives such as the CONSORT statement and efforts by the International Committee of Medical Journal Editors to correct reporting deficiencies found throughout the biomedical literature, but more must be done to ensure guidelines are stringently applied to transplantation trials involving children. Endorsement by journals appears to be insufficient alone, and there is evidence that unfamiliarity with the CONSORT criteria by authors and reviewers can contribute to this problem [46].

Responsibility for ensuring that trial reporting is good quality rests with all involved in clinical research, from funders to publishers. Researchers bear responsibility for conducting their research ethically and responsibly, and ensuring that they report details of their work according to best practice, using the appropriate reporting guidelines for their study design, which for an RCT when writing for journals is the CONSORT statement. Peer reviewers are the expert gate-keepers, who as part of peer review bear responsibility for checking research validity, which includes

assessing study design and reporting, and alerting journal editors where they find this lacking. Ultimate responsibility for reports of RCTs appearing in journals rests with the journal editorial board.

Better training of junior researchers in research methodology might improve the standards of research writing, and peer review. Increasing literacy in trial reporting among trainees, junior researchers, and scientists might be addressed by offering training opportunities as part of postgraduate continuing medical education (CME). Professional societies might endorse this by including trial design and reporting workshops as part of CME education at conferences and scientific meetings.

It is encouraging that there is a movement toward better reporting within the transplant community with CONSORT-derived, transplantation-specific reporting criteria currently being recommended and developed for individual journals [15, 46, 47]. Unfortunately, history has demonstrated that guidelines only benefit the quality of reporting when they are followed.

Acknowledgements We thank Dr. Terry Klassen and Dr. Patricia Caldwell, who gave advice and input to a preliminary version of this work.

Conflicts of interest and funding sources statement None of the authors declare any conflicts of interest in this project. There was no funding for this work. No ethics approval was necessary for this work.

