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Editorial Comment

EDITORIAL COMMENT

Underrepresentation of older patients in clinical trials in nephrology

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One of the major demographic shifts in the last several decades has been population aging. As the population ages, the number of older patients with chronic kidney disease (CKD) is expected to rise, making encounters with these patients increasingly common in healthcare settings. CKD management in older patients is often complex, due in part to multiple comorbidities, polypharmacy, frailty and an increased susceptibility to medication-related complications. In recent years, several large outcome trials have identified novel therapies that reduce the risk of CKD-related complications. However, older patients are frequently underrepresented in clinical trials, resulting in limited evidence on the benefit–risk profile of treatments in this population and, consequently, suboptimal prescribing practices. This editorial explores the extent of older patients in nephrology trials, the scientific and ethical imperatives for their inclusion and practical strategies to improve their representation.

Trials focused on dialysis and transplantation have long been skewed toward younger, healthier participants. In a 2019 meta-analysis of 186 large multicentre randomized controlled trials (RCTs) involving patients undergoing dialysis, trial participants were on average younger than the general end-stage kidney disease population [1]. They also exhibited lower comorbidity burdens and dramatically lower mortality rates—less than half those seen in real-world settings. Among trials in kidney transplant recipients, the mean age was 45 years for trial participants and 50 years for kidney transplant recipients in the general US population [2]. Unfortunately, this discrepancy in age worsened over time. Recent clinical trials in the CKD population not on dialysis or kidney transplantation have been no exception to the trend of underrepresenting older patients. A recent study comparing the characteristics of participants in the CREDENCE (Canagliflozin and Renal Events in Diabetes with Established Nephropathy Clinical Evaluation), DAPA-CKD (Dapagliflozin and Prevention of Adverse Outcomes in Chronic Kidney Disease) and EMPA-KIDNEY (Study of Heart and Kidney Protection with Empagliflozin) trials with trial-eligible CKD patients identified in UK primary care found that real-world patients were, on average, 9, 11 and 14 years older, respectively, than those enrolled in the respective trials [3]. Importantly, real-world trial-eligible patients had a higher burden of cardiovascular disease—a common consequence of CKD—compared with trial participants. For instance, prevalence of cardiovascular disease was 26.1% in the EMPA-KIDNEY participants at baseline and 48.0% in trial eligible real-world patients.

The underrepresentation of older patients in clinical trials is a serious and pervasive challenge. Older patients are not simply older versions of younger patients—they bear a disproportionate burden of CKD and undergo age-related changes in physiology, pharmacokinetics and pharmacodynamics. In addition, they often live with multiple chronic conditions and take numerous medications, while at the same time they vary widely in their levels of frailty and cognitive impairment. These factors can influence both the effectiveness of therapies and the risk of adverse events, highlighting the need for greater personalization in this population [4]. Yet, paradoxically, we have limited data to support informed treatment decisions in older patients. Additionally, underrepresentation in clinical trials raises ethical concerns about fairness in availing potential benefits of trial participation including early access to novel therapies, increased monitoring and the opportunity to contribute to the generation of evidence that may inform future care. Underrepresentation

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in clinical trials also carries significant economic consequences. The lack of diverse and representative enrolment—including of older patients—contributes to persistent health disparities that, in turn, lead to avoidable healthcare costs, reduced productivity and shorter life expectancy. Modelling by the National Academies in the USA has shown that failing to align trial representation with the demographics of the broader population for conditions like diabetes and heart disease could result in missed societal benefits valued at $40–60 billion per disease [5]. While similar cost estimates have not been calculated specifically for CKD, the burden is likely substantial given the high prevalence, clinical complexity and downstream complications of CKD in older patients. Importantly, the report highlighted the continued underrepresentation of key demographic groups—including older patients—in CKD clinical trials.

Frailty and cognitive impairment contribute to several practical challenges in recruiting older patients in clinical trials, including mobility restriction, inability to provide informed consent and limited adherence to trial procedures. Additionally, strict eligibility criteria often exclude older patients. Common criteria—such as thresholds for renal, hepatic or cardiac function—disproportionately affect older populations, who are more likely to present with these conditions. Similarly, age-based criteria also impact inclusion of older patients. About 30% of clinical trials involving kidney transplant recipients included exclusion criteria based on age, with 16% specifically excluding individuals aged 65 years or older [2]. Other barriers include lack of interest or mistrust in research among older patients [6], as well as misconceptions among healthcare providers about their willingness or ability to participate or benefit from treatment. General practitioners managing older patients with early-stage CKD have expressed hesitancy about initiating medications in this group, which may reduce referrals for trial participation [7]. These factors underscore the multifaceted nature of the challenge—but importantly, many of these barriers are modifiable.

