The Number, Quality, and Coverage of Randomized Controlled Trials in Nephrology

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Randomized controlled trials (RCT) are the optimal study design to answer intervention questions. The authors evaluated the number, quality, and coverage of RCT in nephrology. MEDLINE was searched using the relevant medical subject headings for nephrology and 12 major specialties in internal medicine, limited by "randomized controlled trial" as a publication type. A random selection of 160 RCT in nephrology (40 for each decade) published since 1966 and an additional 270 RCT from ongoing or published Cochrane systematic reviews in various areas of nephrology, dialysis, and transplantation were evaluated for quality of reporting using standard criteria. The number of RCT published in nephrology from 1966 to 2002 (2779) is fewer than all other specialties of internal medicine (range: 5335 in hematology to 27109 in cardiology) with the proportion of all citations which are RCT being the third lowest (1.15%). There has been an increase in both indices from 1966 to 1996, but not at a greater rate than other specialties, and there has been no increase over the past 5 yr. Some areas of nephrology, in particular glomerulonephritis, are clear outliers with very low numbers of RCT to guide clinical decision-making. Overall the quality of RCT reporting in nephrology is low and has not improved over the past 30 yr with unclear allocation concealment (89%), lack of reported blinding of outcome assessors (92%), and failure to perform "intention-to-treat analysis" (50%) particularly frequent. The challenges of improving the quality and quantity of trials in nephrology are substantial, but they can be overcome by using standard guidelines and checklists for trial reporting, greater attention to the trial methods and not just the results, involving experts in trial design and reporting, multicenter collaboration, and larger and simpler trials.

Because randomized controlled trials (RCT) are designed to provide unconfounded estimates of intervention effects, they are the ideal study type to answer intervention questions. However, not all RCT provide valid results. Validity of RCT depends on the underlying methodological quality (1). Allocation concealment, blinding, intention-to-treat analysis, and loss to follow-up are the critical items in the design and conduct of RCT, and inadequately conceived and conducted RCT, like observational studies, may overestimate or underestimate true effects of interventions .

To our knowledge, there has never been a systematic evaluation of the number, coverage, and quality of RCT in nephrology. This was the aim of our study. If problems were identified, we also sought to propose feasible solutions.

Discussion

We have found that the number of RCT published in nephrology, and the proportion of citations that are RCT, is very low compared with other internal medicine specialties. Our data suggest that this is primarily because few intervention questions are asked, rather than because intervention questions are not investigated with the appropriate study design (RCT). We have also shown that the number of RCT to inform clinical decision making is very low in some areas of nephrology, particularly glomerulonephritis, that the quality for reporting nephrology RCT is generally suboptimal, and that there has been little improvement over time.

Our study was not designed to determine whether the methodological deficiencies in the reports of RCT also represent problems in design. However, previous studies have shown that poor-quality reports are associated with biased estimates of intervention effects; importantly, on average this leads to overestimating the true effects of interventions (2,11,20□□). These data imply that reporting problems are proxies of design issues.

Studies similar to ours have been conducted in other specialties (3,21–24□□□□). These also show problems in the conduct and design of trials in other specialties.

Our data on the quantity and quality of trials in nephrology is of major concern and suggests that clinical research in nephrology, and trials in particular, is in crisis. This is not a new idea, but this study is the first to provide empiric evidence for this observation. It should be emphasized that this problem is not unique to clinical research in nephrology, but is representative of clinical research in medicine in general (25–28□□□). The Clinical Research Roundtable at the Institute of Medicine was established to address these problems and recently reported. One of the major findings was the block in the translation of basic science to human studies (as well as a block in the translation of new knowledge into clinical practice and health decision making) (25).

Our study does have important limitations. It was designed to evaluate the quality and quantity of trials in nephrology, rather than to identify the mechanisms for a relatively low number of published trials in nephrology compared with other internal medicine specialties. The findings that the quality of trial reporting is suboptimal and that many areas of nephrology are not supported by RCT would not be surprising to many observers. Our analysis of nephrology journals suggests that this is primarily because

non-intervention questions are asked by nephrology researchers rather than non-RCT designs being used to address intervention questions. Why nephrology researchers address fewer intervention questions than researchers in other internal medicine specialties is open for speculation. Clearly adjusting only for the number of citations does not address inequalities across specialties, which may explain these differences, such as number of patients eligible for trial participation, funding (both by the pharmaceutical industry and governmental and other granting bodies), and the number of new pharmaceuticals and devices. It may well be that "adjustment" for these inequalities may mean that nephrology as a community is doing comparatively well. However, the question is, compared with what. Compared with other specialties, perhaps; but if the comparator is the ideal of a firm basis for clinical decision making across all areas of nephrology by well-designed, conducted, and reported trials, there is clear room for improvement. It is likely that the reasons identified for blocks in the translation of basic science to human studies by the Clinical Research Roundtable—lack of willing participants, regulatory burden, fragmented infrastructure, incompatible databases, lack of qualified investigators, career disincentives, practice limitations, high research costs, and lack of funding—are equally true for nephrology as they are for the rest of the medical research community .

Given the findings of our study, what can be done to improve the quality of reporting of RCT in nephrology? This is a problem for triallists, reviewers, and editors of journals, and is clearly not just a problem for nephrology RCT.

Editors from most major biomedical journals have collaborated since 1984 to develop a set of guidelines for the reporting of RCT (31). These Consolidated Standards of Reporting Trials (CONSORT) were revised and published widely in 2001 and provide comprehensive checklists for triallists to ensure that RCT are reported accurately and comprehensively (32,33□). Adoption of these guidelines has resulted in some improvement in the quality of trial reporting (34). It would be feasible for triallists, reviewers, and editors involved in nephrology trials to accept and use these CONSORT guidelines, which to date have been endorsed by 152 major biomedical journals, an exponentially growing list which still does not in-clude nephrology journals (http://www.consort-statement.org/journals.htm).

Other initiatives include the "Protocol Reviews" from The Lancet, which aim to assesses protocols of randomized trials from a clinical and statistical point of view, to encourage good principles in design of clinical research, publicize a list of accepted protocols and make a provisional commitment to publication of the main clinical endpoints of studies (http://www.thelancet.com/info/info.isa?n1=authorinfo&n2= Protocol+reviews).

What can be done to improve the number of trials in nephrology? Does a relatively small specialty with relatively rare diseases mean that trials are impractical? Groups such as the European Vasculitis Study Group and the North American Pediatric Transplant Collaborative Study Group (NAPRTCS; http://spitfire.emmes.com/study/ped/index.htm) have overcome the small-numbers barrier by multicenter collaboration. Another advance in trial design has been the large, simple trial that has been strongly advocated by Peto et al. (35). Costs can be limited and trial design strengthened by only assessing outcomes that are clinically important and that are routinely collected rather than adding in laboratory expensive tests of uncertain clinical significance.

Finally, and perhaps most importantly, there may need to be a cultural change in nephrology toward RCT and the value of medical "evidence," a change which may already be starting to occur. The importance of RCT in nephrology is widely accepted, but there is some way to go before the majority of kidney patients are entered in RCT when it is unclear what the best intervention is. Any additional improvements will be driven by a well-trained workforce available in nephrology clinical research, which will only occur when a track record in trials and clinical research is regarded as equal to a track record in basic science for trainee nephrologists seeking a faculty position and for the promotion of senior nephrologists.

An important agency in the identification, evaluation, and synthesis of available RCT and the promotion of clinical research and research training is the Cochrane Collaboration (37). The Cochrane Renal Group (http://www.cochrane-renal.org/) is specifically responsible for coordinating the production of systematic reviews relating to topics in nephrology, dialysis, and renal transplantation. In addition, this group coordinates and updates the specialist registry of nephrology RCT, which contributes to the Cochrane Central register of Controlled Trials (CENTRAL). Both the production of systematic reviews and the thorough search for RCT to hold and update the renal registry, help to identify those areas where RCT are lacking (both in number and in quality). This ensures further improvement in clinical research and development of a solid base of evidence for decision making.

In conclusion, we have shown that RCT in nephrology are relatively few and the quality of reporting has substantial room for improvement. These observations should be regarded as challenges, not as a blame, for all sectors of the nephrological community: patients, clinicians, triallists, reviewers, and editors. The dual problems of number and quality are both remediable. We would hope that being aware of the problems would prompt improvements by better adherence to the CONSORT guidelines, greater attention to the trial methods and not just the results, involving experts in trial design and reporting, multicenter collaboration, and larger and simpler trials.