

International consensus definitions of clinical trial outcomes for kidney failure: 2020



OPEN

Adeera Levin^{1,30}, Rajiv Agarwal^{2,3,30}, William G. Herrington⁴, Hiddo L. Heerspink⁵, Johannes F.E. Mann^{6,7}, Shahnaz Shahinfar^{8,9}, Katherine R. Tuttle^{10,11}, Jo-Ann Donner¹², Vivekanand Jha^{13,14}, Masaomi Nangaku¹⁵, Dick de Zeeuw⁵, Meg J. Jardine^{16,17}, Kenneth W. Mahaffey¹⁸, Aliza M. Thompson¹⁹, Mary Beaucage^{20,21}, Kate Chong^{22,23}, Glenda V. Roberts^{24,25}, Duane Sunwold²⁶, Hans Vorster²³, Madeleine Warren^{27,28}, Sandrine Damster¹², Charu Malik¹² and Vlado Perkovic²⁹; on behalf of the participant authors of the International Society of Nephrology's 1st International Consensus Meeting on Defining Kidney Failure in Clinical Trials³¹

¹Division of Nephrology, Department of Medicine, University of British Columbia, Vancouver, British Columbia, Canada; ²Department of Medicine, Division of Nephrology, Indiana University School of Medicine, Indianapolis, Indiana, USA; ³Veterans Administration Medical Center, Indianapolis, Indiana, USA; ⁴Medical Research Council Population Health Research Unit, Clinical Trial Service Unit and Epidemiological Studies Unit, Nuffield Department of Population Health, University of Oxford, Oxford, UK; ⁵Department of Clinical Pharmacy and Pharmacology, University Medical Center Groningen, Groningen, The Netherlands; ⁶Department of Medicine, Friedrich Alexander University, Erlangen, Germany; ⁷KfH Kidney Center, Munich, Germany; ⁸S. Shahinfar Consulting, Inc., Philadelphia, Pennsylvania, USA; ⁹Division of Nephrology, Children's Hospital of Philadelphia, University of Pennsylvania, Philadelphia, Pennsylvania, USA; ¹⁰Providence Medical Research Center, Providence Health Care, Spokane, Washington, USA; ¹¹Division of Nephrology, Kidney Research Institute, and Institute of Translational Health Sciences, University of Washington, Seattle, Washington, USA; ¹²International Society of Nephrology, Brussels, Belgium; ¹³George Institute for Global Health India, University of New South Wales (UNSW), New Delhi, India; ¹⁴Manipal Academy of Higher Education (MAHE), Manipal, Karnataka, India; ¹⁵Division of Nephrology and Endocrinology, The University of Tokyo Graduate School of Medicine, Tokyo, Japan; ¹⁶The George Institute for Global Health, Sydney, New South Wales, Australia; ¹⁷Renal Department, Concord Repatriation General Hospital, Sydney, New South Wales, Australia; ¹⁸Stanford Center for Clinical Research, Department of Medicine, Stanford School of Medicine, Stanford, California, USA; ¹⁹Division of Cardiology and Nephrology, Center for Drug Evaluation and Research, Food and Drug Administration (FDA), Silver Spring, Maryland, USA; ²⁰Patient Governance Council, Indigenous Peoples Engagement and Research Council, Can-Solve CKD, Vancouver, British Columbia, Canada; ²¹Provincial Patient and Family Advisory Council, Ontario Renal Network, Toronto, Ontario, Canada; ²²Patient Services, Kidney Foundation, BC & Yukon Branch, Burnaby, British Columbia, Canada; ²³Can-Solve CKD, Vancouver, British Columbia, Canada; ²⁴External Relations and Patient Engagement, Kidney Research Institute, University of Washington, Seattle, Washington, USA; ²⁵Center for Dialysis Innovation, University of Washington, Seattle, Washington, USA; ²⁶Inland Northwest Culinary Academy at Spokane Community College, Spokane, Washington, USA; ²⁷Warren-Charnock Associates, London, UK; ²⁸Kidney Research UK, London, UK; and ²⁹Faculty of Medicine, University of New South Wales (UNSW), Sydney, New South Wales, Australia

Kidney failure is an important outcome for patients, clinicians, researchers, healthcare systems, payers, and regulators. However, no harmonized international consensus definitions of kidney failure and key surrogates of progression to kidney failure exist specifically for clinical trials. The International Society of Nephrology convened an international multi-stakeholder meeting to develop consensus on this topic. A core group, experienced in design, conduct, and outcome adjudication of clinical trials, developed a database of 64 randomized trials and the 163 included definitions relevant to kidney failure. Using an iterative process, a set of proposed consensus definitions were developed and subsequently vetted by the larger multi-stakeholder group of 83 participants representing 18 different countries. The

consensus of the meeting participants was that clinical trial kidney failure outcomes should be comprised of a composite that includes receipt of a kidney transplant, initiation of maintenance dialysis, and death from kidney failure; it may also include outcomes based solely on laboratory measurements of glomerular filtration rate: a sustained low glomerular filtration rate and a sustained percent decline in glomerular filtration rate. Discussion included important considerations, such as (i) recognition of existing nomenclature for kidney failure; (ii) applicability across resource settings; (iii) ease of understanding for all stakeholders; and (iv) avoidance of inappropriate complexity so that the definitions can be used across ranges of populations and trial methodologies. The final definitions reflect the consensus for use in clinical trials.

Correspondence: Adeera Levin, Department of Medicine, Division of Nephrology, University of British Columbia, St. Paul's Hospital, 1081 Burrard Street, Rm 6010A, Vancouver, BC, V6Z 1Y6, Canada. E-mail: alevin@providencehealth.bc.ca

Kidney International (2020) **98**, 849–859; <https://doi.org/10.1016/j.kint.2020.07.013>

³⁰AL and RA contributed equally to this work.

KEYWORDS: continuous kidney replacement therapy; kidney failure; maintenance dialysis; transplantation

³¹Participant authors of the International Society of Nephrology's 1st International Consensus Meeting on Defining Kidney Failure in Clinical Trials are listed in the [Appendix](#).

Copyright © 2020, International Society of Nephrology. Published by Elsevier Inc. This is an open access article under the CC BY-NC-ND license (<http://creativecommons.org/licenses/by-nc-nd/4.0/>).

Received 1 June 2020; revised 1 July 2020; accepted 9 July 2020

Worldwide estimates suggest that 850 million individuals have kidney disease.^{1,2} In 2010, a total of 2.6 million received kidney replacement therapy, and many more died due to lack of access, or other complications such as cardiovascular disease (CVD) and infections.³ Outcomes for patients with chronic kidney disease (CKD) are comparable to, or worse than, those for patients with other serious diseases, including many forms of cancer.^{4,5} Despite the risk, and the wide-ranging impacts of CKD, the numbers of clinical trials in nephrology have lagged behind those in other specialties.^{6,7} Patients with advanced CKD are often systematically excluded from trials of CVD and diabetes interventions, despite the high CKD prevalence among people with such conditions.^{8–10} In CKD populations, only a few large trials have demonstrated benefit of interventions.^{11–14} Patients with CKD often have been considered difficult to recruit in numbers required to identify plausible treatment effects, and variability in outcome definitions makes interpretation of and comparison among trials difficult. Reasons for “negative” trials are multifactorial. Recently, the number of nephrology studies in both preclinical and clinical phases has increased, offering the possibility of improving outcomes for patients with CKD.⁷ With advances in molecular diagnostics and promising new targets for therapies, and efforts to develop new or revisit older therapeutic interventions to tackle kidney diseases and their complications, there is an imperative to enhance the quantity and quality of clinical trials in nephrology worldwide.¹⁵ This need was highlighted in the 2017 “roadmap” for closing the gaps in kidney research, clinical care, and policy.¹

Formalizing the nomenclature of kidney failure for publications has recently been established, after a Kidney Disease: Improving Global Outcomes (KDIGO) Conference.^{16,17} The Kidney Health Initiative has supported a Clinical Data Interchange Standards Consortium (CDISC), developing data standards for kidney failure outcomes for diabetic kidney disease,¹⁸ and extensive analytical work has been conducted with regulators assessing the validity of different surrogates of progression to kidney failure for clinical trials of CKD.¹⁹ However, there are no international consensus definitions for use in clinical trials of kidney failure. Over the years, several different definitions for kidney failure have been used, leading to controversy and confusion. The lack of standard definitions has resulted in challenging discussions in adjudication and steering committees, along with regulatory discussions, and resultant varying prevalence of outcomes which impacts power estimations. The absence of universal definitions of kidney failure for trials contrasts with the specialties that have a successful history of conducting large-scale trials and standardized definitions (e.g., myocardial infarction²⁰ and stroke²¹).

