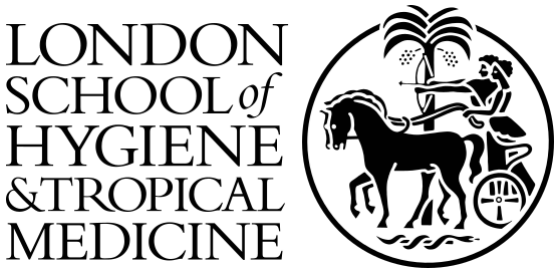

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Implementing core outcomes in kidney disease: report of the Standardized Outcomes in Nephrology (SONG) implementation workshop

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DISCLOSURE

All the authors declared no competing interests.

SUPPLEMENTARY MATERIAL

Supplementary Appendix S1. Workshop program and breakout discussion questions.

Supplementary material is linked to the online version of the paper at www.kidney-international.org.

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Abstract

There are an estimated 14,000 randomized trials published in chronic kidney disease. The most frequently reported outcomes are biochemical endpoints, rather than clinical and patient-reported outcomes including cardiovascular disease, mortality, and quality of life. While many trials have focused on optimizing kidney health, the heterogeneity and uncertain relevance of outcomes reported across trials may limit their policy and practice impact. The international Standardized Outcomes in Nephrology (SONG) Initiative was formed to identify core outcomes that are critically important to patients and health professionals, to be reported consistently across trials. We convened a SONG Implementation Workshop to discuss the implementation of core outcomes. Eighty-two patients/caregivers and health professionals participated in plenary and breakout discussions. In this report, we summarize the findings of the workshop in two main themes: socializing the concept of core outcomes, and demonstrating feasibility and usability. We outline implementation strategies and pathways to be established through partnership with stakeholders, which may bolster acceptance and reporting of core outcomes in trials, and encourage their use by end-users such as guideline producers and policymakers to help improve patient-important outcomes.

Keywords

core outcome sets; implementation; kidney disease; outcomes; patient-centered care; trials

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To date, an estimated 14,000 randomized trials have been published in chronic kidney disease (CKD).[1] Despite this substantive research effort and investment, patients with advanced CKD have mortality rates of up to 100 times higher than that of the general population,[2,3] increased morbidity, and worse quality of life than patients with cancer and

other chronic diseases.[4,5] There remains an urgent need for rigorous, high-quality trials to address these poor outcomes, with greater attention given to the selection, measurement, and reporting of outcomes in trials, to maximize their practice and policy impact and thus their value.[6,7]

The outcomes reported in trials are highly variable and measured in a plethora of ways, often without capturing those that are most meaningful for patients and clinicians for decision making.[8] In a recent analysis of 362 trials in hemodialysis, 81 different outcomes were reported using 10,700 different measures.[9] The 5 most frequently reported outcomes were all biochemical endpoints: phosphate, dialysis adequacy, anemia, inflammatory markers, and calcium.[9] Mortality and cardiovascular disease were reported in only 20% and 12% of trials, respectively. Fatigue, consistently identified by patients as a critically important outcome, even above mortality,[10–12] appeared in only 9% of trial reports.[9] Also, selectively reporting outcomes that favor the intervention or omitting outcomes such as adverse events may be misleading and can potentially cause harm.[13–15] A systematic review found that only 2% of trials of immunosuppressive agents in kidney disease reported a quality of life outcome and almost all reported effect estimates that favored the intervention.[16]

These problems in outcome reporting have also been recognized in other medical specialties and disease areas, including cancer, cardiology, chronic pain, dementia, dermatology, hematology, and otitis media,[17–20] prompting efforts to establish core outcome sets to improve the relevance, certainty, and efficiency of trial-based evidence to reliably inform decision making. Core outcomes sets, as defined by the Core Outcome Measures in Effectiveness Trials (COMET), are “an agreed standardised set of outcomes that should be reported, as a minimum, in all clinical trials in specific areas of health or healthcare.”[21] They may or may not be the primary outcome of trials, which are often selected because of their intervention-responsiveness and feasibility in terms of the resources required to achieve adequate statistical power. Core outcomes are identified through a consensus process to ensure they are critically important to patients and health professionals, with many initiatives drawing from the World Health Organization–endorsed framework developed by the Outcome Measures in Rheumatology (OMERACT) group, which was formed 1992.[22–24]

While core outcomes have the potential to improve the consistency and relevance of outcomes in trials,[14,25,26] trialists have not consistently reported these outcomes when publishing results. The use of core outcomes has increased over time in trials in rheumatoid arthritis, whereas there has been limited change seen in other areas including gout and falls prevention.[25–32] Barriers to implementation by trialists may include lack of awareness about core outcomes among trialists, resource constraints, lack of incentives, and complexities in measuring patient-reported outcomes.[33,34] Without consistent reporting of these core outcomes, there is little scope for end-users such as guideline producers and policymakers to capitalize on their potential benefits. However, little remains known about the perspectives of stakeholders on the use of core outcomes, and frameworks and interventions for the implementation of core outcomes are lacking.[21]

COMET recommends that core outcome developers prepare a dissemination and implementation plan to target potential users of core outcomes.[21] As part of the international