References

1. McTaggart S, Kennedy S, McDonald S, Henning P, Dent H (2008) Pediatric report. In: MacDonald S, Excell L, Livingston B (eds) The thirty-first report: Australia and New Zealand Dialysis and Transplant Registry 2008. ANZDATA Registry, Adelaide
2. Milliner D (2004) Pediatric renal-replacement therapy—coming of age. N Engl J Med 350:2637–2639
3. McDonald S, Craig J (2004) Long-term survival of children with end-stage renal disease. N Engl J Med 350:2654–2662
4. Wilson J (1999) An update on the therapeutic orphan. Pediatrics 104:585–590
5. Caldwell P, Murphy S, Butow P, Craig J (2004) Clinical trials in children. Lancet 364:803–811
6. Altman D, Schulz K, Moher D, Egger M, Davidoff F, Elbourne D, Gøtzsche PC, Lang T; CONSORT Group (Consolidated Standards of Reporting Trials) (2001) The revised CONSORT statement for reporting randomized trials: explanation and elaboration. Ann Intern Med 134:663–694
7. Moher D, Pham B, Jones A, Cook DJ, Jadad AR, Moher M, Tugwell P, Klassen TP (1998) Does quality of reports of randomized trials affect estimates of intervention efficacy reported in meta-analyses? Lancet 352:609–613
8. Moher D, Schulz K, Altman D (2001) The CONSORT statement: revised recommendations for improving the quality of reports of parallel-group randomized trials. Lancet 357:1191–1194
9. Moher D, Jones A, Lepage L (2001) Use of the CONSORT statement and quality of reports of randomized trials: a comparative before-and-after evaluation. The CONSORT Group. JAMA 285:1992–1995
10. Kane R, Wang J, Garrard J (2007) Reporting in randomized clinical trials improved after adoption of the CONSORT statement. J Clin Epidemiol 60:241–249
11. Stinson J, McGrath P, Yamada J (2003) Clinical trials in the Journal of Pediatric Psychology: applying the CONSORT statement. J Pediatr Psychol 28:159–167
12. Al-Namankany A, Ashley P, Moles D, Parekh S (2009) Assessment of the quality of reporting randomized clinical trials in pediatric dentistry journals. Int J Paediatr Dent 19:318–324
13. Moher D, Soeken K, Sampson M, Ben-Porat L, Berman B (2002) Assessing the quality of reports of randomized controlled trials in pediatric complementary and alternative medicine. BMC Pediatr 2:2
14. Anttila H, Malmmivaara A, Kunz R, Autti-Ramo L, Makela M (2006) Quality of reporting randomized controlled trials in cerebral palsy. Pediatrics 117:2222–2230
15. Curtis J, Kaplan B (2004) Transplant immunosuppressive drug trials on trial. Am J Transplant 4:671–672
16. Fritsche L, Einecke G, Fleiner F, Dragun D, Neumayer H, Budde K (2004) Reports of large immunosuppression trials in kidney transplantation: room for improvement. Am J Transplant 4:738–743
17. Moher D, Morrison A, Schulz K, Altman DG, Hill C, Gaboury I (2006) Does the CONSORT checklist improve the quality of reports of randomized controlled trials? A systematic review. Med J Aust 185:263–267
18. Ferraris JR, Pasqualini T, Legal S, Sorroche P, Galich AM, Pennisi P, Domene H, Jasper H (2000) Effect of deflazacort versus methylprednisone on growth, body composition, lipid profile, and bone mass after renal transplantation. The Deflazacort Study Group. Pediatr Nephrol 14:682–688
19. Fine R, Stablein D, Cohen A, Tejani A, Kohaut E (2002) Recombinant human growth hormone post-renal transplantation in children: a randomized controlled study of the NAPRTCS. Kidney Int 62:688–696
20. Sanchez C, Kuizon BD, Goodman WG, Gales B, Ettenger RB, Boechat MI, Wang Y, Elashoff R, Salusky IB (2002) Growth hormone and the skeleton in pediatric renal allograft recipients. Pediatr Nephrol 17:322–328
21. Trompeter R, Filler G, Webb NJ, Watson AR, Milford DV, Tyden G, Grenda R, Janda J, Hughes D, Ehrich JH, Klare B, Zacchello G, Bjorn Brekke I, McGraw M, Perner F, Ghio L, Balzar E, Friman S, Gusmano R, Stolpe J (2002) Randomized trial of tacrolimus versus cyclosporin microemulsion in renal transplantation. Pediatr Nephrol 17:141–149
22. El Husseini A, El Agroudy A, El Sayed M, Sobh M, Ghoneim M (2004) Treatment of osteopenia and osteoporosis in renal transplant children and adolescents. Pediatr Transplant 8:357–361
23. Benfield M, Tejani A, Harmon W, McDonald R, Stablein DM, McIntosh M, Rose S, CCTPT Study Group (2005) A randomized multicenter trial of OKT3 mAbs induction compared with intravenous cyclosporine in pediatric renal transplantation. Pediatr Transplant 9:282–292
24. Grenda R, Watson A, Vondrak K, Webb NJ, Beattie J, Fitzpatrick M, Saleem MA, Trompeter R, Milford DV, Moghal NE, Hughes D, Perner F, Friman S, Van Damme-Lombaerts R, Janssen F (2006) A prospective, randomized, multicenter trial of tacrolimus-based therapy with or without basiliximab in pediatric renal transplantation. Am J Transplant 6:1666–1672
25. Smith J, Wong CS, Salamonik EB, Hacker BM, McDonald RA, Mancl LA, Williams BJ, Ibrahim A, Roberts FA (2006) Sonic tooth brushing reduces gingival overgrowth in renal transplant recipients. Pediatr Nephrol 21:1753–1759
26. Cransberg K, Cornelissen M, Lilien M, Van H, Davin J, Nauta J (2007) Maintenance immunosuppression with mycophenolate mofetil and corticosteroids in pediatric kidney transplantation: temporary benefit but not without risk. Transplantation 83:1041–1047

