# Establishing core cardiovascular outcome measures for trials in haemodialysis: report of an international consensus workshop

**Running title: Cardiovascular outcomes for trials is haemodialysis**


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**ABSTRACT**

Cardiovascular disease (CVD) affects more than two-thirds of patients on haemodialysis, is the leading cause of death in this population and yet, CVD outcomes are infrequently and inconsistently reported in trials in patients receiving haemodialysis. As part of the Standardised Outcomes in Nephrology-Haemodialysis (SONG-HD) initiative, we convened a consensus workshop to discuss the potential use of myocardial infarction (MI) and sudden cardiac death (SCD) as core outcome measures for CVD for use in all trials in people on haemodialysis. Eight patients/caregivers and 46 health-professionals from 15 countries discussed selection and implementation of the proposed core outcome measures. Five main themes were identified. *Capturing specific relevance to the haemodialysis population* acknowledging prevalence, risk, severity, unique symptomology and pathophysiology. *The dilemmas in using composite outcomes* were recognised. *Addressing challenges in outcome definitions*, establishing a common definition, and addressing uncertainty in the utility of biomarkers in haemodialysis. *Ensuring a meaningful metric for decision-making* to facilitate comparison across trials. *Enabling and incentivising* implementation by ensuring cardiologists are involved in development and integration of the outcome measure into registries, trial-design and reporting guidelines. Based on these themes, participants supported the use of *MI* and *SCD* as core outcome measures of CVD to be reported in all haemodialysis trials.

Key words: hemodialysis, outcomes, myocardial infarction, sudden cardiac death

## INTRODUCTION

Cardiovascular disease (CVD) affects more than two thirds of people on haemodialysis and is the leading cause of death in this population [1,2]. CVD also increases their short and long-term morbidity in this population [2]. Traditional risk factors for CVD, including diabetes mellitus, hypertension and dyslipidaemia, are highly prevalent in the haemodialysis population [3] and may act synergistically with non-traditional risk factors including uraemic toxins, electrolyte and fluid imbalance, disordered bone and mineral metabolism and haemodialysis modality [4-8]. Optimal management of CVD in patients on haemodialysis remains uncertain. Evidence from trials to inform decisions is currently limited because patients on haemodialysis are often excluded from cardiovascular trials [9]. Furthermore, cardiovascular outcomes remain infrequently reported, appearing in only 12% of trials in haemodialysis [10].

There is considerable heterogeneity as well as extensive use of surrogate and composite cardiovascular outcomes across trials in haemodialysis [11]. In a recent systematic review of 175 trials in haemodialysis, over 230 measures were used for 26 cardiovascular outcomes such as myocardial infarction, stroke and cardiac arrest [11]. The three most frequently reported outcomes were serum biomarkers (excluding lipids and traditional cardiac biomarkers), cardiovascular composites, and serum lipids [11]. Composite outcomes were highly variable with more than 50 different composite combinations used, with most combinations used only in a single trial [11]. The differing degrees of clinical impact of the individual outcomes incorporated into a composite outcome as well as the difficulty in comparing composites across trials makes estimates of the comparative effectiveness of interventions highly uncertain. This in turn, hinders progress towards improving cardiovascular morbidity and mortality in this high-risk population.

Surrogate markers of CVD, both biochemical (e.g. lipids) and anatomical (e.g. left ventricular mass index), are also frequently used in cardiovascular trials and yet they may not accurately predict the

effect of an intervention on important clinical outcomes such as sudden cardiac death, myocardial infarction or stroke [12,13], nor are they meaningful to patients to support decision-making [14]. CVD has been prioritised by patients, caregivers and health professionals as a critically important outcome for use in all trials in haemodialysis [15]. Specifically, cardiovascular events such as myocardial infarction, sudden cardiac death and stroke, which have direct impact on patients in terms of symptoms and quality of life and survival, and yet these outcomes were reported in less than 10% of trials that report CVD outcomes in haemodialysis [11].

These problems with outcome reporting have driven efforts to develop core outcome sets, defined as an agreed standardised set of outcomes that should be measured and reported, as a minimum, in all clinical trials in specific areas of health or health care [16]. This is a two-step process requiring the identification of the domain, such as myocardial infarction, followed by determining the metric(s) that best defines that domain, such as ECG and cardiac enzyme. In cardiovascular medicine, core outcome sets are being developed in specific populations including pregnant women with CVD [17] and patients undergoing cardiac surgery [18]. In cardiac surgery the core outcome set consists of mortality, quality of life, hospitalisation and cerebrovascular complications [19]. The American Heart Association has developed key data elements and definitions for cardiovascular endpoint events in clinical trials, electrophysiological studies and procedures reporting and a cardiovascular vocabulary for electronic health records [20-22]. Collectively, these efforts endeavour to improve consistency and relevance of cardiovascular events reported in the general population.