Standardized Outcomes in Nephrology (SONG) Initiative, which was founded in 2014 to establish core outcomes across the spectrum of CKD, we convened a workshop with patients, caregivers, and health professionals on the implementation of the core outcomes in trials in CKD. The workshop also included specific reference to core outcome sets that had been established at the time of the workshop (Figure 1a and b) including for patients receiving hemodialysis (fatigue, cardiovascular disease, vascular access function, mortality)[9–12,35–38] and kidney transplant recipients (graft loss, cardiovascular disease, infection, life participation, cancer, mortality).[39–42] These core outcome sets were developed using an evidence- and consensus-based process (systematic review, focus groups with nominal group technique, stakeholder interviews, an international Delphi Survey, and a consensus workshop) involving more than 1300 patients, caregivers, and health professionals from more than 70 countries in each stream (i.e., hemodialysis, kidney transplantation).[10–12,37,38,40,41] The findings from the workshop will inform strategies and pathways for implementing core outcomes, with a focus on trials in nephrology.

SONG IMPLEMENTATION WORKSHOP

Participants and contributors

In total, 82 patients, caregivers, representatives from patient organizations (n =6), and health professionals (n=76)— including nephrologists, nursing and allied health professionals, researchers (including trialists), policy makers, and industry representatives—attended the workshop. Given the focus of the workshop on implementation of core outcomes, we invited patients and caregivers with experience in research or who held advocacy roles in consumer organizations (e.g., National Kidney Foundation, Patient-Centered Outcome Research Institute [PCORI] Home Dialyzors United, American Society of Nephrology /Kidney Health Initiative (ASN/KHI) Patient and Partnership Council, Polycystic Kidney Disease [PKD] International, PKD Foundation) and health professionals with leadership or advisory roles in professional societies (e.g., International Society of Nephrology, ASN, The Transplantation Society), funding agencies, research, regulatory, policy and industry organizations (including but not limited to: US National Institutes of Health, US Food and Drug Administration [FDA], US Centers for Disease Control, US Centers for Medicare and Medicaid Services). Journal editors, trialists and epidemiologists, guideline developers, and those involved in renal registries and trial networks were also invited to attend. The investigators who were unable to attend (n=84) contributed feedback on the workshop program and the draft workshop report by e-mail.

Workshop program and materials

The workshop was held on November 3, 2017, in New Orleans, during the 2017 ASN Kidney Week. A preworkshop survey and the workshop program and materials were sent to all investigators (n = 160) prior to the workshop. The preworkshop survey asked participants to describe how they accessed and used (or plan to use) core outcomes (if applicable); suggest strategies, mechanisms, and actions to promote the use of core outcomes; and describe or explain how they could support the implementation of core outcomes in their role. The initial responses (n=84) informed the questions and prompts for the workshop,

while providing the participants with an opportunity to reflect on the topic in preparation for the breakout discussion groups.

The program is provided in Supplementary Appendix S1 and was structured as follows: a presentation of the SONG Initiative to provide participants with an overview of the process; panel discussion reflecting the patient, professional society, industry, regulator, and trialist perspectives; and breakout discussions on the opportunities, barriers, and strategies for implementing core outcomes in CKD. The attendees were preassigned to one of the 8 breakout groups, which involved 10 to 12 diverse stakeholders (patients or caregivers, physicians, regulators, funders, industry, researchers) to prompt broader and dynamic discussions. Each group was moderated by a facilitator, who used a question guide. After the plenary session, the chairs (J.C., B.M.) asked each group to provide a brief summary.

All the presentations and breakout group discussions were audiotaped and transcribed. The transcripts and survey responses were imported into HyperRESEARCH (Research-Ware Inc., version 3.0; Randolph, MA) software for analysis. The first author (A.T.) coded the transcript line-by-line and inductively identified concepts pertaining to the implementation of core outcomes. All participants were given 2 weeks to provide feedback on the draft workshop report and to confirm that the findings reflected the full range of their perspectives. Any additional comments were synthesized and included in the final report.

SUMMARY OF WORKSHOP DISCUSSION

The participants' perspectives on implementing core outcomes in trials in kidney disease were summarized in 2 overarching themes: socializing the concept (to make the definition and purpose of core outcomes acceptable or considered the norm in the nephrology community), and demonstrating feasibility and usability, which are described in the following section. Selected quotations to support each theme are provided in Table 1. A schema depicting the themes is shown in Figure 2. Key strategies and recommendations for implementing core outcomes are outlined in Table 2.

Socializing the concept

"Socializing the concept, explaining to everybody why it's important, making sure that all of our colleagues understand the advantage of why including core outcomes in clinical trials might actually help us get somewhere quite different in nephrology in a shorter period of time." (Health professional).

Articulating a compelling case for change.—The implementation of core outcomes requires efforts by the community (including professional and patient organizations) to convince health professionals and patients of the "advantages" of core outcomes—"half our colleagues don't even know they have to do clinical trials, let alone why we need to do outcomes" (health professional). They urged that "unless there is some change, some improvement, then we're stuck" (health professional). "Connecting the dots" for everyone would help them realize the lack of evidence about what is important to patients and clinicians—"we don't have answers to questions because we've been mixed up, we don't

have the outcomes that everybody agrees to" (health professional)—and be persuaded of the pressing need for core outcomes.