Our objective was to develop standardized, internationally accepted, consensus definitions for clinical trial kidney failure outcomes and key surrogates that predict progression to kidney failure. To ensure accountability, transparency, and knowledge translation, the definitions presented were

developed with patient partners and a range of stakeholders. This document was reviewed by the collective of meeting participants, and it reflects consensus.

METHODS

The International Society of Nephrology (ISN), through the Research Working Group’s Advancing Clinical Trials (ISN-ACT) Committee, identified the unmet need and facilitated the development of the meeting.

A steering committee composed of nephrology and other specialty clinical trialists, ISN leaders, regulatory representatives, and ISN headquarters staff vetted the concept, and made recommendations as to membership of a core group and invitees to the consensus meeting. The stakeholders included patient partners, clinicians and academic clinical trialists, other researchers, regulators, funder representatives, and industry researchers. Invitees were selected based on expertise, and in keeping with the ISN diversity policy (Appendices 1 and 2).²² A total of 105 people from Asia, Africa, Australasia, Europe, Latin and North America, the Middle East, and Russia were invited: 83 attended the consensus meeting.

The core group consisted of those with experience steering, designing, and conducting clinical trials, and outcome adjudication, and was chaired by Rajiv Agarwal. Its role was to review the literature of consensus definitions in other domains^{20,21,23,24} and develop a scope-of-work document pertinent to nephrology and kidney failure. Table 1^{19,25–27} describes the complete process.

Patient partners

Six patient partners participated in the Consensus Meeting, with diverse perspectives, kidney health journeys, and professional interests. They were oriented to the process and the remit during teleconferences, and at the meeting, they voiced their understanding and supported the need of clear definitions for clinical trial kidney failure outcomes. They contributed to all discussions, with their perspectives presented in plenary sessions and incorporated into the definitions.

RESULTS

Summary of the international consensus definitions of clinical trial kidney failure outcomes

Meeting participants voiced support of concise and clear definitions that could be applied across multiple populations, settings, and a wide range of interventions and trial methodologies. These definitions will support continued efforts to ensure that future clinical trials are comparable, robust, and streamlined.^{11,28} Attendees appreciated that irrespective of the final definitions, there will be situations in which modifications are justified or necessary.

The consensus was that clinical trial outcomes to represent kidney failure should be comprised of a composite including receipt of a kidney transplant, initiation of maintenance dialysis, and death *from* kidney failure, and may also include outcomes based solely on laboratory measurements of glomerular filtration rate (GFR)—a sustained low GFR and a sustained percent decline in GFR (Figure 1). Including these separate outcomes should enable kidney failure in various clinical presentations to be well captured in clinical trials. Depending on the trial setting, different components may be

Table 1 | Development steps for the international consensus definitions of clinical trial outcomes for kidney failure

Step	Activity
1	Systematically generate a list of clinical trials, including cardiovascular disease, diabetes, kidney disease populations, in which kidney failure was an outcome (see Supplementary Table S1).
2	Establish a database of definitions of clinical trial endpoints of kidney failure from available trial protocols and/or adjudication manuals (63 randomized controlled trials, 163 definitions; see Supplementary Table S1) and consider publications from the National Kidney Foundation–US Food and Drug Administration–European Medicines Agency (NKF-FDA-EMA) workshops addressing declines in estimated glomerular filtration rate as surrogates for progression to kidney failure for clinical trials of chronic kidney disease. ^{19,25–27}
3	Generate an independent definition of clinical trial outcomes of kidney failure from each core group member, with attention to modifications that may be required in trials conducted in different settings (high- and low-resource settings).
4	Synthesize a single proposed core group–consensus set of definitions for review at the consensus meeting using an iterative review process.
5	Develop an accompanying set of questions and controversies for discussion in the consensus meeting breakout groups to ensure scrutiny of the proposed definitions.
6	Circulate consensus meeting materials to stakeholders 2 weeks before the meeting.
7	Deliver consensus meeting: <ul style="list-style-type: none"> (i) Present the need, the remit, and the core group–proposed definitions in plenary sessions, followed by 5 facilitated breakout group discussions. (ii) Present and discuss each breakout group’s key comments in a plenary forum.
8	Refine definitions based on feedback during the consensus meeting.
9	Send consensus meeting report and refined definitions for stakeholder comment and public review.
10	Publish and disseminate.

included or omitted (e.g., a particularly long and large trial in those with advanced CKD may not need to include the sustained percent decline in GFR, which is a surrogate of progression to kidney failure rather than evidence of kidney failure itself, whereas a trial with less advanced CKD at entry may use that component to ensure a reasonable study duration). Aligned with current clinical classification systems, GFR <15 ml/min per 1.73 m² is a laboratory-based indicator of kidney failure,¹⁶ although other thresholds may be used in specific circumstances. We propose the concept of a component called “sustained low GFR,” which permits different thresholds to be used, depending on the population studied and the GFR at study enrollment. The last component is a surrogate, which is sustained percent decline in GFR, highly predictive of progression to kidney failure.

Individual outcome components

[Table 2](#) provides a summary of the definitions for components of the kidney failure composite.

Kidney transplantation

Kidney transplantation is defined as receiving a kidney transplant irrespective of source (cadaveric vs. living donor), or successful implantation or graft function. The date of the

procedure constitutes the outcome’s date. No modifications are required for low- or high-resource settings.

Maintenance dialysis

Maintenance dialysis is defined as dialysis (peritoneal or hemodialysis) performed for at least 4 weeks. A number of different confirmatory periods have been used (e.g., 4 weeks; 30, 60, or 90 days) in different trials; we agreed on 4 weeks, for the sake of harmonization, after careful discussion.

There are situations in which the duration of at least 4 weeks may not be met, for example, due to death, or further data are unavailable, but an outcome of kidney failure requiring dialysis can be inferred. These situations include start of dialysis after a trajectory of progressive CKD, discontinuation of dialysis treatment within a few days due to either futility of therapy (dialysis withdrawal) or resource constraints, or kidney transplantation shortly after dialysis initiation. All of these situations constitute reaching a trial outcome of maintenance dialysis (see section on adjudication below).

Special considerations. One point that was highlighted is that although at least 4 weeks of dialysis is recommended for clinical trials, a longer duration (e.g., 90 days) is in keeping with most “registry” definitions of maintenance dialysis. We also acknowledged that the duration of dialysis that confirms it to be maintenance dialysis may differ by the specific patient population under study (e.g., patients with vasculitis or glomerulonephritis may justify a longer duration). Although some patients may recover from dialysis after being on it for 4 weeks,²⁹ practical considerations of timely trial completion, and most importantly, the patient perspective that “any dialysis duration constitutes kidney failure” was appreciated. Thus, we agreed that 4 weeks was a suitable definition in most circumstances and would appropriately exclude most recoverable dialysis-requiring acute kidney injury (AKI) from a maintenance dialysis outcome. Those who recover dialysis-independent kidney function could have this outcome revised and be included in a sensitivity analysis to determine the impact of that change.³⁰

From the patient perspective, any duration of dialysis is a serious failure of their kidneys. Therefore, trials that report kidney failure as an outcome should collect and report information on AKI requiring dialysis or consider reporting a patient-centered outcome of “any dialysis.”

In low-resource settings, no modifications to the definition are required; however, it was recognized that participants on maintenance dialysis may be dialyzed less frequently than those in high-income countries and may discontinue therapy because of non-availability due to financial or other reasons. Dialysis frequency is thus not included in the outcome’s definition.

