Adv Ther (2025) 42:5727–5741
https://doi.org/10.1007/s12325-025-03370-w

ORIGINAL RESEARCH

A Strategic Roadmap to Support Communication on and Acceptance of Surrogate Endpoints: The REnal Surrogacy accEpTance in Chronic Kidney Disease (RESET CKD) Collaboration

Juan José Garcia Sanchez · Marta Trapero-Bertran · Oriana Ciani · Bruno Detournay · Loreto Gesualdo · Hiddo J. L. Heerspink · Lesley A. Inker · Smeeta Sinha · Christoph Wanner · Dustin J. Little · Marvin Sinsakul · You-Seon Nam · Rod S. Taylor

Received: June 23, 2025 / Accepted: September 2, 2025 / Published online: September 23, 2025

ABSTRACT

Introduction: Developing effective treatments in chronic, progressive diseases like chronic kidney disease (CKD) is challenging because patients may only experience relevant outcomes such as kidney failure after long periods of disease progression. Surrogate endpoints provide a valuable alternative to definitive final patient-relevant outcomes, which may accelerate clinical development processes. However, optimal utilization of surrogate endpoints for reimbursement decisions requires alignment across multiple stakeholders, including health technology assessment (HTA) bodies and reimbursement agencies, who are generally more cautious than regulatory bodies in their acceptance of surrogate endpoint evidence. The aim of this paper is to propose a strategic roadmap to facilitate cross-stakeholder collaboration and support the consideration of surrogate endpoints in regulatory and reimbursement decisions.

Supplementary Information The online version contains supplementary material available at https://doi.org/10.1007/s12325-025-03370-w.

J. J. Garcia Sanchez
Health Economics, BioPharmaceuticals, AstraZeneca, Barcelona, Spain

J. J. Garcia Sanchez (✉)
HTA & Modelling Science Team, BioPharmaceuticals Medical, AstraZeneca, Academy House, 136 Hills Road, Cambridge CB2 8PA, UK
e-mail: juanjose.garciasanchez@astrazeneca.com

M. Trapero-Bertran
Department of Economics and Business, Universidad de Lleida, Lleida, Spain

O. Ciani
SDA Bocconi School of Management, Centre for Research on Health and Social Care Management (CERGAS), Milan, Italy

B. Detournay
CEMKA, Bourg-La-Reine, France

L. Gesualdo
Department of Precision and Regenerative Medicine and Ionian Area (DiMePre-J), University of Bari, Bari, Italy

H. J. L. Heerspink
Department of Clinical Pharmacy and Pharmacology, University Medical Center Groningen, Groningen, Netherlands

L. A. Inker
Department of Medicine, Tufts Medical Center, Boston, MA, USA

S. Sinha
Salford Royal Hospital, Northern Care Alliance NHS Foundation Trust, Salford, UK

S. Sinha
Manchester Academic Health Sciences Centre, University of Manchester, Manchester, UK

C. Wanner
Department of Clinical Studies and Epidemiology, Comprehensive Heart Failure Center, University Hospital Würzburg, Würzburg, Germany

***Methods*:** An international group of experts in surrogate endpoints, reimbursement decisions, and kidney disease formed The REnal Surrogacy accEpTance in Chronic Kidney Disease (RESET CKD) Collaboration. This scientific steering committee held several meetings to develop a roadmap of activities with the aim of enabling the appropriate consideration of surrogate endpoints through structured multi-stakeholder engagement involving regulators, clinicians, HTA bodies, payers, industry, and patients.

***Results*:** The strategic roadmap focuses on four areas: identifying the need for evidence; engaging stakeholders; collaborating in regulatory and reimbursement processes; and disseminating evidence. The RESET CKD collaboration is currently implementing the roadmap in the field of CKD through collating relevant evidence for a CKD-relevant surrogate endpoint in a scientific playbook, conducting economic evaluations, developing a position paper, and engaging patient groups.

***Conclusions*:** Disparities between regulatory and reimbursement processes and decisions underscore the need for a structured approach to enhancing transparency, consistency, and timeliness in the use of surrogate endpoint evidence in healthcare decision-making. The roadmap developed through the RESET CKD Collaboration addresses this need and is already demonstrating practical value in its implementation. Although initially focused on CKD, the framework is designed to be transferable to other therapeutic areas. Key challenges remain, including the integration of surrogate endpoints into adaptive pricing models and performance-based agreements.

Keywords: Chronic kidney disease; Health technology assessment; Outcome assessment (health care); Reimbursement mechanisms; Surrogate endpoints

Key Summary Points

Why carry out this study?

Surrogate endpoints may provide an alternative to final trial outcomes, and may accelerate timelines for development of novel therapies for progressive conditions such as chronic kidney disease, allowing timely access to medicines that address unmet needs.

Practical use of surrogate endpoints in decision-making processes requires alignment and collaboration between multiple agencies, based on available evidence.

What was learned from this study?

The REnal Surrogacy accEpTance in Chronic Kidney Disease (RESET CKD) Collaboration has developed a strategic roadmap to support evidence generation and communication and alignment across key stakeholders.

