Celebrating 20 years of evidence from the Cochrane Collaboration: what has been the impact of systematic reviews on nephrology?

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ABSTRACT

It has been 20 years since the Cochrane Collaboration started the global effort to synthesize evidence to improve healthcare. Since 1997, the Cochrane Renal Group has produced over 100 systematic reviews that have collectively had an important impact on nephrology care, guidelines and policy. In this article, we reflect on the ongoing need for randomized trials and systematic reviews in contemporary nephrology and the achievements of the Cochrane Collaboration so far. We also describe some of the challenges in clinical research still faced by the nephrology community today.

Keywords: evidence, meta-analysis, randomized trial, systematic review

COCHRANE: WHY THE NAME? HOW WAS IT FORMED?

Cochrane is named after Archie Cochrane. In 1971, Archie, a Scottish physician and epidemiologist, wrote a book ‘Effectiveness and Efficiency: Random Reflections on Health Services’ [1]. In many ways, he was way ahead of his time, and his arguments are as relevant now as they were then. The book starts with a simple premise that ‘all effective treatment must be free’. This leads on to a discussion of methods for evaluating the effects of healthcare interventions, and he identifies randomized trials as the most reliable way of doing so. He also recognizes in publicly funded healthcare systems that equal attention must be paid to efficiency, ensuring that scarce resources are used to maximize outcomes—perhaps even more relevant now, given the ever-increasing costs of health care in times of austerity. Cochrane noted that the hypertension research community had failed to conduct randomized controlled trials, and attributed this to the tradition of ‘pure’ research that had always considered randomized controlled trials a rather borderline activity. This criticism could be equally levelled at the nephrology community today.

In 1979, Cochrane participated in a forum on ‘Medicines for the year 2000’ organized by the UK Office of Health Economics. During this he commented, ‘It is surely a great criticism of our profession that we have not organized a critical summary by specialty or sub-specialty, updated periodically, of all relevant randomized controlled trials (RCTs)…’. Cochrane also speculated in the same commentary on which branch of medicine was the least scientifically based, judging by the extent that they had used RCTs to evaluate what they were doing and the extent to which they acted on their results’. It was the gynaecologists and obstetricians who received the unwelcome award of ‘the wooden spoon’, because of their failure to randomize home- and hospital-based delivery for low-risk women, cervical cancer screening, induction of labour, use of ultrasound, foetal monitoring and placental function tests. He suggested that GO (gynaecology and obstetrics) could ‘stand for GO ahead without evaluation!’

The challenge brought about by the chagrin of Cochrane’s wooden spoon was taken up by a young British perinatal
TWENTY YEARS ON: STILL THE NEED FOR SYSTEMATIC REVIEWS

The systematic review remains the key methodology to support the vision of the Cochrane Collaboration: providing the highest quality evidence to support health and healthcare. The systematic review of randomized controlled trials provides users with a summary of all the reliable evidence available for research questions that concern interventions. In addition, by combining all the available evidence, a well-conducted systematic review can go beyond the individual trial to show hazardous effects of treatment, assess the quality of the available evidence to give users an understanding of the confidence they might have using the information and identify particular clinical situations in which treatment might be more or less effective. Systematic reviews of randomized trials can then also identify where evidence is missing (for example, lack of evidence for the effects of vitamin D treatment on mortality outcomes in chronic kidney disease [3]), inform practice guidelines and lead ultimately to widespread changes in practice.

Despite Archie Cochrane’s call some 40 years ago to accumulate all available randomized trials and incorporate these into systematic reviews, evidence in nephrology has lagged behind that of all major medical specialties for decades, largely due to the relative lack of high-quality randomized trials. Ten years ago, the number of randomized trials in kidney disease was the fewest of all major subspecialties and the quality was generally low [4]. This trend unfortunately shows no signs of reversing. In 2010, nephrology was well behind the rest of the pack with 6000 randomized trials, compared with 50 000 in cardiology and 30 000 in cancer medicine [5]. And in nephrology, we are relatively over-endowed with small randomized trials that evaluate treatment effectiveness based on biological end points (such as blood pressure, dialysis dose, serum phosphorus and haemoglobin targets). These are not measures of how patients feel, function and survive and may not be valid measures of drug effects. Because of this, individual randomized trials in kidney disease are often ill-equipped to tell us whether treatments work, and equally importantly, whether they are hazardous. Reporting of treatment hazards in randomized trials is notoriously poor [6], and nephrology is no different. Therefore, the systematic review, which collates all available trial data for a specific clinical question (Does treatment A prevent outcome B in adults with disease C?), can overcome many of the challenges borne by numerous smaller trials and may provide sufficient power to identify whether healthcare interventions actually do more harm than good. And for policymakers (but rather less usefully for the clinician), reviews can show when there is no reliable evidence for a given health practice.

