Global Action. Local Change.

KDIGO Controversies Conference on

Challenges in the Conduct of Clinical Trials in Nephrology

September 8-11, 2016

Paris, France

Kidney Disease: Improving Global Outcomes (KDIGO) is an international organization whose mission is to improve the care and outcomes of kidney disease patients worldwide by promoting coordination, collaboration, and integration of initiatives to develop and implement clinical practice guidelines. Periodically, KDIGO hosts conferences on topics of importance to patients with kidney disease. These conferences are designed to review the state of the art on a focused subject and to ask conference participants to determine what needs to be done in this area to improve patient care and outcomes. Sometimes the recommendations from these conferences lead to KDIGO guideline efforts and other times they highlight areas for which additional research is needed to produce evidence that might lead to guidelines in the future.

Background

Chronic kidney disease (CKD) affects approximately 10% of adults worldwide. Compared to those without kidney disease, CKD patients have a substantially increased risk of morbidity and mortality from progressive kidney and cardiovascular disease. Worldwide, the population burden of CKD, and particularly of CKD requiring dialysis and transplantation, is rising. Two of the key drivers are the global epidemic of obesity and associated diabetes and the increasing average age in many populations. The care of

patients with CKD is costly, accounting for over a fifth of Medicare expenditure in 2012(1), yet despite the enormous cost of CKD there is remarkably little reliable information from adequately powered randomized trials to guide treatment. Indeed, the effectiveness and safety of many of the treatments used in the routine care of the patients with CKD are uncertain.(2) This conference aims to discuss current barriers to high-quality trials and to propose how future randomized trials can be improved.

Relevance of the topic and the conference

One of the key issues in understanding the challenges of clinical trials in nephrology is that CKD is an umbrella term for a heterogeneous group of conditions. CKD results from a large number of etiologically distinct diseases (e.g., diabetes, autoimmune-related, hereditary, obstructive) and is managed in a wide range of settings (e.g., primary care and general or specialist hospitals) with a range of treatment modalities (e.g., drug treatment, renal replacement therapy, procedural interventions, dietary interventions, psychological support). Moreover, as well as seeking to prevent or delay the progressive loss of glomerular function (e.g., often through manipulation of the renin-angiotensin system), treatments may aim to prevent or treat comorbidity that is associated with impaired renal function (e.g., cardiovascular disease, anemia, mineral bone disease, and infection) or treat the underlying condition that caused CKD in a particular patient (e.g., diabetes and systemic autoimmune conditions).

For these reasons, any attempt to identify themes that are common to randomized trials in nephrology will need to include a wide ranging discussion among those involved in their design, execution and interpretation. Therefore, to increase the chances of

success, this conference will include among its invited participants representation from various clinical medicine disciplines (e.g., nephrologists, transplant surgeons, diabetologists, cardiologists, pediatricians), epidemiologists and statisticians, trial coordinators, research nursing staff, and representatives from industry, regulators and the patient community. The aim of the conference is not to generate specific recommendations for particular kidney diseases (though these might be implicit in some cases), but instead to identify the barriers common to the design and conduct of the types of trials that are being planned, or likely to be planned, in patients with CKD. Some such barriers (e.g., treatment adherence) are likely to be common to most randomized trials, while other barriers (e.g., disease rarity) may be encountered particularly frequently in nephrology. The conference will discuss examples and look for solutions that might be considered for future trials in nephrology.

Conference Overview

The objective of this KDIGO conference is to gather a global panel of multi-disciplinary clinical and scientific expertise that will identify key issues relevant to design and conduct of clinical trials in nephrology and to suggest how future randomized trials can be improved.

Drs. Colin Baigent (University of Oxford, UK) and John McMurray (University of Glasgow, UK) will co-chair this conference. The format of the conference will involve topical plenary session presentations followed by focused discussion groups that will report back to the full group to build consensus.

The **Appendix: Scope of Coverage** section details the key issues, invited speakers and discussion group topics. The conference output will include publication of a position statement on future nephrology trial design and conduct.

