META-ANALYSIS

Do clinical trials reflect reality? A systematic review of inclusion/exclusion criteria in trials of renal transplant immunosuppression

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SUMMARY

Renal transplant recipients and donors are becoming increasingly more marginal, with more expanded criteria (ECD) and donation after circulatory death (DCD) donors and older recipients. Despite this, high-risk donors and recipients are often excluded from clinical trials, leading to uncertainty about the generalizability of findings. We extracted data regarding inclusion/exclusion criteria from 174 trials of immunosuppression in renal transplant recipients published over a 5-year period and compared criteria with those specified in published trial registries. Frequently reported donor exclusion criteria were age (16.1%), donor type and cold ischaemic time (22.4%). Common recipient exclusion criteria included upper age limit (38.5%), high panel reactive antibody (PRA) (42.5%) and previous transplantation (39.7%). Inclusion/exclusion criteria recorded in trial registries matched those reported in the manuscript in only 6 (7.8%) trials. Of registered trials, 51 (66.2%) trials included additional criteria in the manuscript, 51 (66.2%) were missing criteria in the manuscript specified in the protocol, and in 19 (24.7%) key criteria changed from the protocol to the manuscript. Our findings suggest many recent immunosuppression trials have restrictive inclusion criteria which may not be reflective of current renal transplant populations. Discrepancies between trial protocols and published reports raise the possibility of selection bias.

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Key words
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Introduction

Randomized controlled trials (RCTs) are considered the gold standard in medical research. Around half of the randomized controlled trials published in the field of renal transplantation relate to immunosuppressive interventions, and these trials play a crucial role in informing clinical practice for renal transplant patients [1]. However, overly restrictive eligibility criteria for trials may omit relevant patient populations, thus compromising the generalizability of results to real-world clinical practice.

The success of renal transplantation and improved perioperative management, along with an ageing population, have led to widening of the eligibility criteria for transplantation. Thirty-one per cent of patients in the United Kingdom (UK) transplant waiting list are over the age of 60 [2]. Similarly, in the United States (US)

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22% of patients on the renal transplant waiting list were over the age of 65 in 2015, a 7.5% increase since 2005 [3]. Moreover in 2015, 17.2% of the US transplant recipient population was aged over 65 years [3].

The consideration of greater numbers of patients for transplantation has led to an increasing gap between supply and demand for organs which has resulted in a more liberal criteria for accepting organs by utilization of donors after cardiac death (DCD) and expanded criteria donors (ECD) [4]. The past decade has demonstrated an increase in both DCD and ECD donors, and an increment in both recipient and donor age [5]. From 2006 onwards, a steady increase in DCD donors has been observed in the UK, with 31% of adult kidney-only transplants in 2016/2017 from DCD donors [2]. Age of donor and recipient populations have also significantly increased with the National Health Service Blood and Transplant (NHSBT) reporting 35% of deceased kidney donors and 29% recipients aged 60 years or more for the year 2016/17 [2].

Given the changing demographics of both donors and recipients, it is important that the inclusion criteria in transplant clinical trials reflect these populations. A study conducted by Blosser *et al.* [6] demonstrated the common application of age restrictions in trials of renal transplantation, and the age of kidney transplant recipients included in trials was significantly younger than the average United States kidney transplant population. These findings prompt speculation regarding the generalizability of trials to the present renal transplant populations.

When considering validity and generalizability of trials, another concern is the discrepancy between inclusion/exclusion criteria specified in trial registry records and protocols, and those reported in the final trial manuscripts. Previous studies have found inconsistencies in reporting between trial protocols and final manuscripts [7–9]. Unreported discrepancies, particularly in inclusion/exclusion criteria, may have significant implications for practitioners relying on trial results to inform clinical decision-making. Providing inaccurate or incomplete information of trial participants leads to erroneous assumptions of the applicability of trial results in real-life patients.