The Cochrane Renal Group, tasked with collating the evidence for the Cochrane Collaboration specifically in the field of nephrology, started out life in the ancient city of Lyon, France, in March 1997. Within 9 months of its beginning, 48 collaborators in 16 countries had joined in the effort and 15 reviews were in preparation. By the time the editorial base moved across the world to The Children’s Hospital at Westmead in Sydney, Australia, in 2000, where it has remained ever since, four systematic reviews had been published and 25 more were in the pipeline. At the 20th anniversary in 2013, the group involved 233 contact authors (Figure 1) and 843 authors overall (Figure 2) from all around the world. The number of published reviews has steadily grown to 116, with 143 more in progress (Figure 3). How is clinical practice and policy in nephrology different today as a result of the systematic review and the efforts of Cochrane? What have we learned that would have either remained hidden or its discovery delayed without the methodical
combining of study data? How have systematic reviews in nephrology closed the research–practice gap?

**‘Discovery’ of effective interventions when individual studies have failed to do so**

Systematic reviews in nephrology have allowed us to discover when treatments are effective even when individual studies have not done so. For instance, in 2005 there were already 17 trials of antiviral prophylaxis in recipients of a solid organ transplant who had either positive cytomegalovirus serology or were receiving a cytomegalovirus-positive allograft. In all the existing trials, there was no certainty that antiviral treatment was any more helpful than placebo, and all included fewer than 25 events. It was not at all clear whether treatment improved survival for such patients and whether antiviral treatment really did more good than harm. Elisabeth Hodson and her team did the meta-analysis of these small trials and showed for the first time that antiviral prophylaxis markedly reduced death (by 37% on average) for recipients of a solid organ transplant [7]. And, antiviral prophylaxis acted directly by reducing death related to cytomegalovirus disease. As a result, antiviral prophylaxis became routine and, just as importantly, further larger trials were rendered unnecessary (thereby avoiding future patients being allocated to placebo).

**‘Discovery’ of ineffective/harmful interventions when individual studies show benefit**

Systematic reviews have allowed us to know when treatments for kidney disease might be ineffective for a specific population. By the end of 2011, existing trials of cholesterol lowering in chronic kidney disease were conflicting. Two key trials, 4D and AURORA, revealed that statin therapy did not benefit dialysis patients, even for those patients with extraordinarily high risks of cardiovascular disease [8, 9]. The SHARP trial, the closest we have come to a mega trial in nephrology, subsequently evaluated cholesterol-lowering treatment in nearly 10,000 patients (both dialysis patients and those with less severe kidney disease) and concluded that there was no evidence for different treatment effects in the two different populations [10]. The clinical uncertainty about lipid-lowering treatment for dialysis expanded. Did cholesterol-lowering therapy improve clinical outcomes for dialysis patients or not? Subsequently, a systematic review of statin therapy in individuals with chronic kidney disease could combine all data for statin therapy in 23 dialysis populations to have sufficient power to show that the benefits of
treatment were at best small and uncertain for dialysis patients, and probably non-existent [11].

Systematic reviews also tell us whether treatments are potentially hazardous (and ineffective) when small trials based on surrogate end points are unhelpful and when even large trials are not sufficiently powered to detect treatment harms. Reviews have been done which have identified numerous treatments commonly used in chronic kidney disease that potentially do more harm than good. Although individual trials were nearly all inconclusive or unavailable, by combing published and publicly unavailable data, a review showed that antiplatelet therapy in patients with acute coronary syndromes or undergoing percutaneous angiography, who have kidney disease, increases major bleeding and does not protect against revascularization, cardiovascular events or death [12]. Similarly, cinacalcet, the drug with the greatest annual expenditure in US dialysis patients, more than doubles the risk of harms (nausea, vomiting and hypocalcaemia), but does not improve survival or prevent myocardial infarction or stroke [13].

