Optimizing Enrollment of Patients into Nephrology Research Studies

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Abstract

Advances in medical care and biomedical research depend on the participation of human subjects. Poor patient enrollment in research has limited past clinical and translational research endeavors in nephrology. Simultaneously, patients and their caregivers are seeking better diagnostic, monitoring, and therapeutic approaches to improve or restore kidney and overall health. This manuscript will discuss a framework and strategies to optimize patient enrollment within nephrology research and provide examples of success from existing nephrology research programs.


Introduction

Advances in medical care and biomedical research fundamentally depend on the participation of human subjects in both healthy and diseased states. Many investigators and study sponsors have lamented that poor patient enrollment limits the research necessary to substantially improve health outcomes. Simultaneously, patients and their caregivers are seeking better diagnostic, monitoring, and therapeutic approaches to improve or restore kidney and overall health. A recent household survey of 2150 respondents found that research participation rates were 11% among adults and 5% among children (1). In this same survey, willingness to participate in research ranged from 86% for noninterventional research to 59% for vaccine trials (Figure 1).

Important for investigators of kidney disease, survey respondents with a chronic health condition were more willing for their children to participate in biomedical research compared with individuals without a chronic health condition (1,2). The discrepancy between participation and willingness to participate highlights an opportunity to improve research enrollment and outcomes. This manuscript will discuss a framework and strategies to optimize enrollment within nephrology research and provide examples of success from existing nephrology research programs (Figure 2).

Community Engagement

Partnership with a geographic or patient community can be used to share the rationale and methods of biomedical research, develop research agendas, and design feasible trials (3). Patient advocacy groups, such as the American Kidney Fund, National Kidney Foundation, NephCure Kidney International, and Polycystic Kidney Disease Foundation, may serve as powerful partners in convening or participating in community engagement activities. Research sponsors, networks, and health systems conduct forums for open dialogue, health fairs, and other educational events, where community and research team members have the opportunity to collaborate to improve community awareness and participation in biomedical research (3,4). The Rare Disease Clinical Research Network website provides opportunities for patients to enroll in disease-specific patient contact registries. These contact registries disseminate notifications about research and educational opportunities (5). Other community- and patient-oriented resources include disease- or clinical trial-specific websites, research telephone hotlines, and clinical trial ambassador programs with outreach through peer and patient advocates to support communication regarding available clinical trials. Patient advocacy groups may be particularly effective, because their constituents are often patients and caregivers who are seeking opportunities to improve health outcomes through scientific discovery. By partnering with these communities early in the study development process, the clinical researcher has the opportunity to design trials that are relevant to patient populations, thereby having a greater opportunity for successful enrollment.

Health Care Delivery

A successful integrated clinical care and research environment creates an expectation that every patient has the potential to contribute to research and that every encounter is a research opportunity. This model has been successfully adopted in pediatric cancer research and is representative of a culture that can be adopted by the nephrology community. The Learning Health System expands the model, such that patients, clinicians, data, and tools in the clinical care delivery system are an integral part of the research-quality-clinical care continuum. Furthermore, the Learning Health System has alignment with the health system leadership to maximize the potential
to include discovery as an integral component of the goal to optimize health outcomes. Research partnerships between Learning Health Systems generate results that are generalizable beyond a single care delivery program.

At a health system level, there are multiple benefits of clinical research. Successful clinical research programs have a dual advantage of enriching a health system's reputation in the community, while providing an avenue to improve patient and public health. When the benefits of successful clinical research are recognized, health system resources may be more readily available to support clinical research endeavors. The electronic medical record systems represent a systems-level tool that can be leveraged for research. Programming rules can be developed to generate reports of potential study patients in upcoming visits or generate just-in-time notifications about potentially study-eligible patients in acute or outpatient encounters (6). Additional clinical informatics tools (e.g., i2b2 and PopMedNet) are available to assist with searching clinical health data warehouses to identify cohorts of patients with specified inclusion and exclusion rules (7). These tools enable research teams across distributed sites to use a common query to ascertain the number of potentially eligible patients. In addition, these cohort discovery tools provide researchers information needed for study design and assessment of the feasibility of trial participation. Other tools, such as Trial Prospector, have been developed to generate patient-specific research menus to assist with patient-research study matching. These tools provide an informatics foundation to support successful clinical research programs where every patient has the opportunity to participate in research (8).