Given the changing nature of the donor and recipient population, there is a real risk that the populations recruited to transplant clinical trials are not representative of the prevailing transplant population. The primary aim of this study was to systematically review the inclusion and exclusion criteria of immunosuppression RCTs in renal transplant populations. The secondary aim was to identify the extent of discrepancies in the reporting of inclusion/exclusion criteria of trial registry records and manuscripts.

Methods

This systematic review is reported in line with current Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines [10]. This study was conducted in accordance with an internal protocol that was written prior to study commencement.

Identification of studies

We searched the Transplant Library database (www.transplantlibrary.com) for all randomized controlled trials comparing immunosuppressive interventions in renal transplant recipients published over a 5-year period between 1 January 2010 and 31 December 2014. The Transplant Library database is maintained by the Centre for Evidence in Transplantation and contains all reports from randomized controlled trials in the field of solid organ transplantation published from 1970 to date, sourced from MEDLINE, the Cochrane Library and hand searches of relevant conference abstracts. Filters were applied for renal transplantation, full-text articles (excluding conference abstracts) and date. Search results were screened independently by two reviewers for inclusion in the study. Discrepancies in inclusion were agreed by discussion.

Inclusion/exclusion criteria

All full-text reports from randomized controlled trials comparing two or more immunosuppressive strategies (induction or maintenance) in adult renal transplant recipients were eligible for inclusion. Articles relating to nonimmunosuppressive interventions, paediatric transplantation, and other organ transplant types or published in a language other than English were excluded. We also excluded those studies not providing any clinical outcome data, in particular those only reporting pharmacokinetic data. Conference abstracts were excluded.

Data extraction

Data were extracted from a custom-designed online database. Data extraction was performed by two reviewers (SH and SK) and discrepancies agreed by discussion. Relevant demographic data were extracted from all

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studies to include number of participants, interventions used, number of centres, study design quality, country, funding source and evidence of ethical approval.

Data regarding the inclusion and exclusion criteria for participants in each study were extracted from the full published reports. Donor criteria included donor type [donation after brain death (DBD), DCD, living, ECD], age and cold ischaemia time (CIT). Recipient criteria included recipient type (*de novo* or stable), age, number of previous transplants, immunological risk [HLA mismatches, current and peak panel reactive antibodies (PRA), ABO or HLA incompatibility], body mass index (BMI), virology, previous malignancy, haematological parameters and primary disease. For studies recruiting stable transplant recipients, restrictions regarding transplant function or previous rejection episodes were recorded.

Comparison with trial registry data

Included studies were screened for evidence of trial registration. Where reported, the trial registry record was retrieved and inclusion/exclusion criteria were extracted. These were compared with those reported in the manuscript independently by two reviewers (AAS and SRK). Discrepancies between trial registry record and manuscript were recorded in three groups; criteria included in registry but not manuscript, criteria included in manuscript but not registry, and criteria changed between registry and manuscript.

Risk of bias

Risk of bias for each study was assessed by means of the Jadad score, use of intention-to-treat analysis and description of adequate allocation concealment for each study (Table 1, SDC 1). The Jadad score identifies the risk of bias due to trial methodology, scoring studies between 0 and 5 depending on the presence of an adequate method of randomisation, presence of double blinding and an adequate description of withdrawals and dropouts [11]. These metrics are available for all studies included in the Transplant Library.

Data analysis

Data are presented using simple descriptive statistics using Microsoft Excel version 15 (Microsoft Corporation, Redmond, WA, USA), and the R statistical language (R Foundation for Statistical Computing, Vienna, Austria).

Table 1. Characteristics and study-level quality assessment of included studies.