Participants suggested emphasizing that a core outcome set "ensures consistency across studies, allows us to compare things so we have more knowledge, facilitates the uptake of results, reduces confusion, and ensures that we have relevance—to clinicians, patients, regulators, in a very real way" (health professional). Trials would capture outcomes that have a direct impact on patients—"pain, infection, anxiety … all these things not included in trials," and ultimately "accelerate quality research" (patient). To have core outcomes available would "save" trialists from "thrashing about looking for an outcome because it's been devised" (health professional).

Core outcomes could identify "unforeseen consequences" of an intervention, even if there was "not a direct link to the intervention" and that this could be "leveraged." Health professionals remarked: "we all get sort of strange and unexpected findings; unless you measure it, or report it, you don't know." Also, it was noted that while an effect may not be seen in a single trial, consistent reporting of core outcomes would be important "because when you do a meta-analysis, perhaps you could get a positive result" (health professional).

Clarifying the intent and meaning.—Coherent communication about the definition and purpose of core outcomes was needed because the concept could be new and unfamiliar to some patients and health professionals. Researchers were concerned about the feasibility and relevance of using core outcomes as primary outcomes, and that they may not be responsive to the study intervention. Thus, it was important to explain that core outcomes "need not be the primary outcome," rather they were to be "collected and reported as part of that study even if they are not the primary outcome," because they were critically important to stakeholders. They suggested to frame the use of core outcomes as an "add on": in other words, "you come up with your own outcomes, that are nuanced towards your intervention, but then you add these extra [core] outcomes so you can at least say it made no difference to fatigue, cardiovascular disease as far as our trial is concerned" (health professional). Also, to reiterate that core outcomes were included on the basis of their importance to patients and health professionals, irrespective of the intervention and the size and duration of the trial: "it's about research to inform decision-making rather than the trialists finding something positive or responsive to their interventions" (health professional).

Ensuring trust and credibility.—Recognizing that the core outcomes were "internationally derived, used respected methodology, accredited, peer-reviewed, and non-commercial" (patient) would promote trust and uptake. Researchers would need to have confidence in the consensus process, international and cross-cultural applicability, and reassurance that patients were involved in a meaningful and substantial way. There had to be consistency in the definition and interpretation of outcomes (and outcome measures), and validation and endorsement by relevant groups would strengthen credibility. Part of "selling core outcomes" entailed making transparent the rigor of the process, explaining "how did we get to here, who made these decisions, are they valid?" (health professional).

Fostering community ownership.—Stakeholder groups (e.g., payers, regulators, industry organizations, trialists, and consumers) had to be engaged early and "buy in" to the process, to strengthen impetus for implementing core outcomes: "the big danger is dissemination by lamination. It's got to come from the ground up. People have got to own the message" (health professional). Participants suggested to "tailor the message to people, and to get the attention of patients through networks, and have patients tell the patients, we as the individual as well as our colleagues should own the message and distribute it from the ground up" (health professional).

Health professionals recognized that conflicting agendas between stakeholder groups may be potential barriers to implementation: "pharmaceutical companies have agendas to bring drugs on the market as quickly as possible and to generate profits and sometimes we are not in agreement that the outcomes chosen are necessarily in alliance with what might be the priorities of patients and health care providers." Further efforts were needed to "spread it [core outcomes] into [industry] organizations" (health professional).

Participants posited that "competition" among researchers and societies could be a barrier to "accepting [the core outcomes] because they feel they weren't at the table" (health professional). They thought it may be challenging to "get other groups (non-nephrology societies)" to agree on the harmonization of definitions for core outcomes and measures identified, for example, cardiovascular disease (cardiology), and agreed that "heavy hitters like oncology and cardiology needed to be on board and be in parallel doing similar things" (health professional) to gain broader acceptance and uptake.

Modeling on exemplars of culture shift.—Highlighting prior successes of implementing similar or related initiatives in trials was identified as a strategy for promoting the uptake of this newer concept of core outcomes. Participants referenced cardiology "where they had clear definitions of their key outcomes that they routinely use that have really helped to move the field forward" (health professional). The requirements to register trials, obtain Institutional Review Board approval, and report according to the Consolidated Standards of Reporting Trials (CONSORT) were given as examples of "very significant brain shifts that have now been adopted very widely" (health professional) despite initial concerns of the added burden these would impose.

Reinforcing with authoritative advisory support.—Mandating or insisting on the use of core outcomes in grant applications, journal publications, and regulatory approvals would force researchers "to toe the line" with efforts focused "further upstream" expected to be more effective. Trial registries (e.g., ClinicalTrials.gov) and funding agencies (e.g., National Institutes of Health [NIH]) would be the "stronger levers" for implementation because the use of core outcomes would be considered at the design phase of the trial. Trial registries could list the core outcomes to provide a "systematic way of making trialists think about it before they start the trial" (health professional). Trial networks were also identified as a potential opportunity to provide trialists with guidance on using core outcomes. Explicit support from regulators (e.g., US Food and Drug Administration [FDA], European Medicines Agency [EMA]) would be a catalyst for implementation. Even if regulators "suggested" the use of core outcomes, sponsors would feel compelled to adopt them: "they

will walk away with a strong message—'we have to do it, we can't not do it'" (health professional). There were concerns that mandating the use of core outcomes may be "too prescriptive" and that researchers could be encouraged rather than forced to use core outcomes; whereas others argued that "there must be not a carrot but a stick to implement it."