Death from kidney failure

This component usually represents a small proportion of kidney failure outcomes. Its inclusion allows recognition that those participants who progressed to a GFR <15 ml/min per 1.73 m², and often one much lower, and died as a result of

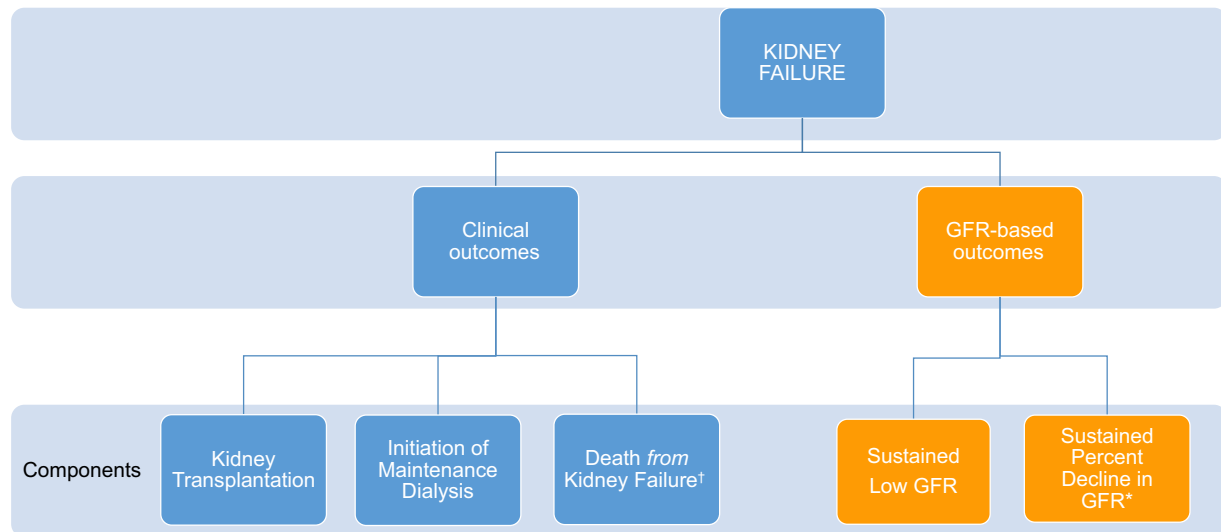


Figure 1 | Individual components of a composite outcome of kidney failure for use in clinical trials. GFR, glomerular filtration rate. †Death *from* kidney failure differs from death *with* kidney failure. We consider death *with* kidney failure to include a death from any cause among those who have a clinical outcome of kidney failure or a sustained low GFR (but not a sustained percent decline in GFR alone). *Sustained percent decline in estimated GFR has been demonstrated to be a surrogate of progression to kidney failure.

non-availability of kidney replacement therapy or a personal decision to not pursue dialysis, have reached the outcome. This is analogous to the KDIGO nomenclature of death from “kidney failure without replacement therapy.” In these situations, the underlying cause of death (i.e., the disease that initiated the train of morbid events leading directly to death³¹) is advanced CKD. In the context of trials, distinguishing between death *with* kidney failure and death *from* kidney failure is important.

The death *from* kidney failure concept presumes that the driver of death is the low kidney function (irrespective of specific mechanisms, such as hyperkalemia, fluid overload, etc.). There is no need for modification of this definition for

different resource settings, but we recognized that death *from* kidney failure may be more common in lower-resource settings. It is noted that those who develop AKI with no pre-existing CKD, and who either are not offered dialysis or refuse it, or for whom it is unavailable, and subsequently die, may or may not be considered an instance of death *from* kidney failure, depending on circumstances, and study design. In the conduct of the trial, this should be prespecified.

Special considerations. Meeting attendees deliberated on the concepts of death *from* kidney failure, and death *with* kidney failure. There was extensive debate, but there was some agreement that death *with* kidney failure should not be recommended to be a standard component of the kidney failure outcome definition (Figure 1). There is a need to differentiate deaths from other causes (e.g., overwhelming sepsis or fatal CVD) in people *with* kidney failure, from the deaths of those who die *from* kidney failure (due to non-provision of replacement therapy for any reason AND advanced CKD). We appreciate the sometimes subtle differences and recommend that death *with* kidney failure be considered as a subsidiary outcome in clinical trials. Death *with* kidney failure includes death, irrespective of cause, among those who have a clinical outcome of maintenance dialysis, kidney transplantation, or a sustained low GFR (but, importantly, not a sustained percent decline in GFR alone). Because an increasingly high proportion of patients with CKD in developed countries are elderly and multimorbid, death *with* kidney failure may become more common.

Table 2 | Summary international consensus definitions of clinical trial outcomes for kidney failure

Components	Definition
Kidney transplantation	Receipt of a kidney transplant
Maintenance dialysis	Dialysis performed for at least 4 wk
Death <i>from</i> kidney failure	The participant dies, AND kidney replacement therapy was never started (irrespective of reason), AND advanced chronic kidney disease is the underlying cause of death
Sustained low GFR	GFR <15 ^a ml/min per 1.73 m ² sustained over at least 4 wk
Sustained percent decline in GFR	Percent decline in GFR of ≥40% ^b from a baseline start point sustained over at least 4 wk ¹⁹

GFR, glomerular filtration rate.

^aA GFR of <10 ml/min per 1.73 m² may be used in certain situations.

^bA ≥30%, ≥40%, ≥50%, or ≥57% decline in GFR (a 57% decline in estimated GFR approximately corresponds to a doubling of serum creatinine) may be considered surrogates for progression to kidney failure depending on the trial population and acute effects of study intervention on GFR. A doubling of creatinine is the most well established, whereas a ≥30% decline, in comparison, is the least reliable of these (putative) surrogates.

GFR-based outcomes and surrogates of progression to kidney failure

GFR-based outcomes represent nonclinical laboratory outcomes that are acceptable in clinical practice and trials. Some laboratory-based outcomes have been shown to strongly

predict progression to clinical outcomes of kidney failure (i.e., percent decline in estimated GFR [eGFR]). They may also predict other serious complications (e.g., CVD) that patients and clinicians view as a “poor” outcome. Sustained low GFR, irrespective of need for dialysis, is one outcome. A sustained percent decline in GFR is offered here as another “acceptable” GFR-based surrogate for the clinical trial outcome of kidney failure in specific circumstances.

We extensively discussed the use of the terms “eGFR” and “GFR,” with no clear consensus as to what was preferred. The validation work on surrogates of progression to kidney failure is based on eGFR, and practical considerations for trials would favor the use of eGFR instead of measured GFR. However, we recognized that there are situations in which one might measure GFR. There were extensive discussions about formulae to be used and the need for validated equations.

Sustained low GFR

The outcome of sustained low GFR is reached when the participant has a low GFR (e.g., to <15 ml/min per 1.73 m²) sustained over at least 4 weeks, evidenced by 2 consecutive measurements; GFR <15 ml/min per 1.73 m² is considered acceptable in most circumstances as it represents a substantial loss of kidney function and is concordant with current guideline definitions.¹⁶

Special considerations. The group recognized that the presence of symptoms is important (see Patient-reported outcome measures section below), and it is highly variable within and between populations. Some people with kidney failure have few symptoms and can maintain acceptable quality-of-life at a GFR of <15 ml/min per 1.73 m².

The validity of the specific threshold was extensively discussed, and given that there is increasing interest in including people with a wide range of GFR in clinical trials, we recognized the need to consider lower thresholds in specific circumstances. For example, in trials enrolling people with GFRs of 20 ml/min per 1.73 m² or less, a GFR threshold that defines sustained low GFR may be lower than the <15 ml/min per 1.73 m² value (e.g., to <10 ml/min per 1.73 m²). We acknowledge that the KDIGO definition¹⁶ of kidney failure is a GFR of <15 ml/min per 1.73 m².

The eGFR is estimated by measuring reproducible markers of kidney function, most often serum creatinine, using isotope dilution mass spectrometry–traceable methods.³² We acknowledged that other validated serum markers can be used to estimate kidney function. We discussed the use of central laboratories versus local clinical laboratories, and calibrated point-of-care testing. Central laboratory measurements are considered to be more trustworthy, but they can cause added challenges (time and resources) and may not always be truly “standardized” (due to long sample transit times or different assays run across different central laboratories). There also may be an under-recognition of the protection that large-scale randomization offers against small errors in measurements. These issues require further research, and individual studies

should consider the best possible methodology for their planned study population and regions.

The group recognized the potential limitations of including the 4-week timeline of repeated laboratory measurements for use in observational studies or administrative datasets. Investigators may need to modify this definition for use in studies other than clinical trials.

