### Standardized Outcomes in Nephrology – Glomerular Disease (SONG-GD): establishing a core outcome set for trials in patients with glomerular disease

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| Complete List of Authors: | Carter, Simon; University of Sydney, School of Public Health; Children's Hospital at Westmead Centre for Kidney Research  
Lightstone, Liz; Imperial College School of Medicine, Centre for Inflammatory Disease, Faculty of Medicine  
Cattran, Daniel; University of Toronto, Faculty of Medicine; Toronto General Research Institute  
Bagga, Arvind; All India Institute of Medical Sciences, Pediatrics  
Barbour, Sean; University of British Columbia, Division of Nephrology, Department of Medicine  
Barratt, Jonathan; University of Leicester College of Medicine Biological Sciences and Psychology, Infection, Immunity & Inflammation; Leicester General Hospital, John Walls Renal Unit  
Boletis, John; Laiko Hospital, Nephrology Department and Renal Transplantation Unit  
Caster, Dawn; University of Louisville, Division of Nephrology  
Coppo, Rosanna; Regina Margherita Children Hospital, Fondazione Ricerca Molinette  
Fervenza, Fernando; Mayo Clinic, Nephrology and Hypertension  
Floege, Juergen; Rheinisch Westfalische Technische Hochschule Aachen Fachgruppe Biologie, Nephrology  
Hladunewich, Michelle; University of Toronto, University Health Network and Sunnybrook Health Sciences Centre, Faculty of Medicine  
Hogan, Jonathan; University of Pennsylvania Perelman School of Medicine, Medicine  
Kitching, A Richard; Monash Health, Nephrology; Monash University, Centre for Inflammatory Diseases, Department of Medicine  
Lafayette, Richard; Stanford University Medical Center; Stanford University, Division of Nephrology, Department of Medicine  
Malvar, Ana; Hospital Fernandez, Nephrology  
Radhakrishnan, Jai; Colombia University Medical Centre; New York Presbyterian Hospital, Division of Nephrology  
Rovin, Brad; Ohio State University, Internal Medicine-Nephrology  
Zhang, Hong; Peking University Institute of Nephrology, Renal Division; Gutman, Talia; University of Sydney, School of Public Health; The Children's Hospital at Westmead, Centre for Kidney Research  
Howell, Martin; University of Sydney - Camperdown and Darlington Campus, School of Public Health; Children's Hospital at Westmead Centre for Kidney Research |
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<td>Teixeira-Pinto, Armando; University of Sydney School of Public Health; Children's Hospital at Westmead Centre for Kidney Research</td>
</tr>
<tr>
<td>Alexander, Stephen; Children's Hospital at Westmead, Centre for Kidney Research</td>
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<tr>
<td>Cho, Yeoungjee; Princess Alexandra Hospital, Department of Nephrology; University of Queensland, Australasian Kidney Trials Network; Translational Research Institute</td>
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<td>Harris, David; University of Sydney, CTRR</td>
</tr>
<tr>
<td>Johnson, David; University of Queensland School of Medicine; Translational Research Institute; Metro South and Ipswich Nephrology and Transplant Services (MINTS), Princess Alexandra Hospital</td>
</tr>
<tr>
<td>Kerr, Peter; Monash Medical Centre, Department of Nephrology; Monash University, Southern Clinical School</td>
</tr>
<tr>
<td>Ryan, Jessica; Monash University, Medicine; Monash Health, Department of Nephrology</td>
</tr>
<tr>
<td>Viecelli, Andrea; Princess Alexandra Hospital, Nephrology; University of Queensland, Australasian Kidney Trials Network</td>
</tr>
<tr>
<td>Wang, Angela; Queen Mary Hospital, University of Hong Kong, Department of Medicine</td>
</tr>
<tr>
<td>Wilkie, Martin; Northern General Hospital, Sheffield UK, Renal Sorby E Floor; Scholes-Robertson, Nicole; The Children's Hospital at Westmead, Centre for Kidney Research</td>
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<td>Tong, Allison; The Children's Hospital at Westmead, Centre for Kidney Research</td>
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Standardized Outcomes in Nephrology – Glomerular Disease (SONG-GD): establishing a core outcome set for trials in patients with glomerular disease

Authors
Simon A. Carter MBBS,1,2 Liz Lightstone MBBS,3 Daniel Catran MD,4,5 Arvind Bagga MD,6 Sean J. Barbour MD,7 Jonathan Barratt PhD,8,9 John Boletis MD,10 Dawn Caster MD,11 Rosanna Coppo MD,12 Fernando C. Fervenza MD, PhD,13 Jürgen Floege MD,14 Michelle Hladunewich MD,4,15 Jonathan J. Hogan MD,16,17 A. Richard Kitching PhD,18,19 Richard Lafayette MD,21,22 Ana Malvar MD,23 Jai Radhakrishnan MD,24,25 Brad H. Rovin MD,26 Hong Zhang PhD,27 Talia Gutman MPH,1,2 Martin Howell PhD,1,2 Charlotte Logeman MPH,2 Jenny I. Shen MD,28 Armando Teixeira-Pinto PhD,1,2 Stephen I. Alexander PhD,2 Yeoungjee Cho PhD,29,30,31 Jonathan C. Craig PhD,32 David Harris MD,33,34 David W. Johnson PhD,29,30,31 Peter G. Kerr PhD,18,19 Jessica Ryan PhD,18,20 Andrea K. Viecelli MD,29,30 Angela Yee-Moon Wang PhD,35 Martin Wilkie MD,36 Nicole Scholes-Robertson,2 Allison Tong PhD1,2 for the SONG-GD Initiative