Characteristic	All studies *N* (%)
Recipient type	
de novo	123 (71.0)
Post-transplant	51 (29.3)
Number of centres	
Single	77 (44.3)
Multiple	97 (55.7)
Ethics approval	
Yes	154 (88.5)
No	20 (11.5)
Funding source	
Industry	94 (54.0)
Nonindustry	33 (18.9)
Mixed	15 (8.6)
No external funding	7 (4.0)
Not described	25 (14.4)
Jadad score	
0	1 (0.6)
1	21 (12.1)
2	63 (36.2)
3	79 (45.4)
4	2 (1.1)
5	8 (4.6)
Adequate allocation concealment	
No	92 (52.8)
Yes	82 (47.1)
Intention-to-treat analysis	
Available case analysis	27 (15.5)
Intention-to-treat	34 (19.5)
Modified intention-to-treat	59 (33.9)
Per protocol analysis	54 (31.0)

Results

Characteristics of included studies

The literature search identified 213 manuscripts from 174 unique studies that met the inclusion criteria (Fig. 1). Characteristics of the included studies are described in Table 1. The median number of centres in each trial was 4 (range 1–111), and the median length of follow-up in weeks was 52 (range 1–932). Median number of participants was 115 (range 9–1640).

Donor criteria

One hundred and twenty-four (71.3%) trials recruited both living (LD) and deceased donor (DD) recipients, with 27 (15.5%) recruiting only DD recipients and 23 (13.2%) recruiting only LD recipients (Fig. 2). Exclusion criteria relating to donor characteristics were

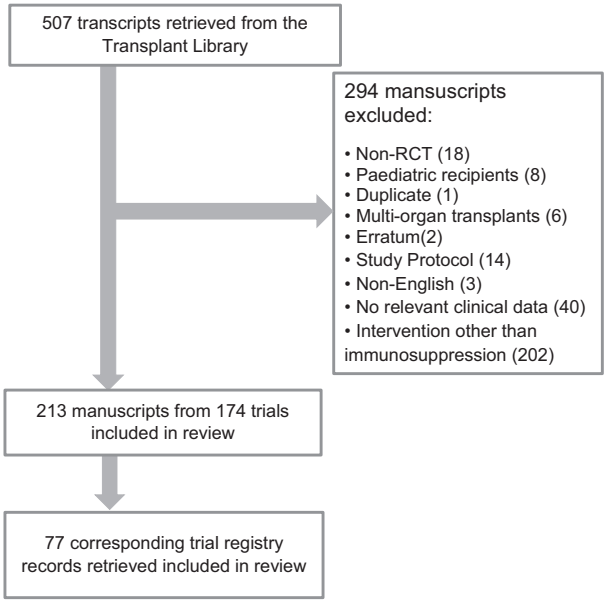

Figure 1 Flow chart to demonstrate inclusion/exclusion of studies during the review process. RCT, randomized controlled trial.

common, with 42 (24.1%) and 10 (5.7%) trials excluding DCD and ECD donors, respectively. Donor age was an exclusion criterion in 28 (16.1%) trials. Thirty-eight (21.8%) trials were restricted by maximum cold ischaemic time (CIT) with a median CIT of 30 (range 24–48).

Recipient criteria

One hundred and twenty-three (70.7%) studies recruited *de novo* recipients with 51 (29.3%) recruiting stable patients post-transplant (Fig. 3). Recipient age was a common restriction, with 67 studies (38.5%) specifying an upper age limit for inclusion. The proportion of studies excluding patients over 60, 65 and 70 years was 2.9%, 17.2% and 28.2%, respectively.

Exclusion based upon immunological risk was also common. The most common exclusion criteria were panel reactive antibody level (PRA), with 74 (42.5%) studies excluding patients with a median cut-off at 30% (range 20-85%). Fifty-one (29.3%) studies excluded blood group (ABO) or HLA incompatible recipients. Sixty-nine studies (39.7%) excluded patients by number of previous transplants, with 37 (21.3%) limiting inclusion to recipients of a first transplant only. Of 51 studies recruiting stable patients post-transplant, 38 (74.5%) excluded recipients with previous rejections and 48 (94.1%) restricted by transplant function.

Other common recipient exclusion criteria included haematological parameters (21.3%), current infection (21.3%), positive viral serology (22.4%) and previous malignancy (27.0%). Nine (5.2%) studies defined a maximum body mass index (BMI) in recipients, with the median cut-off at BMI greater than 32 (range 25–40). A small number of studies (5.2%) excluded recipients with particular aetiology of renal failure, most commonly glomerulonephritis with the potential for recurrence in the graft.