27. Johnson C, Ahsan N, Gonwa T, Halloran P, Stegall M, Hardy M, Metzger R, Shield C 3rd, Rocher L, Scandling J, Sorensen J, Mulloy L, Light J, Corwin C, Danovitch G, Wachs M, van Veldhuisen P, Salm K, Tolzman D, Fitzsimmons WE (2000) Randomized trial of tacrolimus (Prograf) in combination with azathioprine or mycophenolate mofetil versus cyclosporine (Neoral) with mycophenolate mofetil after cadaveric kidney transplantation. Transplantation 69:834–841
28. Kahan B (2000) Efficacy of sirolimus compared with azathioprine for reduction of acute renal allograft rejection: a randomised multicenter study. Lancet 356:194–202
29. Legendre C, Norman D, Keating M, Maclaine G, Grant D (2000) Valaciclovir prophylaxis of cytomegalovirus infection and disease in renal transplantation: an economic evaluation. Transplantation 70:1463–1468
30. Antonopoulos I, Nahas W, Mazzucchi E, Ianhez L, Saldanha L, Arap S (2001) Comparison of palpation-guided and ultrasound-guided biopsies in transplanted kidneys. Clin Transplant 15:393–396
31. Henry M, Pelletier R, Elkhammas E, Bumgardner G, Davies E, Ferguson R (2001) A randomized prospective trial of OKT3 induction in the current immunosuppression era. Clin Transplant 15:410–414
32. Johnson R, Kreis H, Oberbauer R, Brattstrom C, Claesson K, Eris J (2001) Sirolimus allows early cyclosporine withdrawal in renal transplantation resulting in improved renal function and lower blood pressure. Transplantation 72:777–786
33. Kahan B, Kaplan B, Lorber M, Winkler M, Cambon N, Boger R (2001) RAD in de novo renal transplantation: comparison of three doses on the incidence and severity of acute rejection. Transplantation 71:1400–1406
34. MacDonald A (2001) A worldwide, phase III, randomized, controlled, safety and efficacy study of a sirolimus/cyclosporine regimen for prevention of acute rejection in recipients of primary mismatched renal allografts. Transplantation 71:271–280
35. Montagnino G, Tarantino A, Segoloni GP, Cambi V, Rizzo G, Altieri P, Castagneto M, Salvadori M, Cossu M, Pisani F, Carmellini M, Mastrangelo F, Ferrara R, Ponticelli C (2001) Long-term results of a randomized study comparing three immunosuppressive schedules with cyclosporine in cadaveric kidney transplantation. J Am Soc Nephrol 12:2163–2169
36. Zhang X, Ardissino G, Ghio L, Tirelli AS, Daccò V, Colombo D, Pace E, Testa S, Claris-Appiani A (2001) L-arginine supplementation in young renal allograft recipients with chronic transplant dysfunction. Clin Nephrol 55:453–459
37. Kumana C, Tong M, Li C, Lauder IJ, Lee JS, Kou M, Walley T, Haycox A, Chan TM (2003) Diltiazem co-treatment in renal transplant patients receiving microemulsion cyclosporin. Br J Clin Pharmacol 56:670–678
38. Ciancio G, Burke G, Gaynor JJ, Ruiz P, Roth D, Kupin W, Rosen A, Miller J (2006) A randomized long-term trial of tacrolimus/sirolimus versus tacrolimus/mycophenolate versus cyclosporine/sirolimus in renal transplantation: three-year analysis. Transplantation 81:845–852
39. El Dahshan K, Bakr M, Donia A, Badr A, Sobh M (2004) Co-administration of ketoconazole to tacrolimus-treated kidney transplant recipients: a prospective randomized study. Nephrol Dial Transplant 19:1613–1617
40. Machado P, Felipe CR, Hanzawa NM, Park SI, Garcia R, Alfieri F, Franco M, Silva HT Jr, Medina-Pestana JO (2004) An open-label randomized trial of the safety and efficacy of sirolimus vs. azathioprine in living related renal allograft recipients receiving cyclosporine and prednisone. Clin Transplant 18:28–38
41. Nashan B, Curtis J, Ponticelli C, Mourad G, Jaffe J, Haas T (2004) Everolimus and reduced-exposure cyclosporine in de novo renal-transplant recipients: a three-year phase II, randomized, multicenter, open-label study. Transplantation 78:1332–1340
42. Lorber M, Mulgaonkar S, Butt KM, Elkhammas E, Mendez R, Rajagopalan PR, Kahan B, Sollinger H, Li Y, Cretin N, Tedesco H, B251 Study Group (2005) Everolimus versus mycophenolate mofetil in the prevention of rejection in de novo renal transplant recipients: a 3-year randomized, multicenter, phase III study. Transplantation 80:244–252
43. Gurkan A, Yakupoglu YK, Dinckan A, Erdogdu T, Tuncer M, Erdoğan O, Demirbas A, Akaydin M (2006) Comparing two ureter reimplantation techniques in kidney transplant recipients. Transpl Int 19:802–806
44. Silva H, Yang H, Abouljoud M, Kuo PC, Wisemandle K, Bhattacharya P, Dhadda S, Holman J, Fitzsimmons W, First MR (2007) One-year results with extended-release tacrolimus/MMF, tacrolimus/MMF and cyclosporine/MMF in de novo kidney transplant recipients. Am J Transplant 7:595–608
45. Moher D, Fortin P, Jadad AR, Jüni P, Klassen T, Le Lorier J, Liberati A, Linde K, Penna A (1996) Completeness of reporting of trials published in languages other than English: implications for the conduct of systematic reviews. Lancet 347:363–366
46. Budde K, Fritsche L (2005) Proposal for guidelines for publication of randomized trials in the American Journal of Transplantation. Am J Transplant 5:644–647
47. Martini S, Glander P, Fritsche L, Fleiner F, Budde K (2007) Suggested guidelines for reporting clinical results in transplantation trials. Transplant Rev 21:136–142