Author Affiliations
1 Sydney School of Public Health, The University of Sydney, Australia
2 Centre for Kidney Research, The Children’s Hospital at Westmead, Sydney, Australia
3 Centre for Inflammatory Disease, Faculty of Medicine, Imperial College London, United Kingdom
4 Faculty of Medicine, University of Toronto, Toronto, Canada
5 Toronto General Research Institute, Toronto, Canada
6 All India Institute of Medical Sciences, Department of Pediatrics, New Delhi, India
7 Division of Nephrology, Department of Medicine, University of British Columbia
8 Department of Infection, Immunity and Inflammation, University of Leicester, Leicester, United Kingdom

9 John Walls Renal Unit, Leicester General Hospital, Leicester, United Kingdom

10 Nephrology Department and Renal Transplantation Unit, Laiko Hospital, Athens, Greece

11 University of Louisville, Division of Nephrology, Kentucky, United States

12 Fondazione Ricerca Molinette, Regina Margherita Hospital, Turin, Italy

13 Division of Nephrology and Hypertension, Department of Internal Medicine, Mayo Clinic, Minnesota, United States

14 Department of Nephrology and Clinical Immunology, RWTH University Hospital, Aachen, Germany

15 Sunnybrook Health Sciences Centre, Toronto, Canada

16 Hospital of the University of Pennsylvania, Philadelphia, United States

17 Perelman School of Medicine, University of Pennsylvania, Philadelphia, United States

18 Department of Nephrology, Monash Health, Victoria, Australia

19 Centre for Inflammatory Diseases, Monash University Department of Medicine, Victoria, Australia

20 Department of Medicine, Monash University, Victoria, Australia

21 Stanford University Medical Center, Stanford, California, United States

22 Department of Medicine, Division of Nephrology, Stanford University, California, United States

23 Hospital Fernández, Nephrology, Buenos Aires, Argentina

24 Colombia University Medical Center, New York, United States

25 Division of Nephrology, New York Presbyterian Hospital, New York, United States

26 Department of Internal Medicine, Division of Nephrology, Ohio State University Wexner Medical Center, Ohio, United States
27 Renal Division of Peking University First Hospital, Beijing, China

28 Division of Nephrology and Hypertension, Los Angeles Biomedical Research Institute at Harbor-UCLA Medical Center, Torrance, United States

29 Department of Nephrology, Princess Alexandra Hospital, Brisbane, Australia

30 Australasian Kidney Trials Network, University of Queensland, Brisbane, Australia

31 Translational Research Institute, Brisbane, Australia

32 College of Medicine and Public Health, Flinders University, Adelaide, Australia

33 Westmead Institute for Medical Research, The University of Sydney, Australia

34 Sydney Medical School, The University of Sydney, Australia

35 Department of Medicine, Queen Mary Hospital, University of Hong Kong, Hong Kong

36 Department of Nephrology, Sheffield Teaching Hospitals NHS Foundation Trust, Sheffield, United Kingdom

Corresponding author
Dr Simon A. Carter MBBS FRACP
Centre for Kidney Research
The Children’s Hospital at Westmead, NSW
Australia 2145

Phone: +61 2 9845 3431
Fax: +61 2 9845 3432
Email: simon.carter@health.nsw.gov.au

Keywords: Core outcome set, Outcomes research, Patient-centered outcomes, Clinical trials, Chronic kidney disease, Glomerulonephritis
Glomerular diseases (GD) impose a substantial burden on patients and health systems, and are a major cause of end stage kidney disease (ESKD) worldwide.\textsuperscript{1} The causes and clinical features of GD are diverse yet as a group they share many symptoms, treatments and outcomes (Table 1). Patients with primary and secondary GD have mortality rates 2.7 and 3.9-fold higher than the general population respectively, have higher rates of cardiovascular events and report impaired quality of life.\textsuperscript{1} Treatment side effects may include diabetes, poor bone health, obesity, infection, reduced fertility, cancer and impaired quality of life. Prognostic uncertainty and the potential for disease progression contribute to a substantial psychological burden for patients with GD.

While mortality and ESKD rates in patients with some types of GD have shown improvement over the past three decades, this has not been observed for other outcomes. This may be due to limitations in the design of trials, and in particular with respect to outcome reporting. Outcomes of critical importance to patients and clinicians may not be currently reported in trials as these have not been explicitly identified. In other areas of nephrology, there is inconsistent measurement and reporting of trial outcomes, and they are likely subjected to outcome reporting bias.\textsuperscript{2}

Many outcomes directly relevant to patients are not reported in trials. Surrogate biochemical endpoints are frequently used to avoid the large sample sizes and long follow-up required to detect a change in clinical outcomes (e.g. ESKD and mortality).\textsuperscript{3} However patients with GD identify fatigue, pain, weight gain, financial impact and anxiety as major concerns yet these outcomes remain largely absent from many trial reports.
The inconsistency of reporting in GD trials limits our ability to compare the effects of interventions. Three recent trials in IgA nephropathy (STOP-IgAN, NEFIGAN and TESTING) each used different composite outcome measures of estimated glomerular filtration rate (eGFR) and proteinuria as their primary outcome. Kidney function may be reported as change in creatinine, 1/creatinine, creatinine clearance or eGFR with the method of aggregation given as a mean, categorical or percentage change from baseline. Likewise, proteinuria has been reported as mean change in spot albumin:creatinine ratio, protein:creatinine ratio or 24 hour urine protein. Definitions of complete or partial remission are based on proteinuria alone, or as part of a composite outcome incorporating kidney function with differing cut-offs.

Outcome reporting bias is a form of selective reporting that results in published outcomes being those more likely to show an effect favoring the intervention or overstating the effect size. There is often simultaneous underreporting of adverse events, which may lead to patients being inadvertently exposed to the harmful effects of an intervention. Apart from overestimation and distortion of the true effect, there is loss of information from unpublished (negative) outcomes, duplication of effort and inefficiency, with limited contribution to systematic reviews and reduced precision of meta-analyses.

