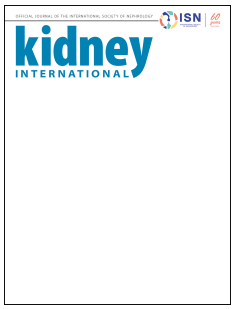

The International Society of Nephrology Advancing Clinical Trials (ISN-ACT) Network: current activities and future goals

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Title: The International Society of Nephrology Advancing Clinical Trials (ISN-ACT) Network: current activities and future goals

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Cardiovascular disease, chronic kidney disease, diabetes, education, phosphate binders

Introduction

The value of randomized trials as the optimal method for determining the benefits of healthcare interventions in clinical practice has been highlighted repeatedly during the current COVID-19 pandemic. Despite being considered an 'academic specialty', nephrology lags behind its internal medicine counterparts in the conduct of high-quality clinical trials. As a result, many of the treatments used in routine nephrology care (e.g. phosphate binders) remain poorly supported by evidence from randomized trials.

The International Society of Nephrology (ISN) established the Advancing Clinical Trials (ISN-ACT) initiative in 2013 to expand the scope and number of high-quality clinical trials in nephrology in order to fill some of the knowledge gaps. In this article, we describe the evolution of ISN-ACT, highlight its current activities, and outline its future goals.

Aims and objectives of ISN-ACT

ISN-ACT was established to serve two main purposes: firstly to ensure independent and industry investigators have access to timely and unbiased expert advice; and secondly to facilitate the development and execution of high-quality clinical trials within in an ethical framework, with a particular focus on promoting and expanding capacity for clinical trials in developing countries[1]. Membership of ISN-ACT is open to all ISN members, regardless of profession, career stage, or region of practice, and applications to join can be made quickly online (https://theisn-community.force.com/Join/s/act). Led by a core committee, ISN-ACT currently has 304 members ~~from~~ all ISN regions and we actively encourage anyone interested in ~~the~~ undertaking ~~of~~ clinical trials in nephrology to join this network. By sustainably connecting the international nephrology community, our ultimate aim is that clinical trials become part of the ethos of the specialty.

ISN-ACT activities

ISN-ACT undertakes activities focused on 4 distinct working groups (**Table 1**).

1. *Trial toolkit development working group*

With some exceptions, most trials in nephrology are relatively small and many have methodological shortcomings[4]. ISN-ACT recognizes, however, the challenges involved in developing, or even simply participating in, a clinical trial, particularly in settings where research infrastructure or experience might be limited. To meet this need, ISN-ACT developed an accessible and evolving clinical trial toolkit. This educational and reference resource provides detailed information about all aspects of clinical trial design and conduct, with the aim of supporting both new and experienced investigators and institutions wishing to start a clinical trial or to participate as a trial site. The toolkit was launched in April 2020 and is openly accessible online (https://www.theisn.org/isn-act-toolkit). The key components of the toolkit are outlined in **Table 2**.

2. *Patient engagement in kidney research working group*

Historically, clinical trials have been designed and led by clinicians with limited involvement of patients and hence research questions that are important to patients may not be answered. This ISN-ACT working group recognizes the importance and challenges of expanding meaningful patient involvement in all stages of renal research. To understand the existing nature of patient involvement in clinical research globally, the working group conducted an international survey, which highlighted the absence of formal mechanisms for patient involvement in most regional ISN boards and the requirement to unify processes to improve patient involvement in clinical trials across ISN regions[2]. The development of tools and platforms that are sensitive to culture and language differences is a challenge that will be tackled regionally, and shared to enhance interactions with patients in all countries in clinical trials.

3. *Capacity building and clinical trial networks working group*

Trials are frequently conducted in a single or relatively small number of countries. There is limited capacity in the kidney community to develop or

perform large randomized trials on a global scale, with many regions of the world being underrepresented in randomized populations[5]. The overarching objective of the ISN-ACT Capacity Building working group is to improve the connections, skills, abilities, and resources of interested healthcare providers to design and conduct randomized controlled trials at the local, national and international level. Having assessed facilitators and barriers to participation in clinical trials, the Capacity Building working group aims to increase networking opportunities to enable the conduct of trials in kidney disease. Initiatives include: 1) hosting round-table events with investigators conducting or planning trials, allowing them the chance to provide a brief overview of their trial followed by multi-stakeholder feedback; 2) developing of an online curriculum on clinical trials in order to expand the global network of clinicians versed in trial design and conduct; and 3) supporting the development of an international network of clinical trial investigators.