Recently, the Standardised Outcomes in Nephrology Haemodialysis (SONG-HD) initiative was launched to establish a set of core outcomes for trials in haemodialysis. Based on a consensus process involving more than 1200 patients, caregivers and health professionals from over 70 countries, CVD (together with vascular access, fatigue and mortality) was identified as a core outcome. As part of the SONG-HD Initiative to establish core outcome measures for CVD, we administered an international survey to stakeholders to rank in order of importance ten cardiovascular

outcomes derived from a recently published systematic review. Survey respondents (n=676) comprised healthcare professionals, patient/caregivers, policy makers, and industry representatives from 53 countries[23]. The outcomes myocardial infarction, sudden cardiac death, heart failure and stroke were consistently identified as the most important CVD outcomes, across all stakeholder groups. We convened a consensus workshop in New Orleans in November 2017 during the American Society of Nephrology Kidney Week Conference with patients, caregivers, and health professionals to discuss the identification and implementation of a core outcome measure for CVD to be reported in all trials in haemodialysis populations. This report provides a summary of the workshop discussion and outlines recommendations for establishing core CVD outcome measures in haemodialysis.

## SONG-HD CARDIOVASCULAR DISEASE WORKSHOP

### Context and scope

The SONG-HD Cardiovascular Disease consensus workshop was held on November 1st, 2017 in New Orleans, USA in conjunction with the American Society of Nephrology Kidney Week Conference 2017. The workshop brought together stakeholders (patients, caregivers, and health professionals) to discuss the identification and implementation of a core outcome specifically for CVD to be reported in all haemodialysis trials. Participants were presented the results of the systematic review [11] and interim results from an international survey on CVD outcomes completed by patients/caregivers and health professionals prior to the workshop[23]. The interim survey results suggested that the most important CVD outcomes across stakeholders were myocardial infarction, sudden cardiac death, stroke and heart failure[24]. The two most highly prioritised cardiovascular outcomes were myocardial infarction and sudden cardiac death and discussion focused on these.

### Participants and contributors

Patients and caregivers with experience of haemodialysis, and health professionals (nephrologists, cardiologists, researchers, trialists, regulators, funders, and policy makers) were invited to the workshop. Invitations were also extended to representatives of professional societies (e.g. American Society of Nephrology), regulatory agencies (e.g. Food and Drug and Administration [FDA], Centers for Medicare and Medicaid Services [CMS]), journal editors, registries, funding organisations (e.g. National Institutes for Health [NIH]), industry, and guideline organisations (e.g. Kidney Disease Improving Global Outcomes).

**Workshop program and materials**

The workshops materials were circulated to all investigators two weeks prior to the workshop. The materials included an overview of the SONG-HD process, results of the systematic review of cardiovascular outcomes in haemodialysis trials, and interim results of an international online survey with patients/caregivers and health professionals who ranked the importance of cardiovascular outcomes (e.g. myocardial infarction, sudden cardiac death) to be reported in trials in haemodialysis. We also included definitions of myocardial infarction currently used including the Third Universal Definition [25] and the definitions used in a number of landmark cardiovascular trials in patients with end-stage kidney disease (ESKD) [26-29].

Participants were allocated to one of six break-out discussion groups with 7-10 members. Each group had at least one patient/caregiver and the group participants are characterised in Supplementary Table 1. The groups were facilitated by EO, AKV, JCC, WW, AL and DW. The facilitator asked participants to discuss: the interim results of the survey (which is beyond the scope of the current report and will be published separately); the potential use of myocardial infarction and sudden cardiac death as core outcome measures including the definition, feasibility, validity and discrimination; how they should be reported, including metric, comprehensibility for patients;

and implementation. In the plenary session, one member from each group presented the main points of their discussion. The Chair of the workshops (DCW) summarised the presentations across the groups. The group discussions and the plenary sessions were audio-taped and transcribed.

The transcripts were entered into HyperRESEARCH (ResearchWare Inc. United States; Version 3.0.) to facilitate coding and analysis of the data. The first author (EO) read and coded the transcript line-by-line, using inductively identified codes. Similar codes were then sorted into preliminary themes that reflected the concepts expressed by participants relating to the identification and implementation of a core outcome measure for CVD to be reported in trials in haemodialysis. The themes identified from the comments were cross checked by a second investigator (AT) to ensure they captured the breadth and depth of the discussion. All participants and contributors received a draft workshop report to provide feedback within a two-week timeframe to ensure that the findings reflected participants' perspectives. Additional comments were integrated into the final report.

In total, 46 healthcare professionals (nephrologists, cardiologists, researchers [including trialists], journal editors, policy makers and industry representatives) and eight patients/caregivers attended the workshop. The participants were from 15 countries. Additional investigators who were unable to attend (n=58) contributed feedback on the workshop program and the draft workshop report by email.

**Summary of the workshop discussion**

We identified five main themes (Figure 1): capturing specific relevance to the haemodialysis population; dilemmas in using composite outcomes; addressing challenges in outcome definition; ensuring a meaningful metric for decision-making; and enabling and incentivising implementation. The respective subthemes are described below. Selected illustrative quotations for each theme are shown in Box 1. Recommendations from the workshop discussions are summarised in Box 2.