Core outcome sets are an agreed upon standardized set of outcomes that should be measured and reported in all trials in a specific clinical field. They can increase the relevance of trials to patients as well as improve trial efficiency and evidence synthesis through the consistent, transparent and comprehensive reporting of outcomes. The Standardized Outcomes in Nephrology (SONG) initiative commenced in 2014 to establish core outcome sets for trials in
nephrology (Figure 1) and has developed core outcome sets for hemodialysis (SONG-HD), kidney transplantation (SONG-Tx) and peritoneal dialysis (SONG-PD).\textsuperscript{S7,S8,S38} SONG-GD is a new endeavour that aims to establish a consensus-based core outcome set to be reported in all trials in patients with GD. We have used the term GD rather than glomerulonephritis, as it is a more accurate and appropriate term for this group of diseases and more comprehensible by patients.

The SONG-GD core outcome set will consist of approximately five outcomes that are critically important to patients with GD, caregivers and health professionals irrespective of the intervention. The initial and main focus of SONG-GD will be to establish core outcome domains common to all GD. This is justifiable as the first practical and logical step because there is reasonable shared patient experience of disease and treatments across all GD types. Core outcomes do not have to be the primary outcome of a trial - and other outcomes that are sensitive or responsive to the specific intervention can be added.

The aims of SONG-GD are to: describe the scope and consistency of outcomes reported in trials in GD; identify and prioritize outcomes important to patients with GD and their caregivers; determine health professionals’ perspectives on outcomes in GD; develop a consensus-based set of core outcomes of key importance to all stakeholders; and establish a set of outcome domains to be reported in trials of patients with GD.

The SONG-GD methodological framework will be based on the previous SONG projects and adapted from that of Outcome Measures in Rheumatology (OMERACT)\textsuperscript{S1} and Core Outcome
Measures in Effectiveness Trials (COMET). S2 SONG-GD will consist of five phases which are outlined below (Figure S1). A more detailed project plan is provided in the online supplement accompanying this editorial.

The types of GD to be included are shown in Table 1. We will exclude glomerular diseases that do not have common disease manifestations and treatment (e.g. post-infectious glomerulonephritis without alternative complement dysregulation, atypical hemolytic uremic syndrome, hepatitis and HIV-associated disease, collagenopathies, amyloidosis, diabetic and hypertensive nephropathies, storage diseases). Any patient or physician-identified kidney involvement from the included diseases will be considered for the nominal group and Delphi phases. Children will be excluded as they will be addressed in the upcoming SONG-Kids core outcome set.

**Phase 1:** We will conduct a systematic review to assess the scope and heterogeneity of outcome domains and measures reported in contemporary trials of all interventions for adult patients with GD.

**Phase 2:** We will conduct focus groups using nominal group technique with patients who have GD and their caregivers to identify and rank important outcomes that they believe should be reported in trials and discuss the reasoning behind their choices.

**Phase 3:** Semi-structured interviews will be conducted with health care professionals caring for patients with GD to describe their beliefs, values and attitudes about outcomes in GD. We will
specifically sample those with expertise in trials and health policy.

**Phase 4:** An international online Delphi survey of at least 1000 respondents from 70 countries (including low and middle income countries) will be conducted to achieve consensus among patients, caregivers and health professionals on outcomes to be reported in GD trials. The proposed core outcomes will be taken forward for review in Phase 5.

**Phase 5:** A consensus workshop of patients, carers and health professionals (clinical roles, guideline production, GD trial experience, research funding, advisory and regulatory representatives) will be held to review and discuss the proposed core outcome set.

The proposed core outcomes will be made public on the SONG website for four weeks and the website link will be distributed through the SONG Initiative database to invite further feedback. Upon review, the SONG-GD set of core outcome domains will be finalized.

SONG-GD will establish a new core set of outcome domains for all trials in GD through a comprehensive, transparent and equitable process accounting for the shared priorities of patients, caregivers, clinicians, researchers and policy makers. Following consensus on the SONG-GD core outcome set, outcome measures will then be identified or developed as necessary for each domain.

We acknowledge the heterogeneity present across the glomerular diseases. SONG-GD will identify some differences in priorities for outcomes and outcomes unique to different diseases or
treatments. Three broad subgroups may be defined according to their presentation and outcome: GD with the kidneys as the main organ type involved, nephrotic syndrome with the kidneys as the main organ type involved, and systemic disease with kidney involvement. Outcomes relevant and important to specific subgroups in SONG-GD may be captured in the middle and outer tier outcomes (Figure 1). Trialists may include these outcomes as necessary if they are considered appropriate for a certain disease or individual trial. This is especially true for surrogate outcomes, such as proteinuria, where the response to treatment may have different prognostic implications depending on GD type. SONG-GD does not preclude – but rather is a prelude to – the subsequent development of outcome sets specific to different types of GD.

Potential barriers to the uptake of core outcome sets in trials include lack of awareness, limited incentives for their use and added complexity in measuring patient-reported outcomes. A recent SONG implementation workshop identified two main strategies to support implementation of the core outcomes: promoting a culture shift through ‘socialization’ and demonstrating their feasibility and usability.4 Key aspects of implementation will include addressing the knowledge gap around core outcome sets; establishing the credibility of the development process; operationalizing and minimizing the burden of measurement, and embedding the core outcomes in registries and clinical practice.

Through better outcome measurement and reporting in trials, SONG-GD aims to increase the applicability, integrity and contribution of research to patients with GD and their shared treatment decisions.
DISCLOSURE

The authors declare that they have no competing interests.

SUPPLEMENTARY MATERIAL

SONG-GD study protocol. SONG-GD design and study protocol outlining the five phases and methodological framework.

Figure S1. Standardized Outcomes in Nephrology-Glomerular Disease (SONG-GD): study design to derive a core outcome set for trials conducted in people with glomerular disease.

Supplementary references.

