Composing a new song for trials: the Standardised Outcomes in Nephrology (SONG) Initiative

Authors

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Randomised trials provide the most reliable evidence about the safety and effectiveness of interventions to improve healthcare and patient outcomes. Unfortunately, the potential for trials to inform treatment decisions remains limited because the outcomes reported often do not resonate with what is directly meaningful and relevant to patients and their clinicians[1-3]. Further, inconsistent reporting of outcomes across trials prevents assessment of the comparative effect of interventions[4]. Outcome reporting bias, whereby authors cherry pick the outcomes they report on the basis of favourable results, may also occur when there is not a standardised list of outcomes measured and reported [5, 6]. Collectively these problems may undermine the reliability of published trials, leading to inefficient use of scarce research and healthcare resources, and unintended harm to patients [6].

Such dissonance in outcomes reported in trials is widespread and evident across all medical specialties. The growing recognition of the problem has prompted large-scale efforts to establish core outcome sets. Core outcome sets are an agreed standardised set of outcomes for a specific clinical area that are to be reported as a minimum in all trials in that area[7]. Outcomes are selected because they are critically important to all stakeholders – namely patients, their clinicians, and policy makers – for decision-making. Core outcomes sets are not designed to be comprehensive or exclusive. Typically they include only 3-5 outcomes. Other outcomes that are identified to be important (i.e. to some stakeholder groups) may also be recommended for some trials (Figure 1). The designated primary outcome of any given trial may be outside the core outcome set, and researchers may also opt to add other, trial-specific outcomes, chosen for reasons including responsiveness to the intervention and feasibility.

Attempts to standardise outcomes began 50 years ago when the World Health Organization published recommendations for the minimum requirements for data collection in cancer trials[8]. In the 1990s the Outcome Measures in Rheumatology (OMERACT) initiative was formed, and is perhaps the most widely recognised and largest initiative in the field of core outcome development. OMERACT
engages patients and health professionals to standardise outcome measures for trials in rheumatology[9], and has pioneered methodologies for developing core outcome sets. The uptake of the OMERACT core outcome sets has improved the consistency of outcomes reported in trials[10]. In the past decade, core outcome sets in diverse medical specialties, including cardiology, dermatology, surgery, oncology, women’s health, and respiratory disease, have progressively been developed[7, 9-11].

The use of core outcome sets is also increasingly being advocated by funders to ensure the relevance and potential impact of research. In the United Kingdom, funding organisations including the National Institute for Health Research and the Health Research Board (Ireland) advise researchers to include core outcome sets if they are available, and highlight the Core Outcome Measures in Effectiveness (COMET) database of core outcomes as a key resource[7]. The COMET initiative was recently launched to facilitate the development, implementation and evaluation of core outcome sets[7].

There has been a long-standing need in nephrology to develop core outcomes[12-14]. More than 14,000 randomised trials are available in the Cochrane Kidney and Transplant Specialised Register[15] and a search in ClinicalTrials.gov trials for “kidney disease” yields over 3000 ongoing trials. Despite this considerable investment into trials in nephrology, improvements in outcomes for patients with kidney disease have been modest at best. Across all stages of chronic kidney disease, patients still have a markedly higher risk of mortality and serious comorbidities including cardiovascular disease, diabetes, cancer, and infection, compared with the general population[16-18]. Patients with chronic kidney disease have poor quality of life, particularly if they are on dialysis, to the extent that many patients with a kidney transplant have indicated that graft survival is of a higher priority outcome (avoiding a return to dialysis) than death[19].
It is difficult to estimate the impact that the lack of core outcomes in nephrology has had on patient care and outcomes, but a comparison between the huge research effort and the relatively small health gains would suggest some impact is likely. Examples of missed opportunities abound. In kidney transplantation, complete reporting of mortality, graft loss, and graft function (creatinine and estimated glomerular filtration rate) occurred in only 16% of trials on immunosuppressive therapy[20]; only two per cent of trials reported quality of life [21]. Quality of life outcomes, when reported, were almost always shown to favour the intervention, which is almost certainly due to selective reporting of outcomes, rather than near universal benefits of specific immunosuppressive agents [21]. Graft survival, mortality, life participation (ability to participate in usual activities) were both identified as core outcomes in the SONG-Tx (kidney transplantation process) – critically important to stakeholders for informing decision-making[22].

