EHR-Based Clinical Trials
The Next Generation of Evidence

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Introduction
The nephrology community has been vexed by the dearth of randomized, controlled trials (RCTs) to guide the generation of clinical practice guidelines and wider health care policy (1,2). Multiple factors have contributed to this problem, including the lack of adequate research funding, scarcity of nephrology investigators at each stage of the translational research spectrum, and feasibility barriers such as difficulty with patient recruitment, substantial crossover between treatment arms, and limited adherence to interventions. Although the nephrology community has recently achieved several significant advances in kidney disease care, the rates of poor outcomes associated with kidney disease indicate an exigent need for more progress. As electronic health records (EHRs) become ubiquitous in more economically developed countries, there has been growing momentum to leverage them to facilitate the conduct of RCTs, including functions that extend beyond their familiar role as sources of secondary data.

Kidney Disease Research and EHRs
Mirroring the rising prevalence of EHRs has been an explosion in EHR-based clinical research. The field of nephrology is uniquely well suited to conduct EHR-based research because of the (1) high prevalence of AKI and CKD, (2) ability to detect AKI and CKD with routinely collected biomarkers (i.e., creatinine/eGFR, urine albuminuria, urine protein by dipstick), (3) frequent measurement of these biomarkers as part of routine clinical care, (4) capture of common contributing risk factors as structured data (e.g., comorbidities, medications, BP, laboratory values, and procedure codes), (5) provision of a large proportion of dialysis services by a small number of organizations that use a common EHR product within their respective organization, and (6) availability of registries and databases for linkage to enhance ascertainment of relevant clinical outcomes (e.g., death, dialysis, and kidney transplant). Notably, recent efforts to establish standardized CKD electronic phenotypes should further strengthen the existing foundation for conducting valid and reproducible EHR-based kidney research across health systems (3).

An EHR-based RCT leverages the EHR as a platform to identify and enroll participants and conduct nearly all aspects of an RCT, including allocation assignment, intervention delivery (e.g., decision support), and data collection, with high fidelity, accuracy, and efficiency. Most EHR-based RCTs are pragmatic trials. Key components of a pragmatic RCT include nonrestrictive eligibility criteria, implementation of the intervention under “real-world” conditions by providers, comparison with usual care, and outcomes that are usually ascertained using data collected during routine clinical care (4). We highlight the novel approaches and raise questions and limitations that will need to be addressed to enable further advances in pragmatic EHR-based RCTs.

An EHR-Based RCT in the Inpatient Setting
The Isotonic Solutions and Major Adverse Renal Events Trial (5) was a single-center, pragmatic, cluster-randomized, multiple crossover, comparative effectiveness trial of balanced crystalloids versus saline to prevent major adverse kidney events in patients with critical illness. EHR-based participant enrollment allowed the study to include nearly 16,000 patients in under 2 years. Allocation assignment and delivery of the intervention was coordinated through the EHR with the use of real-time decision support to guide the ordering clinician. Additionally, all routinely collected clinical data were abstracted from the EHR, thus minimizing potential for data entry errors, although raising concerns regarding ascertainment bias. Notably, the trial was deemed minimal risk because of the lack of data regarding a superior crystalloid and safeguards present in the EHR decision-support process to check for potential contraindications to the fluid chosen by allocation assignment. These factors allowed the institutional review board to grant a waiver of informed consent.

This study raises several questions. Can comparable, future trials be conducted while incorporating participant informed consent, potentially through electronic means (e.g., e-consent)? If not, similar trials would be limited to interventions that are inarguably minimal risk. Further, as EHR infrastructure grows and EHR-based trials become more commonplace, how should the smallest clinically important difference in outcomes be viewed (6)? In this study, an approximate 1% lower rate of major adverse kidney
events was noted in the balanced fluid arm. Is this clinically important and was a larger treatment effect diluted by the highly pragmatic nature of the trial? It seems unlikely that a traditional clinical trial would have been powered for a similarly small treatment effect; however, should our expectations change as our tools change?