**Discovery of widespread risk of bias in existing studies**

The information from systematic reviews is not limited to whether treatments are effective, ineffective, uncertain or frankly harmful. They can also methodically evaluate the quality of the evidence for a clinical question and provide an estimate of how confident we can be in estimated treatment effects reported by randomized trials. For example, if we are not certain how investigators concealed the treatment assignment for each patient in a randomized trial (so we could not be sure whether investigators might have influenced the specific treatment given to specific participants), then we might have less confidence in the results of that trial. Or, equally, if patients are more likely to drop out of follow-up after receiving a new experimental treatment and these participants are excluded from the trial analysis, it might seem like that the treatment is less hazardous because the patients who potentially have come to harm are not counted. These ‘risks of bias’ in randomized trials, among others, have been shown to lead to unreliable estimates of the benefits or harms of treatment, which are more often than not biased in favour of the novel intervention. A recent example, in nephrology, is the effects of haemodiafiltration for the outcome of cardiovascular death [14]. In two of the three largest trials of haemodiafiltration (ESHOL and Turkish OL-HDF), between 20 and 40% of patients were excluded from the analyses, downgrading the confidence we might have in the 25% reduction on cardiovascular mortality to low (‘our confidence in the effect estimate is limited: The true effect may be substantially different from the estimate of effect’ [15]). So despite six trials in nearly 3000 dialysis patients, the evidence from primary trials for haemodiafiltration is not sufficiently reliable to inform consumer preferences, clinical practice or guideline policies.

**Discovery of widespread evidence gaps**

Systematic reviews can also show policy makers and practitioners when there is little evidence to support common clinical practice. A systematic review has shown that there are no robust data supporting the common practice and guideline suggestions to control levels of serum phosphorus, parathyroid hormone or calcium within specified target ranges [16]. Systematic review and meta-analysis have additionally shown that there is no evidence that vitamin D treatment to lower parathyroid hormone levels in kidney disease patients prevents death and cardiovascular events [3]. Despite a widespread belief...
and earlier analyses, cranberry products do not appear to pre-
vent urinary tract infections [17].

**Impact on guidelines and policy**

Ultimately, to be useful, systematic reviews must facilitate the
inclusion of effective interventions into healthcare practice and
policy (and vice versa). Beneficial treatments need to be used,
and ineffective or harmful treatments need to be discontinued.
When there are clear gaps in the evidence shown by systematic
reviews for the available literature, clinical practice needs to
change and new research priorities need to close the gaps.

As an example, shortly after a systematic review showed that
the benefits of lipid-lowering therapy for patients treated with
dialysis were small or non-existent in 2012 [11], the Kidney
Disease Improving Global Outcomes (KDIGO) group suggested in
its 2013 clinical guideline that dialysis patients not be initiated
on statin/ezetimibe therapy and that patients might be confi-
dent that little or no benefit would be received from treatment
(although patients might reasonably choose to have treatment
through personal preference) [18]. By combining existing data
from studies at generally lower risks of bias, we could be collect-
ively confident that no further trials were needed. In a second
example, during a period of widespread global use of erythro-
poietin agents to correct the anaemia that complicates chronic
kidney disease, systematic reviews that revealed worse health
outcomes occurred with higher haemoglobin targets [19, 20]
contributed to an FDA black box warning and change in global
practice to lower haemoglobin values.

**FUTURE CHALLENGES FOR COCHRANE AND NEPHROLOGY**

Despite the steady progress achieved by systematic reviews on
practice and policy, there are many challenges still ahead for
the Cochrane Collaboration. Specifically, the Collaboration
needs to continue contributing to global efforts to maximize
value and reduce wastage in biomedical research [21].

**Relying on published data**

Systematic reviews rely on published data and on the willing-
ness of investigators to provide unpublished data from their re-
search studies. Only about half of all trials are eventually
published in full [22], and fewer than half of all trials are ade-
quately registered with a trial registry [23]. When outcomes
are published eventually, statistically significant results are
commonly favoured and selective reporting of outcomes is
prevalent [24]. Publicly available sources of data (such as jour-
nal articles) provide much less information on patient out-
comes than unpublished clinical study reports [25], and
systematic reviews which rely solely only on published informa-
tion draw different conclusions compared with those in which
unpublished results can be included [26]. For systematic re-
views to provide the most robust information possible, a collect-
eive effort from all investigators to provide data from all
randomized participants for pre-specified outcomes is needed.
When it is not, then our confidence in the results of the trials
and the reviews based on those trials will always be sub-optimal.
To enhance the availability of data for systematic review, the Co-
chrane Renal Group has cumulated a large registry of 12 270
randomized controlled trials relevant to nephrology through
a dedicated and consistent community effort to identify trial
data from electronic sources and handsearching (Figures 4
and 5).