**Capturing specific relevance to the haemodialysis population**

*"It's a different conversation with somebody on dialysis, and I don't believe that that's always acknowledged, that dialysis patients are unique. Not just in their risk factors [for CVD], but in how they can and should be treated and take care of themselves."* (Health professional, Group 3)

Prevalence, risk and severity of the cardiovascular outcome: Participants considered whether the core CVD outcome should be based on prevalence in the haemodialysis population (i.e. myocardial infarction), its specificity to a haemodialysis population (i.e. sudden cardiac death) or the impact of the outcome to patients (i.e. heart failure or stroke), "There is a difference between importance versus frequency" (Health professional, Group 1), and "I'm okay with the fact that it's [*myocardial infarction]* the most frequently measured, but I'm not okay with the fact that probably it's not really the most relevant" (Health professional, Group 1).. The relevance of the CVD outcomes was argued to be fundamental to the decision – "My understanding is that pretty much every dialysis run damages the cardiovascular system" (Patient/caregiver, Group 1),

Complex symptomology and diagnosis: It was emphasised that CVD in a patient on haemodialysis did not often present in a classical way, and the ability to diagnose CVD in the haemodialysis population was particularly difficult. Patients were not always aware that a heart attack may present differently, "that's a good question, my gut feeling is no [i wasn't aware]" (Patient/caregiver, Group 1). Heart failure could be misdiagnosed in a patient with fluid overload and a sudden cardiac death could be misclassified as a myocardial infarction. A myocardial infarction could be missed in a patient without chest pain, "you can get them by chest pain, certain back pains, your arms, whatever" (Patient/caregiver, Group 6). The core outcome measure for CVD had to be carefully

established for the specific population, “that sudden cardiac death in someone who is on dialysis, if you were to use the general population term, probably you would think this is a myocardial infarction death. When in actual fact you realise in the years that pass that actually a very large proportion may not be myocardial infarction” (Health professional, Group 3).

Considering consequences on quality of life: CVD could impact quality of life, which was a key consideration as patients “want to be able to survive and have some semblance of quality of life” (Health professional, Group 2). Silent or recurrent myocardial infarction was felt to contribute to long term poor outcomes and quality of life, “you were saying about quality of life and heart failure, it [*myocardial infarction*] is crucial in the development of heart failure and it does impact on functional cardiovascular reserve, so it is sensitive to have it in there because it will ultimately impact adversely on function.” (Health professional, Group 2) Stroke and heart failure were also highlighted as having a potentially more severe and immediate impact on function and overall quality of life day-to-day. “Most of my patients put a stroke ahead of everything, ahead of sudden cardiac death, myocardial infarction, because it’ll be the thing with the most obvious change in quality of life because it’s immediate” (Health professional, Group 2). Patients also considered long term implications of an event, “You have that longevity with stroke disability, with heart failure disability” (Patient/caregiver, Group 2).

Accounting for geographic variation: The variation in prevalence of CVD across countries was recognised – “Like in Japan, strokes are a lot more common *[than MI*]." (Health professional, Group 4). Treatment could vary depending on the healthcare context – “hospitalisation is region-dependent, because in some regions, patients are going to be hospitalised earlier than in other regions” (Health professional, Group 5). A core outcome for CVD in haemodialysis had to be feasible to measure internationally, for example “countries around the world where you cannot measure troponin” (Health professional, Group 6).

Having potential for intervention: There was some concern that establishing a core outcome in CVD may drive research in a futile direction, particularly if they expected there to be little potential for interventions to change the outcome – "MIs, heart attacks are clearly important. My concern is that by reporting them in every trial, they're so poorly modifiable that it's not going to get us where we want to go in terms of getting better, patients better at the end of the day" (Health professional, Group 5). It was speculated that sudden cardiac death and heart failure might be more modifiable than myocardial infarction. Participants realised that trialists may not want to include an outcome which is unlikely to be responsive to their particular intervention but agreed that outcomes of critical importance to patients and clinicians' decision making should still be measured and reported, irrespective of whether they may respond to the intervention.

**Dilemmas in using composite outcomes**

Obfuscation and misinterpretation of findings: For a core CVD outcome, "having a composite outcome would be very complex" (Health professional, Group 4). The combination of outcomes used in composites (presented during the workshop) was extremely heterogenous, making comparisons across trials impossible – "it would be great if everybody used the same definition of MACE and MACE-plus.....even imperfect, at least we could compare results" (Health professional, Group 4). Issues discussed also included: the potential to "cherry pick" components for a composite cardiovascular disease outcome in the attempt to demonstrate a positive effect for an intervention, and combining outcomes of varying prevalence and importance to patients could dilute the relevance of the results, and be potentially misleading. For these reasons, it was "not actually appropriate to combine [*outcomes*], or it may not be smart to do so [*for a core outcome*]" (Health professional, Group 4). Reporting an individual specific CVD outcome would make results more transparent and thus preferable as a core outcome.

Benefits to trialists: It was acknowledged that "as much as we might not want to encourage the use of a composite endpoint, the reality is regulatory agencies, that's exactly what they demand" (Health professional, Group 5). The use of composite outcomes could reduce cost by reducing the required sample size – "you have to have a composite outcome in order to have statistical significance with a smaller sample size" (Health professional, Group 5). Some thought it may be important to report more than one CVD outcome, and to "try and define what the composite outcome should be" (Health professional, Group 5).