An EHR-Based RCT in Outpatient Dialysis

Maintenance dialysis is well suited for pragmatic trials because EHRs are widely utilized to document and store a multitude of clinical measurements, including patient-reported outcomes. The near-universal availability of granular and relatively uniform data across patients in this setting is an extraordinary feature. Further, because most ESKD care is provided by a small number of large dialysis organizations, large-scale studies can be efficiently organized and executed using a small number of EHR platforms as the main source for clinical measurements of interest. The Time to Reduce Mortality in ESKD trial leveraged these resources to significantly facilitate the conduct of a large, pragmatic, cluster RCT that examined outcomes in participants randomized to receive 4.25 hours of hemodialysis and those who received a duration determined by usual care (4). In <3 years, the investigators enrolled 266 dialysis facilities and 7035 patients with ESKD.

The study was remarkable for several reasons. First, in part related to the minimal risk designation of the intervention, the study was granted a waiver of participant informed consent. Instead, an opt-out approach was used for all patients (i.e., patients were given study information and contact numbers to opt out of data sharing). Second, the study used routinely collected clinical data from the dialysis providers’ EHRs to determine baseline characteristics, intervention fidelity, outcomes, and safety. Third, the study was conducted without dialysis facility research staff. Notably, the study succeeded in reaching its enrollment targets (using fewer dialysis facilities than anticipated), implementing the opt-out approach (with only 17 patients choosing to opt out), obtaining data with a high level of completeness, harmonizing data across EHR platforms, and monitoring safety using aggregate data from the EHRs. Certainly, the infrastructure created as part of this study should be useful in future studies in this clinical environment. Unfortunately, this trial was stopped early because of a 10-minute difference in delivered hemodialysis session duration between treatment arms. In this study, intervention fidelity encompassed both the prescription time ordered by the provider as well as the actual dialysis time completed by the patient. This raises a critical issue of whether additional research partners, staff, or infrastructure are needed to champion local implementation and augment intervention fidelity in similar pragmatic EHR-based trials that test interventions deemed burdensome and compete with treatment norms that are convenient (to patients, providers, or both).

An EHR-Based RCT for Outpatient CKD Care

In the United States, >37 million adults have CKD, leading to substantial morbidity, mortality, and health care costs (7,8). Given a growing CKD population, the relative dearth of nephrologists, and the fragmented care that high-risk patients receive, novel tools are needed to improve the quality of CKD care and clinical outcomes in the primary care setting, where most CKD care is delivered. One strategy to improve chronic disease care is population health management, which seeks to improve health by aggregating and analyzing data across a population to drive consistent, evidence-based care. In the National Institutes of Health–funded Kidney-Coordinated Health Management Partnership study (ClinicalTrials.gov identifier NCT03832595), CKD population health management is being performed using routinely collected EHR data to risk stratify the population, identify patients with high-risk CKD, facilitate the delivery of evidence-based treatments, and track patients longitudinally in a resource efficient and sustainable fashion (9). In this ongoing, EHR-based, pragmatic, cluster-randomized trial, investigators are examining whether population health management can improve outcomes in patients with high-risk CKD through the delivery of targeted automatic electronic consults (i.e., Targeted Automatic Electronic Consultations) (10) by nephrologists to primary care clinicians, medication therapy management delivered by pharmacists, and education of patients with CKD. Like other EHR-based trials, the study has a waiver of participant informed consent and uses an opt-out approach. In addition, the EHR is being leveraged both for delivery of key components of the intervention and longitudinal tracking, as well as for nearly all data collection for the study. The study results should inform strategies to deliver efficient, high-quality, cost-effective CKD care in the primary care setting.

Conclusion

EHR-based clinical trials can accelerate the pace of research discoveries in nephrology and generate evidence to inform treatment strategies, patient safety, and the delivery of evidence-based, high-quality care to patients with AKI, CKD, and ESKD, as well as patients who are at risk for developing these conditions. EHRs can provide a powerful platform to enroll and randomize patients and deliver interventions, thus lowering the cost and enhancing the feasibility of conducting a clinical trial. Issues that will need to be addressed include concerns regarding patient consent, ascertainment bias with the use of secondary data, and challenges with the uptake and fidelity of interventions implemented through the EHR. Investigators must consider their research design carefully to ensure that EHR-based intervention trials are relatively convenient for patients and providers (e.g., align with provider workflow, provide ongoing engagement and education to patients and providers, and obtain patient and provider feedback to improve acceptability). Despite these potential barriers, EHR-based clinical trials will continue to grow, answering many research questions that were impractical to address before, and providing opportunities to enrich the quality of evidence that informs nephrology care and health policy decisions.

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