4. Trial design working group

The Trial Design working group aims to identify and foster trial designs that promote the successful conduct of trials generating evidence for people with kidney disease. Identified barriers include the lack of global clinical trial networks, high costs, the relatively low incidence of some diseases or small accessible patient populations, the lack of appropriately validated biomarkers, and the inefficiencies of recurrently re-establishing trial infrastructure. Trial designs and infrastructures that address these barriers would find more efficient ways to connect interested patients with trials. They would deliver robust evidence while minimizing required sample size and maximizing trial efficiency. The working group identified the value of creating enduring platform structures to support trials by generating efficiencies, minimizing site workload and allowing sites, sponsors and patients some predictability for activity. These structures could, for example, involve the creation of a large network of ‘trial ready’ patients who could then be quickly offered relevant trials as they became available. Moreover, the group also identified value in multi-arm, Master Protocol trials that have common trial procedures and

endpoints. The trials group has charged a small team with developing these concepts further to design a trial infrastructure.

The ISN-ACT Global Trials Focus

ISN-ACT's flagship educational initiative is the Global Trials Focus (GTF; formerly the ISN-ACT Trial List). Since 2017, ISN-ACT has produced a monthly summary of the latest randomized trials in nephrology from around the world. The literature is systematically searched each month with randomized trials in nephrology being identified for inclusion. The trials are selected so as to highlight those with impact, with novelty, and with an emphasis on trials from regions of the globe that are underrepresented in the literature. GTF is published on the ISN website each month (https://www.theisn.org/research/isn-act#isn-act-global-trials-focus-gtf) and has received 4854 views to date. Future goals include expanding the pool of junior nephrologists contributing trial summaries, providing the GTF in multiple languages and, importantly, making the GTF more accessible to patients.

International Consensus Definitions of Clinical Trial Outcomes for Kidney Failure

The use of standardized definitions of endpoints for use in clinical trials allows comparison of the effectiveness of drugs and devices within and across research programs, and avoids disparities in outcomes, which may subsequently affect risk and power estimations, as well as subsequent interpretation. Whilst there are well-established definitions, many with multiple iterations, for trial endpoints within other specialties (e.g. myocardial infarction and stroke), there has been no accepted definition of kidney failure for use in clinical trials. ISN-ACT recognized the need for an internationally vetted and approved definition of kidney failure when it was initially formed[1]. To help achieve this aim, ISN-ACT organized a multi-stakeholder consensus meeting earlier this year with 83 attendees from diverse regions of the world. The meeting was preceded by work of a core group leading to a draft consensus definition, which was subsequently modified and agreed upon by the wider

group. The consensus definition has recently been published with subsequent audit of its use planned[3].

Future goals of ISN-ACT

The ultimate measure of success for ISN-ACT will be an increase in the number of patients who benefit from the translation of findings from trials into standard clinical practice. Despite several recent trials (e.g. CREDENCE, DAPA-CKD, FIDELIO-DKD, SONAR) demonstrating benefit of interventions for patients with kidney disease, uptake of findings remains variable. Through its educational and advocacy initiatives, alongside the fostering of international networks, ISN-ACT aims to build on these recent successes by creating an environment that encourages and supports the conduct of similar high-quality clinical trials that have meaningful benefit for patients. ISN-ACT, however, also recognizes areas where improvement is needed. These include the undertaking of clinical trials in low- and middle-income countries, and the development of the next generation of researchers interested in clinical trials.

Maximum benefit of any intervention requires it to be generalizable, which requires testing in diverse populations around the world. Few trials are undertaken in low- and middle-income countries despite this being where the majority of the world's population lives. Limited experience and confidence in undertaking research, lack of existing research structures and ethics committees, limited funding opportunities, and few specialists with significant clinical care demands all contribute. ISN-ACT aims to focus on initiatives to overcome these challenges in its future work, through inclusion of all regions in activities, and ongoing commitment to education and dissemination using ISN platforms, programs and communication channels. In parallel, ISN-ACT aims to increase the focus on the training and mentorship of young investigators throughout the world. Limited opportunities for training and experience in clinical trials in fellowship programs, and the length of time and funding often required to undertake a trial, means that clinical trial research does not easily fit within a time-limited higher degree. ISN-ACT is working on methods by which there can be an increase the accessibility of clinical trials

research to young investigators as well as to patient partners, in all resource settings worldwide. Ultimately, ISN-ACT aims to remain ~~nimble~~, responding on an ongoing basis to emerging needs in evidence generation for people with kidney disease, as defined by the communities that we serve and our members.