Demonstrating feasibility and usability

"We don't want them misused or used inappropriately, we want some tools for implementation" (health professional).

Providing proof of concept.—Empiric data to confirm that the "quality of studies improves after the implementation," of core outcomes would "show that it's not just a theoretical concept" (health professional), and thus provide a strong reason for their use. Pilot testing core outcome sets in some trials was suggested. Another idea was to "go back to some trials, pharmaceutical trials through to some registry trials, to see what the effect would be if we have these core outcomes and test whether they work or not … to demonstrate benefit from having done this" (health professional). For pragmatic trials, some health professionals suggested to evaluate "what would we have had to have done, what would the benefits be" if core outcomes were used.

Readily accessible and visible.—Making core outcomes prominent by "publishing in journals, and also [presenting them] in workshops and educational activities" (health professional) would support uptake. Providing direct access to core outcomes (e.g., on the website) meant researchers could easily "download" the core outcome set when writing grant applications or trial protocols. The core outcomes and their respective measures had to be "readily available in different formats where it's easy to pluck out from the web and use within your own structure of clinical trials" (health professional). Participants suggested submitting core outcomes to relevant organizations such as the US National Quality Forum or the NIH Common Data Elements repository because researchers "go looking for measures—they go there and pull it off the shelf" (health professional).

Maximizing operationalizability.—Core outcomes require firmly established definitions and measures, otherwise they would be too ambiguous to implement. For example, cardiovascular disease was a broad outcome domain (e.g., could include myocardial infarction, sudden cardiac death) and could be measured in multiple ways. A core outcome had to be stable over a reasonable time frame and be "definitive because the trials we are doing now, another one is done in 10 years, 15 years, some of these outcomes change, of course mortality cannot change, before we call them core outcomes, we should have a very good crystal clear definition that doesn't change" (health professional). It was important to specify "how you ask the question, who delivers it."

Being able to integrate core outcomes into case report forms and "documented" in electronic health records and databases using classification codes, for example the *International Classification of Diseases,* would facilitate efficient data collection on core outcomes in trials. "Micro-specification" of core outcomes would enable researchers to enter and extract

data on core outcomes efficiently and in a reproducible way. This could be challenging for patient-reported outcomes such as fatigue: “to define them in a very granular way is absolutely excruciating” (health professional). Health professionals noted the increasing number of trials using quality-adjusted life years in cost-effectiveness analyses, and thus advocated that quality of life domains had to be “built in at the very beginning of study design.”

Training researchers in how to use core outcome measures in trials would “speed up the implementation,” and this could be delivered through tutorials and resources: “if there is a centralized way that you can go to the website to see how to administer the tool [e.g., paper versus electronic tablet], then you are more likely to have some standardization of measurement” (health professional). Systemic lupus erythematous was given as an example where researchers had to be trained to assess and score disease activity using measures such as the SLE Disease Activity Index (SLEDAI) and British Isles Lupus Activity Group (BILAG): “we all deliver it in the same way, and actually we all use the same program to analyze it so it does introduce uniformity” (health professional).

Allowing adaptation when necessary.—Health professionals identified circumstances in which core outcomes could not be feasibly or appropriately implemented. Pragmatic or registry trials typically used “data that’s already being collected” as part of routine care or in registries, which may not currently include core outcomes and thus could not be feasibly included in such trials. An “opt out” approach could be considered whereby core outcomes would be “strongly encouraged and trialists would be expected to use them,” and researchers requested to provide a justification to seek exemption (e.g., from funders, trial registration organizations) from using core outcomes. In grant applications, trialists could indicate whether core outcomes have been included and if not to provide the reason, similar to tick boxes used (e.g., to indicate whether the study had equal representation of sexes, or Institutional Review Board approval). However, they noted that “to come down really hard is going to be difficult but we are going to have flexibility in the appropriateness in the implementation of these, but then it’s very hard to call them ‘core’” (health professional).

Guaranteeing minimal burden, cost, and consequence.—Health professionals emphasized that core outcomes had to be “measured relatively easily, simply and cheaply.” Imposing an undue “extra burden” to trials would be a barrier to implementation and “people would resent it.” In particular, trials “where you don’t have an a *priori* concern or it’s not your efficacy outcome, you don’t want to attach a lot of burden” in measuring the core outcomes. They cautioned that increased cost and resources to include core outcomes may potentially “inhibit the conduct of high quality trials, which would be counter to what we are trying to do.” Objections to the use of core outcomes were expected if they were seen as “a disincentive to running trials because it’s an extra bureaucratic layer they feel they have to jump through.” The resource implications of implementing core outcomes, particularly in low-income countries, had to be considered. Also, core outcomes should not “distract people, including the patients, from what the trial is about.”

Health professionals also recognized that in the current academic environment, “we are perpetuating research careers and science that is overdriven by biomarkers and surrogates,

because they are a great track record, [you get] a lot of publications" and early career researchers in particular may not be able to invest the extra resources and time to measure and report core outcomes in their studies.