Discrepancies between trial registry record and final manuscript

Seventy-seven (44.3%) studies had a published trial registry record available. Inclusion/exclusion criteria recorded in the trial registration matched those reported in the final manuscript in only six (7.8%) trials. Of those with published registry records, 51 (66.2%) included additional criteria in the final manuscript, 51 (66.2%) were missing criteria in the manuscript that were specified in the registry, and in 19 (24.7%) of the trials key criteria changed from the trial registry to the manuscript.

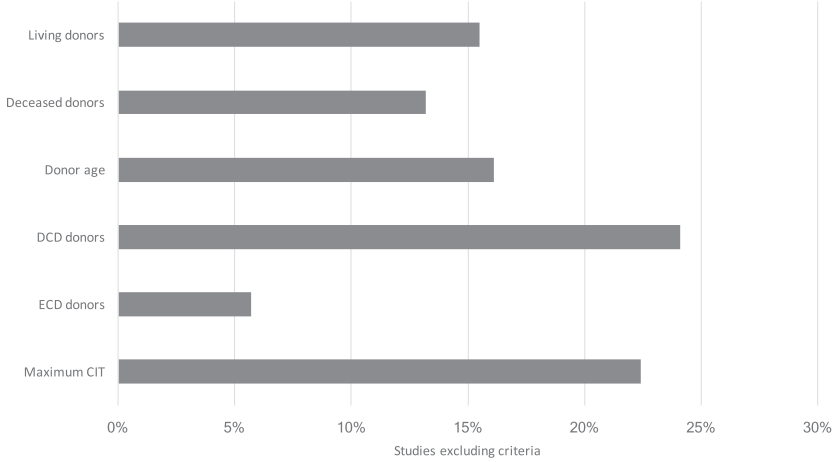

Figure 2 Commonly reported donor exclusion criteria. DCD, Donor after cardiac death; ECD, expanded criteria donor; CIT, cold ischaemic time.

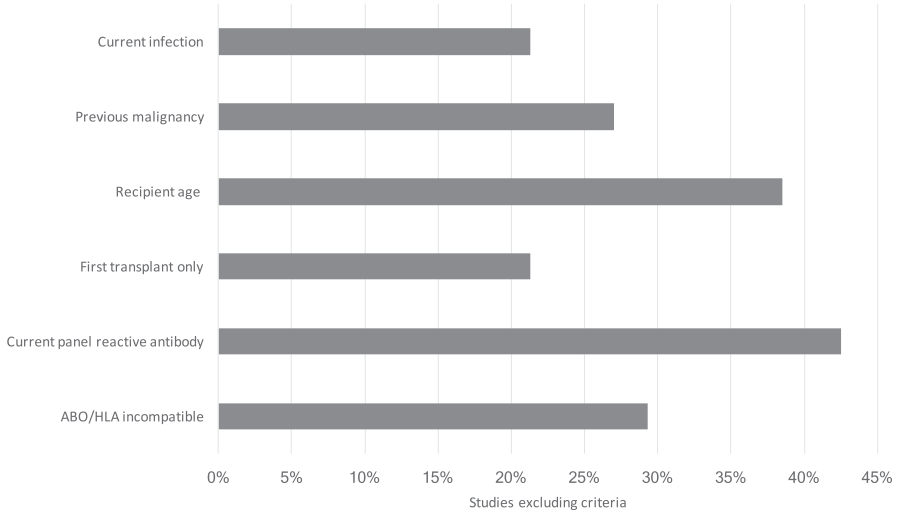

Figure 3 Commonly reported recipient exclusion criteria. HLA, human leukocyte antigen.