The framework for this roadmap is adaptable and may be transferred to support integration of surrogate endpoints into decision-making processes for other therapeutic areas.

D. J. Little
Late-Stage Development, Cardiovascular, Renal and Metabolism (CVRM), BioPharmaceuticals R&D, AstraZeneca, Gaithersburg, MD, USA

M. Sinsakul
Early Clinical Development, Research and Early Development, Cardiovascular, Renal and Metabolism (CVRM), BioPharmaceuticals R&D, AstraZeneca, Gaithersburg, MD, USA

Y.-S. Nam
Global Medical Affairs, BioPharmaceuticals Medical, AstraZeneca, Gaithersburg, MD, USA

R. S. Taylor
MRC/CSO Social and Public Health Sciences Unit & Robertson Centre for Biostatistics, School of Health and Well Being, College of Medical, Veterinary and Life Sciences, University of Glasgow, Glasgow, UK

INTRODUCTION

The development of innovative and effective treatments remains a priority [1, 2], especially for chronic and progressive diseases associated with high morbidity and mortality despite current therapies [3–6]. Demonstrating the definitive benefit of new interventions on patient-relevant final outcomes such as survival or major morbidity often requires trials with extended follow-up periods and large sample sizes, potentially delaying regulatory decisions and reimbursement processes and, ultimately, patient access to innovative treatments [7, 8]. This is especially true for conditions such as chronic kidney disease (CKD), where the progression toward patient-relevant adverse clinical outcomes, such as kidney failure or mortality, can span several years. Furthermore, ethical concerns may arise when using trial outcomes relying on patients to experience detrimental reductions in kidney function, or even progression to kidney failure, to provide sufficient evidence of treatment benefit.

Surrogate endpoints have emerged as a potentially valuable alternative to address these challenges, offering the opportunity to predict clinical benefit [9, 10]. In contrast to patient-relevant clinical endpoints that reflect how a participant "feels, functions, or survives" [9], surrogate endpoints are biomarkers, such as a laboratory measurement or a physical sign, or measures of function or symptoms that replace the outcome of interest. Surrogate endpoints that reliably predict benefit or harm on the basis of epidemiologic, therapeutic, pathophysiologic, or other scientific evidence [10, 11] can accelerate clinical development, reduce trial duration, and facilitate earlier decision-making on market access [7, 8]. The value of surrogate endpoints was first established during the development of antiretroviral drugs for human immunodeficiency virus (HIV) during the 1990s. Initially, antiretroviral approvals were based on clinical endpoints, such as an acquired immunodeficiency syndrome-defining event or death, but these endpoints relied on patients progressing, and it was not considered ethical for this process to form the basis of drug approvals [12]. As treatment-associated decreases in a surrogate biomarker (HIV load) were found to be associated with risk of disease progression, HIV load was accepted as a relevant endpoint for regulatory purposes in place of the traditional clinical endpoint [12]. In CKD, kidney failure is a significant morbidity, and reliance on such an outcome should also be reduced.

Although regulatory bodies increasingly accept common surrogate endpoints for drug approval [13, 14], health technology assessment (HTA) agencies and payers often remain cautious in their funding decisions when these have been based on surrogate evidence [15]. A white paper on surrogate endpoints in cost-effectiveness analysis for use in HTAs developed through a collaboration between the National Institute for Health and Care Excellence (NICE) and other HTA agencies highlights the lack of clear guidance on the optimal use of surrogate endpoints for reimbursement decision-making [16].

Ciani et al. [10] provide a conceptual framework to define, classify, and interpret surrogate endpoints across different decision-making contexts. This work underscores the need for clarity on the strength of the surrogate relationship and the importance of aligning the perspectives of regulators, HTA bodies, and other stakeholders. However, conceptual clarity alone is not sufficient; practical guidance is needed to navigate the complexities of multi-stakeholder decision-making and inform the appropriate consideration of surrogate endpoints in healthcare decisions.

The aim of this paper is to address this implementation gap by proposing a strategic roadmap to facilitate cross-stakeholder collaboration and support the consideration of surrogate endpoints in access and reimbursement decisions. We present the experience of the REnal Surrogacy accEpTance in CKD (RESET CKD) Collaboration as a case study within nephrology, where patients require interventions at disease stages prior to the late-stage clinical outcomes that have traditionally formed the basis of clinical trials. These circumstances necessitate the use of surrogate endpoints to support the timely development of new treatments in clinical trials and consideration of resultant regulatory and reimbursement decisions. By bridging the theoretical

insights of Ciani et al. [10] with a practical governance approach, we hope this roadmap can support stakeholder discussions around the value of surrogate endpoints, enabling transparent, coordinated, and timely decision-making, with a focus on scientifically validated surrogate endpoints that reliably predict patient-relevant final outcomes.