Incentives for implementing core outcomes had to be "nonpunitive" such that providers or sponsors would not be "punished" based on their data pertaining to core outcomes. For example, with the increased use of extended criteria kidneys for transplantation, some health professionals observed that the commencement of dialysis posttransplant (due to delayed graft function) was sometimes deliberately delayed in order to achieve center-based performance indicators and targets. As a consequence, transplant recipients became volume overloaded for a longer period of time, which could lead to serious adverse effects. They remarked that health professionals may fear "that if core outcomes were going to get mandate, it's going to be used against them, they will be called bad citizens" and urged that regulators (e.g., CMS) would have to guarantee that "negative or neutral results are not going to affect their registration."

Integrating into infrastructure.—Embedding core outcomes in registries, epidemiological cohort studies, and routine care(i.e., as quality indicators) would subsequently facilitate their uptake particularly in pragmatic trials "where we are trying to minimize the burden of data collection and use existing infrastructure." Registries were somewhat "messy" with variable definitions and measures used for many outcomes including kidney function, which could be ascertained using different equations (e.g., Modification of Diet in Renal Disease, Cockcroft Gault). Health professionals suggested to "embed core outcomes in registries so that every six months patients are asked about fatigue, myocardial infarction, stroke, the data are all automatically recorded, its automatically in the electronic system" (health professional). Having core outcomes embedded into routine clinical care could then be leveraged as part of clinical trials. Also, "if we can actually integrate these [core outcomes] into clinical care, it's going to be easier for regulatory agencies to access them. If you collect it for post-market outcome assessment, it's a lot easier for industry to collect if it's something that's captured as part of routine clinical care."

DISCUSSION

A multipronged approach to socialize the concept and demonstrate the feasibility and usability of core outcomes in nephrology studies could motivate trialists and facilitate the implementation of core outcomes in trials. This would involve advocating the need for improved consistency and relevance of research and addressing potential skepticism by ensuring trust in the process of establishing core outcomes, buy-in from stakeholders, demonstrating the impact of similar initiatives, and securing support from authoritative bodies. The core outcomes should be readily accessible, clearly defined with validated measures, applicable, and of minimal burden to implement in trials internationally. Particularly for novel trial designs such as registry or pragmatic trials, core outcomes would need to be integrated into clinical care infrastructures or research registries.

Publishing core outcomes, communicating with relevant stakeholders groups, and involving potential users in the development process, have been identified by core outcome developers

as strategies for dissemination and implementation.[21] Our workshop discussions indicate the need to make clear the goal and definition of core outcomes, framed in such a way that would be acceptable to researchers, and to address concerns about feasibility and applicability. Core outcomes are critically important to patients and clinicians for decision making and should be considered for use as primary outcomes where possible, otherwise they should be added and tracked with primary outcomes that trialists have selected to be relevant to their intervention. In addition, core outcomes have potential benefits for other end-users such as guideline producers and policymakers.

Strategies to promote uptake of core outcomes can be conceptualized as “push” (directly encouraging trialists to collect and report data on core outcomes) or “pull” (encouraging end-users to highlight the need for these outcomes so that they can be used to benefit patients, such as in practice guidelines or quality measures or both). Likely both types of strategies will be required to effect meaningful change.

Partnerships with stakeholders and relevant organizations are needed to support and to expedite the uptake of core outcomes. COMET has identified trialists, trial registries, funders, research registries, journals, and systematic review organizations as having a role in the implementation of core outcomes.[21] In addition, participants in the workshop recognized that professional societies and consumers (i.e., patients, caregivers) could also help to educate and advocate for the use of core outcomes. Patient organizations liaise with clinicians, academic, industry, and government and regulatory agencies to promote research.[43] Patients and patient organizations also increasingly participate in guideline production and thus are strongly positioned to support the implementation of core outcomes by appealing to both trialists and end-users.

There have been a few initiatives aimed at promoting the uptake of core outcomes in research proposals. The Standard Protocol Items: Recommendations for Interventional Trials (SPIRIT) checklist recommends to use a common set of key outcomes in trials to “deter selective reporting of outcomes and to facilitate comparisons and pooling of results across trials in a meta-analysis.”[44] In the UK, the National Institute for Health Research guidance notes for applicants submitting a proposal for funding states that “where established Core Outcomes exist they should be included amongst the list of outcomes unless there is good reason to do otherwise”[45] and advises applicants to refer to the COMET database of core outcomes. While there is currently no regulatory mandate specific to implementing core outcomes, regulators are seeking increased clarity about what outcomes matter to patients that could be submitted for review and potential marketing approval, and there have been initiatives to improve outcome reporting in trials. The US NIH recommends the use of common data elements in NIH-funded projects or registries.[46] FDA and EMA have produced guidance documents on the use of patient-reported outcome measures in trials. EMA and FDA can issue a qualification opinion on the acceptability of a specific use of a method (including outcome measures) for use in trials.[47,48] These examples indicate that regulatory agencies or policy organizations have a potential role in supporting the implementation of core outcomes in trials.

Despite these promising initial efforts, the potential benefits of adopting core outcomes do not appear to have been fully recognized by guideline producers or other end-users such as policymakers. Further efforts are needed to develop and evaluate training resources (e.g., tools, tutorials) to collect and report data on core outcomes, as well as educate trialists and end-users about their benefits for patients. Table 2 outlines implementation strategies and pathways covering education, dissemination, and resources and infrastructure for efficient operationalization of core outcomes, which may be established through partnership with stakeholders.