Discussion

This study sought to systematically review the inclusion and exclusion criteria of immunosuppression RCTs in renal transplant populations. Our results demonstrate that many recent RCTs have highly restrictive inclusion/exclusion criteria for both donors and recipients. Older and marginal donor populations (DCD, ECD) were omitted in a substantial proportion of studies, with maximum CIT and DCD donors the most common criteria for exclusion. Similarly, exclusion based on recipient age, particularly over 65, was prevalent as was exclusion of recipients with immunological risks such as history of previous transplant and blood group (ABO)/HLA incompatibility.

These findings highlight the lack of generalizability and congruity of results from immunosuppressive RCTs to the current 'real-world' kidney transplant population. The past decade has observed a shift in the demographics of renal transplant donors and recipients to include many older and marginal patients. Frequent exclusion of these populations from immunosuppressive trials limits the ability to extend study findings to patients seen in routine clinical practice. Transplant registry data from the USA and UK provide some insight into the extent of the problem [2,3]; 24% of the trials in this analysis excluded DCD donor organs, despite the fact that these organs make up over 30% of adult kidney transplants in the UK and 18% in the USA; 38% of trials reported an upper age limit for inclusion, despite an increasingly ageing wait-list population. Current data suggest that 22% of the kidney USA waiting list are aged over 65, and 31% of the UK waiting list are over the age of 60. Exclusion of recipients by immunological risk is also common, with over 20% studies excluding patients with a previous transplant, a population that makes up 24% of the UK waiting list. Sensitized patients are often excluded from participating in trials, despite 30% of US transplant recipients having a PRA >20% at the time of transplant.

Stringent inclusion/exclusion criteria introduce selection bias by excluding complex or difficult to treat patients. This is likely to exaggerate positive study outcomes and benefits expected from treatments [12]. Moreover, as a result of strict inclusion criteria, the study sample may not be truly representative of the target population, thus compromising trial generalizability.

Rigorous entry criteria are often set by trialists to ensure safety of trial participants to the new intervention as well as maximize chances of observing a treatment effect in optimal conditions. However, this comes with the inevitable cost of risking exclusion of participants that are more likely to represent 'real-life' populations encountered in clinical settings, limiting the ability to assess the effectiveness of the intervention [13]. A requisite for a useful RCT is to be both internally and externally valid [14], although achieving a balance between internal and external validity is often challenging [15]. However, it is necessary that the spectrum of patients recruited to the trial is extensive enough to reflect the target population and subgroups [16]. Thus, the selective exclusion of older and marginal kidney transplant populations in immunosuppressive trials may have serious consequences when extrapolating study findings to the wider clinical population. Results from such RCTs may not capture the overall view of efficacy and safety of intervention in many renal transplant patients. As such, there is a risk of unintended harm to

renal transplant subgroups (e.g., those who are older, with comorbidities or those with high immunological risk) commonly excluded from RCTs.

Concerns regarding restrictive inclusion/exclusion criteria and lack of external validity have been previously flagged across several medical disciplines including heart failure, stroke, cancer, rheumatoid arthritis and psychological disorders including depression [17–23]. A number of studies in various clinical populations are consistent with our findings that restrictive eligibility criteria of clinical trials omit substantial proportions of relevant patient groups that are representative of real-life patient populations [24–28]. A systematic sampling review demonstrated age, sex, common medical conditions and commonly prescribed medication to be typical grounds for exclusion in RCTs published in high-impact medical journals [13]. Less than half of the exclusion criteria assessed in the review were graded as strongly justified in the context of the specific RCT. Taylor *et al.* [29] used cardiac rehabilitation as an example to demonstrate that outcomes from RCTs are often not observed when applied to clinical populations with differences in patient characteristics. It is therefore imperative to carefully consider the risks posed when clinical practice is based on RCTs recruiting only stable and low-risk kidney transplant donors and recipients that are not representative of the wider transplant population.

The secondary aim of this study was to identify the extent of discrepancies in the reporting of inclusion/exclusion criteria of trial registries and published manuscripts in immunosuppressant RCTs in renal transplantation. We found substantial differences between inclusion and exclusion criteria submitted to trial registries and published reports for the majority of studies. Only 8% (6/77) were classified as matching, with the remainder classified as reporting additional criteria in the manuscript, modified criteria from registry to manuscript or missed criteria in the manuscript that was listed in the trial registry. Many studies were a combination of the above classifications. It is worth noting that only 44% of the RCTs included in review had a trial registry record available. The above figures were apparent despite recommendations by guidelines and journals for RCTs to prospectively register trial information and provide complete, clear and transparent reporting [30–32].