**Addressing challenges in symptomatology, definition and utility of outcomes**

Consistency, applicability and specificity of definitions: Given the wide heterogeneity in definitions for cardiovascular outcomes in trials, establishing a consistent definition was thought to be paramount. Patients believed consistency gave "a transparency level" (Patient/caregiver, Group 6). There were conflicting views on the current definitions available: The Third Universal definition for myocardial infarction was suggested as a gold standard and whilst "there's a strength in a gold standard if you will, that is internationally accepted; rather than reinventing the wheel and defining this from scratch which may take decades" (Health professional, Group 6), some health professionals argued that the current definition had "to be adapted for the haemodialysis population" (Health professional, Group 3). This was on the basis of the different symptomatology and diagnostic criteria in haemodialysis: "they often don't have pain, so that's the first criteria. Their troponin's elevated anyway, that's the second criteria, troponin's up at baseline in many patients, no?" (Health professional, Group 2); and that "the type-2 MI is predominant, not the type-1" (Health professional, Group 4). The definition had to be practical, comprehensible to patients, and validated in the haemodialysis population, "it's good to be adapted, it's more important to be validated" (Health professional, Group 3).

Recognising variability in symptoms: In the haemodialysis population, the symptoms of MI and heart failure differed, "I didn't have a sharp pain, but I had difficulty breathing and stuff like that" (Patient/caregiver, Group 3). A health professional further explained, "because in our population, a lot of the heart attacks are actually silent, so actually it's quite different from the general heart attack that we see in the usual population. Most patients may manifest heart failure rather than classical heart attack symptoms or chest pain. That is one important consideration when you diagnose a heart attack in a classical way where you need to have the symptoms, chest pain" (Health professional, Group 4). It was also difficult to differentiate heart failure from fluid overload in haemodialysis.

Uncertainty in the clinical utility of biomarkers specific to haemodialysis: The limitations of biomarkers in haemodialysis were recognised – "biomarkers which are very useful in general population cannot be truly interpreted in renal patients" (Health professional, Group 6). Troponin levels were not standardised in a haemodialysis population and each assay and lab performs differently. The timing of a biomarker, whether it was before or after dialysis and what constituted a significant change in troponin levels was uncertain in the context of haemodialysis – "we don't know what a significant delta is, right?" (Health professional, Group 1)

Clarity for adjudication: The definition of the core CVD outcome in haemodialysis had to have potential for use not only by clinicians as a diagnostic tool but also by trialists and registries, "frankly the definition comes a bit too late. It's already been defined by the local doctor" (Health professional, Group 4). The ability to use the definition in the context of clinical care and in trials was suggested to align outcome ascertainment based upon clinical diagnosis and by trial outcome adjudicators, "It turns out only about two-thirds to three-quarters of what the investigators reporting as an MI is finally adjudicated positively as an MI … you're limited in your data that you get in a clinical trial setting, because often times heart attacks are happening in the hospital. The

investigator's not there, and you're limited by the data that you're getting" (Health professional, Group 4).

**Selecting a meaningful metric for decision-making**

Comprehensible and meaningful to patients: The core outcome for CVD had to be simple and readily understood by patients so that it could inform decision-making, "I wonder whether the definition of 'heart attack' to a patient is different as well, whether any condition involving the heart, including sudden cardiac death that we define differently, could mean heart attack for patients" (Health professional, Group 1). "The simpler you can make it for the average patient the better, because remember when you're giving them information, the vast majority of them are being overwhelmed by the process itself" (Health professional, Group 2). Making it simple "would be a great way of, you know, getting the patients' attention, in language we understand" (Patient/caregiver, Group 1). Patients and caregivers wanted to be told the specific risks of CVD, "I'd rather know the numbers and know the facts so that I can do my best to prevent that [*myocardial infarction]* from happening to me." (Patient/caregiver, Group 2). However, using risk as a metric did not always help the individual,"a group risk does not mean that you, as an individual, are going to have that, statistically" (Group 2, Patient). Some suggested providing information in a visual format and to "use numbers, not percentages when describing anything" (Patient/caregiver, Group 6) and "you should always be grounded in the absolute [*risk*]" (Patient/caregiver, Group 6). Personalising cardiovascular risk was important to patients, "there's ways of putting it that you give that information, and yet you're actually personalising it as well" (Patient/caregiver, Group 2).

Distinguishing severity and recurrence: The outcome measure for CVD needed to capture the severity of an event, mainly in terms of its clinical consequences and impact on quality of life, "you could have someone who has a very large MI and develops heart failure and other complications,

arrhythmias, and then you can have another patient who meets the criteria but just squeaks by and doesn't have a lot in terms of effects, in terms of quality of life, and in terms of function" (Health professional, Group 5). The outcome measure should capture severity by defining a clear threshold after which the event fulfils the definition. "If we want to assess severity at the same time, it has to have some sort of a consequence, either needing an intervention or needing hospitalisation" (Health professional, Group 5) and trialists may want to add this outcome to the core outcome. The recurrence of events also had to be considered – "it matters to people if they had one heart attack or three" (Group 6), though the same definition could be used by trialists to capture recurrence.

Comparability across trials: A single metric would facilitate ease of comparison across trials and patients considered this to be patent, "wouldn't it be better to have something that we could compare?" (Patient/caregiver, Group 2). Some particular metrics may lead to further inconsistencies. For example, CVD-related hospitalisation would lead to undue variability across trials because "hospitalisation is region-dependent, in some regions patients are going to be hospitalised earlier than in other regions" (Health professional, Group 5). Using a time-to-event metric may be simpler and would mean that "you could still infer your proportion of events. You could extract whatever other metric you want" (Health professional, Group 2), however this would miss subsequent events. Ultimately the metric should facilitate collection of a minimum dataset with minimal flexibility because "if we say leave it to trialists, we'll just get the same mess we've got now" (Health professional, Group 2).