METHODS

The steps involved in the development of the RESET CKD strategic roadmap are schematically summarized in Fig. 1. The first steps were to carry out a desktop search and interviews with key stakeholders to explore the position of regulatory bodies and HTA agencies on the use of surrogate endpoints for reimbursement decisions. Following this, the RESET CKD Collaboration was established with the formation of a dedicated scientific steering committee (SSC) comprising an international group of experts in surrogate endpoints, reimbursement decisions, and kidney disease. This committee held a series of meetings to develop the RESET CKD roadmap and oversee its progress.

This article is based on previously conducted studies and does not contain any new studies with human participants or animals performed by any of the authors.

Exploring the Current Landscape

An initial desktop search focused on the use of surrogate endpoints in the development, regulatory approval, and reimbursement of new medicines. This task included an analysis of guidelines or recommendations for the use of surrogate endpoints published by several regulatory, HTA, and reimbursement agencies from the USA, Japan, China, and key European countries [13, 17–27]. A sample of evidence submission packages based on surrogate endpoints and payer critique of these packages were also examined, along with publicly available pricing and reimbursement decision documents (see Table S1 in the electronic supplementary material for details). A convenience sample of 14 HTA and reimbursement experts from six countries (England, France, Germany, Italy, Spain, and the USA) were invited to participate in 1:1 interviews, based on prior collaborations and recent involvement in reimbursement decision-making. The purpose of the interviews was to discuss and validate the findings of the preliminary desktop search. Discussions focused on key drivers of regulatory and payer approvals, the role of surrogate endpoints, the types and sources of supporting evidence, and the extent to which position of other regulatory or HTA agencies influence final decisions.

The desktop search and subsequent 1:1 interviews established that, although surrogate endpoints are commonly used by regulatory bodies to make approval decisions, global HTA and reimbursement agencies are generally more cautious in their acceptance of surrogate endpoint evidence. Many regulatory decisions by the Food and Drug Administration and the European Medicines Agency have been based on surrogate endpoint evidence [13, 28]. Although there is consistent recognition of the value of surrogate endpoints by HTA agencies, there appears to be considerable variation in how individual agencies handle the use of surrogate endpoints in their decision-making. For example, the HTA agency of England and Wales (NICE) appears more likely than the German Institute for Quality and Efficiency in Health Care (IQWiG) to accept the use of surrogate endpoints for reimbursement decisions. Although NICE recognizes a hierarchy of evidence for validation of surrogate endpoints that can be applied according to the decision context [20], IQWiG has established more restrictive evidentiary requirements, based on the need to demonstrate a high correlation between the treatment effects on the surrogate and the treatment patient-relevant endpoint [21]. To date, IQWiG has only approved a limited number of therapies on the basis of such evidence.

Forming the RESET CKD Collaboration

The RESET CKD Collaboration was established as a coordinated effort between industry and key