Supplementary information is available at Kidney International’s website.
ABBREVIATIONS

COMET  Core Outcome Measures in Effectiveness Trials

eGFR  Estimated glomerular filtration rate

ESKD  End stage kidney disease

GD  Glomerular disease

KDIGO  Kidney Disease: Improving Global Outcomes

OMERACT  Outcome Measures in Rheumatology

SONG-GD  Standardized Outcomes in Nephrology-Glomerular Disease

SONG-HD  Standardized Outcomes in Nephrology-Hemodialysis

SONG-Kids  Standardized Outcomes in Nephrology-Children and Adolescents

SONG-PD  Standardized Outcomes in Nephrology-Peritoneal Dialysis

SONG-Tx  Standardized Outcomes in Nephrology-Kidney Transplantation
REFERENCES


Table 1. Common features of the major glomerular diseases in adults for inclusion in Standardized Outcomes in Nephrology-Glomerular Disease (SONG-GD)

<table>
<thead>
<tr>
<th>Renal-limited glomerular diseases</th>
<th>Clinical features</th>
<th>Clinical course</th>
<th>Treatment</th>
<th>Renal outcome</th>
<th>Risk of transplant loss</th>
</tr>
</thead>
<tbody>
<tr>
<td>IgA nephropathy</td>
<td>Hematuria/proteinuria; nephritic syndrome; rarely nephrotic</td>
<td>Benign; relapsing-remitting; progressive</td>
<td>Supportive; immunosuppression</td>
<td>Highly variable; CKD and ESKD common</td>
<td>Low</td>
</tr>
<tr>
<td>Membranous nephropathy</td>
<td>Proteinuria; nephrotic syndrome</td>
<td>Benign; relapsing-remitting; progressive</td>
<td>Supportive; treat underlying cause; immunosuppression</td>
<td>Complete and partial remission common; ESKD</td>
<td>Low</td>
</tr>
<tr>
<td>Minimal change disease</td>
<td>Nephrotic syndrome</td>
<td>Relapsing-remitting</td>
<td>Supportive; immunosuppression</td>
<td>ESKD rare</td>
<td>Not applicable</td>
</tr>
<tr>
<td>Focal segmental glomerulosclerosis</td>
<td>Proteinuria; nephrotic syndrome</td>
<td>Progressive</td>
<td>Supportive; immunosuppression</td>
<td>Variable depending on treatment response; often progresses to ESKD</td>
<td>Variable</td>
</tr>
<tr>
<td>Complement-mediated glomerulopathy*</td>
<td>Hematuria/proteinuria; rarely nephrotic</td>
<td>Relapsing-remitting, progressive</td>
<td>Supportive; complement blockade or immunosuppression; plasmapheresis</td>
<td>Variable; risk of CKD and ESKD</td>
<td>Variable</td>
</tr>
<tr>
<td>Idiopathic immune complex mediated membranoproliferative glomerulonephritis</td>
<td>Hematuria/proteinuria; nephritic-nephrotic syndrome</td>
<td>Relapsing-remitting, progressive</td>
<td>Supportive; treat underlying cause; immunosuppression</td>
<td>CKD common; ESKD</td>
<td>Moderate</td>
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Glomerular diseases with systemic involvement
<table>
<thead>
<tr>
<th>Glomerular Disease</th>
<th>Presenting Symptoms</th>
<th>Course</th>
<th>Management</th>
<th>Risk of CKD and ESKD</th>
</tr>
</thead>
<tbody>
<tr>
<td>Anti-neutrophil cytoplasmic antibody-associated vasculitis</td>
<td>Hematuria/proteinuria; nephritic syndrome; respiratory symptoms; multi-system involvement</td>
<td>Rapidly progressive; relapsing-remitting</td>
<td>Supportive; immunosuppression; plasmapheresis</td>
<td>High risk of CKD and ESKD</td>
</tr>
<tr>
<td>Lupus nephritis</td>
<td>Hematuria/proteinuria; nephritic syndrome; nephrotic syndrome; multi-system involvement</td>
<td>Relapsing-remitting</td>
<td>Supportive; immunosuppression</td>
<td>Variable; significant risk of CKD and ESKD</td>
</tr>
<tr>
<td>IgA vasculitis (Henoch-Schoenlein purpura)</td>
<td>Hematuria/proteinuria; nephritic syndrome; rarely nephrotic</td>
<td>Benign; relapsing-remitting; progressive</td>
<td>Supportive; immunosuppression</td>
<td>Highly variable; risk of ESKD</td>
</tr>
<tr>
<td>Anti-glomerular basement membrane disease</td>
<td>Nephritic syndrome; pulmonary hemorrhage</td>
<td>Rapidly progressive; low relapse rate</td>
<td>Plasmapheresis; immunosuppression</td>
<td>Highly variable; risk of ESKD</td>
</tr>
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</table>

*Glomerular disease arising from dysregulation and activation of the solid phase of the alternative complement pathway, including those with a membranoproliferative pattern on histology. Post-infectious glomerulonephritis that does not have alternative complement pathway dysregulation will be excluded.

CKD: chronic kidney disease; ESKD: end stage kidney disease.
**Figure 1.** Schema for a Standardized Outcomes in Nephrology (SONG) core outcome set for trials, adapted from Tong *et al.*[^5]
1 CORE OUTCOMES
Critically important to all stakeholder groups. Report in all trials.