**Enabling and incentivising implementation**

Integration into registries: Recognising the growing interest in conducting registry-based trials to increase efficiency and reduce the burden to trialists, the core outcome measure had to be applicable and feasibly integrated in registries across healthcare contexts - "to do more efficient trials....to

build your outcome measures so they can be used across borders as in across different healthcare systems" (Health professional, Group 4).

Incorporating into clinical care: The definition for the core CVD outcome had to be readily embedded into routine clinical care, "definitions for MI which we could standardise in administrative data sets" (Health professional/regulatory body, Group 6) then "if this was adopted by regulators or registry trials, ....healthcare systems or registry systems could participate, and may actually have an incentive to be competitive and implement [*the definition]* into the clinical, everyday care setting" (Health professional, Group 6).

Seeking authoritative endorsement: Buy-in and endorsement by journals and guidelines would support implementation of the core outcome measure for CVD, incorporating them into trial reporting guidelines "just as journal editors now require a CONSORT diagram, perhaps we could convince the journal editors that using standard definitions is also going to be important to be published in that particular journal" (Health professional Group 5). It also requires uptake by those involved in trial design, "bring in some of the thought leaders that design these trials, you need to bring in the regulatory agencies. They all need to come together and hash it out, and comment on the feasibility of doing this and the appropriateness of doing this. If you don't have the buy-in from those who are designing the trials, you don't have the buy-in in the regulatory agencies, it's not going to happen" (Health professional, Group 4). They questioned, "how much is [*the core outcome measure to be used as*] a guideline, how much is it something we aspire to, and how much is going to be mandated?" (Health professional, Group 6), and some contended that the measure should be compulsory to ensure uptake, "prescriptive is usually the best vehicle towards implementing and making change happen" (Health professional, Group 6). They suggested to: "[*make*] it be part of the requirements for FDA approval, that trials have actually measured these core outcomes?"(Health Professional, Group 5). They thought it would be similar to implementing "mandatory trial

registration, everybody was like, 'Ugh, this is horrible. It's so much extra work,' and now we don't think twice. We just do it." (Health professional, Group 6) Alternatively an "opt in" system could be considered, "maybe provide a checklist that investigators have to [*fill in*]" (Health professional, Group 5).

Requiring cardiology input and buy in: Cardiologists needed to be integrally involved in the development of the core outcome measure for CVD in haemodialysis to support implementation – "it's of great value to have an expert group of cardiologists look at these things (Health professional, Group 4) so the measure would be "accepted into the cardiology community" (Health professional, Group 1). The involvement of cardiologists would facilitate acceptance and ensure that both nephrology- and cardiology-led trials could be effectively compared and would be relevant to the haemodialysis population, "It would be very difficult to extrapolate anything if we don't have a common language with the cardiologists" (Health professional, Group 1).

## DISCUSSION

The Consensus workshop attendees agreed that myocardial infarction and sudden cardiac death are important CVD outcomes to report in all trials in hemodialysis and provides considerations on their rationalisation and implementation. CVD outcomes such as heart failure and stroke were recognised as important but consensus was achieved for myocardial infarction and sudden cardiac death for a number of patient-centred, clinical and pragmatic reasons. They are of high importance to patients and health professionals, and there is an increased risk in, and are of specific relevance to, patients on haemodialysis. Myocardial infarction is particularly relevant because it is associated with high mortality, functioning, quality of life, and had long-term health and psychosocial consequences in patients on haemodialysis.

Health professionals' comments focussed on severity and impact of an event as well as practical measures for implementation. Health professionals noted that heart failure may not be feasible as a *core* CVD outcome because of the difficulties in diagnosing heart failure in the hemodialysis population. They also stated that heart failure is often secondary to ischaemic heart disease, and thus the potential inclusion of MI as a core CVD outcome was regarded a reasonable decision. Similarly stroke, would not be a simple outcome (due to the extensive investigations required to accurately diagnose) to adjudicate in people on haemodialysis.

Patients and caregivers comments reflected a need for the core outcome to be be "user friendly", this applied to the outcome as well as the metric. This will enable the consumer to easily interpret the results of trials and make comparisons between interventions.

Composite outcomes are frequently used in cardiovascular trials, because they can minimise resources and increase power in a trial. However, they should not be used as core outcomes because of the challenges they pose for interpretation of the findings. Even the frequently used composite endpoint "Major adverse cardiovascular events (MACE)" demonstrates substantial heterogeneity in the study-specific individual outcomes used to define MACE, with substantially different results and conclusions across trials [30]. A recent systematic review found similar heterogeneity across other CVD composite endpoints used in trials in haemodialysis [11]. The CVD core outcomes should be simple and the data for the outcomes should be able to be collected in all trials in haemodialysis regardless of the intervention. Using well-defined individual CVD outcomes would therefore be preferable to a composite when selecting core outcomes for CVD in trials in haemodialysis.