Acceptable surrogate: sustained percent decline in GFR as predictive of progression to kidney failure

Sustained percent decline in GFR is defined as relative decline from baseline in GFR of $\geq 40\%$ or other thresholds (30%, 50%, 57%), depending on circumstances. This component is important given the relatively high correlation between the percent decline and risk of progression to kidney failure. The baseline for determining GFR decline may depend on study populations and mechanisms of drug therapy action. A sustained percent decline in GFR should generally be based on follow-up measurements after a baseline assessment prior to randomization, sustained over at least 4 weeks as evidenced by 2 consecutive measurements. The date of the outcome is the onset of when the first decline occurred (not the date of confirmation). Considerations for use of local versus isotope dilution mass spectrometry–traceable central laboratories are the same for this outcome as for sustained low GFR, with the additional proviso that declines in GFR are calculated based on measurements using the same methods.

Special considerations. All recognized that a sustained percent decline in GFR is not a clinical outcome, but rather a surrogate that predicts progression to kidney failure. Nevertheless, meeting attendees considered its value in reducing samples sizes and durations of follow-up for kidney failure trials.²⁵ Extensive analyses, supported by the National Kidney Foundation–US Food and Drug Administration–European Medicines Agency workshops, have established the validity of eGFR-based surrogates.¹⁹ These findings include the following:

- (i) The strong association between a decline in eGFR and risk of end-stage kidney disease in observational analyses. Compared to those with a stable eGFR, a 40% eGFR decline over 2 years is associated²⁷ with a 10-fold increased risk of kidney failure in those with an eGFR of <60 ml/min per 1.73 m².
- (ii) A $\geq 40\%$ decline in eGFR provides consistent assessment of treatment effects compared to a doubling of creatinine in re-analyzed trials, using a range of different interventions.²⁶
- (iii) Simulation studies to advise on what percentage decline in eGFR to select for an intervention in various scenarios—populations with different rates of CKD progression, choice of start point eGFR, and using interventions with different acute effects on eGFR.²⁵ The selection of $\geq 30\%$, $\geq 40\%$, $\geq 50\%$, or $\geq 57\%$ eGFR decline is dependent on these factors. For example, trials in people without diabetes or without albuminuria may

need to use a $\geq 40\%$ decline because the time to a $\geq 57\%$ decline may be too long. Acute effects of the study intervention on eGFR are critical to consider.^{25,26} In some situations (e.g., when the test intervention does not acutely affect eGFR), a $\geq 30\%$ decline in GFR may be an acceptable surrogate of progression to kidney failure, though it is not as reliable or strong an indicator as larger declines.

We noted that a doubling of creatinine was a particularly strong predictor of end-stage kidney disease. A 57% eGFR decline over 2 years (i.e., about a doubling of creatinine) is associated with a 32-times increased risk for kidney failure²⁷ in those with an eGFR < 60 ml/min per 1.73 m². This surrogate may be particularly suitable for trials using routine healthcare data for follow-up, in which it is not always possible to collect additional measurements.

The concept of “sustained” decline in GFR does add specificity to this outcome compared to basing the percent decline on a single follow-up GFR.³³ However, it was also recognized that to ensure the simplicity of study design, and consistency with clinical care, it is reasonable to confirm sustained declines in GFR (or sustained low GFR) at the next scheduled study visit in certain circumstances. Extra confirmation visits may be problematic as they add to participant burden and trial costs. With regular and relatively frequent follow-up, the definition of “sustained” could be applied without need for additional trial-specific confirmatory measurements.

Blood for a baseline analysis of GFR should be drawn prior to randomization. It is recognized that an average of 2 measurements a few weeks apart may increase the precision of measurement of baseline GFR, but these may not be mandatory, depending on the purpose of the clinical trial, as the benefits of that precision may not outweigh the burden of extra measurements and visits, particularly in larger streamlined trials.

It is noted that GFRs should continue to be collected, even after this outcome is confirmed, in order to record a greater percent decline in GFR (e.g., a $\geq 57\%$ decline after a $\geq 40\%$ decline) or a sustained low GFR, or for accompanying pre-specified GFR slope analyses. Follow-up for all outcomes (dialysis, transplant, or other) should continue for the full duration of any trial.

We have used the term “outcome” intentionally throughout this document, instead of “endpoint.” The term “endpoint” is a misnomer, as trial follow-up usually continues for any given participant who has “met an endpoint,” until study end.

Out of scope: other outcomes and kidney populations

For the purposes of clarity, in the following 3 sections, we describe those concepts that were out of scope.

GFR slopes and changes in albuminuria. It has been recognized that total or chronic eGFR slope analyses and changes in albuminuria may fulfill the criteria for surrogacy

for CKD progression.³⁴ Such GFR slope analyses are particularly useful in early kidney disease and interventions with acute effects on GFR. Given that the meeting focused on the clinical outcome of kidney failure *per se*, and even though progression of CKD is on the pathway to kidney failure, we did not address progression specifically.

Patient-reported outcome measures for kidney failure. We recognize that symptoms of kidney failure may present at different levels of GFR with variability among patients. Symptoms of kidney failure (e.g., fatigue, cognition issues³⁵) have been identified as important potential trial outcomes for people with CKD, including those on dialysis.³⁶ When relevant and reliable patient-reported outcome measures have been developed, have been shown to be feasible to implement, and are responsive to interventions, they should be included as outcomes in ongoing trials in CKD populations. This work is currently in progress. Patient-reported outcome measures are extremely important, but they were considered out of scope for this meeting.

Pediatric populations. We recognized that there is a current unmet need for clinical trials in pediatric patients with kidney disease. Pediatric populations are highly heterogeneous, have variable causes of disease across age groups, and have different methods to estimate GFR.³⁷ The meeting was focused on clinical trials in adults. However, the framework and key concepts are adaptable to pediatric nephrology clinical trials, and a process to engage the pediatric community will be undertaken.

Other considerations

The definitions above are designed for implementation into clinical trials and do not change or challenge existing KDIGO definitions of kidney failure.¹⁶ The proposed definitions do not address details nor specificity of data recording during conduct of a trial. Although good guidance exists on how kidney outcomes data should be stored in trial datasets,¹⁸ there are no standardized consensus methods for collecting kidney failure outcome during participant follow-up visits or review of health records. Timelines of kidney disease status and other diagnoses in computer systems have long been used by nephrologists and may be a simple option to adopt.³⁸

The need for adjudication (i.e., clinician-based verification) of kidney failure outcomes was discussed. Although consistent attribution of an underlying cause of death in kidney trials usually requires a clinician-led adjudication process, there are examples from kidney populations in which adjudication of kidney replacement therapy had no major impact on kidney failure outcomes (unpublished data).¹⁴ Many past trials examining the outcome of kidney failure have been small and used different methods of data collection, necessitating adjudication. We also recognize that in trials anticipating fewer kidney failure events, in populations without kidney disease, or those conducted by investigators without expertise in kidney disease, the adjudication of

kidney failure in trials may be necessary. Death within 4 weeks of starting dialysis may also be an example of when adjudication is necessary to distinguish maintenance from acute dialysis. The group concluded that the role of event adjudication for kidney failure needs to be evaluated within the specific context of the study planned.

Important future research

The value of adopting these simple kidney failure outcome clinical trial definitions to support and encourage the conduct of larger clinical trials, including pragmatic trials, remains to be seen. Although there is much discussion about the precision of measurements and need for adjudication, further research is needed into when the use of central laboratories or adjudication of kidney failure outcomes is justified or needed. We need to review methods used to measure serum creatinine and other kidney markers, including point-of-care testing, which may be somewhat less reproducible and robust than gold-standard assays, but provide potential to facilitate large sample sizes, reduce trial costs, and/or increase participation. Such research could offer major scientific value in terms of the scalability of clinical research, and inclusivity around the world.

We acknowledged that there are differences in precision of CKD–Epidemiology Collaboration (CKD-EPI) eGFR equations across different regions. Future research may evaluate the impact of using region- or population-specific eGFR equations in international trials in a rigorous manner. Clinical trials assess differences in treatment effects between allocated groups, so that regional differences should not bias a randomized comparison; however, this question continues to perplex many. There is interest in examining potential differences in GFR equations in study populations in different regions, so as to test the assumption that there is no bias due to those differences.

Dissemination

We wish to emphasize the role of patient partners and all relevant stakeholders in adopting these consensus definitions for clinical trial outcomes of kidney failure. The shared understanding of this work will enhance broad uptake. We need to engage the pediatric nephrology community, and to educate the diabetes and CVD communities regarding these definitions, given that people with CKD and those conditions are often recruited into their clinical trials.

Summary

At an international multi-stakeholder consensus meeting of patient partners, clinicians and academic trialists, other researchers, regulators, funder representatives, and industry researchers, international consensus definitions of clinical trial outcomes for kidney failure were developed, based on available literature, using an iterative and inclusive process. These outcome definitions should enhance the ability to conduct clinical trials, harmonize and compare results, and improve the amount of reliable evidence to determine the best therapies for individuals living with kidney diseases.

APPENDIX 1

List of International Society of Nephrology's 1st International Consensus Meeting on Defining Kidney Failure in Clinical Trials participant authors

Shuchi Anand, Stanford University School of Medicine, Palo Alto, California, USA
 Nicholas Argent, Office of Clinical Trials, Health Canada, Ottawa, Ontario, Canada
 Elena Babak, Cardiorenal, AstraZeneca Canada Inc., Mississauga, Ontario, Canada
 Debasish Banerjee, Renal and Transplantation Unit, St George's University Hospitals National Health Service Foundation Trust, London, UK; and Molecular and Clinical Sciences Research Institute, St George's, University of London, London, UK
 Jonathan Barratt, University of Leicester and John Walls Renal Unit, University Hospitals of Leicester National Health Service Trust, Leicester, UK
 Amino K. Bello, Division of Nephrology and Immunology, Department of Medicine, University of Alberta, Edmonton, Alberta, Canada
 Angelito A. Bernardo, Global Clinical and Medical Affairs, Baxter Healthcare Corporation, University of Illinois-Chicago, River Forest, Illinois, USA
 Jaime Blais, Janssen Pharmaceutical LLC, Raritan, New Jersey, USA
 William Canovatchel, Janssen Pharmaceutical LLC, Raritan, New Jersey, USA
 Fergus J. Caskey, Population Health Sciences, University of Bristol, Bristol, UK; and The Richard Bright Renal Unit, Southmead Hospital, North Bristol National Health Service Trust, Bristol, UK
 Josef Coresh, Johns Hopkins University Bloomberg School of Public Health, George W. Comstock Center for Public Health Research and Prevention, Baltimore, Maryland, USA; and Johns Hopkins University School of Medicine, Welch Center for Prevention, Epidemiology and Clinical Research, Baltimore, Maryland, USA
 Ian H. de Boer, Division of Nephrology, Department of Medicine, University of Washington, Seattle, Washington, USA; and Kidney Research Institute, University of Washington, Seattle, Washington, USA
 Kai-Uwe Eckardt, Department of Nephrology and Medical Intensive Care, Charité – Universitätsmedizin Berlin, Berlin, Germany
 Rhys DR Evans, Department of Renal Medicine, University College London, London, UK
 Harold I. Feldman, Department of Biostatistics, Epidemiology, and Informatics and the Center for Clinical Epidemiology and Biostatistics, Perelman School of Medicine at the University of Pennsylvania, Philadelphia, Pennsylvania, USA
 Agnes B. Fogo, Department of Pathology, Microbiology and Immunology, Vanderbilt University Medical Center, Nashville, Tennessee, USA
 Hrefna Gudmundsdottir, Icelandic Medicines Agency, Reykjavik, Iceland; and Department of Nephrology, Landspítali—The National University Hospital of Iceland, Reykjavik, Iceland
 Takayuki Hamano, Department of Nephrology, Nagoya City University Graduate School of Medical Sciences, Nagoya, Japan
 David C.H. Harris, Centre for Transplantation and Renal Research, Westmead Institute for Medical Research, University of Sydney, Westmead, New South Wales, Australia
 Sibylle J. Hauske, Boehringer Ingelheim International GmbH, Ingelheim, Germany; and Vth Department of Medicine, University Medical Center Mannheim, University of Heidelberg, Mannheim, Germany
 Richard Haynes, Nuffield Department of Population Health, University of Oxford, Oxford, UK; and Oxford Kidney Unit, Oxford University Hospital, Oxford, UK
 Charles A. Herzog, Hennepin Healthcare, University of Minnesota, Minneapolis, Minnesota, USA
 Thomas Hiemstra, Cambridge Clinical Trials Unit, Division of Experimental Medicine, Department of Medicine, University of Cambridge, Cambridge, UK
 Thomas Idorn, GLP-1, CV & Outcomes, Novo Nordisk A/S, Soeborg, Denmark
 Lesley Inker, Division of Nephrology, Tufts Medical Center, Boston, Massachusetts, USA
 Julie H. Ishida, Inflammation Clinical Research, Gilead Sciences Inc., Foster City, California, USA
 David W. Johnson, Centre for Kidney Disease Research, University of Queensland, Brisbane, Australia; Translational Research Institute, Brisbane, Australia; and Metro South and Ipswich Nephrology and Transplant Services (MINTS), Princess Alexandra Hospital, Brisbane, Australia
 Charlotte Jones-Burton, Global Clinical Development, Nephrology, Otsuka Pharmaceutical Development & Commercialization, Princeton, New Jersey, USA
 Amer Joseph, Cardiology & Nephrology Clinical Development, Bayer AG, Berlin, Germany

Audrey Koitka-Weber, TA CardioMetabolism Respiratory Medicine, Boehringer Ingelheim International GmbH, Ingelheim, Germany; Division of Nephrology, University Hospital Würzburg, Würzburg, Germany

Matthias Kretzler, Department of Internal Medicine, University of Michigan, Ann Arbor, Michigan, USA; and Department of Computational Medicine and Bioinformatics, University of Michigan, Ann Arbor, Michigan, USA

Robert Lawatscheck, Cardiology & Nephrology Global Medical Affairs, Bayer AG, Berlin, Germany

Adrian Liew, The Kidney & Transplant Practice, Mount Elizabeth Novena Hospital, Singapore

Louise Moist, Division of Nephrology, Schulich School of Medicine and Dentistry, Western University, London, Ontario, Canada

Saraladevi Naicker, Department of Internal Medicine, School of Clinical Medicine, Faculty of Health Sciences, University of the Witwatersrand, Johannesburg, South Africa

Reiko Nakashima, Office of New Drug 1, Pharmaceuticals and Medical Devices Agency, Tokyo, Japan

Uptal Patel, Inflammation Therapeutic Area, Gilead Sciences Inc., Foster City, California, USA; and Department of Medicine, Duke University, Durham, North Carolina, USA

Roberto Pecoits Filho, School of Medicine, Pontifícia Universidade Católica do Paraná, Curitiba, Brazil; and Arbor Research Collaborative for Health, Ann Arbor, Michigan, USA

Jennifer B. Rose, Medical Affairs, Janssen Inc., Toronto, Ontario, Canada

Noah L. Rosenberg, Retrophin, Inc., San Diego, California, USA

Marvin Sinsakul, Clinical Development, AstraZeneca, Gaithersburg, Maryland, USA

William E. Smoyer, Nationwide Children's Hospital, The Ohio State University, Columbus, Ohio, USA

Laura Sola, Dialysis Unit, Centro Asistencial del Sindicato Médico del Uruguay Institución de Asistencia Médica Privada de Profesionales Sin Fines de lucro, Montevideo, Uruguay

Amy R. Sood, Canadian Agency for Drugs and Technologies in Health (CADTH), Ottawa, Ontario, Canada

Benedicte Stengel, Center for Research in Epidemiology and Population Health (CESP), National Institute of Health and Medical Research (INSERM), Villejuif, France; University Paris Sud, Villejuif, France; Université de Versailles Saint-Quentin-en-Yvelines (UVSQ), Villejuif, France; and University Paris Saclay, Villejuif, France

Maarten W. Taal, Department of Renal Medicine, Royal Derby Hospital, Derby, UK; and Division of Medical Sciences and Graduate Entry Medicine, University of Nottingham, Nottingham, UK

Mototsugu Tanaka, Office of New Drug 1, Pharmaceuticals and Medical Devices Agency, Tokyo, Japan

Marcello Tonelli, Department of Medicine, University of Calgary, Calgary, Alberta, Canada; and Pan American Health Organization/World Health Organization's Collaborating Centre in Prevention and Control of Chronic Kidney Disease, University of Calgary, Calgary, Alberta, Canada

Allison Tong, Sydney School of Public Health, The University of Sydney, Sydney, New South Wales, Australia; and Centre for Kidney Research, The Children's Hospital at Westmead, Sydney, New South Wales, Australia

Robert Toto, Department of Internal Medicine, University of Texas Southwestern Medical Center, Dallas, Texas, USA; and Department of Population and Data Sciences, University of Texas Southwestern Medical Center, Dallas, Texas, USA

Michele Trask, School of Nursing, University of British Columbia, Vancouver, British Columbia, Canada; and Provincial Health Services Authority, Vancouver, British Columbia, Canada

Ifeoma I. Ulas, Renal Unit, Department of Medicine, College of Medicine, University of Nigeria, Ituku Ozalla, Enugu State, Nigeria; Department of Medicine, University of Nigeria Teaching Hospital Ituku Ozalla, Enugu State, Nigeria; and Department of Internal Medicine, Alex Ekwueme Federal University Teaching Hospital Abakaliki (AEFUTHA), Ebonyi State, Nigeria

Christoph Wanner, Division of Nephrology, University Hospital Würzburg, Würzburg, Germany

David C. Wheeler, Department of Nephrology, Royal Free Campus, University College London, London, UK; and George Institute for Global Health, Oxford, UK

Benjamin O. Wolthers, Novo Nordisk A/S, Copenhagen, Denmark

Harold M. Wright, Translational Medicine, Retrophin, Inc., San Diego, California, USA

Yoshihisa Yamada, Department of Renal and Cardiovascular Research, Otsuka Pharmaceutical Co., Ltd., Tokushima, Japan

Elena Zakharova, Department of Nephrology, Moscow City Hospital named after S.P. Botkin, Moscow, Russian Federation; Department of Nephrology, Moscow State University of Medicine and Dentistry, Moscow, Russian Federation and Department of Nephrology, Russian Medical Academy of Continuous Professional Education, Moscow, Russian Federation

Participant author disclosures

SA reports grants from Normon S. Coplon Satellite Healthcare Applied Pragmatic Research Grant, outside the submitted work. EB reports personal fees from AstraZeneca Canada, outside the submitted work. DB reports grants from Wellcome ISSF 204809/Z/16/Z, Kidney Research UK ID-01520190403, and AstraZeneca ESR ESR-19-20174, outside the submitted work. AAB reports personal fees from Baxter Healthcare Corporation, outside the submitted work. WC reports personal fees from Johnson & Johnson, outside the submitted work. FC reports personal fees from Baxter Healthcare, outside the submitted work. ID reports personal fees from Boehringer-Ingelheim, George Clinical, Goldfinch Bio, and Ironwood, outside the submitted work. KE reports grants from AstraZeneca, Bayer, Fresenius, Vifor, Amgen, Genzyme, and Shire, and personal fees from Akebia, Bayer, Fresenius, and Vifor, outside the submitted work. HF reports grant from the National Institutes of Health, personal fees from the National Kidney Foundation, Kyowa Kirin Inc., and InMed, Inc., and honorarium from the University of California, Los Angeles, outside the submitted work. SH reports personal fees from Boehringer Ingelheim, outside the submitted work. RH reports grants from Boehringer Ingelheim and Novartis, outside the submitted work. CH reports personal fees from AbbVie, AstraZeneca, Corvidia, Diamedica, FibroGen, Janssen, NxStage, Pfizer, Sanofi, University of Oxford, and UpToDate, a grant from the National Institute of Diabetes and Digestive and Kidney Diseases /National Institutes of Health (USRDS Contract), a grant and personal fees from Amgen, Relypsa, Inc., and the National Heart Lung and Blood Institute (NHLBI/NIH), a grant and stocks from Bristol-Meyer Squibb, personal fees and stock from Merck, a grant from the University of British Columbia, and stocks from Boston Scientific, General Electric, Johnson & Johnson, and Hennepin Healthcare, outside the submitted work. LI reports grants from Retrophin and Reata Pharmaceuticals, a grant and consulting agreement from Omeros Corporation, and a consulting agreement with Tricida, Inc., outside the submitted work. JI reports personal fees from Gilead Sciences, Inc., outside the submitted work; and is a volunteer Workgroup Co-Chair for the Kidney Health Initiative. DWJ reports grants and personal fees from Baxter Healthcare and Fresenius Medical Care, personal fees from AstraZeneca, AWAK, and Ono, travel sponsorship from Amgen, and a grant from the National Health and Medical Research Council of Australia, personal fees from Ono, outside the submitted work. CJB reports personal fees from Otsuka Pharmaceutical Development & Commercialization, Inc., outside the submitted work. AJ reports personal fees from Bayer AG, outside the submitted work. AKW reports personal fees from Boehringer Ingelheim, outside the submitted work. MK reports grants from AstraZeneca, Gilead Sciences, Inc., Novo Nordisk, Eli Lilly and Co., Janssen, Merck, Elpidera, Certa, Goldfinch Bio, Boehringer Ingelheim, the National Institutes of Health, JDRF, and Angion, outside the submitted work, and has a patent PCT/EP2014/073413 "Bio-markers and methods for progression prediction for chronic kidney disease" issued. RL reports personal fees and other stocks from Bayer AG, outside the submitted work. SN reports a research grant funded by the Newton Fund, Medical Research Council (UK and South Africa), and GlaxoSmithKline, outside the submitted work. UP reports personal fees from Gilead Sciences, Inc., outside the submitted work and is a member of the Board of Directors for Kidney Health Initiative. RPF reports grants from Baxter Healthcare and Fresenius Medical Care, personal fees from AstraZeneca and Akebia, outside the submitted work. JR reports personal fees and stock from Janssen Inc., Canada, outside the submitted work. NR reports personal fees Retrophin, Inc., outside the submitted work. MS reports personal fees and other stocks from AstraZeneca, outside the submitted work. CW reports grant from Boehringer-Ingelheim, personal fees from Boehringer-Ingelheim, Gilead Sciences, Inc., GlaxoSmithKline, and MSD, outside the submitted work. DW reports personal fees from Amgen, AstraZeneca, Bayer, Boehringer Ingelheim, GlaxoSmithKline, Janssen, Napp, Mundipharma, Reata, Vifor Fresenius, and Merck Sharpe and Dohme, outside the submitted work. BW reports personal fees Novo Nordisk A/S, outside the submitted work. HW reports personal fees and stocks from Retrophin, Inc., outside the submitted work. YY reports personal fees and stocks from Otsuka Pharmaceutical Co., Ltd., outside the submitted work. All the other authors declared no competing interests.

APPENDIX 2

List of meeting attendees

First name	Last name	Country—role
Meg	Jardine	Australia—Steering Committee
Vivekanand	Jha	India—Steering Committee; ISN President
Adeera	Levin	Canada—Steering Committee; Chair, ISN Research Working Group
Charu	Malik	Belgium—Steering Committee; ISN Executive Director
Masaomi	Nangaku	Japan—Steering Committee; Deputy Chair, ISN Research Working Group
Vlado	Perkovic	Australia—Steering Committee; Chair, ISN-ACT Committee
Aliza	Thompson	USA—Steering Committee
Rajiv	Agarwal	USA—Core Group
William	Herrington	UK—Core Group
Johannes	Mann	Germany—Core Group
Shahnaz	Shahinfar	USA—Core Group
Katherine	Tuttle	USA—Core Group
Shuchi	Anand	USA
Nicholas	Argent	Canada
Elena	Babak	Canada—AstraZeneca
Debasish	Banerjee	UK
Jonathan	Barratt	UK
Mary	Beaucage	Canada
Aminu	Bello	Canada
Angelito	Bernardo	USA—Baxter
Jaime	Blais	USA—Janssen
Geoffrey A.	Block	USA—REATA
William	Canovatchel	USA—Janssen
Fergus	Caskey	UK
Kate	Chong	Canada
Joe	Coresh	USA
Sandrine	Damster	Belgium—ISN staff
Ian	de Boer	USA
Jo-Ann	Donner	Belgium—ISN staff
Kai-Uwe	Eckardt	Germany
Rhys	Evans	UK
Harold	Feldman	USA
Agnes	Fogo	USA
Hrefna	Gudmundsdottir	Iceland
Takayuki	Hamano	Japan
Heather	Harris	Canada
David	Harris	Australia
Sibylle	Hauske	Germany—Boehringer Ingelheim
Richard	Haynes	UK
Peter	Heerma	Netherlands—Retrophin
Jens	Heisterberg	Denmark—Novo Nordisk
Charles	Herzog	USA
Thomas	Hiemstra	UK
Thomas	Idorn	Denmark—Novo Nordisk
Lesley	Inker	USA
Julie	Ishida	USA—Gilead
David	Johnson	Australia
Charlotte	Jones-Burton	USA—Otsuka
Amer	Joseph	Germany—Bayer
Audrey	Koikta	Germany—Boehringer Ingelheim
Robert	Lawatscheck	Germany—Bayer
Kelli	Lester	USA—Baxter
Adrian	Liew	Singapore
Louise	Moist	Canada
Saraladevi	Naicker	South Africa
Reiko	Nakashima	Japan
Uptal	Patel	USA—Gilead
Roberto	Pecoits-Filho	Brazil
Glenda V.	Roberts	USA
Jennifer	Rose	Canada—Janssen
Noah	Rosenberg	USA—Retrophin

Appendix 2 | (Continued)

First name	Last name	Country—role
Friedrich	Schultze	Germany—Boehringer Ingelheim
Marvin	Sinsakul	USA—AstraZeneca
William	Smoyer	USA
Sara	Snow	USA—Gilead
Laura	Sola	Uruguay
Amy	Sood	Canada
Robert	Star	USA
Benedicte	Stengel	France
Duane	Sunwold	USA
Maarten	Taal	UK
Mototsugu	Tanaka	Japan
Marcello	Tonelli	Canada
Allison	Tong	Australia
Robert	Toto	USA
Michele	Trask	Canada
Ifeoma	Ulesi	Nigeria
Hans	Vorster	Canada
Michael	Walsh	Canada
Christopher	Wanner	Germany
Madeleine	Warren	UK
David	Wheeler	UK
Benjamin	Wolthers	Denmark—Novo Nordisk
Harold	Wright	USA—Retrophin
Yoshi	Yamada	Japan—Otsuka
Helena	Zakharova	Russia

ACT, Advancing Clinical Trials; ISN, International Society of Nephrology.

DISCLOSURE

RA reports personal fees and travel support from Relypsa, Inc., AbbVie, Amgen, AstraZeneca, Bayer, Boehringer Ingelheim, Celgene, Daiichi Sankyo, Eli Lilly and Co., Gilead Sciences, Inc., GlaxoSmithKline, Johnson & Johnson, Merck, Novartis, Sandoz, ZS Pharma, Inc., Akebia, Takeda, Sanofi, Reata, Ironwood Pharmaceuticals, Otsuka, Opko, and Birdrock Bio; and grants from the National Institutes of Health (NIH) and the Veterans Administration Medical Center, outside the submitted work. SD reports personal fees from The International Society of Nephrology, outside the submitted work. DDZ reports advisory and speaker fees to himself and his institution from Fresenius, Boehringer Ingelheim, and Bayer; Steering Committee fees to himself and his institution from Janssen; advisory and speaker fees from Mitsubishi Tanabe and Mundipharma; and Steering Committee fees to his institution from AbbVie, outside the submitted work. JD reports personal fees from The International Society of Nephrology, outside the submitted work. HLH reports personal fees from AbbVie, AstraZeneca, Boehringer Ingelheim, Bayer, Chinook, CSL Behring, Fresenius, Janssen, Gilead Sciences, Inc., Merck, Mitsubishi Pharma, and Retrophin; and grant support from AstraZeneca, Boehringer Ingelheim, and Janssen, outside the submitted work. WH reports grants from Boehringer Ingelheim, Eli Lilly and Co., Novartis, Medical Research Council UK, and Kidney Research UK, outside the submitted work (and is supported by an MRC-Kidney Research UK Professor David Kerr award). MJ reports consultancy fees, honoraria, and/or travel support paid to her institution from Akebia, Amgen, AstraZeneca, Baxter, Boehringer Ingelheim, Commonwealth Serum Laboratories, and Vifor, outside the submitted work. VJ reports grants from GlaxoSmithKline and Baxter Healthcare, and provides scientific leadership to George Clinical and consultancy for Biocon, Zudis Cadilla, and NephroPlus, outside the submitted work. KM reports personal fees from Abbott, Ablynx, Baim Institute, Boehringer Ingelheim, Bristol Myers Squibb, Elsevier, GlaxoSmithKline, Mederger, Medscape, Mitsubishi, Myokardia, Novo Nordisk, Portola, Radiometer, Regeneron, SmartMedics, Springer Publishing, and University of California, San Francisco; grants and personal fees from AstraZeneca, Johnson & Johnson, the National Institutes of Health (NIH), and Novartis; and grants from Afferent, Amgen, Apple, Inc., Cardiva Medical, Inc., Daiichi, Ferring, Google (Verily), Luitpold, Medtronic, Merck, Sanofi, St. Jude, and Tenax, outside the submitted work. CM reports personal fees from The International Society of Nephrology, outside the submitted work. MN reports grants and personal fees from Kyowa Kirin, Astellas, Daiichi Sankyo, Mitsubishi Tanabe, JT, Chugai, Takeda, and MSD; personal fees from GlaxoSmithKline, Boehringer Ingelheim, Torii, AstraZeneca, Akebia, and Bayer; grants from Ono, Ostuaka, Dainippon

Sumitomo, outside the submitted work. SS reports personal fees from Amgen, Johnson & Johnson, and Tricida, Inc., outside the submitted work. KT reports personal fees from Eli Lilly and Co., Boehringer Ingelheim, AstraZeneca, Gilead Sciences, Inc., Goldfinch Bio, Novo Nordisk, and Bayer, outside the submitted work. MW reports personal fees from Quanta Dialysis Technologies, Pathfinder Medical, and Clinical Reference Group (National Health Service England), outside the submitted work. VP reports personal fees from Servier, Retrophin, Merck, and Janssen; a Research Fellowship from the National Health and Medical Research Council; a grant from the National Health and Medical Research Council paid to his institution; grants, honoraria, and support for clinical trials from GlaxoSmithKline, Pfizer, and Janssen paid to his institution; and advisory fees, honoraria, and/or travel support paid to his institution from Bayer, Bristol-Myers Squibb Company, Eli Lilly and Co., Boehringer Ingelheim, AstraZeneca, Novo Nordisk, Pharmalink, Relypsa, Inc., Baxter, Sanofi, Gilead Sciences, Inc., Novartis, Durect, Astellas, Tricida, Inc., Dimetrix, and AbbVie. All the other authors declared no competing interests.

ACKNOWLEDGMENTS

Support for the 1st International Consensus Meeting on Defining Kidney Failure in Clinical Trials was made possible by various organizations (listed in alphabetical order): AstraZeneca LP, Baxter, Bayer, Boehringer Ingelheim, Gilead, Janssen Inc. (a pharmaceutical company of Johnson & Johnson), Novo Nordisk, Otsuka, REATA, Retrophin, and Tourism Vancouver. In addition, support “in kind” was provided from Can-SOLVE CKD Network (CIHR SPOR Network), and those representing regulatory bodies, national research organizations, or other research organizations that supported representative attendance at the meeting. The International Society of Nephrology thanks the following people and organizations for reviewing the manuscript: Dr. Robert Star; Dr. Rosanna Coppo; Dr. Hong Zhang; the Venezuelan Society of Nephrology; the Russian Dialysis Society; the Canadian Nephrology Trials Network; the Japanese Society of Nephrology; the Korean Society of Nephrology; the French Society of Nephrology, Dialysis and Transplantation; the Hellenic Society of Nephrology; the Norwegian Society of Nephrology; the Swedish Society of Nephrology; the Renal Association; and the Nigerian Association of Nephrology. This work was supported by the International Society of Nephrology. The views expressed in this article are solely the responsibility of the authors and they do not necessarily reflect the views, decisions, or policies of the institutions with which they are affiliated.

SUPPLEMENTARY MATERIAL

Supplementary File (PDF)

Table S1. Trials that have evaluated kidney failure endpoints.