2 MIDDLE TIER
Critically important to some stakeholder groups. Report in some trials.

3 OUTER TIER
Important to some or all stakeholder groups. Consider for trials.

**Figure 1.** Schema for a Standardized Outcomes in Nephrology (SONG) core outcome set for trials, adapted from Tong et al.\textsuperscript{5}

99x30mm (300 x 300 DPI)
Standardized Outcomes in Nephrology – Glomerular Disease (SONG-GD):

Study Protocol and Design

The SONG-GD methodological framework will be based on the previous SONG projects and adapted from that of Outcome Measures in Rheumatology (OMERACT) and Core Outcome Measures in Effectiveness Trials (COMET).\(^1\),\(^2\) This methodology is endorsed by the World Health Organization as a valid approach for establishing core outcome sets.\(^3\) SONG-GD will consist of five phases: a systematic review, focus groups with nominal group technique, semi-structured interviews, international Delphi survey with best/worst choice experiments and a consensus workshop (Supplementary Figure 1). Reporting for this study will follow the Core Outcome Set-Standards for Reporting (COS-STAR) statement.\(^4\) SONG-GD is registered in the COMET database (1153; June 4, 2018).\(^5\)

Scope

The initial and main focus of SONG-GD will be to establish core outcomes “shared” across types of GD to be reported in randomized trials. This justifiable as the first practical and logical step because there is reasonable commonality of patient experience and treatments across the types of GD. We will include IgA nephropathy, membranous nephropathy, focal segmental glomerulosclerosis, minimal change disease, IgA vasculitis (Henoch-Schoenlein purpura), complement-mediated glomerulonephritis, membranoproliferative glomerulonephritis, AAV, lupus nephritis and anti-glomerular basement membrane disease (Table 1). In AAV and systemic lupus erythematosis renal involvement is a dominant clinical manifestation; the treatments are
shared with other GD and thus both will be included. Any patient or physician-identified kidney involvement for the included diseases will be considered for the nominal group and Delphi phases. We will exclude other GD that do not have sufficiently similar disease manifestations and treatment (e.g. post-infectious glomerulonephritis without alternative complement dysregulation, atypical hemolytic uremic syndrome, hepatitis and HIV-associated disease, collagenopathies, amyloidosis, diabetic and hypertensive nephropathies, storage diseases). Children will be excluded as they will be addressed in the SONG-Kids core outcome set.\textsuperscript{S6}

**Phase 1: Systematic review of outcome domains reported in GD trials**

We will conduct a systematic review to assess the scope and heterogeneity of outcome domains and measures reported in contemporary trials of interventions for patients with GD.

**Study search strategy**

We will use a sensitive search strategy devised by the Cochrane Kidney and Transplant Information Specialist to identify all randomized controlled trials (RCT) involving adult patients (aged 18 years and over) that enrolled patients with GD. The searches will be conducted in the Cochrane Kidney and Transplant Specialized Register, MEDLINE, Embase, and trial registers including ClinicalTrials.gov, EU clinical trials register (www.clinicaltrialsregister.eu) and Australian and New Zealand Clinical Trials Registry (ANZCTR; www.anzctr.org.au).
We will include all published reports and protocols of RCT focusing on contemporary trials from the past five years; January 2013 to December 2017 inclusive. We will exclude abstracts and conference reports as these do not provide a comprehensive or reliable report of all outcomes measured in trials. We will not apply any language restriction.

**Types of interventions**

We will include all interventions for GD, which may include but are not limited to pharmacological, lifestyle, psychosocial and health service interventions.

**Types of participants**

We will include trials with participants aged more than 18 years. We will exclude trials that only enrolled children less than 18 years of age. The inclusion and exclusion criteria for the types of GD to be considered are provided in Table 1.

**Eligibility of studies**

All records retrieved from the sensitive search strategy will be independently assessed by two reviewers for inclusion. Full text reports will then be independently assessed by two reviewers. Resolution of any disagreements between reviewers regarding study eligibility will be resolved in discussion, and if necessary with the involvement of a third reviewer.
Data extraction

Data extraction will be performed using a standardized data extraction form adapted from previous SONG systematic reviews.\textsuperscript{S7-9} We will extract the trial characteristics including: the trial name, first author, date published, trial duration, funding source, country, participating sites, participant characteristics (disease type, age, sex, ethnicity, baseline kidney function, degree of proteinuria), intervention and comparator used. We will extract all outcomes and outcome measures (both primary and secondary outcomes), which will include the authors’ original description of outcomes, definitions, measurement instruments, thresholds, units, method of aggregation, and time points. Selective reporting of outcomes will be assessed by comparing trial registration with the published reports. Two reviewers will cross-check the extracted data.

Data analysis and presentation

The outcomes will be classified as surrogate, clinical or patient-reported as per previous SONG streams\textsuperscript{S10} in line with similar recently published taxonomies.\textsuperscript{S11} Surrogate outcomes are any biochemical indicator or derived value used as a proxy for a clinical outcome (e.g. blood pressure, estimated glomerular filtration rate or proteinuria).\textsuperscript{S9, S12, S13} Clinical outcomes will be considered any medical outcome usually diagnosed by a clinician (e.g. relapse or remission, mortality, cardiovascular disease). Patient-reported outcomes are those that reflect how the patient feels or functions (e.g. fatigue, pain) obtained by direct report from the patient without interpretation or interference.\textsuperscript{S14} The SONG-GD Steering Committee will review the classification of outcomes. We will assess the number of trials, number of outcomes and the
measures used as well as the domain of the primary outcome. Areas of deficient reporting will be specifically identified. Statistical analysis will be performed using R version 3.5.1 (R Foundation for Statistical Computing, Vienna, Austria).

**Phase 2. Focus groups using nominal group technique with patients and caregivers**

Participants with GD and their caregivers (i.e. family members) will identify and rank the importance of outcomes that they believe should be reported in trials and discuss the reasoning behind their choices. A combined focus group/nominal group technique will ensure that the outcome domains important to the patients and caregivers will be grounded in their own accounts of what matters to them about their GD. The nominal group technique is a transparent and equitable process to work towards consensus based on a structured group discussion. This is an efficient and valid technique for generating ideas and priorities, prevents dominant participants from controlling the discussion, and allows participants the opportunity to raise views and suggestions without direct criticism or rejection of other participants. To address the opinions and priorities of patients unwilling to participate in a focus group setting, we will also use an online Delphi survey in Phase 4.

