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

Authors

Allison Tong[1,2], Jonathan C Craig[1,2], Evi V Nagler[3,4], Wim Van Biesen[3,4] for the SONG Executive Committee and the European Renal Best Practice Advisory Board*

*A complete list of the members of the SONG Executive Committee and European Renal Best Practice Advisory Board is provided in the Acknowledgements section.

Details of all authors:

[1]Sydney School of Public Health, University of Sydney, Sydney, NSW, Australia

[2]Centre for Kidney Research, The Children's Hospital at Westmead, Sydney, NSW, Australia

[3]Renal Division, Ghent University Hospital, Ghent, Belgium

[4]European Renal Best Practice, London, UK

Name and address for correspondence:

Allison Tong

Centre for Kidney Research, The Children's Hospital at Westmead, Westmead, NSW 2145, Sydney, Australia

Phone: +61 2 98451482 Fax: +61 2 9845 1491 Email: allison.tong@sydney.edu.au

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

SONG Executive Committee*

Jonathan C Craig (Chair), Sydney School of Public Health, The University of Sydney
Braden Manns, Departments of Medicine and Community Health Science, The University of Calgary
Brenda Hemmelgarn, Departments of Medicine and Community Health Science, The 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 Paraná
Sally Crowe, Crowe Associates Ltd
Tess Harris, Patient representative, PKD International
Wim Van Biesen, Renal Division, Ghent University Hospital
Wolfgang C Winkelmayer, Section of Nephrology, Baylor College of Medicine
Angela Yee Moon Wang, Department of Medicine, The University of Hong Kong
Allison Tong, Sydney School of Public Health, The University of Sydney

European Renal Best Practice Advisory Board*

Jonathan Fox (Chair), The 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 Heimburger, 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 in 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
Andrezj Wiecek, Department of Nephrology, Endocrinology and Metabolic Diseases, Medical University of Silesia
Carmine Zoccali, Nephrology, Dialysis and Transplantation Unit, Ospedali Riuniti,

References

1. Ghandi GY. Patient-important outcomes in registered diabetes trials. JAMA 2008;299(21):2543-2549

2. Yudkin JS, Lipska KJ, Montori VM. The idolatory of the surrogate. BMJ 2011;343(d7995)

3. Hedayati SS, Minhajuddin AT, Afshar M, *et al.* Association between major depressive episodes in patients with chronic kidney disease and initiation of dialysis, hospitalization, or death. J Am Med Assoc 2010;303(19):1946-1953

4. Hirsch BR, Califf RM, Cheng SK, *et al.* Characteristics of oncology clinical trials: insights from a systematic analysis of ClinicalTrials.gov. JAMA Intern Med 2013;173(11):972-979

5. Dwan K, Gamble C, Williamson PR, *et al.* Systematic review of the empirical evidence of study publication bias and outcome reporting bias - an updated review. PLoS One 2013;8(7):e66844

6. Chan AW, Song F, Vickers A, *et al.* Increasing value and reducing waste: addressing inaccessible research. Lancet 2014;383(9913):257-266

7. Williamson PR, Altman DG, Bagley H, *et al.* The COMET Handbook: version 1.0. Trials 2017;18:280

8. Miller AB, Hoogstraten B, Staquet M, *et al.* Reporting results of cancer treatment. Cancer 1981;47(1):207-214

9. OMERACT. The OMERACT Handbook available at http://www.omeract.org/pdf/OMERACT_Handbook.pdf.

10. Kirkham JJ, Boers M, Tugwell P, *et al.* Outcome measures in rheumatoid arthritis randomised trials over the last 50 years. Trials 2013;14:324

11. Kirkham JJ GS, Altman DG, Blazeby JM, Clarke M, Devane D, Gargon E, Moher D, Schmitt J, Tugwell P, Tunis S, Williamson PR. Core Outcome Set-STAndards for Reporting: The COS-STAR Statement. PLoS Med 2016;13:e1002148

12. Cochrane Library available at http://www.cochranelibrary.com (Accessed March 29th, 2017). Cochrane; 1999 - 2017.

13. Knight S, Morris PJ, Schneeberger S, *et al.* Trial design and endpoints in clinical transplant research. Transplant Int 2016;29(8):870-879

14. Chong LSH SB, Tong A, Hanson CS, Samuel S, Zappitelli M, Dart A, Furth S, Eddy AA, Groothoff J, Webb NJA, Yap HK, Bockenhauer D, Sinha A, Alexander SI, Goldstein SL, Gipson DS, Raman G, Craig JC. Range and heterogeneity of outcomes in randomized trials of pediatric kidney disease. J Pediatr 2017;186:110-117.e.111

15. Cochrane Kidney and Transplant Specialised Register available at http://kidneyandtransplant.cochrane.org/cochrane-kidney-and-transplant-specialised-register (Accessed 12th July 2017). Sydney, Australia2017.

