Composing a new song for trials: the Standardized Outcomes in Nephrology (SONG) initiative

Allison Tong1,2, Jonathan C. Craig1,2, Evi V. Nagler3,4 and Wim Van Biesen3,4, for the SONG Executive Committee and the European Renal Best Practice Advisory Board*

1Sydney School of Public Health, University of Sydney, Sydney, NSW, Australia, 2Centre for Kidney Research, Children’s Hospital at Westmead, Sydney, NSW, Australia, 3Renal Division, Ghent University Hospital, Ghent, Belgium and 4European Renal Best Practice, London, UK

Correspondence and offprint requests to: Allison Tong; E-mail: allison.tong@sydney.edu.au
*A complete list of the members of the SONG Executive Committee and European Renal Best Practice Advisory Board is provided in the Acknowledgements section.

Randomized trials provide the most reliable evidence about the safety and effectiveness of interventions to improve health care 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 standardized 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 health care 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 standardized set of outcomes for a specific clinical area that are to be reported as a minimum in all trials in that area [7]. Outcomes of any given trial may be outside the core outcome set 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 standardized 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 health care 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 standardized 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 policymakers—for decision making. Core outcome sets are not designed to be comprehensive or exclusive. Typically they include only three to five 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 standardize 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 recognized and largest initiative in the field of core outcome development. OMERACT engages patients and health professionals to standardize 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 UK, funding organizations, 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 randomized trials are available in the Cochrane Kidney and Transplant Specialised Register [15] and a search of ClinicalTrials.gov trials for ‘kidney disease’ yields >3000 ongoing trials. Despite this considerable investment in trials in nephrology, improvements in outcomes for patients with kidney disease have been modest at best. Across all stages of chronic kidney disease (CKD), 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 CKD 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 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 2% of trials reported quality of life [21]. Quality of life outcomes, when reported, were almost always shown to favor the intervention, which is almost certainly due to selective reporting of outcomes, rather than universal benefits of specific immunosuppressive agents [21]. Graft survival, mortality and life participation (ability to participate in usual activities) were identified as core outcomes in the Standardized Outcomes in Nephrology kidney transplantation (SONG-Tx) process, which is critically important to stakeholders for informing decision making [22].

A recent systematic review of 205 trials in children with CKD showed that the majority of outcomes reported were biochemical endpoints (including biochemical or physiological outcomes, i.e. 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 SONG initiative was launched in 2014 to establish core outcomes across all stages with CKD. In a synchronized effort, more than 2500 patients, caregivers, physicians, nurses and allied health professionals, regulators, funders, researchers and industry partners from >80 countries have been involved in developing core outcomes. To date, these have included SONG hemodialysis, SONG-HD [23–27], SONG kidney transplantation (SONG-Tx) [22, 28], SONG peritoneal dialysis, (SONG-PD) [29], children and adolescents (SONG-Kids) [14, 30] and SONG 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 SONG hemodialysis (fatigue, vascular access, cardiovascular disease, mortality) [24–28] and SONG-Tx (graft health, cardiovascular disease, cancer, infection, life participation and mortality) [22, 28], identifying core validated outcome measures for each outcome is under way.

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 organizations, trial networks, registries, journals, funders, regulators and patient organizations to disseminate and encourage use of the SONG core outcomes. European Renal Best Practice, an advisory board of the European Renal Association and European Dialysis and Transplant Association, produces evidence-based guidelines for health care professionals involved in the care of patients with kidney disease. In July 2017, European Renal Best Practice endorsed the SONG core outcome domains, which will be used in relevant guidance. Other societies and organizations, including the International Society of Nephrology, Canadian Society of Nephrology, Australian and New Zealand Society of Nephrology, The Transplantation Society, Kidney Disease Improving Global Outcomes 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 outcome domains across all stages of CKD. Patients with CKD, family members, clinicians, researchers, policymakers and industry are invited to be part of the SONG initiative by registering their details via http://songini tiative.org/get-involved/. Working in concert and singing from the same song sheet, we hope to see transformative changes in

FIGURE 1: SONG core outcomes.
the relevance and consistency of trial outcomes to better support shared decisions, which will expedite improvements in patient care and outcomes in CKD.

ACKNOWLEDGEMENTS

SONG Executive Committee*: Jonathan C. Craig (Chair), Sydney School of Public Health, University of Sydney; Braden Manns, Departments of Medicine and Community Health Science, University of Calgary; Brenda Hemmelgarn, Departments of Medicine and Community Health Science, University of Calgary; David C. Wheeler, Centre for Nephrology, Division of Medicine, University College London; John Gill, Division of Nephrology, University of British Columbia, St. Paul’s Hospital; Peter Tugwell, Epidemiology and Community Medicine, Centre for Global Health, University of Ottawa; Roberto Pecoits-Filho, School of Medicine, Pontifícia Universidade Católica do Parana; Sally Crowe, Crowe Associates Ltd; Tess Harris, patient representative, PKD International; Wim Van Biesen, Renal Division, Ghent University Hospital; Wolfgang C. Winkelmaier, Section of Nephrology, Baylor College of Medicine; Angela Yee Moon Wang, Department of Medicine, University of Hong Kong; Allison Tong, Sydney School of Public Health, University of Sydney.

European Renal Best Practice Advisory Board*: Jonathan Fox (Chair), Glasgow Renal Unit, University of Glasgow; Daniel Abramowicz, Department of Medicine, Université Libre de Bruxelles; Jorge Cannata-Andia, University of Oviedo; Adrian Covic, University of Medicine and Pharmacy Romania; Lucia Del Vecchio, Department of Nephrology and Dialysis, Alessandro Manzoni Hospital; Denis Fouque, Department of Nephrology, Hopital Edouard Herriot; Olof Heimbuer, Karolinska Institutet; Kitty Jager, Faculty of Medicine, University of Amsterdam; Elisabeth Lindley, Department of Renal Medicine, Leeds Teaching Hospitals NHS Trust; Anna Marti-Monros, Nephrology Department, Consorcio Hospital; Evi V. Nagler, Renal Division, Ghent University Hospital; Rainer Oberbauer, University of Vienna Medical Center; Ivan Rychlik, Charles University, Prague; Goce Spasovski, Department of Nephrology, University of Skopje; James Tattersall, Department of Renal Medicine, St James University Hospital; Wim Van Biesen, Renal Division, Ghent University Hospital; Raymond Vanholder, Renal Division, Ghent University Hospital; Christoph Wanner, Division of Nephrology and Hypertension, University of Wuerzburg; William Whithers, patient representative; Andrzei Wieczek, Department of Nephrology, Endocrinology and Metabolic Diseases, Medical University of Silesia; Carmine Zoccali, Nephrology, Dialysis and Transplantation Unit, Ospedali Riuniti.

CONFLICT OF INTEREST STATEMENT

None declared. The results presented in this article have not been published previously in whole or part, except in abstract format.

REFERENCES


Received: 11.8.2017; Editorial decision: 11.9.2017