In summary, core outcome sets are being developed to improve the relevance, consistency, and reliability of trial evidence to inform decision making and to systematically include the patient perspective. However, overcoming potential barriers to uptake necessitates partnerships with key stakeholders (including trialists and end-users) to "socialize" the concept of core outcomes and demonstrate that they can be feasibly applied in trials. Also, efforts will be needed to ensure ongoing monitoring and evaluation of the use and impact of core outcomes.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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ESRD, end-stage renal disease; INI-CRCT, Investigation Network Initiative—Cardiovascular and Renal Clinical Trialists; NHS, National Health Service; PKD, polycystic kidney disease; SONG, Standardized Outcomes in Nephrology; UCLA, University of California, Los Angeles; VA, Veterans Health Administration.

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Figure 1 |. Core outcome sets for Standardized Outcomes in Nephrology (SONG).
Outcome sets for (a) SONG-Hemodialysis (SONG-HD) and (b) SONG–Kidney Transplantation (SONG-Tx) are shown.

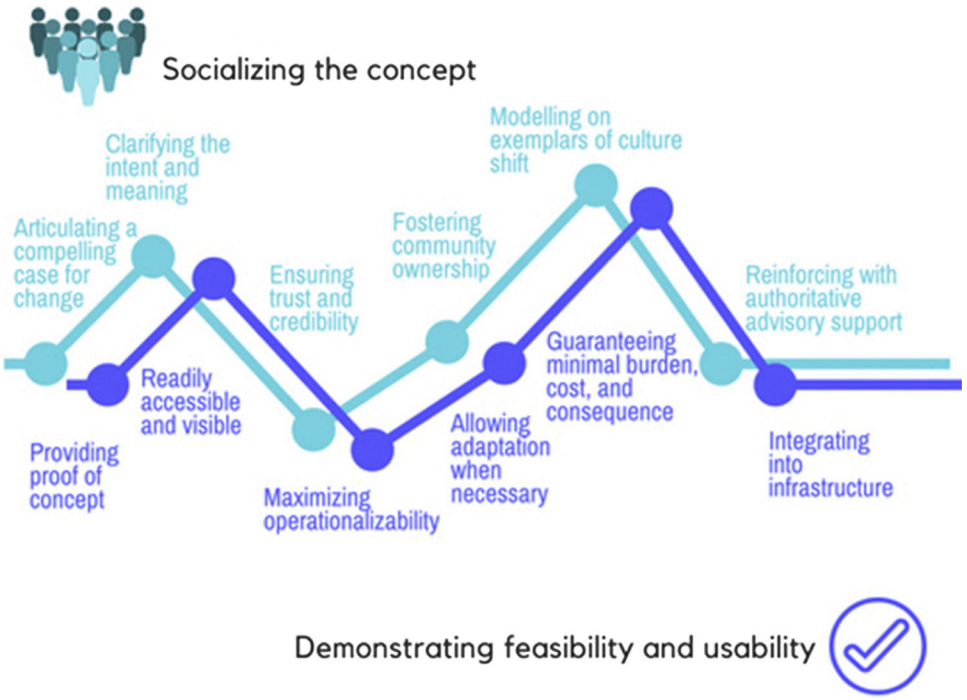

Figure 2 |.
Thematic schema.

Table 1 |

Selected quotations from the workshop discussions on the identification and implementation of core outcomes in hemodialysis

Theme	Quotations	Group ID
Articulating a compelling case for change	Socializing the concept This initiative is critical because it's highlighted what is really important and help us prioritize where the unmet needs are and in general standardization and moving towards standardization is a good thing. (Health professional) There's been a history of what we referred to initially as bad research and then later as inadequate research, or uninformed trials, and we need to shift culture to include these core outcomes. (Health professional) We have a problem in nephrology because we don't have answers to questions, because we don't have outcomes that everybody agrees to, and we are trying to get the outcome right. (Health professional)	1,2,3,4,6,7,8
Clarifying the intent and meaning	The intervention is not necessarily the important thing, the intervention is kind of by the by. You come up with your own outcomes, that are nuanced towards your intervention, but then you add these extra outcomes, you can at least say it made no difference to fatigue, as far as our trial is concerned, it made no difference to cardiovascular disease as far as our trial is concerned. (Health professional) If you look at these, hemodialysis, there isn't a surrogate there, and if you look at the transplantation, there isn't a surrogate there because clinicians and patients basically uniformly deprioritized them. We need to focus on that which is important, responsiveness in any given situation we can come back to, but it is what's important, and measured in a standard way. (Health professional) Trialists want to find a positive outcome, from a clinician perspective and from a patient perspective they don't care whether their pain, or their graft is achieved with this, this, or that [intervention]. What's important to them is that it improves, so if we don't have the outcomes which are relevant, then it's not addressing the things that matter to them. It's about research to inform decision making rather than the trialist finding something that is positive or responsive to their interventions. (Health professional) The sense from the patients was that they wanted to know the information even if it wasn't powered. (Health professional)	1,2,3,4,5,6,7,8
Ensuring trust and credibility in the process	It includes patients', carers', and clinician[s'] input, it's international, it uses respected methodology, accredited, it's on the COMET database, it's peer-reviewed, it's noncommercial, so the advantage of that is that it delivers consistency, it's comprehensive, reduced bias, and is trustworthy, which means that the benefits for me, the patient group, it's real world. (Patient) You have to overcome everyone's reluctance to use them, they don't understand the development, validity … there's going to be a lot of advocacy needed, and a lot of trust in the methodology in the development for any one of these measures. (Health professional) In order to be really accepted, make sure that the tools that are used are validated and are calibrated for the different populations in different countries, in different settings. (Health professional)	2,4,5,6,7,8
Fostering community ownership	You have this problem of competition with nonnephrology societies, and there is sort of a "this is my crossing over to my kind of territory." I'm not sure how you are going to get other groups to agree, the harmonization of the definitions, that's a huge challenge, and we see that in KDIGO. (Health professional) We've ignored the role of the payers which in many ways are more important than the regulators these days because they are the ones who make the decisions about whether the treatments are actually paid for and therefore used, so getting them on board is really important. (Health professional) Before you disseminate you have to bring all the stakeholders together to put their approval on that if you will. Because there are many groups that will disseminate various measures and guidelines but you need to involve all the stakeholders, and government authorities, pharmaceutical companies, trialist[s]. One potential way of doing that is once a group comes up with a set of guidelines and going out and going to these individuals and asking them to comment on it, what they see as good aspects as well as aspects that need to be tweaked. (Health professional) The heavy hitters like oncology and cardiology need to be on board and need to be in parallel doing similar things. (Health professional)	1,3,4,5,7
Referencing convincing examples of culture shift	Look at the cardiovascular community where they for decades now, had clear definitions of their key outcomes that they routinely use that have really helped to move the field forward. (Health professional) Government agencies are now insisting you have open access trials, everybody is toeing the line, consumer engagement, that's all considered very important. Maybe having funders insist that these are part of the strategy to fund. They insist on trial registration, that's a burden but everyone does it, it's a requirement. (Health professional) The need to include things like CONSORT, these were very significant brain shifts that have now been adopted very widely. (Health professional) If we can offer a powerful argument for, from a different field like cardiology or oncology, where a core outcome was developed and implemented, and how that was useful to, then this is definitely sellable. (Health professional) A diabetes drug needs to have cardiovascular outcomes. That is also something which evolved over time. (Health professional)	1,3,4,7,8

Theme	Quotations	Group ID
Requiring authoritative support	And when we do have bodies within our societies that might be reviewing clinical protocols or clinical trials to see whether or not you can advocate for the use of them in those trials, think of us as professional advisors and consultants, and sort of engage some our society members in helping with the rolling out of core outcomes. (Health professional) We [regulators] have opportunities when we meet with sponsors, we try to make sure that they are aware of other efforts that are going on that have bearing on their development programs so certainly that's an opportunity for us to share this important work and highlight the core outcomes that you've identified. (Health professional) The funding agencies are actually the stronger lever rather than the journals, certainly the regulators for the trials that are relevant. (Health professional) Trial registration might be a useful way of encouraging people to use these outcomes by listing it there and asking are you using these outcomes —that would be a systematic way of making trialists think about [core outcomes] before they start the trial. (Health professional) This may be something that the journal editors may want to take on because if the journal editors say we recommend that we follow these outcomes, just as they now say you need to have a CONSORT diagram, you have to follow these core outcomes, or perhaps if you register in clinicaltrials.gov, you need to say that you are using those outcomes, that's a way that you could potentially promote this. (Health professional) In some funding agencies, the program officer participates and overseas protocol development and that individual could insist on the use of standardized outcomes. (Health professional)	1,2,3,4,5,6,7,8
Providing proof of concept	Demonstrating feasibility and usability There's going to be some skepticism that these core outcome measures are going to work. I wonder if we could go back to some trials and just demonstrate within a number of different types of trials, some pharmaceutical trials through to some registry trials, what would be the effect if we have these core outcomes, and sort of test whether they do work or not. (Health professional) If you can show that the quality of studies improves after the implementation of these core outcomes, that's a no brainer. (Health professional) Maybe do pilot testing, if we come out with a first set of outcomes, let's do some pilot testing, a few different trials, small groups of patients, and prove to ourselves that what we chose makes sense. (Health professional)	1,4,5,6
Accessible, applicable, and practical	Have [core outcomes] readily available in different formats where it's easy to pluck out [of] the web and use within your own structure of your clinical trials so if it's electronic that you could have a sort of an app or an iPad but you would also have the paper versions available, you would also have the various different formats available, for implementation of these outcomes. (Health professional) If you are going to all the effort, of actually developing the tool, submit the measure to a measure organization like the National Quality Forum. When people look for stuff, they actually go look there, the government goes looking there, others go looking there for measure, because it's all validated so if you wanted to use you can pull it off the shelf. (Health professional)	1,2,3,4,5,6,7,8
Maximizing operationalizability	They should be definitive because the trials that we do are done now, another one is done in 10 years, 15 years, some of these outcomes change … before we call them core outcomes, we also have a very good crystal clear definition that doesn't change. (Health professional) We almost all use CRFs now and it's generated code so whatever database you are going to be able to use, you could just use, "here you are, here's our key core outcomes" and if you are going to do this trial, if you said I've just got the code for you, here it is, it is easy. (Health professional) Is there going to be some kind of tutorial or something? If there is a centralized way that you can go to the website of how to administer the tool, then you are more likely to have some standardization of measurement rather than saying, well measure this, this and this, how are you going to measure it, I ask my coordinators to do certain measurements, and they are going to do it 5 different ways unless I train them and say this is the way. (Health professional) Create a micro specifications manual so if someone actually wanted to implement this, it would be done consistently. (Health professional) You can have cardiovascular disease as your outcome but what exactly is your cardiovascular disease that you are talking about, so that [is] granulatory. That is an issue for fatigue as well. So if people do report cardiovascular disease, they are using the patient's ICD-9 codes, ICD-10 codes. (Health professional)	1,2,3,4,5,6,7,8
Allowing adaptation when necessary	We are moving to more efficient trial conduct where we are looking to use data that's already being collected as much as possible and in that situation there's no way we go back and redefine the outcomes, so we need to allow some flexibility in terms of how we use outcomes. (Health professional) [We] are going to have to have flexibility in the appropriateness in the implementation of these, but then it's very hard to call them core. (Health professional) The core outcome measure should be flexible, and pragmatic enough, we have to allow some flexibility and leave it to some degree to the local practice, how to measure something, but it still has to be a standardized definition. (Health professional)	1,2,3,7
Guaranteeing minimal burden, cost and consequence	If you're in a setting where you don't have *a priori* concern or it's not your efficacy outcome, obviously you don't want to attach a lot of burden in trying to characterize these endpoints. (Health professional)	1,2,3,4,5,6,7

Theme	Quotations	Group ID
Integrating into infrastructure	We are looking at trials that can be done around the world and the resources implications of what we are asking people to do in trials that may be for example run in low-income countries with very limited resources, every additional thing that has to be collected has important cost and resource implications, that may inhibit the conduct of high-quality trials which would be counter to what we are trying to do. (Health professional) There's got to be some kind of nonpunitive incentive … how can regulators protect them from negative or neutral results [for the core outcomes], it's not going to affect your registration? (Health professional) The issue of cost, and cost not just in terms of financial terms, but cost in time with interaction with patients and the burden of implementing some measures and reporting data. (Health professional) One challenge is the tension between trying to be uniform across all trials and include this core set across all trials but not have it overwhelm the real goal of a particular trial… so it doesn't add so much burden to the trials and doesn't distract people, including the patients, from what the trial is about. (Health professional) From a pragmatic trials perspective, we are trying to minimize the burden of data collection and use existing infrastructure. Another stakeholder are people in administrative registry type roles where it may not be readily apparent that these are outcomes that are necessarily relevant but certainly need to [be] thought about prospectively in their implementation. A good example for me is the PDOPPS study, whatever information we learn from SONG-PD should be incorporated. (Health professional) If we are trying to make trials simpler, just make the data collection simpler, to the extent that these things could get incorporated into routine clinical care, this task would be much easier. (Health professional) If you come up with a set of care outcomes and they're a reasonably short list and they are very simple, that you could embed them in registries so that every 6 months patients are asked about fatigue, MI, stroke, the data is all automatically recorded, if it's a very small number, its automatically in the electronic system … the trials don't need to necessarily have to ask the patients the whole time, how do you feel fatigue, fill out our questionnaire, its done automatically by the nurses and you download it. (Health professional)	3,4,5,6,7

CONSORT, Consolidated Standards of Reporting Trials; CRF, case report form; ICD, *International Classification of Diseases*; MI, myocardial infarction; PDOPPS, Peritoneal Dialysis Outcomes and Practice Patterns Study; SONG-PD, Standardized Outcomes in Nephrology Peritoneal Dialysis.

Table 2 |

Implementation strategies and pathways through partnership with stakeholders

Strategy/pathway	Professional societies	Consumers including consumer organizations	Trial networks/trialists	Research funders	Regulators/policymakers	Trial registries	Administrative datasets/patient registries	Journals	Evidence synthesis groups (guidelines, systematic reviews)
Educate about the need, definition, and purpose of core outcomes[a]	●	●	●					●	●
Highlight examples of prior success in implementing related initiatives and impacts of core outcomes[b]	●	●							
Provide training in the use of core outcomes (tools, resources, tutorials)	●	●	●						●
Demonstrate feasibility, in other words, pilot test and evaluate use of core outcomes (including in pragmatic trials)			●						
Publish or provide a reference to core outcome sets	●	●	●	●	●	●		●	●
Recommend or mandate the use of core outcomes			●	●	●	●	●	●	●
Embed core outcomes into infrastructure (databases)					●		●		●

OMERACT, Outcome Measures in Rheumatology.

[a]Improve consistency and relevance of outcomes reported in trials; identify through a systematic and transparent international consensus process; add to outcomes that trialists want to include in their trials (and does not have to be the primary outcome); have measures that are easy, simple, and inexpensive to use; include on the basis of importance to patients and caregivers for decision making (not based on expected response to the intervention).

[b]Implementation of reporting guidelines, trial registration; improved reporting of OMERACT core outcomes in rheumatoid arthritis.