16. de Jager DJ, Grootendorst DC, Jager KJ, *et al.* Cardiovascular and noncardiovascular mortality among patients starting dialysis. J Am Med Assoc 2009;302(16):1782-1789

17. Robinson BM, Akizawa T, Jager KJ, *et al.* Factors affecting outcomes in patients reaching end-stage kidney disease worldwide: differences in access to renal replacement therapy, modality use, and haemodialysis practices. Lancet 2016;388(10041):294-306

18. Stewart JH, Vajdic CM, van Leeuwen MT, *et al.* The pattern of excess cancer in dialysis and transplantation. Nephrol Dial Transplant 2009;24(10):3225-3231

19. Howell M, Tong A, Wong G, *et al.* Important outcomes for kidney transplant recipients: a nominal group and qualitative study. Am J Kidney Dis 2012;60(2):186-196

20. Masson P, Duthie FA, Ruster LP, *et al.* Consistency and completeness of reported outcomes in randomized trials of primary immunosuppression in kidney transplantation. Am J Transplant 2013;13(11):2892-2901

21. Howell M, Wong G, Turner RM, *et al.* The consistency and reporting of quality of life outcomes in trials of immunosuppressive agents in kidney transplantation: a systematic review and meta-analysis. Am J Kidney Dis 2016;67(5):762-774

22. Sautenet B TA, Manera KE, Chapman JR, Warrens AN, Rosenbloom D, Wong G, Gill J, Budde K, Rostaing L, Marson L, Josephson MA, Reese PP, Pruett TL, Hanson CS, O’Donoghue D,

Tam-Tham H, Halimi JM, Shen JI, Kanellis J, Scandling JD, Howard K, Howell M, Cross N, Evangelidis N, Masson P, Oberbauer R, Fung S, Jesudason S, Knight S, Mandayam S, McDonald S, Chadban S, Rajan T, Craig JC. Developing consensus-based priority outcome domains for trials in kidney transplantation: a multinational Delphi survey with patients, caregivers and health professionals. Transplant 2017:Accepted 2nd March 2017

23. Evangelidis N, Tong A, Manns B, *et al.* Developing a set of core outcomes for trials in hemodialysis: an international Delphi survey. Am J Kidney Dis 2017:doi: 10.1053/j.ajkd.2016.1011.1029 (online first)

24. Tong A, Manns B, Hemmelgarn B, *et al.* Establishing core outcome domains in hemodialysis: report of the Standardised Outcomes in Nephrology – Hemodialysis (SONG-HD) consensus workshops. Am J Kidney Dis 2017;69(1):97-107

25. Tong A, Manns B, Hemmelgarn B, *et al.* Standardised outcomes in nephrology – haemodialysis (SONG-HD): study protocol for establishing a core outcome set in haemodialysis. Trials 2015;16:364

26. Tong A, Winkelmayer WC, Wheeler DC, *et al.* Nephrologists' perspectives on defining and applying patient-centered outcomes in hemodialysis. Clin J Am Soc Nephrol 2017;12(3):454-466

27. Urquhart-Secord R, Craig JC, Hemmelgarn B, *et al.* Patient and caregiver priorities for outcomes in hemodialysis: an international nominal group technique study. Am J Kidney Dis 2016;68(3):444-458

28. Tong A GJ, Budde K, Marson L, Reese PP, Rosenbloom DL, Rostaing L, Wong G, Josephson MA, Pruett TL, Warrens AN, Craig JC, Sautenet B, Evangelidis N, Ralph AF, Hanson CS, Shen JI, Howard K, Meyer K, Perrone RD, Weiner DE, Fung S, Ma MKM, Rose C, Ryan J, Chen LX, Howell M, Larkins N, Kim S, Thangaraju S, Chapman JR. Toward establishing core outcome domains for trials in kidney transplantation: Report of the Standardized Outcomes in Nephrology – Kidney Transplantation (SONG-Tx) Consensus workshops. Transplant 2017:Accepted 13th March 2017

29. Manera KE, Tong A, Craig JC, *et al.* Standardised Outcomes in Nephrology – Peritoneal Dialysis (SONG-PD): study protocol for establishing a core outcome set in peritoneal dialysis. Perit Dial Int 2017:Accepted 2nd May 2017

30. Tong A SS, Zappitelli M, Dart A, Furth S, Eddy A, Groothoff J, Webb NJA, Yap HK, Bockenhauer D, Sinha A, Alexander S, Goldstein SL, Gipson D, Hanson CS, Evangelidis N, Crowe S, Harris T, Hemmelgarn B, Manns B, Gill J, Tugwell P, Van Biesen W, Wheeler DC, Winkelmayer WC, Craig JC. . Standardised Outcomes in Nephrology – Children and Adolescents (SONG-Kids): a protocol for establishing a core outcome set for children with chronic kidney disease. Trials 2016;17:401

31. SONG Initiative. The SONG Handbook (Version 1.0) available at http://songinitiative.org/reports-and-publications/ (Accessed 12th July 2017). Sydney, Australia2017.

Conflict of interest statement

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