**Participants and recruitment**

Patients diagnosed with GD and their caregivers aged 18 years and older and who speak English and Spanish will be eligible (Spanish and English-speaking sessions will be run in the United States). Initially, we will aim to conduct 14 focus groups involving approximately 10 participants...
(total n=140) in Australia, United States, United Kingdom and Hong Kong. Patients will be purposively sampled to achieve maximum diversity based on demographics (age, gender, socioeconomic status, ethnicity, location of residence) and clinical characteristics (cause and duration of GD, stage of kidney disease and prior treatment exposures). We will convene focus groups until data saturation is achieved and no new concepts emerge. Participants will be provided AUD $50 (or local currency equivalent) reimbursement for their travel expenses. Written voluntary and informed consent will be obtained from all participants.

**Data collection**

Each focus group using nominal group technique will be two hours in duration and held in a location external to hospital or clinical settings to encourage open and uninhibited discussion. A facilitator will conduct the groups using the question guide outlined below, and a co-facilitator will be present to assist, observe and record non-verbal and contextual details. The run sheet and question guide will be adapted from previous SONG nominal group studies in hemodialysis and transplantation and informed by relevant literature on patients’ perspectives in GD.

*Introduction (10 minutes):* The facilitator will explain the purpose of the session; outline the diversity of experiences possible in GD, clinical trials, and outcomes; and ask participants to introduce themselves.

*Focus group discussion (25 minutes):* Participants will discuss their experiences and major impacts of their disease. In particular, they will consider the benefits and harms of treatment and
what they consider to be most important in making treatment decisions. The facilitator will identify and note outcomes during this discussion, which may be used as examples during the nominal group exercise.

**Nominal group technique (70 minutes):** Participants will be asked to identify up to three outcomes they believe are the most important and relevant to be reported in trials in GD. Using a round-robin approach, participants will in turn suggest one outcome at a time and the facilitator will write them on a flipchart/whiteboard until they are all recorded. Outcomes identified from prior GD trials and previous nominal groups will be added. The list of outcomes will be discussed to ensure that all participants understand the definition of the outcomes. We will print a list of the outcomes for participants to individually rank in order of importance – at least the top 10, from 1 (most important) through X (least important as determined by the number of outcomes listed). The facilitator will ask for the participant’s top three outcomes, indicate these on board and then ask the group to discuss any difference/similarities of the group’s top priorities. All discussions will be audiotaped and transcribed verbatim.

**Data analysis**

**Quantitative analysis**

An importance score will be calculated for each outcome that is based on the Expected Reciprocal Rank Evaluation Metric, as used in previous SONG nominal group analyses. The importance score is the mean of the reciprocal ranks for each outcome, i.e. if a participant ranked
an outcome at rank $\chi$, then their reciprocal rank for that outcome would be $1/\chi$. Outcomes not ranked by participants will be assigned a reciprocal rank of 0. The importance score will therefore rank outcomes between 0 and 1 accounting for the individual rankings of the outcomes and also the frequency of being nominated in the groups. More frequently ranked and highly valued outcomes identified by participants will have a value closer to 1, with inconsistently nominated or poorly ranked outcomes being closer to 0. Standard errors for the importance scores will be generated by bootstrapping and hypothesis testing, and then used to calculate confidence intervals. Outcome rankings will be reported for all participants as well as for the following subgroups: age, sex, ethnicity, caregivers or patient, disease type, immunosuppression type, stage of kidney disease and time since diagnosis. Formal comparisons between subgroups will be performed using a $t$-test with the significance level set at $p<0.05$. Statistical analysis will use R version 3.5.1 (R Foundation for Statistical Computing, Vienna, Austria).

Qualitative analysis

The transcripts will be imported into the HyperRESEARCH program for qualitative analysis (ResearchWare Inc., www.researchware.com, version 3.7.3). We will use thematic analysis and adapted grounded theory. Two researchers will independently read through the transcripts line-by-line to identify concepts and group them into preliminary themes that underpin the rationale for the selection and ranking of outcomes. A coding schema will be inductively generated through re-reading and discussing the transcripts. The coding schema will be reviewed by the research team to ensure that the full range and depth of the data are captured in the themes. Reporting will follow the Consolidated Criteria for Reporting Qualitative Health
Research (COREQ) recommendations.

Phase 3. Semi-structured key informant interviews

Semi-structured interviews will be conducted with health care providers to describe the beliefs, values and attitudes about outcomes in GD.

Participants and recruitment

Health care professionals caring for patients with GD, including nephrologists, nurses, and allied health staff (psychologists, social workers, dietitians and pharmacists) with expertise and interest in GD, will be eligible to participate. We will specifically sample key informants with expertise in conducting clinical trials and in health policy relating to GD. Recruitment will occur internationally through the networks of the Steering Committee and collaborators. We will recruit at least 50 participants and continue interviewing until we achieve data saturation. Purposive sampling and snowballing strategy (i.e. current participants can suggest other potential participants) will be employed to ensure a broad range of perspectives representing different professional roles, level of experience and demographics. Participants will provide informed consent before the interview.

Data collection

Outcomes from the systematic review and nominal groups will inform the content of the semi-
structured interview question guide. Each interview will last approximately 40 minutes.

Interviews will be face-to-face where feasible/preferred by the participant, otherwise the interview will be conducted by videoconference or telephone. Participants will reflect on their experience with patients with GD and be asked to provide their perspectives on:

- their role and experience in the provision of care to patients with GD,
- challenges in providing care and treatment,
- shared decision-making in the setting of GD,
- outcomes they consider to be important for trials in GD and the rationale,
- results from the nominal group technique (phase 2), and the development of, and implementation strategies for a core outcome set for trials in GD.

All interviews will be recorded and transcribed verbatim.

**Data Analysis**

Transcripts will be imported into HyperRESEARCH software (ResearchWare Inc., www.researchware.com, version 3.7.3), and a list of suggested outcomes will be extracted. We will use thematic analysis to analyze the data and identify themes. At least two investigators will be involved in the data analysis and review the preliminary findings to ensure the coding framework encompasses the spectrum as well as depth of the data collected. The preliminary findings will be circulated to all participants for their feedback to ensure comprehensive and accurate interpretation of the data (member checking). Any additional perspectives will be incorporated to strengthen the analytic framework. Reporting will follow the COREQ statement.\textsuperscript{27}
Phase 4. International online Delphi consensus survey

An international online Delphi survey will be conducted to achieve consensus among patients, caregivers and health professionals on the critically important outcomes to be reported in trials in GD. The Delphi technique is a well-recognized and successful method to achieve consensus on core outcome sets in a variety of health conditions, and was used in the development of the previous SONG core outcome sets for kidney transplant and hemodialysis. The Delphi method usually consists of iterative rounds of surveys completed anonymously by individuals with relevant perspectives on an area of study. The survey allows the equitable expression of opinion from all participants as it prevents direct criticism and confrontation from others whilst generating a consensus. In each round, respondents provide their opinion or perspective on a number of areas (e.g. the relative importance of health outcomes for trials). In each subsequent round, respondents have the option to review their previous scores as well as the group aggregate scores and then revise their opinion. We have shown that whilst respondents do alter their responses during subsequent Delphi rounds, they do not appear to be unduly influenced by the group opinion.

Participants and recruitment

Based on respondent rates from prior SONG Delphi surveys, we will target a minimum of 1000 respondents from 70 countries including low and middle income countries. We will aim to include similar numbers of patients/caregivers and healthcare professionals (nephrologists,
nurses, dieticians, psychologists, researchers, industry and policy makers). We will use an opt-in strategy with multiple sampling techniques. This will include purposive sampling and snowballing to include a diverse range of opinions as is feasible based on gender, professional role and ethnicity; for patients, this will also include type of GD, stage of disease and treatment. We will disseminate study information and invitations to participate in the Delphi survey through the networks of the Steering Committee, existing SONG collaborative networks (including collaborating hospitals, universities and patient organizations) and patient/consumer groups. All participants will be aged 18 years or over and be required to register through the SONG website (www.songiniative.org) using their name and email address, read a standard study information sheet and then provide informed consent.

**Data collection**

The Delphi survey will initially include approximately 20-30 outcome domains identified from the first three SONG-GD phases. The survey will be administered in at least two languages – English and Chinese. A plain language description will accompany each outcome. The Delphi survey will be administered online and consist of at least two rounds. Previous SONG Delphi surveys found stability of participant opinion after round two (e.g. the top 10 outcomes remained the same between rounds two and three); however, we will perform an interim analysis to determine the need for a subsequent round. The draft survey will be reviewed by the SONG-GD Steering Committee and piloted with at least 10 patients/caregivers before launch. The survey will be programmed through Qualtrics; each respondent will be assigned a unique identifier to link their responses across rounds. A minimum of three reminders will be sent to each participant.
per round, with the aim of a minimum 70% response rate across the rounds.

**Round 1.** Participants will be asked to rate the importance of each of the 20-30 outcomes on the GRADE nine-point Likert scale.\textsuperscript{33} Ratings 1-3 indicate the outcome is of limited importance, ratings 4-6 indicate the outcome is important but not critical, and ratings 7-9 indicate that the outcome is critically important. Participants may also select an ‘unable to score’ option. Outcome domains will be randomized between participants and rounds to minimize ordering bias. Participants will have the option of providing further comments regarding their choices as well as suggesting additional outcomes. New outcome domains suggested by more than 10% of respondents and that do not duplicate existing domains will be included in Round 2.

The investigators will review the outcome scores prior to Round 2 by the two stakeholder groups: patient/caregiver and healthcare professionals. Outcomes with a median and mean of more than 7 will be carried forward to Round 2, although the final threshold based on the mean, median and proportion of participants scoring the outcome from 7-9 may have to be determined post-hoc based on the distribution. This is in line with the approach taken for previous SONG Delphi surveys.\textsuperscript{31,32} Excluded outcomes will be included as either outer tier outcomes (those important to some or all stakeholder groups and to be considered in trials) or middle tier outcomes (those that are critically important to some stakeholder groups and to be reported in some trials, see Figure 1).

**Round 2.** Participants will be shown their previous rating for each outcome and a histogram of the distribution of scores from all participants, equally weighted by stakeholder group. There will
be accompanying plain language explanation and an example to aid interpretation of the graph. Patient/caregiver or health professional comments from the prior round will also be presented next to this in a scroll-down text box. Participants will then be asked to score outcomes again on the GRADE nine-point Likert scale with a text box available for any (optional) comments regarding the rationale for their ratings.

Round 2 will also include a Best-Worst Scale (BWS) survey to quantify the relative importance of the different outcomes.\textsuperscript{34} Similar to discrete choice experiments, the BWS is a preference elicitation method but with better discrimination, less cognitive burden and higher information retrieval.\textsuperscript{35-37} The BWS will be conducted by providing participants with a series of six blocks of six randomly selected outcomes selected from the outcome set carried forward to round 2. They will be asked to select the most important and the least important outcome from each block of six. To reduce survey burden, we will use a balanced incomplete block design composed of four blocks where participants will be randomly assigned to complete one of the four blocks.\textsuperscript{34}

\textbf{Data analysis}

For each outcome from each round, we will evaluate the distribution of the scores and calculate the mean, median and proportion of participants who rated the outcome of critical importance (i.e. scores from 7 to 9). To analyze the BWS survey, we will perform multinomial logistic regression modeling to calculate the relative importance score for the outcomes, normalized to a range from 1 (least important) to 9 (most important).\textsuperscript{25, 38} These will be calculated for health professionals and patients/caregivers.
In considering the feasibility for implementation, the final core outcome set will consist of three to five outcome domains.\textsuperscript{S10, S29} Outcomes not included in the core set will be classified in the middle and outer tiers (Figure 1). However, more than five outcomes of critical importance may be generated, as determined by the pre-specified SONG criteria. Therefore, for inclusion in the core outcome set an outcome will have: a median score greater than or equal to 8; a mean score greater than or equal to 7.5; the percentage of participants rating the outcome 7 to 9 (critically important) will be at least 75% and a median score of less than 10 in the forced ranking question. These thresholds for core outcome inclusion may need to be altered post hoc depending on the distribution of the final rankings. The proposed core outcomes and any post hoc alteration of the inclusion thresholds will be recorded and taken forward for review in the Phase 5 consensus workshop. Subgroup analysis will be performed by gender, disease type, stage of kidney disease and stakeholder role. GN subtype rankings will be grouped into the following categories: nephritis – kidney only (e.g. IgA nephropathy, complement-mediated and membranoproliferative glomerulonephritis), nephrotic syndrome – kidney only (e.g. FSGS, minimal change and membranous nephropathy), and systemic disease with kidney involvement (e.g. lupus, AAV, IgA vasculitis, anti-GBM disease).