The 2017 KDIGO Controversies Conference on ‘Challenges in Conducting Clinical Trials in Nephrology’ identified potential solutions to overcome barriers to trial participation and emphasized the importance of designing trials that are relevant to the broad population of patients who may ultimately receive the intervention under study [8]. Indeed, for nephrology trials to be relevant to older patients with comorbidities, they must be deliberately structured to accommodate the health profiles and practical needs of this population. Incorporating insights from other disciplines can be instrumental when designing trails. Flexible trial designs, such as the cohort multiple RCT (cmRCT) used in aging research, can enhance access to eligible older patients and improve participation [9]. The cmRCT model involves recruiting a large cohort of individuals with a specific condition—such as frailty—who consent to be considered for future trials. Participants are regularly assessed for outcomes relevant to clinical research with minimal additional burden (e.g. extra visits) beyond routine care and preventing scheduling conflicts with other medical appointments. Because they are not approached for each individual trial, this design can reduce the fatigue and confusion often experienced by older adults. To address mobility and transportation barriers, offering round-trip transport can significantly improve participation and attendance, especially for those with impaired mobility and cognition and those living farther from recruitment sites, thus also enhancing representativeness within older age group [10]. Additional supportive strategies, such as patient navigators, flexible scheduling and home visits, can further improve recruitment and retention of older adults, especially among those with cognitive or physical impairments. Moreover, to address misconceptions about research, involving older patients in study design and recruitment strategies that involve face-to-face contact in trusted clinical settings can be more effective in patient recruitment than impersonal or solely digital approaches [6]. To address issues related to communication and consent, it is recommended that communication materials be adapted to meet age-appropriate literacy and sensory needs. Additionally, addressing gaps in provider education around geriatrics and relaxing exclusion criteria related to common age-associated conditions such as comorbidities or polypharmacy can help ensure that older patients are not unintentionally excluded from trial discussions, referrals or participation.

Unfortunately, none of these observations or recommendations is new and despite repeated calls to improve the representation of key populations, including older patients, in clinical trials, these recommendations have not translated into consistent changes in practice. This persistent inertia underscores that guidance alone is not enough and implementation is now imperative. The nephrology community must lead the shift toward inclusive trial designs that actively facilitate the enrolment of older patients. Importantly, site selection for clinical trials should be guided by the representativeness of the local patient population relative to the target population, rather than by convenience or existing affiliations with principal investigators. The Global Kidney Patient Trials Network, a form of cmRCT established in 2020, represents a promising step forward—it enables real-world clinic integration, minimizes restrictive eligibility criteria and aligns study procedures with routine care, all of which can significantly improve the inclusion of older patients [11].

In parallel, clinical trials need to begin to routinely report quantitative measures of representativeness, such as the participation-to-prevalence ratio (PPR), enrolment fractions by age group, and raw counts of older participants. Despite their limitations, together these metrics can provide valuable insights into both the inclusiveness of trial design and the effectiveness of recruitment strategies. These tools can help identify where in the trial process recruitment of older patients is negatively impacted—whether at the stage of site selection, initial outreach or actual enrolment. It is encouraging that the Global Cardiovascular Clinical Trialists Forum, in their recent call to action for improving trial representativeness, recommended achieving a PPR of 0.8–1.2 across key demographic groups, including age [12]. Nephrology trials should likewise set clear representativeness targets and hold themselves accountable for meeting them. Finally, funders, journals and regulatory bodies must move beyond encouragement and begin to require the use and reporting of representativeness metrics when reviewing trials for funding, publication or approval for use in practice. With enforceable standards and stronger accountability, nephrology has the real opportunity to lead the way in shaping a future of kidney care that truly meets the needs of older patients with CKD.

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AUTHORS’ CONTRIBUTIONS

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CONFLICT OF INTEREST STATEMENT

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