References

1. Collins, A.J.F.; Foley R.N.; Herzog, C; et al. US Renal Data System 2012 annual data report. American journal of kidney diseases. 2013; 61(1 (Suppl 1)):A7, e1-e476.
2. Inrig J.K.C.; Califf R.M.; Tasneem, A.;et al. The Landscape of Clinical Trials in Nephrology: A Systematic Review of ClinicalTrials.gov. American journal of kidney diseases. 2014;63(5):771-80.

Appendix: Scope of Coverage

Overview and objectives

There have been notable nephrology trial successes, but the amount of reliable information available to guide patient care for commonly used treatments in nephrology is limited.

There are several features in the nephrology specialty which may predispose to this situation, including the difficulty in identifying large numbers of patients with often rare diseases, slow disease progression, poorly defined outcomes, low medication compliance, and treatments which may be less effective than in other populations. Consequently hard outcome trials in nephrology may need to be somewhat larger than is often appreciated. Since large trials are challenging and expensive to conduct, many treatments are assessed in small trials, which may not be able to detect treatments with moderate (but still worthwhile) effects. There is an urgent need for a discussion about how we can optimize trial methods in nephrology.

Plenary session 1: Reflections on trials in nephrology: Past successes and future challenges

Speaker: Jonathan Craig

This talk will provide context for the subject of the conference and consider the specialty's past experience of randomized trials, reflect on some of the lessons that have emerged, and suggest how the renal community (including patients) can become more active in seeking evidence from randomized trials.

Plenary session 2: Defining optimal outcomes in trials assessing kidney disease progression

Speaker: Lesley Inker

This talk will consider key issues when designing trials to assess effects on kidney disease progression, in particular the search for appropriate eGFR-based surrogates for end-stage renal disease to allow the timely emergence of evidence about new treatments (this will include the outcome of work performed in collaboration with the FDA).

Plenary session 2: Defining appropriate non-renal outcomes in renal trials

Speaker: Michael Walsh

This talk will consider how major non-renal outcomes (including cardiovascular outcomes) might be chosen when designing trials. It will include a discussion of the sensitivity of outcomes for measuring an impact on the target disease; composite outcomes (including a discussion about appropriate components); and surrogate outcomes.

Plenary session 3: Optimizing trial design

Speaker: Martin Landray

This talk will cover the question of how to improve the quality of trials in nephrology, beginning with the precept that quality is the absence of errors that matter to decision-making. In trials, random errors are avoided by adequate sample size and systematic errors are avoided by proper randomization, appropriate follow-up and unbiased ascertainment and analyses of study outcomes. Each of these elements will be considered, and some general lessons for the design of future renal trials will be proposed.

Plenary session 3: Optimizing trial execution

Speaker: Vlado Perkovic

Trials in renal populations present particular challenges because of the limited size of the target population in any single center (and hence the need for large international collaborations), poly-pharmacy and hence often poor adherence, and the greater potential for drug toxicity. This talk will review some of the lessons of recent years on how to improve trial execution while limiting costs, including the increasing interest in electronic health records for recording outcomes.

Plenary session 4: Lessons learned from recent trials: Case studies

Speaker: Reshma Kewalramani

The presenter will draw on her experience in Amgen working on a range of large trials in nephrological populations to identify some common themes and lessons from the perspective of a large pharmaceutical company.

Plenary session 4: Lessons learned from recent studies in dialysis units: Case studies

Speaker: Frank Maddux

Dr. Maddux is the Chief Medical Officer of Fresenius Medical Care North America. He will review the lessons learned using examples of studies that Fresenius Medical Care have conducted, reflecting on the challenges the community faces in conducting clinical trials in nephrology, the use of large observational data sets and collaborative research models. He will also introduce the breadth of data captured and utilized by Fresenius Medical Care worldwide and suggest techniques where such data might be used to increase efficiency in clinical trial conduct.

Plenary session 4: Interpreting clinical trials in nephrology: A regulator's perspective

Speaker: Romaldas Mačiulaitis

Drawing on experiences working with the European Medicines Agency, the issues regulators have faced during last 5 years while working on the design and interpretation of clinical trials in nephrology will be presented. Areas where consensus between academia and industry are still required will also be highlighted.