REFERENCES

- Levin A, Tonelli M, Bonventre J, et al. Global kidney health 2017 and beyond: a roadmap for closing gaps in care, research, and policy. *Lancet*. 2017;390:1888–1917.
- Jager KJ, Fraser SDS. The ascending rank of chronic kidney disease in the global burden of disease study. *Nephrol Dial Transplant*. 2017;32(suppl 2):ii121–ii128.
- Liyanage T, Ninomiya T, Jha V, et al. Worldwide access to treatment for end-stage kidney disease: a systematic review. *Lancet*. 2015;385:1975–1982.
- Heerspink HJ, de Zeeuw D. The kidney in type 2 diabetes therapy. *Rev Diabet Stud*. 2011;8:392–402.
- Afkarian M, Sachs MC, Kestenbaum B, et al. Kidney disease and increased mortality risk in type 2 diabetes. *J Am Soc Nephrol*. 2013;24:302–308.
- Palmer SC, Sciancalepore M, Strillpoli GF. Trial quality in nephrology: how are we measuring up? *Am J Kidney Dis*. 2011;58:335–337.
- Chatzimanouli MKT, Wilkens L, Anders HJ. Quantity and reporting quality of kidney research. *J Am Soc Nephrol*. 2019;30:13–22.
- Ishida JH, Johansen KL. Exclusion of patients with kidney disease from cardiovascular trials. *JAMA Intern Med*. 2015;176:124–125.
- Maini R, Wong DB, Addison D, et al. Persistent underrepresentation of kidney disease in randomized, controlled trials of cardiovascular disease in the contemporary era. *J Am Soc Nephrol*. 2018;29:2782–2786.
- Zoccali C, Blankestijn PJ, Bruchfeld A, et al. Children of a lesser god: exclusion of chronic kidney disease patients from clinical trials. *Nephrol Dial Transplant*. 2019;34:1112–1114.
- Baigent C, Herrington WG, Coresh J, et al. Challenges in conducting clinical trials in nephrology: conclusions from a Kidney Disease: Improving Global Outcomes (KDIGO) Controversies Conference. *Kidney Int*. 2017;92:297–305.
- Perkovic V, Jardine MJ, Neal B, et al. Canagliflozin and renal outcomes in type 2 diabetes and nephropathy. *N Engl J Med*. 2019;380:2295–2306.
- Heerspink HJL, Parving HH, Andress DL, et al. Atrasentan and renal events in patients with type 2 diabetes and chronic kidney disease (SONAR): a double-blind, randomised, placebo-controlled trial. *Lancet*. 2019;393:1937–1947.
- Baigent C, Landray MJ, Reith C, et al. The effects of lowering LDL cholesterol with simvastatin plus ezetimibe in patients with chronic kidney disease (Study of Heart and Renal Protection): a randomised placebo-controlled trial. *Lancet*. 2011;377:2181–2192.
- Herrington WG, Staplin N, Haynes R. Kidney disease trials for the 21st century: innovations in design and conduct. *Nat Rev Nephrol*. 2020;16:173–185.
- Kidney Disease: Improving Global Outcomes (KDIGO) CKD Work Group. KDIGO 2012 Clinical Practice Guideline for the Evaluation and Management of Chronic Kidney Disease. *Kidney Int Suppl*. 2013;3:1–150.
- Levey A, Eckardt K, Dorman N, et al. Nomenclature for kidney function and disease: report of a Kidney Disease: Improving Global Outcomes (KDIGO) Consensus Conference. *Kidney Int*. 2020;97:1117–1129.
- Kidney Health Initiative Clinical Data Interchange Standards Consortium. Diabetic kidney disease therapeutic area user guide v1.0. Available at: www.cdisc.org/standards/therapeutic-areas/diabetic-kidney-disease. Accessed February 16, 2020.
- Levey AS, Inker LA, Matsushita K, et al. GFR decline as an end point for clinical trials in CKD: a scientific workshop sponsored by the National Kidney Foundation and the US Food and Drug Administration. *Am J Kidney Dis*. 2014;64:821–835.
- Thygesen K, Alpert JS, Jaffe AS, et al. Fourth universal definition of myocardial infarction (2018). *J Am Coll Cardiol*. 2018;72:2231–2264.
- Sacco RL, Kasner SE, Broderick JP, et al. An updated definition of stroke for the 21st century: a statement for healthcare professionals from the American Heart Association/American Stroke Association. *Stroke*. 2013;44:2064–2089.
- International Society of Nephrology. ISN position statement on diversity. Available at: www.theisn.org/images/Diversity%20Statement/ISN%20Position%20Statement%20on%20Diversity%20%20v3%2022%20Sept%202011.pdf. Accessed March 9, 2020.
- Hicks KA, Mahaffey KW, Mehran R, et al. 2017 cardiovascular and stroke endpoint definitions for clinical trials. *Circulation*. 2018;137:961–972.
- Leon MB, Piazza N, Nikolsky E, et al. Standardized endpoint definitions for transcatheter aortic valve implantation clinical trials: a consensus report from the Valve Academic Research Consortium. *Eur Heart J*. 2011;32:205–217.
- Collins R, Bowman L, Landray M, et al. The magic of randomization versus the myth of real-world evidence. *N Engl J Med*. 2020;382:674–678.
- Pajewski R, Gipson P, Heung M. Predictors of post-hospitalization recovery of renal function among patients with acute kidney injury requiring dialysis. *Hemodial Int*. 2018;22:66–73.
- Siew ED, Abdel-Kader K, Perkins AM, et al. Timing of recovery from moderate to severe AKI and the risk for future loss of kidney function. *Am J Kidney Dis*. 2020;75:204–213.
- World Health Organization. ICD-10. International Statistical Classification of Diseases and Related Health Problems. 10th Revision. Vol. 2. 2nd Ed. Available at: www.who.int/classifications/icd/ICD-10_2nd_ed_volume2.pdf. Accessed February 16, 2020.
- Levey AS, Stevens LA, Schmid CH, et al. A new equation to estimate glomerular filtration rate. *Ann Intern Med*. 2009;150:604–612.
- Greene T, Teng CC, Inker LA, et al. Utility and validity of estimated GFR-based surrogate time-to-event end points in CKD: a simulation study. *Am J Kidney Dis*. 2014;64:867–879.
- Coresh J, Turin TC, Matsushita K, et al. Decline in estimated glomerular filtration rate and subsequent risk of end-stage renal disease and mortality. *JAMA*. 2014;311:2518–2531.
- Inker LA, Lambers Heerspink HJ, Mondal H, et al. GFR decline as an alternative end point to kidney failure in clinical trials: a meta-analysis of

- treatment effects from 37 randomized trials. *Am J Kidney Dis.* 2014;64:848–859.
33. Perkovic V, Koitka-Weber A, Cooper ME, et al. Choice of endpoint in kidney outcome trials: considerations from the EMPA-REG OUTCOME trial. *Nephrol Dial Transplant.* <https://doi.org/10.1093/ndt/gfz179>. Accessed May 20, 2020.
 34. Levey AS, Gansevoort RT, Coresh J, et al. Change in albuminuria and GFR as end points for clinical trials in early stages of CKD: a scientific workshop sponsored by the National Kidney Foundation in collaboration with the US Food and Drug Administration and European Medicines Agency. *Am J Kidney Dis.* 2020;75:84–104.
 35. Gonzalez AM, Gutman T, Lopez-Vargas P, et al. Patient and caregiver priorities for outcomes in chronic kidney disease: a multinational nominal group technique study [e-pub ahead of print]. *Am J Kidney Dis.* <https://doi.org/10.1053/j.ajkd.2020.03.022>. Accessed May 20, 2020.
 36. Ju A, Unruh M, Davison S, et al. Establishing a core outcome measure for fatigue in patients on hemodialysis: a Standardized Outcomes in Nephrology–Hemodialysis (SONG-HD) Consensus Workshop report. *Am J Kidney Dis.* 2018;72:104–112.
 37. Schwartz GJ, Munoz A, Schneider MF, et al. New equations to estimate GFR in children with CKD. *J Am Soc Nephrol.* 2009;20:629–637.
 38. Will EJ (Ed). Perspectives on UK clinical renal computing 1979–1994. Available at: <https://renal.org/wp-content/uploads/2018/12/Clinical-Renal-Computing-Witness-Seminar.pdf>. Accessed February 16, 2020.