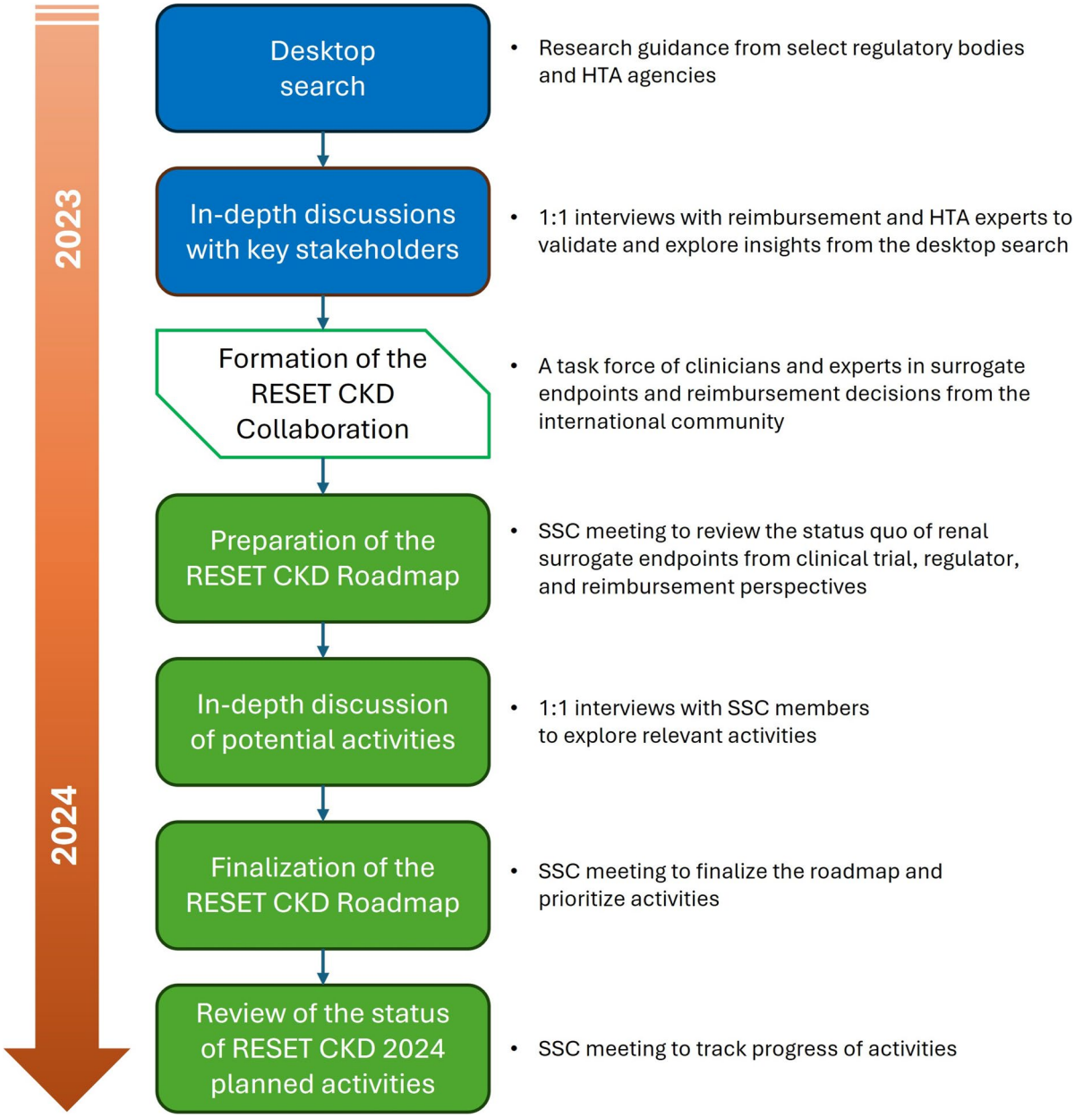

Fig. 1 Overall process of the RESET CKD Collaboration. Blue boxes represent initial work before the formation of the RESET CKD SSC. Green boxes represent work by the SSC. *HTA* health technology assessment, *RESET CKD* REnal Surrogacy accEpTance in Chronic Kidney Disease, *SSC* scientific steering committee

experts in reimbursement decisions, surrogate endpoints, and kidney disease to increase the visibility and understanding of the appropriate use of surrogate endpoints in clinical trials for HTA and reimbursement decision-making in kidney disease. A number of reimbursement experts, clinicians, and experts in surrogacy (based on previous collaborations and recent professional activities in the field of surrogate endpoints) were invited to form the RESET CKD SSC. This international task force shaped and

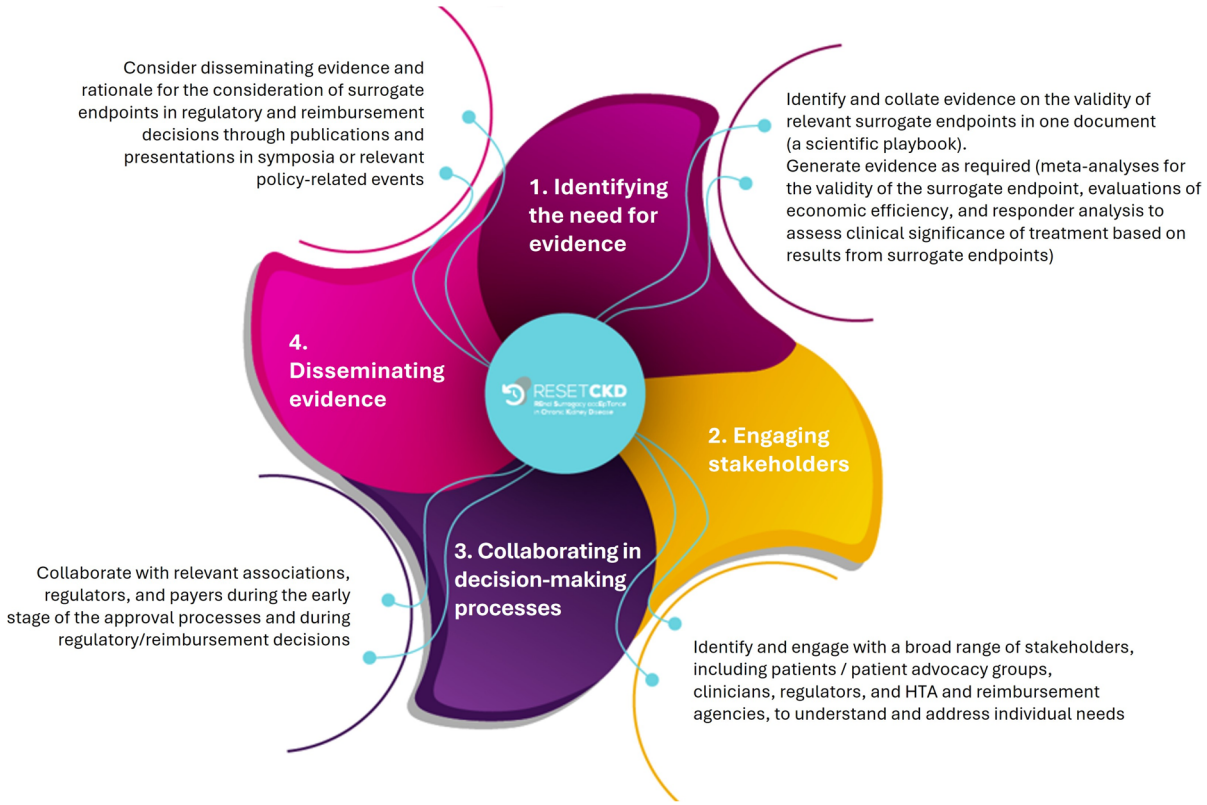

Fig. 2 A strategic roadmap to facilitate cross-stakeholder collaboration and support the use of surrogate endpoints in access and reimbursement decisions. *HCP* healthcare professional, *HTA* health technology assessment

coordinated the activities of the wider collaboration through regular meetings.

