International consensus definitions of clinical trial outcomes for kidney failure

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

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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.

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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 infarction[20] and stroke[21]).

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: (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 m^2 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 m^2, and often one much lower, and died as a result of

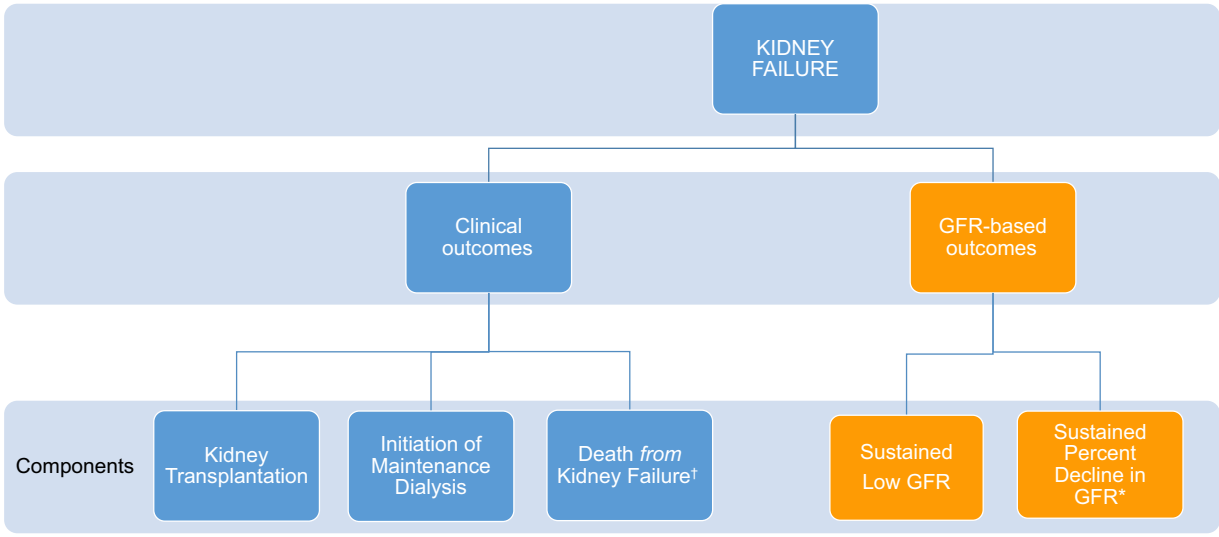

Figure 1 | Individual components of a composite outcome of kidney failure for use in clinical trials. GFR, glomerular filtration rate. †Death *from* kidney failure differs from death *with* kidney failure. We consider death *with* kidney failure to include a death from any cause among those who have 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 death[31]) 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 *from* 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 $\geq 40\%$[b] from a baseline start point sustained over at least 4 wk[19]

GFR, glomerular filtration rate.
[a]A GFR of <10 ml/min per 1.73 m^2 may be used in certain situations.
[b]A $\geq 30\%$, $\geq 40\%$, $\geq 50\%$, or $\geq 57\%$ 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 $\geq 30\%$ 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 m^2) sustained over at least 4 weeks, evidenced by 2 consecutive measurements; GFR <15 ml/min per 1.73 m^2 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 m^2.

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 m^2 or less, a GFR threshold that defines sustained low GFR may be lower than the <15 ml/min per 1.73 m^2 value (e.g., to <10 ml/min per 1.73 m^2). We acknowledge that the KDIGO definition[16] of kidney failure is a GFR of <15 ml/min per 1.73 m^2.

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 ≥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 associated[27] with a 10-fold increased risk of kidney failure in those with an eGFR of <60 ml/min per 1.73 m^2.

(ii) A ≥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 ≥30%, ≥40%, ≥50%, or ≥57% eGFR decline is dependent on these factors. For example, trials in people without diabetes or without albuminuria may

need to use a ≥40% decline because the time to a ≥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 ≥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 failure[27] in those with an eGFR <60 ml/min per 1.73 m^2. 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 ≥57% decline after a ≥40% decline) or a sustained low GFR, or for accompanying prespecified 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 issues[35]) 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

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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
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.

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SUPPLEMENTARY MATERIAL

Supplementary File (PDF)

Table S1. Trials that have evaluated kidney failure endpoints.

REFERENCES

1. 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.
2. 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.
3. 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.
4. Heerspink HJ, de Zeeuw D. The kidney in type 2 diabetes therapy. *Rev Diabet Stud*. 2011;8:392–402.
5. 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.
6. Palmer SC, Sciancalepore M, Strillpoli GF. Trial quality in nephrology: how are we measuring up? *Am J Kidney Dis*. 2011;58:335–337.
7. Chatzimanouli MKT, Wilkens L, Anders HJ. Quantity and reporting quality of kidney research. *J Am Soc Nephrol*. 2019;30:13–22.
8. Ishida JH, Johansen KL. Exclusion of patients with kidney disease from cardiovascular trials. *JAMA Intern Med*. 2015;176:124–125.
9. 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.
10. 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.
11. 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.
12. 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.
13. 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.
14. 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.
15. 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.
16. 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.
17. 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.
18. 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.
19. 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.
20. Thygesen K, Alpert JS, Jaffe AS, et al. Fourth universal definition of myocardial infarction (2018). *J Am Coll Cardiol*. 2018;72:2231–2264.
21. 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.
22. 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.
23. Hicks KA, Mahaffey KW, Mehran R, et al. 2017 cardiovascular and stroke endpoint definitions for clinical trials. *Circulation*. 2018;137:961–972.
24. 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.
25. 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.
26. 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.
27. 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.
28. 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.
29. Levey AS, Stevens LA, Schmid CH, et al. A new equation to estimate glomerular filtration rate. *Ann Intern Med*. 2009;150:604–612.
30. 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.
31. 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.
32. 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.