**Phase 5. Consensus workshop**

A face-to-face stakeholder consensus workshop will be held to review and discuss the proposed core outcomes for trials in GD. The SONG-GD Steering Committee members will chair and facilitate the workshop, which will be held at an international nephrology conference in order to
maximize engagement and attendance. On the basis of prior consensus workshops, and in order to ensure feasibility and effective group management, there will be approximately 60 participants, which will include a minimum of 20 patients with GD and their caregivers. Health professionals with clinical roles managing patients with GD, including nephrologists, nurses and allied health staff, will be invited. In addition, professionals with experience in conducting clinical trials in GD, guideline production, roles in research funding, advisory or leadership, and regulatory body representatives will also be invited. Reimbursement will be provided for patients and caregivers to cover the costs of transportation and parking.

The results from Phases 1-4 will be circulated to participants two weeks prior to the workshop. This allows participants to prepare and familiarize themselves with the consensus approach being taken and allow troubleshooting of any questions they may have. This will ensure better engagement in the process and maximize the productivity of the workshop. The workshop will consist of three sessions.

Session 1: Introduction

We will provide an introduction to the SONG-GD process and present the results from Phases 1-4. The aims and process of the workshop will be described in full. The proposed core set of outcome domains, working thresholds as well as the rationale for their inclusion will be described.

Session 2. Breakout group discussion

Participants will be divided into six groups of up to 12 individuals, and each group will also be
allocated a moderator and facilitator. Groups will be composed such that there is balanced representation of various roles within them, with each group having a minimum of three patients/caregivers. This will encourage a range of perspectives and opinions being presented in each group. Facilitators will attend a briefing session and be provided with a question guide in order to guide and prompt the discussion. Participants will be presented with the proposed core outcomes domains and then asked to reflect and discuss their perspectives on them.

Session 3. Plenary discussion

The breakout groups will reconvene and the workshop Chair will moderate the final plenary discussion. Individual groups will nominate a member to present a summary of their discussion to the workshop. There will be the opportunity for the collective group to respond to and discuss any issues raised. The Chair will summarize the key points raised from the summaries and subsequent discussions.

All breakout sessions will be audiorecorded and transcribed verbatim. Transcripts will be imported into HyperRESEARCH software for qualitative data management and analysis. One investigator (SC) will read and code the transcripts line-by-line identifying themes relevant to establishing core outcome domains for GD. A draft workshop report in plain language will then be circulated to participants and collaborators from phases 1-4 for feedback over a two week period. Feedback received will then be collated and integrated into the final report.

Establishing the SONG-GD core outcome domains
The proposed core outcome domains for SONG-GD will be made public on the SONG website (www.songiniative.org) for four weeks in order to invite further feedback. The website link will be distributed through the SONG Initiative database to over 1000 patients and 3000 health care professionals, the Steering Committee and participating organizations. Feedback will be collated and reviewed with Steering Committee. Upon review, the SONG-GD set of core outcome domains will be finalized.

**Ethics and consent to participate**

Ethics approval has been obtained from the following sites for this study. Hong Kong (NTWC/CREC/17049); Los Angeles BioMedical Research Institute at Harbor-UCLA Medical Center (31147-01); United Kingdom (IRAS 247081); Westmead Hospital, Sydney (HREC2009/6/4.15), Monash Health, Melbourne (13082B); Princess Alexandra Hospital, Brisbane (HREC/17/QPAH/112). We will obtain informed consent from all participants in the study.

**Study status**

The systematic review including search strategy and data abstraction form have been designed. Recruitment and data collection for focus groups with nominal group technique has commenced but analysis is not complete.

**Abbreviations**
AAV    Anti-neutrophil cytoplasmic antibody-associated vasculitis
ANCA  Anti-neutrophil cytoplasmic antibodies
ANZCTR Australian and New Zealand Clinical Trials Registry
BWS   Best-Worst Scale
CKD   Chronic kidney disease
COMET Core Outcome Measures in Effectiveness Trials
COREQ Consolidated Criteria for Reporting Qualitative Health Research
COS-STAR Core Outcome Set- Standards for Reporting
eGFR  Estimated glomerular filtration rate
ESKD  End stage kidney disease
GD    Glomerular disease
KDIGO Kidney Disease: Improving Global Outcomes
OMERACT Outcome Measures in Rheumatology
RCT   Randomized controlled trial
SONG-GD Standardized Outcomes in Nephrology-Glomerular Disease
SONG-Kids Standardized Outcomes in Nephrology-Children and Adolescents

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Disclosure

The authors declare that they have no competing interests.

Authors’ contributions

SAC, AT and JC contributed to the study design and drafted the protocol manuscript; LL, DC, AB, SJB, JB, DC, RC, FF, JF, MH, JH, ARK, RL, AM, JR, BHR, HZ, TG, MH, CL, JIS, ATP, SIA, YC, JCC, DH, DWJ, PGK, JR, AKV, AYMW, MW, NS and AT revised the protocol and the manuscript.
**Supplementary Figure 1.** Standardized Outcomes in Nephrology-Glomerular Disease (SONG-GD): study design to derive a core outcome set for trials conducted in people with glomerular disease.

79x50mm (300 x 300 DPI)
**Supplementary references**