Unreported discrepancies in inclusion and exclusion criteria have several implications for renal transplant patients. Firstly, inaccurate or incomplete information of participant characteristics leads to erroneous assumptions regarding the applicability and generalizability of trial results in real-life patients [33,34]. For example, in one trial multiple organ transplant was listed under the exclusion criteria on the trial registry record, but not on the published report, which may lead to false assumptions of a broader study population. Secondly, inaccurate reporting of inclusion/exclusion of populations with comorbidities such as previous malignancies could cause unintended harm to routine clinical patients administered the study drugs, due to the lack of precise safety information. Thirdly, policy decisions such as patient age ranges or subgroups a new drug or intervention is approved for would be based on ambiguous participant characteristic information [33]. Fourthly, unreported changes made to the eligibility criteria during the trial allow for selection bias, by inclusion of favourable patient characteristics. For this reason, outcomes from RCTs with changes made to inclusion/exclusion criteria that are not justified or acknowledged should be considered with a degree of apprehension.

Previous studies of discrepancies and inconsistencies between trial protocols and published articles have reported issues similar to our findings [35,36]. Ghandi *et al.* [34] found substantial gaps in eligibility criteria reporting between publications of RCTs in HIV-positive patients and protocols. A Cochrane review reported three studies that compared eligibility criteria and found that between 0% and 63% of RCTs reported all eligibility criteria in the published reports that were listed in the protocol. Two of the aforementioned studies found differences in eligibility criteria between trial protocols and published reports of 19% (6/32) and 100% (52/52) [37]. One of these studies also reported that 86% of the RCTs added new criteria to the published reports that were not declared in the trial. Similarly, a study by Zhang *et al.* [38] reported substantial differences in trial registries, protocols and published articles of cancer clinical trials. Almost all discrepancies in eligibility criteria suggested inclusion of a broader study population to readers of the published report. While our study focused on comparing trial registry records to published reports in renal transplantation immunosuppressant trials, findings from the literature highlight the wider issue of discrepant reporting of eligibility criteria in trial registry records, protocols and published reports.

The main strength of this study is the systematic methodology used, including a cross-section of contemporary randomized trials published over a 5-year period. We included all published reports from these trials and also sought additional information from supplementary digital content where available. It is possible

that inclusion/exclusion criteria applied during the trial were not reported in the final manuscript due to word limits, which we were unable to explore. Only 44% of the present studies reported protocols published in accessible trial registries – it is possible that this sample was not representative. We did not have the resources available to contact authors to identify reasons for discrepancies between published protocols and final manuscripts.

This review highlights discrepancies between the inclusion/exclusion criteria in randomized controlled trials of renal transplant immunosuppression and the changing nature of transplant donor and recipient populations. Clinicians are advised caution when applying findings from RCTs to inform clinical decision-making for renal transplant subgroups that are poorly represented in existing trials. We also found substantial discrepancies in reporting of inclusion and exclusion criteria in trial registries and published reports. It is recommended that full disclosure of eligibility criteria and discrepancies are provided as supplementary data in appendices as advised by Consolidated Standards of Reporting Trials (CONSORT) guidelines [31]. For changes to inclusion/exclusion criteria after trial registration, data logs of modifications should be maintained and changes should be justified, to ensure transparent reporting. Future trials should consider broadening inclusion criteria to encompass all clinically relevant renal transplant populations.

Authorship

AAS: participated in data extraction, data analysis and preparation of the manuscript. SH: participated in study design, literature searches and data extraction. SRK: designed the study and participated in data extraction, data analysis and preparation of the manuscript.

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Conflicts of interest

The authors have declared no conflicts of interest.

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