As recognised by the workshop attendees, defining the core outcomes would be difficult given that current definitions for CVD outcomes in the general population could not be readily extrapolated and applied in patients on haemodialysis. This is because of the variability in clinical presentation of CVD, uncertainty in the clinical utility of CVD biomarkers, and problems with the interpretation of diagnostic tests in the haemodialysis population.

Myocardial infarction and sudden cardiac death are not only frequent events in HD, these outcomes have specific relevance to the haemodialysis population. Patients on dialysis are more likely to die during hospitalisation for acute MI than patients with normal kidney function [31] and one year mortality following acute myocardial infarction approaches 60% in patients with ESKD [32] compared to less than 10% in the general population [33,34]. Sudden cardiac death accounts for nearly 30% of all-cause mortality in prevalent haemodialysis patients and around 35% of all-cause mortality in patients initiating dialysis [2,35]. The annual risk of sudden cardiac death is almost three-fold higher in haemodialysis patients (5-7%) compared to the general population (1.5-2.7%) [36].

There are several challenges in defining myocardial infarction and sudden cardiac death for the haemodialysis population. The current components of the Fourth Universal definition of myocardial infarction includes symptoms, biomarker increments and ECG changes[37]. These may not always apply to people on haemodialysis because chest pain is not always present in patients on haemodialysis and troponin levels can be raised at baseline and altered by haemodialysis. A specialist group will be convened to determine how the Fourth Universal definition can be used or adapted in the haemodialysis population.

The heterogeneity in the events ascribed to sudden cardiac death, particularly in the haemodialysis population, also poses a major challenge. The practicality of collecting these data is also problematic often because of variations in how cause of death is recorded in different countries. The recent Kidney Disease: Improving Global Outcomes (KDIGO) Controversies Conference on Chronic kidney disease and arrhythmias similarly highlighted the need to refine the definitions of sudden cardiac death in ESKD patients, emphasising the unexpected nature of sudden death to avoid misclassifications. This international group have proposed definitions of sudden death, sudden cardiac death, and aborted cardiac arrest pertinent for ESKD patients [36]. Our future work

will focus on how the definition of sudden cardiac death might be utilised as the core outcome measure and best implemented into clinical trials.

Both outcome measures require a meaningful and simple metric to allow comparability across trials. Implementation of core outcomes for CVD in haemodialysis trials would require input from cardiologists and support from registries, guidelines, journals; and should be feasibly implemented in routine clinical practice.

The consensus workshop was conducted in English and therefore potentially limited input from non-English speaking participants. However, representatives from 15 countries, both developed and developing, attended the workshop which we hope does make our work more generalisable. A further limitation is that only two nurses (both of whom had other primary roles as patient or caregivers) no other allied health professionals, and only two participants from regulatory bodies, attended this workshop..

Recommendations from the workshop are summarised in Box 2. To address the challenges in the measurement of the core outcomes *myocardial infarction* and *sudden cardiac death,* an expert working group will be convened to derive universally agreed upon definitions for use in the haemodialysis population. These definitions will need to be globally feasible and of minimal burden to implement in trials. Making these definitions as pragmatic as possible will support implementation. These measures will need to be assessed based upon the Core Outcome Measures in Effectiveness Trials (COMET) criteria including content and structural validity, responsiveness and measurement error [38] and then validated by using them as outcome measures in historical trials to ensure they are fit for purpose. The ability to accurately compare data across trials using core CVD outcomes will optimise shared decision making and likely contribute to improved cardiovascular morbidity and mortality in this very high risk population.

## Article Information


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**Figure Legends**

**Figure 1.** Summary of theme derived from the Consensus workshop

HD-haemodialysis, ESKD – end stage kidney disease

**Box 1 Illustrative quotations**

| Theme | Quotation |
|---|---|
| **Capturing specific relevance to the haemodialysis population** | |
| Prevalence, risk and severity of the cardiovascular outcome | I'm okay with the fact that it's the most frequently measured, but I'm not okay with the fact that probably it's not really the most relevant. (Group 1, health professional)<br>There is a difference between importance versus frequency. Something that is most frequent may not be considered the most important. (Group 3, health professional)<br>From a public health standpoint in dialysis patients, what's more prevalent or what's more disabling? (Group 4, health professional)<br>My understanding is that pretty much every dialysis run damages the cardiovascular system (Patient/caregiver, Group 1) |
| Complex symptomology and diagnosis | Sudden cardiac death in someone who is on dialysis, if you were to use the general population term, probably you would think this is a myocardial infarction death. When in actual fact you realise in the years that pass that actually a very large proportion may not be myocardial infarction. The nomenclature is very difficult. (Group 3, health professional)<br>Heart failure is very difficult to define in the dialysis population. The question that many adjudication committees have is, is it patient heart failure, or is it simply that the patient is at the incorrect dry weight, or the patient has missed a dialysis treatment, and that's why their fluid overloaded (Group 5, health professional)<br>I don't think a lot of patients do know what a heart attack is, because you… you get them in different ways and different forms. You can get them by chest pain, certain back pains, your arms, whatever. (Group 6, patient) |
| Considering consequences on quality of life | You have that longevity with stroke disability, with heart failure disability. It impacts every single aspect of life. I guess that's where I was coming from and I agree with you with the stroke. It's devastating, it's catastrophic. (Group 2, patient) |
| Accounting for geographic variation | Different cultures may present, say their symptoms differently. (Group 3, health professional)<br>In Japan, strokes are a lot more common than in other parts. (Group 4, health professional)<br>What you can also have is that the hospitalisation is region-dependent, because in some regions, patients are going to be hospitalised earlier than in other regions. (Group 5, health professional)<br>Then they'll agree with the decision and be consistent across the world, worldwide. Nobody will argue the patient over in Germany had a bypass, had a heart attack, or in the United States, a bypass is a bypass. But just mild elevation in troponin, how much, one, two, three, which has high degree of heterogeneity in this population. (Group 5, health professional) |
| Having potential for intervention | Whatever we do, does it prevent or improve the outcome with MI? (Group 1, health professional)<br>I find heart failure to be the outcome that is not only most applicable, but most potentially modifiable when we do interventional trials. (Group 5, health professional) |