Disclosure

The authors do not have any disclosures that are relevant to this manuscript. Details of commercial relationships for each of the authors will be provided by the corresponding author on direct request.

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Table 1: Summary of ISN-ACT activities

ISN-ACT Theme	Trial Toolkit Development	Patient Engagement in Renal Research	Capacity Building and Clinical Trial Networks	Trial Design	Global Trials Focus	Development of Kidney Failure Endpoints for use in clinical trials
Link / reference	https://www.theisn.org/isn-act-toolkit	Banerjee et al, International perspectives on Patient Involvement in Clinical Trials in Nephrology, Kidney International[2]			https://www.theisn.org/research/isn-act#isn-act-global-trials-focus-gtf	Levin et al, International Consensus Definitions of Clinical Trial Outcomes for Kidney Failure: 2020, Kidney International[3]
Aim	Provide guidance for anyone wishing to start a clinical trial or to participate as a trial site	Expand meaningful patient involvement in international renal research	Improve the skills, abilities, and resources of interested healthcare providers to design and conduct randomized controlled trials	Improve the efficiency of renal trials and promote mechanisms that facilitate the integration of research into routine clinical activities. Create a worldwide platform and infrastructure for efficiently executing new trial designs	Drive improvement and promote greater engagement in trial activity by showcasing the latest clinical trials within nephrology	Development of a consensus definition of kidney failure for use in clinical trials

Description of completed activity	Development of a comprehensive online resource outlining the phases of clinical trials, what is required to become a trial site, and how to begin setting up a clinical trial of your own	Global survey of patient involvement in clinical trials; publication of results as part of review of patient involvement in renal research	Assessment of the facilitators and barriers to participation in clinical trials. Organization of networking meetings to facilitate undertaking of clinical trials.	Group of interested investigators formed to develop a trial infrastructure	Monthly appraisal of clinical trials disseminated via the ISN website, ISN Academy and ISN communication channels	Consensus definition agreed during an international meeting of 83 stakeholders, January 2020.
Future Goals	Audit use of the online resource and improve content in light of user feedback; expand trial toolkit use through webinars and other dissemination activities.	Activities to promote awareness of the value of patient involvement; development of tools and platforms to facilitate patient involvement in clinical trials.	Development of an online clinical trials curriculum and efforts to support the development of an international network of clinical trial investigators	Develop a network of trial-ready patients to support traditional trials and master trial protocols.	Inclusion of studies from all ISN regions and settings; improve accessibility of GTF to patients.	Dissemination of the definition and audit of its use.

Table 2*:* Components of the ISN-ACT Clinical Trials Toolkit

ISN-ACT CLINICAL TRIALS TOOLKIT
INTRODUCTION:
What is a Clinical Trial?
Phase I
Phase II
Phase III
Phase IV
Being a Clinical Trials Site
Checklist of typical requirements
Getting set up
Conducting the trial
Starting a New Trial
STUDY STAGES
STAGE I: DESIGN
Developing your ideas
Trial Design
Endpoints and Outcomes
Sample Size Calculation
Randomisation
Protocol Development
Funding
Involving Patients in the Research Process
STAGE II: ETHICS AND REGULATORY REQUIREMENTS
Sponsors, Investigators and other Key Study Roles
Contracts and Trial Agreements
Insurance and indemnity
Trial Registration
Ethics and Institutional Board Review
Consent
Regulatory Approval
STAGE III: CONDUCTING A CLINICAL TRIAL
Good Clinical Practice
Project Management
Documents and Procedures
Data Collection and Management
Adverse Event Management and Reporting
Recruiting Sites and Participants
Trial Monitoring
Closing Down a Trial
STAGE IV: ANALYSIS AND REPORTING
Statistical Analysis
Reporting and Publication
Data Sharing