A recent systematic review of 205 trials in children with chronic kidney disease showed that the majority of outcomes reported were biochemical endpoints (including biochemical or physiological outcomes, ie, pathophysiological manifestations of health conditions). The most frequently reported outcome was blood pressure (37% trials), which was defined by 56 different outcome measures [14]. Only 14% of trials reported mortality, 4% reported cardiovascular disease, and 1% reported quality of life, fatigue, depression, school, or physical function [14]. These data are unconscionable. Patients, clinicians and research funders have a legitimate right to ask the nephrology research community a number of questions. Why are these outcomes chosen? Is it because of their importance to decision making or because of feasibility and their likelihood of being ‘positive”? Why is the same outcome measured in so many different ways?

It is now time to break the status quo in nephrology – and perhaps we can do so with a SONG. The Standardised Outcomes in Nephrology (SONG) initiative was launched in 2014 to establish core outcomes across all stages with chronic kidney disease. In a synchronised effort, more than 2500
patients, caregivers, physicians, nurses and allied health professionals, regulators, funders, researchers, and industry partners from more than 80 countries have been involved in developing core outcomes. To date, these have included hemodialysis (SONG-HD)[23-27], peritoneal dialysis (SONG-PD), kidney transplantation (SONG-Tx)[22, 28], peritoneal dialysis (SONG-PD)[29], children and adolescents (SONG-Kids)[14, 30], and polycystic kidney disease (SONG-PKD).

The core outcomes are developed through a validated and transparent process based on the OMERACT[9] and COMET[7] initiatives. The framework for establishing core outcomes involves systematic reviews of outcome reporting in trials, focus groups with nominal group technique with patients and caregivers, stakeholder interviews, an international online Delphi survey, and consensus workshops. The detailed methods are available in the SONG Handbook, published in June 2017[31]. With the core outcomes now established for haemodialysis (SONG-HD: fatigue, vascular access, cardiovascular disease, mortality)[24-28] and kidney transplantation (SONG-Tx: graft health, cardiovascular disease, cancer, infection, life participation, and mortality)[22, 28], identifying core validated outcome measures for each outcome is underway.

The uptake of core outcomes will help to ensure that trials report outcomes that are directly relevant for decision-making, and thereby contribute to patient care. However, establishing and implementing core outcomes is not without challenges and will require engagement, dialogue, and support among stakeholders. We are now working with professional societies, guideline and research organisations, trial networks, registries, journal, funders, regulators, and patient organisations to disseminate and encourage the use of the SONG core outcomes. European Renal Best Practice (ERBP), an advisory board of the European Renal Association and European Dialysis and Transplant Association (ERA-EDTA), produces evidence-based guidelines for healthcare professionals involved in the care of patients with kidney disease. In July 2017, ERBP endorsed the SONG core outcome domains, which will be used in relevant guidance. Other societies and organisations, including the International
Society of Nephrology, Canadian Society of Nephrology, the Australian and New Zealand Society of Nephrology, and Cochrane Kidney Transplant have also endorsed the SONG core outcomes.

There are ongoing opportunities to be involved in the SONG initiative and we welcome input from the nephrology community to identify and implement core outcomes domains across all stages of chronic kidney disease. Patients with chronic kidney disease, family members, clinicians, researchers, policy makers, and industry, are invited to be part of the SONG initiative by registering their details via http://songinitiative.org/get-involved/. Working in concert and singing from the same song sheet, we can hope to see transformative changes in the relevance and consistency of trial outcomes to better support shared decisions, which will expedite improvement in patient care and outcomes in chronic kidney disease.
Acknowledgements

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Conflict of interest statement

The results presented in this paper have not been published previously in whole or part, except in abstract format.