Research Networks

Most successful clinical research studies require multisite, and, often, multinational involvement. A recent Institute of Medicine report recognized the tremendous value in establishing and maintaining research networks to improve research efficiency of study implementation, conduct, and quality in oncology (9). Similarly, kidney disease-related networks, such as the Australasian Kidney Trials Network (AKTN), the Nephrotic Syndrome Study Network (NEPTUNE), the Midwest Pediatric Nephrology Consortium (MWPNC), and the Dialysis Access Consortium, have been established to provide an enduring infrastructure for the conduct of research with a targeted scientific, therapeutic, or age-specific field (10–15). Networks can provide a number of opportunities for the efficient conduct of research, including expertise to optimize protocol design, support to maintain a stable study team for patient enrollment, common data collection procedures, and biobanking capacity (16–20). In the most efficient networks, umbrella contracts are in place that require a simple amendment when new studies are deployed. Similarly, networks may use central or reliance institutional review board (IRB) models to gain efficiencies in regulatory review without compromising ethical oversight. Reliance IRBs use one of the network site's IRBs as the IRB of record for a network study. The IRB of record may stay at a single-network institution or rotate to align with the project principal investigator. With greater quality in study design and greater efficiency in study implementation, study team members...
have the opportunity to focus their efforts on participant enrollment and study conduct.

**Study Design and Procedures**

To optimize enrollment into research, the study design must be carefully developed with input from clinicians and patients. This begins with a research question that is scientifically valuable, clinically feasible, and of importance to the patient population in question. Inclusion of patients and clinicians in the study development team will generate insight into acceptable study end points, study burden, and identification of patient or clinician participation barriers that can be addressed before a protocol is finalized and implemented. Successful studies often align with the expected patient clinical pathway, which includes an understanding of typical patient touch points with the health care environments as well as accepted standards of care. Studies designed to optimize enrollment and generalizability include inclusion/exclusion criteria that are as broad as possible while maintaining scientific integrity. Pragmatic designs are often well aligned with usual clinical care and have broad eligibility criteria. Adaptive, Sequential, Multiple Assignment, Randomized Trials, and enriched trial designs may reduce the number of patients required for an individual study. These designs have been reviewed in recent publications (21–24).

Consent forms should be concise and clear, and they should adhere to the principles of plain language (25) to support a transparent discussion of research participation (26). Supplemental educational material can provide information about the underlying disease, available therapies, and prognosis as well as study-related information. Supplemental education materials may allow for shortening of the consent form while improving patient understanding of the research study (27,28). Alternate methods of consenting patients through web-based informed consents for minimal risk studies may promote enrollment and participation in internet-based studies, such as registries or surveys. Staged consent strategies may also be used to increase enrollment. In a staged consent, participants are initially consented to a research study that is minimal risk, such as an observational study. When subsequent eligibility criteria are met, a second consent may be offered for a second phase of the study, which may include an intervention or study procedures where study risks and benefits are aligned with the status of the patient. When researching interventions in emergent or life-threatening situations, consent of the patient may not be possible. In these situations, such as acute renal replacement therapy, consent from a surrogate or delayed consent from the patient may be part of the approved study procedures when aligned with federal and local regulatory requirements (29–31).

Studies nearly always add burden, such as extra or prolonged visits, travel, procedures, or data collection. Patient acceptance of these research activities is greater when the burden is minimized and when study procedures or visits align with routine clinical care. Whenever possible, offer extended hours for research visits, including evenings or weekends, to minimize work or school absences for the subject and family caregiver. Alternatives to traditional study visits may include studies in which patient-reported information through text messaging, smartphones, or other home monitoring devices optimizes prospective data collection while minimizing study burden (32–34). The electronic medical record may be used to simultaneously collect clinical and research data, or collected data may be accessed for subsequent research endeavors. Effective use of the electronic medical record may reduce data collection redundancies and promote clinician and patient research participation.