Establishing a core SSC with a long-term commitment was essential to ensure a coordinated approach around the use of surrogate endpoints. Engaging with stakeholders on an ad hoc basis through one-to-one interactions or advisory boards could have provided advice on specific points. However, the strategic direction and long-term decision-making needed for our collaboration required a dedicated, multidisciplinary SSC while initiating, implementing, and evolving the activities of the collaboration. As the scope of the work required is defined, the SSC will reach out to additional individuals or teams to tackle specific activities as needed, expanding the RESET CKD Collaboration.

Developing the Roadmap

The SSC conducted a comprehensive review of the evidence supporting the use of surrogate endpoints in kidney disease, alongside an assessment of the positions adopted by regulatory authorities, HTA bodies, and reimbursement agencies regarding their acceptance. Through a series of group discussions and individual meetings, the SSC identified the key stakeholders to be involved; evidence requirements; clinical, regulatory, and reimbursement pathways to be considered; and strategies for evidence dissemination and education. These insights informed the development of the strategic roadmap outlining a set of activities designed to support decision-making processes for future medicines evaluated on the basis of surrogate endpoints.

RESULTS

The Roadmap

The roadmap brings together four linked themes improving the use and access of surrogate endpoints in HTA and reimbursement decisions (Fig. 2): (1) identifying the need for evidence; (2) engaging stakeholders; (3) collaborating in decision-making processes; and (4) disseminating evidence. For each of these areas, specific activities and corresponding recommendations were proposed, as detailed in Table 1.

A multidisciplinary SSC is often required to hold overarching responsibility and provide guidance on project selection, prioritization, execution, and review [29, 30]. In this case, experts in the disease area, reimbursement, and policy decisions should be involved. Such experts can be identified through recent publications on the subject, professional societies, academic institutions, payer organizations, and health policy bodies to ensure comprehensive and credible input. Representation by a range of countries can further enhance the team's ability to explore the best approaches for addressing the diverse opinions of international reimbursement agencies. By bringing together experts from various fields with unique insights, committees can provide guidance on project selection, execution, and review.

The Four Domains

Identifying the Need for Evidence

The primary objective is to collate available evidence to support the validation of a surrogate endpoint and its appropriate use for regulatory, HTA, and reimbursement decisions. This exercise should consider following the three-step framework to surrogate validation described by Ciani et al. [31]. This includes demonstration of biological plausibility of a surrogate endpoint and the observational (prognostic) and treatment effect associations (causality) between a surrogate endpoint and a patient-relevant target outcome. Ideally, a repository or 'playbook' providing the key supporting evidence and rationale for surrogate endpoints that have been evaluated and demonstrated to have acceptable validity should be established and maintained as a living document, providing the foundation to engage in discussions on surrogacy with technical stakeholders and lay audiences.

Validation of a surrogate endpoint can be provided commonly by meta-analyses of randomized clinical trials and large-scale studies to assess correlations between the surrogate and patient-relevant clinical outcomes at both patient level (within trials) and trial level (across trials). Patient-level data can show that the surrogate predicts individual outcomes, whereas trial-level data can confirm that treatment effects on the surrogate translate into actual clinical benefits. Economic evaluations to project clinical and economic benefits of treatment over different time horizons in terms of clinical outcomes, survival, quality-adjusted life years, and healthcare costs based on the surrogate endpoint may also have a role in some countries. These should account for potential differences between the size of treatment effect on the surrogate and the treatment effect on the final patient-relevant outcomes. Long-term data on target outcomes (e.g., mortality, morbidity) must also be collected, even for accepted surrogate endpoints, to confirm the effectiveness of drugs, requiring robust post-marketing surveillance systems and real-world evidence programs. Finally, it is important to encourage sharing of trial data, as this is instrumental to perform surrogate validation studies.

Engaging Stakeholders

Mapping regional and global stakeholders is essential to ensure the project is supported by relevant experts with diverse opinions, and that the needs of all those with a vested interest in drug approval and reimbursement decisions are addressed. Engaging with patients, clinicians, regulators, and HTA and reimbursement experts as early as during the design and development stage will be pivotal when identifying research gaps, defining the most meaningful outcomes,

Table 1 Roadmap activities and recommendations

Category	Recommendations
Identifying the need for evidence	Collate evidence on the validity of relevant surrogate endpoints, from biological plausibility to individual patient-level meta-analyses Identify gaps in evidence based on regulatory and HTA requirements around associations between surrogates with final patient-relevant outcomes or understanding the healthcare and societal benefits of reducing the final outcomes via surrogate endpoints Generate required evidence to fill these gaps, e.g., meta-analyses, economic evaluation Prepare a living document (or playbook) to gather relevant information and act as a reference tool for other documents, such as policy briefs or scientific education material Demonstrate that the surrogate endpoint is a validated patient-relevant outcome and confirm it is applicable to a range of patient subgroups and phenotypes Emphasize the ethical aspects of different trial designs and the inclusion of surrogate endpoints
Engaging stakeholders	Engage early with a broad range of stakeholders to explore their needs and viewpoints (note that this could differ across countries and regions) Relevant stakeholders could include patients, clinicians, pharmacists, policymakers, regulators, HTA and reimbursement agencies Seek early scientific advice from HTA committees to understand priority steps that may need to be addressed Foster collaboration between different stakeholders via educational and scientific activities on surrogate endpoints
Collaborating in decision-making processes	Confirm whether guidelines for the assessment of surrogate endpoints exist, and support their development and/or use in regulatory and HTA contexts (international and country level) Engage in early scientific advice discussions with regulators and HTA and reimbursement agencies to understand and address their specific requirements Educate stakeholders on surrogate endpoints and their use, including ethical aspects of different trial designs

Table 1 continued

Category	Recommendations
Disseminating evidence	Develop a publication plan to facilitate the dissemination of evidence as it is generated, aiming to increase awareness of the surrogate endpoint and provide a critical appraisal of the evidence available in the context of requirements by and advice from regulators and HTA and reimbursement agencies Ensure the communication is tailored to different audiences on the basis of stakeholder needs and background, e.g., lay or technical audiences Critically review the surrogate endpoint in the form of a position paper—this can illustrate alignment between academia, HCPs, patients, and payers Encourage collaboration between industry, academia, HCPs, patients, and payers through multidisciplinary expert panels and workshops Communicate the validity of surrogate endpoints via evidence-based, peer-reviewed publications Consider the most appropriate types of evidence to present at academic-led symposia; disease-specific symposia and congresses; healthcare reimbursement, health economics, and HTA congresses; and policy-related events

HCP healthcare professional, *HTA* health technology assessment

and drafting a rationale for the use of specific surrogate endpoints. For patients who are not fully informed on surrogate measures and how they correlate with more familiar health outcomes, clear communication and informed consent are essential [32]. In such cases, patient representatives can help create plain language, accessible materials that define surrogate endpoints, and explain how they work and their limitations.

Some stakeholders, including patients, may be skeptical of surrogate endpoints, viewing them as less meaningful than outcomes such as survival or quality of life scores. Overcoming this skepticism requires robust evidence and education that shows these endpoints are reliable in predicting treatment effects on patient-relevant target outcomes across diverse patient populations and healthcare settings. Integrating patient input through focus groups or surveys can help ensure that surrogate endpoints align with patient priorities and preferences. Widespread educational initiatives can also ensure that healthcare professionals and decision-makers understand and interpret surrogate endpoint data. Effective communication should account for differences in practices for measuring and interpreting surrogate endpoints, healthcare infrastructure, regulatory processes, and cultural factors between countries.

Collaborating in Decision-Making Processes

It is important to support the decision-making processes of regulatory, HTA, and reimbursement agencies based on robust evidence from surrogate endpoints. This support includes educational efforts, aiding the development of evidence-based guidelines on the use of surrogate endpoints, and engaging early with regulators and HTA and reimbursement agencies to understand their information needs. Collaboration with other groups, such as the International Society for Pharmacoeconomics and Outcomes Research (ISPOR), EU Joint Clinical Assessment groups, and relevant medical societies, can further bolster the evidence for and guidance on the use of surrogate endpoints. Endorsement of patient-centered surrogate endpoints by patient representatives can further support the consideration of such endpoints during decision-making processes. This includes sharing testimonials, lived experience narratives, or patient-generated data, as well as active participation in

advisory panels and regulatory or reimbursement discussions.

Currently, ISPOR has established a taskforce to provide guidance on good practices for the evaluation, validation, and health economic modeling of the relationship between surrogate endpoints and outcomes to inform HTA decisions [33]. In addition, NICE produced a white paper on surrogate endpoints in cost-effectiveness analyses for use in HTA [16]. In kidney disease, international collaborations such as the CKD Epidemiology Collaboration are focusing their efforts on the evaluation of surrogate endpoints for clinical trials in CKD.

Disseminating Evidence

Peer-reviewed publications are crucial for consolidating evidence on surrogate endpoints, and congresses provide a strategic platform for stakeholder engagement through symposia and scientific presentations. A position statement can be an important initial document to consolidate evidence gaps, establish research priorities, and formally align strategy across different stakeholders. Disease-specific congresses are ideal for reaching and educating clinicians, whereas Health Economics and Outcomes Research or policy-specific congresses, such as those organized by ISPOR or Health Technology Assessment international, are appropriate for raising awareness among reimbursement experts and payers. A publication plan is crucial for highlighting opportunities to communicate evidence and engage with stakeholders. Patient input through advisory boards, steering committees, or 1:1 interviews is critical to ensure their priorities and concerns are addressed and aligned with the proposed value of surrogate endpoints throughout the collaboration.

Prioritization of Activities

The definition and prioritization of specific activities to support the adoption of surrogate endpoints in regulatory, access, and reimbursement decisions largely depend on the evidence validating the surrogate endpoint and the attitudes of regulatory authorities, HTA bodies, and reimbursement agencies toward its use. In situations where there are clear but strict requirements on the use of surrogate endpoints and there is a paucity of acceptable evidence, significant initial effort may be required for evidence identification and generation. In other cases where the evidence is robust and available, engaging and educating stakeholders would be a priority.

Application of the Roadmap in CKD

Within the RESET CKD Collaboration, the primary focus has been placed on the estimated glomerular filtration rate (eGFR) slope (mean decline of eGFR over time, typically over 1–3 years) [34, 35] as a surrogate endpoint for patient-relevant kidney outcomes. This endpoint is supported by robust evidence from large-scale individual patient-level meta-analyses that demonstrate a consistent association between changes in eGFR slope and the risk of progression to kidney failure requiring kidney replacement therapy, supporting the use of eGFR slope as a primary endpoint for clinical trials of CKD progression [34–36]. In this context, key priorities include enhancing the communication of this evidence and the potential value of eGFR slope for reimbursement decisions to all relevant stakeholders while simultaneously reinforcing the link between trial-based GFR slope outcomes and long-term clinical and economic benefits for healthcare systems.

To operationalize this approach, the team is developing a scientific playbook, which maps the current evidence of surrogacy in CKD and documents the needs, progress, and future directions of the collaboration. A multidisciplinary group of experts and clinicians developed and published a position paper that synthesizes the available evidence supporting a surrogate endpoint and articulates how this evidence aligns with the evaluation criteria of HTA and reimbursement bodies [37].

Furthermore, an economic evaluation analysis is underway to project the downstream impact of slowing eGFR decline on key outcomes such as kidney failure, quality of life, and healthcare

costs. The aim of this work is to demonstrate that therapies approved based on eGFR slope not only confer clinical benefit but also deliver tangible value to healthcare systems. Finally, engagement with patient advocacy groups is ongoing to ensure that patient perspectives and preferences are adequately represented and integrated into the evaluation process.

DISCUSSION

Ensuring timely access to safe and effective treatments for patients with unmet needs remains a critical challenge, requiring robust evidence generation based on high-quality trial design. Surrogate endpoints offer a potentially valuable and ethical approach in clinical trials to expedite clinical development, particularly in chronic, progressive diseases such as CKD, where definitive patient-relevant outcomes may take years to materialize. However, some HTA bodies and reimbursement agencies may be reluctant to rely on surrogate endpoints for their reimbursement decisions, which must balance clinical benefit, economic value, and healthcare system sustainability.

In the current landscape of regulation, market access, and reimbursement processes of drugs, biologics, and medical devices, the need for a structured and transparent approach to the evaluation and acceptance of surrogate endpoints has become increasingly evident [13, 14]. Such an approach requires a collaborative and multi-stakeholder effort involving regulators, policymakers, HTA bodies, clinicians, academics, industry, and, crucially, patients. Each stakeholder brings unique insights and priorities, which should be aligned across all stages of the drug development and evaluation continuum to facilitate patient access to that technology.

The RESET CKD Collaboration represents a timely example of how early cross-stakeholder alignment can be operationalized in practice, offering a coordinated framework to align perspectives and streamline decision-making processes regarding surrogate endpoints. Although the roadmap and associated activities were developed within the context of kidney disease, they were deliberately designed to be disease-agnostic and process-oriented. This approach acknowledges that surrogate endpoints vary widely across therapeutic areas and therefore should be appraised within their specific clinical and evidentiary context. However, applying the roadmap to other diseases would not constitute a direct replication. While the overarching categories are broadly applicable, the proposed tactics should be critically assessed. Several may be adapted and expanded, with additional strategies incorporated as needed to address disease-specific considerations. This flexibility enables the roadmap to serve as a transferable model, fostering a paradigm shift toward more transparent, evidence-informed, and collaborative decision-making across stakeholders.

Adapting the roadmap requires consideration of country-specific factors. For instance, some countries' reimbursement agencies have developed specific guidelines for surrogate validation that should be adhered to during reimbursement decisions, whereas others decide the value of a surrogate endpoint on a case-by-case basis. Although clinical experts, medical societies, and patient advocacy groups are important stakeholders across all countries, allied health professionals (such as pharmacists) may also play an additional crucial role in certain countries.

The success of the roadmap should not be assessed solely by the increased use of surrogate endpoints in regulatory and payer decisions or by tangible improvements in drug development or access times. Rather, its impact must be understood in a broader context, recognizing several key challenges. Substantial variation across therapy areas affects both the availability and utility of surrogate endpoints. In some areas, significant resources may be invested in evidence generation without a clear understanding of when, or if, these efforts will lead to the timely and appropriate application of surrogate endpoints. Furthermore, a variety of factors can introduce delays in drug development, regulatory review, and reimbursement processes. For example, improvements in the standard of care may require larger and longer trials to demonstrate incremental benefit, despite the use of surrogate endpoints. Therefore, additional indicators of successful implementation include robust data generation on surrogate

endpoints, positive outcomes from educational initiatives, enhanced stakeholder communication, and improved understanding of surrogate endpoints among decision-makers.

Limitations

The scope of this collaboration was to provide a foundation and a framework of activities that can be individualized according to specific needs rather than cover the surrogacy validation requirements of every possible regulatory, HTA, or reimbursement agency. Furthermore, we focused on activities that communicate the value of surrogate endpoints in reimbursement decisions, and we have not covered specific topics involving pricing, market access, and public health. Although incorporating these aspects could have offered a more comprehensive view of the entire market access pathway, it might have also added complexity to the roadmap and diverted the focus from the primary objective of fostering acceptance of surrogate endpoints across stakeholders. Additionally, pricing and access strategies often differ widely across countries, making it challenging to develop a one-size-fits-all approach in a multi-jurisdictional context. Nonetheless, we acknowledge that surrogate endpoints can play a key role in facilitating adaptive pricing models, performance-based agreements, and early access schemes in certain cases. These areas represent important avenues for future work. Despite this defined scope, the roadmap provides a transferable blueprint for any collaborative effort aiming to enhance patient care across medical fields and geographic regions.

CONCLUSION

There are significant disparities in the use of surrogate endpoint evidence in healthcare decision-making between regulatory and reimbursement agencies, both within and across regions. These differences highlight the need for a structured approach to enhancing transparency, consistency, and timeliness in how surrogate endpoint evidence is evaluated and applied. To that end, the strategic roadmap developed by the RESET CKD Collaboration offers a framework to support multi-stakeholder engagement, including regulators, clinicians, HTA bodies, payers, industry, and patients. Its implementation in the field of CKD is already demonstrating value through the development of a scientific playbook for a CKD-related surrogate endpoint, economic evaluations, a position paper, and active engagement with patient groups. Although rooted in the field of kidney disease, the roadmap is designed to be transferable to other therapeutic areas facing similar challenges, by remaining disease-agnostic and process-oriented.

Medical Writing/Editorial Assistance. Medical writing support under the guidance of the authors was provided by Constantinos Bezos and Emma Conran of Porterhouse Medical, UK, in accordance with Good Publication Practice (GPP 2022) guidelines, and funded by AstraZeneca.

Author Contributions. All authors (Juan Jose Garcia Sanchez; Marta Trapero-Bertran; Oriana Ciani; Bruno Detournay; Loreto Gesualdo; Hiddo J. L. Heerspink; Lesley A. Inker; Smeeta Sinha; Christoph Wanner; Dustin J. Little; Marvin Sinsakul; You-Seon Nam; Rod S. Taylor) contributed to drafting and approving the manuscript for submission and meet the ICMJE criteria for authorship.

Funding. AstraZeneca sponsored the steering committee meetings and medical writing. AstraZeneca is also funding the journal's Rapid Service and Open Access Fees.

Data Availability. Data sharing is not applicable to this article as no datasets were generated or analyzed during the current study.

Declarations

Conflict of Interest. Christoph Wanner has received honoraria for steering committee membership, advisory board participation, and lecturing from Alexion, Amgen, Amicus, AstraZeneca, Bayer, Boehringer Ingelheim, CSL Vifor,

Eli Lilly, GSK, Idorsia, Novartis, Novo Nordisk, and Sanofi. Oriana Ciani has received honoraria for advisory board participation and consultancy from AstraZeneca, MSD, Lumanity, and Cencora. Bruno Detournay has received personal compensation for advisory board participation and speaker fees from Abbott, AstraZeneca, CEMKA, Cerba, Novo Nordisk, Sanofi Winthrop Industrie, Eli Lilly, Lumanity, Janssen, MSD, Continuum+, and Pfizer. Marta Trapero-Bertran has received honoraria for advisory board participation from AstraZeneca and Boehringer Ingelheim, and from Novartis for in-company teaching on economic evaluation methods. Smeeta Sinha has received honoraria from AstraZeneca, Boehringer Ingelheim, CSL Vifor, Novartis, GSK, Sanofi-Genzyme, Inozyme Pharma, Menarini, Amicus, Stada, Chiesi, Bayer, and Santhera; and grant funding from AstraZeneca, Novartis, CSL Vifor, Johnson & Johnson, and Sanofi-Genzyme. Loreto Gesualdo has received research grants from Abionix, Sanofi and Astrazeneca payed to his institution; He has received speaker honoraria from Bayer and Werfen; served as consultant for Baxter, Tavere, