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

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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.

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Keywords

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Glomerular diseases (GD) impose a substantial burden on patients and health systems, and are a major cause of end stage kidney disease (ESKD) worldwide.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.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.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).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).^{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)^{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.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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

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

Table 1.

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

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

* 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.