**Patient Engagement**

Partnerships with patients through patient advisory groups, focus groups, or interviews may help to define unmet medical needs and provide insight into research design. Patients and their caregivers are often willing to describe symptoms, signs, and adverse reactions to therapies and rank health challenges to inform research priorities (3,35,36). Tremendous examples exist of patients as members of study development and design teams, study steering committees, and oversight committees, such as data safety and monitoring boards and IRBs (37–41). Patient advisory groups are also effective partners to help formulate patient-facing communication to return the results of research. Nascent partnerships between patients, clinicians, and clinical researchers often require careful selection, training, and facilitation for all stakeholders to maximize the likelihood of success. Approaches for identification and inclusion of patients in research leadership have been developed and disseminated through the Patient-Centered Outcomes Research Institute (PCORI.org).

**Clinician Engagement**

It is important to recognize that the successful conduct of clinical research relies at least as much on the engagement of clinicians as it does on the enrollment of patients. Therefore, it is important to understand the challenges that clinicians may encounter in study participation and interventions that can serve to mitigate them. The loss of clinician autonomy is cited as one of the reasons that physicians choose not to participate in clinical trials (42,43). Indeed, physicians may be unwilling to give up control of clinical decision-making, even when evidence does not exist or outcomes are suboptimal for the condition under study. Recognizing these issues, clinical researchers can take steps to improve clinician participation by including clinicians in clinician advisory boards, study design discussions, and leadership roles. Clinicians will often recognize a potential conflict between standard medical care and study designs, such as prolonged off-therapy run-in periods, and may help to inform strategies that promote best standards of clinical care while still addressing the primary study objective. The recognition and mitigation of these factors are essential steps in the design of a successful study.

Pragmatic trial designs provide an opportunity to further improve clinician participation in clinical trials (44,45). Pragmatic trials, such as the Cluster-randomized, Pragmatic Trial of Hemodialysis Session Duration (TiME) Trial (NCT02019225; see below for examples), are designed to assess the effectiveness of study interventions in typical clinical practice conditions and use data routinely captured as
part of the standard of care. Eligibility criteria tend to be inclusive, and therefore, research findings from pragmatic trials are often more readily generalizable to the clinical practice than explanatory trials (46).

Successful programs often have research advocates among physician and nursing teams who have the responsibility to efficiently incorporate clinical research into clinical care, discuss research in faculty and staff meetings, and establish processes for review and selection of studies and mentor colleagues. These research advocates create a culture of research within a clinical practice. Clinicians have an established relationship with their patients; therefore, they may be best suited to assist with prescreening of patients for study eligibility and may serve as a trusted entity for the patient for initial study introductions. At the conclusion of the study, the study team is responsible for dissemination of study results and implications for future health care to clinicians as well as patient participants. These clinician engagement strategies will foster patient enrollment and may increase participation in future research.

Nephrology Examples

NEPTUNE

The Rare Disease Clinical Research Networks were formed with federal funding to gather patients, advocacy groups, researchers, and clinicians to address specific rare diseases. The NEPTUNE (NEPTUNE-study.org) is one of these rare disease networks that launched in 2010 to bring a systems biology approach to redefining the conditions leading to nephrotic syndrome from phenotypic, molecular, and genetic bases (12). The network was established with 22 academic partners, including internal medicine and pediatric nephrology programs, pathologists, and patient and research advocacy foundations. The NEPTUNE developed and implemented a framework to facilitate research by making biospecimens, phenotypic data, and research infrastructure available for the scientific community within and beyond the NEPTUNE Consortium. Initial recruitment targets were met on time through the engagement of every NEPTUNE site. Presently, the NEPTUNE is actively following over 450 patients with FSGS, minimal change disease, membranous nephropathy, and other proteinuric kidney diseases. The initial study reached and expanded the enrollment target, approved over 50 ancillary studies (including six clinical trials), and provided career development awards to five young investigators. The second 5-year phase of the NEPTUNE Study was approved in 2014.

ESRD

The TIME trial (NCT02019225; principal investigator L. Dember) is a cluster-randomized, pragmatic clinical trial of hemodialysis session duration. The ongoing trial was launched in 2013 in dialysis facilities that were randomized to the intervention arm or standard of care arm. The facilities randomized to the intervention arm recommend dialysis session duration of at least 4.25 hours for all new patients on hemodialysis. Usual care facilities maintain their existing approaches to prescribing dialysis session duration. The end points include mortality, hospitalization rate, and quality of life, and the study relies on the data obtained through routine clinical care captured within the dialysis facilities. The decision to randomize at the level of the dialysis facility provides a strategy for enrollment of every incident patient entering the dialysis facility during the study period with minimal effect on clinical care.

MWPNC

In 2004, the MWPNC was established in response to the recognition that a multicenter collaboration is necessary to provide sufficient patient numbers for successful research in pediatric nephrology. The stated aim of the group is, “To develop and perform multi-center prospective clinical and translational studies addressing important clinical problems unable to be adequately addressed at a single center.” The MWPNC, composed of over 50 centers across North America, has developed a committee structure, including protocol, development, study participation, and deployment. This group has been successful, with over 20 publications and 20 ongoing studies (mwpnc.com).

AKTN

In 2005, the AKTN was established amid growing concerns about the increasing public health burden of CKD and the relative paucity of successful clinical trials (10). The group was formed after the successful completion of the Initiating Dialysis Early and Late Study. The AKTN developed a governance structure with a goal to provide a central hub for clinical research among participating institutions. As part of the mission, the AKTN has established research priorities and increased collaboration and access to patients while identifying funding opportunities and improvements throughout clinical trial development. As of 2015, the AKTN reports five completed clinical trials, with three trials currently recruiting participants (47,48). The AKTN has recognized early on in their development the need for collaboration to allow for successful patient enrollment and the completion of clinical trials. Beginning at the study development phase, clinician investigators have access to biostatistical support and clinical trial expertise to allow for optimal and realistic trial design. The AKTN includes international and collaborative sites outside the network to optimize success rates. Finally, to ensure the development of nephrology clinician scientists, the network has actively promoted educational and career opportunities for junior faculty.

Conclusions

Optimal enrollment of patients with kidney disease into clinical research studies requires strategic planning. Investigators are encouraged to engage the community, patients, and clinicians to participate in research priority setting, assist with study design, and share in outreach endeavors. Health care delivery systems provide an infrastructure that can be used for the dual purpose of clinical care and research. The integration of these endeavors can establish a culture of a Learning Health System to benefit health outcomes through discovery, dissemination, and implementation of actionable findings. Research networks can accelerate enrollment through the development and implementation of high-quality study designs and the establishment of an enduring team of research investigators and coordinators.
with efficient contract and regulatory processes. Successful clinical research programs in nephrology are already using these strategies and may serve as exemplars for emerging programs. The time has come to transform our nephrology practices so that every patient is given the opportunity to participate in scientific discovery and the generation of solutions to their most pressing health challenges.

Disclosures

Contracts exist between the University of Michigan and GlaxoSmithKline (for clinical trial enrollment strategies and site participation into clinical trial [NCT02000440], Mayo Clinic (for site participation [capitated fees] for enrollment into investigator-initiated clinical trial [NCT0118036]), Retrophin (for site participation in clinical trial [NCT01613118]), Janssen (2014; completed; advisory board for development of global pediatric clinical trials network), and NephCure Kidney International (for development of a clinical trials network for glomerular disease).

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Published online ahead of print. Publication date available at www.cjasn.org.