**Systematic reviews are large and not user-friendly**

Systematic reviews can be unwieldy in size and rather im-
penetrable because of their effort to be transparent. Although
Cochrane summaries win awards from plain English
campaigners (www.plainenglish.co.uk), many are still hard to digest for readers and consumers. Clinicians typically have an hour or less for reading each week and although they formulate two questions for every three patient encounters, these queries frequently go unanswered because information flows do not work to help clinicians change their practice [27]. We have known for a long time that there can be up to 20 years between findings from clinical research being implemented in clinical guidelines and practice. New ways to harness user-friendly methods that disseminate information from within systematic reviews beyond the PDF format and from behind firewalls are needed. Even now, half of the world’s population does not have free access to The Cochrane Library when they need it. We need to loosen the traditional models of publishing and journal-based knowledge translation to allow the knowledge produced by systematic reviews to be much more applicable in every day practice when decisions are being made.

**Traditional systematic reviews of trials alone cannot answer the full range of questions asked**

The systematic review itself is evolving and needs to. The traditional Cochrane review of interventions, where one treatment is compared with another treatment, simply cannot answer all the clinical questions we have. Patients and health systems are increasingly complex, and systematic reviews that evaluate complex interventions and healthcare strategies would help [28]. The ever-increasing number of alternative treatment options means that traditional meta-analysis does not have the statistical grunt to understand the relative efficacy and safety of all treatments for a particular condition. The next generation of evidence synthesis is the network meta-analysis, which for the first time will allow us to rank multiple different treatments for a single condition even when individual head-to-head trials are not available. Recent examples of network analyses in the general literature have been the ranking of effectiveness and tolerability of antidepressants [29] or even exercise versus pharmacological interventions on mortality [30]. In nephrology, for instance, network meta-analysis could answer which is the most effective and safest antihypertensive agent for individuals with diabetes and kidney disease?

Or, are biosimilar epoetins equivalent to proprietary epoetin formulations (or even placebo) for preventing blood transfusion?

**Acknowledging consumer values**

Increasingly, our top-down approach to priority setting in medical research is being appropriately challenged [31]. Increasingly, outcomes reported in trials diverge from the aspects of care that patients value most; while dialysis trials tend to focus on biochemical and cardiovascular outcomes, dialysis patients value survival, convenience and dialysis-free days [32]. Thus, patient involvement in identifying and prioritizing research topics can facilitate practice and policy that meets consumer’s needs and improves compliance and patient satisfaction. Qualitative research, which identifies consumer preferences, experiences and concerns, is at the heart of understanding the impact and relevance of medical care and can help drive sensible research outcomes. And one step further, the thematic synthesis of qualitative studies can draw together data from a wide range of clinical settings to draw a much larger conceptual understanding than each individual data sets. For example, qualitative synthesis has shown that when making decisions about chronic kidney disease care, patients are strongly influenced by the experiences of their peers and that the timing of information may inhibit patient choices about dialysis modality and palliative care [33]. For the first time in September 2013, the Cochrane Library dipped its toe in this water and published a synthesis of qualitative studies. Notably, Cochrane Renal Group contributors have been fundamental in developing guidelines for transparent reporting of qualitative research [34].

**The Next 20 Years**

Despite enviable progress for Cochrane and the systematic review, there is much still to be done. Evidence synthesis shows we still have important gaps in knowledge for large populations affected by chronic kidney disease. We need more trials for children with kidney disease [35]. And, trials in low- and middle-income settings are badly underrepresented for all non-communicable diseases [36]. Cochrane reviews take on average over 2 years to complete and are often out of date on arrival, and currently, about one-third of the reviews in The Cochrane Library are in need of updating. Priority setting for the most urgent and relevant topics, patient priority setting and updating of reviews that will have substantively new conclusions from newly published trials are all approaches being adopted by the Collaboration. In addition, individual patient data meta-analysis from existing nephrology trials may add to our understanding of benefits and harms of the treatments we use but require community collaboration.

In recognition of the central role that the systematic review has had in providing reliable actionable evidence in chronic kidney disease, we will be publishing a series of educational articles over the next few months about how to read and appraise the different types of systematic reviews available. We will include in this series, reader guides to systematic reviews of (i) interventions, (ii) network analyses, (iii) prognosis and...
prevalence, (iv) qualitative studies, (v) health economics and (vi) diagnostic test accuracy studies. In these, we will provide a relevant clinical scenario, appraise a relevant published systematic review and in doing so, discuss how a systematic review is done and interpreted.

Happy 20th birthday, Cochrane Collaboration.

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CONFLICT OF INTEREST STATEMENT

All authors are affiliated with the Cochrane Renal Group. The information presented in this paper has not been published previously in whole or in part, except in abstract format.

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