Breakout Group A: Renal Outcomes including CKD Progression
Group Leaders: Joe Coresh, Peter Rossing

Breakout group A will discuss the challenges raised in the plenary session on "Defining optimal outcomes in trials assessing renal disease progression." Discussion topics will include:

1. Is there now consensus on the optimum outcome for CKD progression trials and how it should be assessed?
2. Is there consensus on how to measure change in GFR efficiently during trial follow-up (e.g., slopes)?
3. Under what circumstances is directly measured glomerular filtration rate necessary?
4. Under what circumstances could albuminuria be accepted as a marker of CKD progression?
5. Is there consensus on the most appropriate surrogate outcomes for specific renal conditions:
    a. Glomerulonephritides
    b. Polycystic kidney disease
    c. Transplantation
    d. Acute kidney injury prevention and treatment

Breakout Group B: Non-Renal Outcomes in Nephrology Trials
Group Leaders: Michael Walsh, Vlado Perkovic

Breakout group B will discuss the challenges raised in the plenary session on "Defining appropriate non-renal outcomes in renal trials" with particular attention to cardiovascular outcomes. Discussion topics will include:

1. What is the appropriate process for choosing endpoints (e.g., what components of what composites? Should we use cardio-renal composite outcomes?), and how should effects on mortality be assessed (cardiovascular versus non-cardiovascular)?
2. What is the role of surrogate outcomes?
3. How can we ensure that outcomes important to patients are measured and do these include patient reported outcome measures?
4. Is there consensus on the key outcomes for:
    a. Anemia trials?
    b. Vascular access trials?
    c. Safety (i.e., toxicity and adverse events including bleeding and infection)?
    d. Mineral-bone disease trials?
5. Can we record information in trials to assist in assessment of health economic impact of a particular treatment?

Breakout Group C: Optimizing Trial Design
Group Leaders: Martin Landray, Marc Pfeffer

Breakout group C will discuss the challenges raised in the plenary session on 'Optimizing trial design'. Discussion topics will include:

1. What is the optimum choice of trial population?
    a. Key inclusion criteria (e.g., relevant disease, possibility of benefit from intervention; narrow vs broad population; special groups or regions)
    b. Key exclusion criteria (i.e., based on safety or other issues)
2. What are the key issues when selecting active & comparator treatments (e.g., dose selection, placebo, blinding, factorial designs)?
3. Why are "run-in" periods important in renal trials and what is their optimal duration?
4. What are the principles behind selection of trial endpoints (i.e., what to include in primary, key secondary and safety endpoints; and the use of composite outcomes)?
5. How should sample size calculations be done to minimize risk of false negative trials, including:
    a. Estimating a realistic event rate
    b. Estimating a realistic treatment effect
    c. Determining follow-up duration
    d. Estimating the impact of non-adherence, incomplete follow-up or missing data?
6. What types of statistical analyses are the most robust, including:
    a. Intention-to-treat principles
    b. Appropriate and inappropriate subgroup analyses and their interpretation?

Breakout Group D: Optimizing Trial Conduct
Group Leaders: Adeera Levin, Christoph Wanner

Breakout Group D will discuss the challenges raised in the plenary session on 'Optimizing trial conduct'. Discussion topics will include:

1. What is the optimum method to identify potential participants? Can disease registries and other electronic healthcare records be used for identifying and inviting patients to participate in randomized trials, and recording patient outcomes?
2. What are the opportunities to improve both data quality and streamline its collection (including laboratory analyses)?
3. How can the model of trials be changed so large numbers are recruited per study center?
4. How can the common problem of loss of treatment adherence (i.e., drop-out and drop-in) and loss to follow-up be tackled?
5. How might trial monitoring procedures be made more efficient (e.g., statistical monitoring)?
6. How can safety reporting/pharmacovigilance be streamlined?
7. How should adjudication be more focused and streamlined?