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| | MIs, heart attacks are clearly important. My concern is that by reporting them in every trial, they're so poorly modifiable that it's not going to get us where we want to go in terms of getting better, patients better at the end of the day. Heart failure to me is a better outcome measure. (Group 5, health professional) |
| **Dilemmas in using composite outcomes** | |
| Obfuscation and misinterpretation of findings | Having a composite outcome would be very complex. (Group 4, health professional)<br>It would be great if everybody used the same definition of MACE and MACE-plus, so that as complicated as defining heart failure is, if we all used the same one, even imperfect, at least we could compare results. (Group 6, health professional)<br>Lots of reasons why composite outcomes are potentially bad to put up there, but there's a whole series of reasons why they could be really important. (Group 4, health professional) |
| Benefits to trialists | Not only do you have a regulatory issue in terms of the need for composite, but also most dialysis trials other than some of the very large pharmaceutical trials are not powered to look at this, so you have to have a composite outcome in order to have statistical significance with a smaller sample size. (Group 5, health professional)<br>Regulatory agency demanding a composite endpoint that includes death, all-cause death, MI, and stroke. As much as we might not want to encourage the use of a composite endpoint, the reality is regulatory agencies, that's exactly what they demand. (Group 5, health professional)<br>Maybe SONG should consider acknowledging this composite is going to happen, and trying to put some sort of, maybe we all should use the same definitions for the composite. (Group 5, health professional) |
| **Addressing challenges in outcome definitions** | |
| Consistency, applicability and specificity of definitions | We have an issue of whether or not the definition needs to be modified in the dialysis patient, who may have a slightly elevated troponin level. To get to your point in terms of the biomarkers, one of the questions we'll need to discuss is whether or not the definition is cardiac biomarker as one of the choices, but not a required choice. (Group 5, health professional)<br>There's a strength in a gold standard if you will, that is internationally accepted. Rather than reinventing the wheel and defining this from scratch which may take decades. (Group 6, health professional/regulatory body)<br>The so-called validating, making sure that that universal definition, which was never developed in the dialysis patient, is actually applicable to it. Because the danger is, let's adopt it, and then find out that it actually doesn't work that way. (Group 6, health professional) |
| Recognising variability in symptoms | It's expected that men are more likely to have cardiac disease than women, and so symptoms are interpreted differently. (Group 3, health professional)<br>Patients who do come in with MI who are on dialysis often don't have classical symptoms of angina. Chest pain, no numbness, all of the classical symptoms we see in non-dialysis patients are not there. (Group 1, health professional)<br>Because in our population, a lot of the heart attacks are actually silent, so actually it's quite different from the general heart attack that we see in the usual population. Most patients may manifest heart failure rather than classical heart attack symptoms or chest pain. That is one important consideration when you diagnose a heart attack in a classical way where you need to have the symptoms, chest pain. (Group 4, health professional) |

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| Uncertainty in the clinical utility of biomarkers specific to haemodialysis | In terms of this description, it says 'detect a rise of one' but maybe we're going to have to consider doing two, right. The delta is probably more important than the absolute level, right. (Group 1, health professional)<br>We're trying to define thresholds based on level of kidney function in CKD and potentially dialysis, but the problem is that it's not measured in a lot of dialysis patients, but we are trying to come up with absolute thresholds. (Group 1, health professional)<br>The problem with looking for change is that it involves time, but what we don't want is time to pass. You want patients with an MI to get to cardiology as quickly as possible. (Group 1, health professional) |
| Clarity for adjudication | It turns out you're limited in your data that you get in a clinical trial setting, because heart attacks are happening in the hospital. The investigator's not there, and you're limited by the data that you're getting. (Group 4, health professional)<br>It turns out only about two-thirds to three-quarters of what the investigators reporting as an MI is finally adjudicated positively as an MI. I think it's important to bear that in mind, how we're adjudicating. (Group 4, health professional)<br>Frankly the definition comes a bit too late. It's already been defined by the local doctor. (Group 4, health professional) |
| **Selecting a meaningful metric for decision-making** | |
| Comprehensible and meaningful to patients | There's ways of putting it that you give that information, and yet you're actually personalising it as well. (Group 2, patient)<br>Typically on dialysis we expect five episodes per ten years, whatever it is, one episode per ten years. With the treatment we could reduce that to one every thirteen years or fourteen years, so you get an idea of the magnitude of the difference. (Group 2, health professional)<br>Express it to me where, in my terms, where I can understand it. Don't come and tell me in doctors' terms. No, because I'm not a physician. Break it down and tell me. (Group 6, patient)<br>[Making it simple] "would be a great way of, you know, getting the patients' attention, in language we understand" (Patient/caregiver, Group 1). |
| Distinguishing severity and recurrence | This is a difficult question because you could have someone who has a very large MI and develops heart failure and other complications, arrhythmias, and then you can have another patient who meets the criteria but just squeaks by and doesn't have a lot in terms of effects, in terms of quality of life, and in terms of function. (Group 5, health professional)<br>If we want to assess severity at the same time, it has to have some sort of a consequence. Either needing an intervention or needing hospitalization (Group 5, health professional)<br>It would be really challenging to incorporate a severity measure in standardised reporting. One option would be why not ask that they record both? (Group 5, health professional)<br>A group risk does not mean that you, as an individual, are going to have that, statistically so (Group 2, Patient) |
| Comparability across trials | Wouldn't it be better to have something that we could compare? (Group 2, patient)<br>We also want to be able to compare to other fields and it's important that we have consistency. (Group 4, health professional) |

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| | We want to be able to pool trials together to really get more from the evidence than any single trial. I totally agree with that. (Group 6, health professional)<br>If we say leave it (*choosing a metric)* to trialists, we'll just get the same mess we've got now. (Group 2, health professional) |
| **Enabling and incentivising implementation** | |
| Integration into registries | If you're requiring the full list of troponins and ECGs, that's a big burden and that would strike out a lot of trials, let's say registry-based trials, trials that are not in the position where they can get that level of detail. (Group 6, health professional)<br>What's going to be considered acceptable as an outcome? How high do you have to set the bar for evidence to be acceptable at the FDA? (Group 4, health professional) |
| Incorporating into clinical care | If for example this were adopted by regulators or registrational trials, although it can never match in a registration trial being a registry trial, but still. Let's assume that they do so, then actually healthcare systems or registry systems participate, may actually have an incentive to be competitive to implement that in the clinical, everyday care setting. (Group 6, health professional)<br>Definitions for MI we could standardize in administrative data sets, so it might be an opportunity for more of that. (Group 6, health professional/regulatory body) |
| Seeking authoritative endorsement | Should it be part of the requirements for FDA approval, that trials have actually measured these core outcomes? (Group 5, health professional)<br>How much is it a guideline, how much is it something we aspire to, and how much is going to be mandated. That's an important issue. (Group 6, health professional)<br>Being prescriptive is usually the best vehicle towards implementing and making change happen. An example that was mentioned earlier was mandatory trial registration at the time when clinical trials registration became mandatory, everybody was like, 'Ugh, this is horrible. It's so much extra work,' and now we don't think twice. We just do it. (Group 6, health professional) |
| Requiring cardiology input and buy in | We should bring all the stakeholders to the table. You need to bring the cardiologists to the table, you need to bring not only the MI, but the heart failure and whatever else is going to be in the composite. You need to bring in some of the thought leaders that design these trials, you need to bring in the regulatory agencies. They all need to come together and hash it out, and comment on the feasibility of doing this and the appropriateness of doing this. Because if you don't have the buy-in from those who are designing the trials, you don't have the buy-in in the regulatory agencies, it's not going to happen. (Group 5, health professional)<br>Approach the cardiologists and maybe to become a stakeholder in the process [*of writing the next Universal Definition]*, and make sure that the kidney perspective gets heard and potentially implemented in future iterations of it. (Group 6, health professional)<br>It's of great value to have an expert group of cardiologists look at these things, because even they tend to disagree sometimes, and at least what you have finally is a consensus opinion. (Group 4, health professional) |

Abbreviations: CKD – chronic kidney disease; ECG – electrocardiogram; FDA – Food and Drug Administration.

**Box 2. Recommendations from the Consensus Workshop on selecting, defining and implementing a core outcome measure for cardiovascular disease in trials in haemodialysis**

**Selecting a core CVD outcome**

1. Myocardial infarction (MI) as the core outcome measure for cardiovascular **disease**
2. Sudden cardiac death (SCD) as the core outcome measure for cardiovascular **death**.

Reasons

- High prevalence in the haemodialysis population
- Direct consequences on quality of life, function and long term-outcomes
- Feasible to be measured across countries
- Potential to be modified by intervention
- Individual CVD outcome for transparency and accurate interpretation (not a composite outcome)

**Developing a core outcome measure**

- Requires consideration of the complex symptomology and diagnosis
- Establish a consistent, standardised definition (may need to be adapted for the haemodialysis population due to different symptomatology and diagnostic criteria)
- Consider variability in symptoms (e.g. myocardial infarctions may be "silent")
- Recognize limitations in the clinical utility of biomarkers specific to haemodialysis
- Definition to be used in the context of routine clinical care and trials
- Needs to be meaningful and comprehensible to patients

**Implementation of a core outcome measure**

- Integrate into registries and routine clinical care
- Obtain endorsement by journals, guidelines, regulatory agencies
- Ensure joint development with cardiologists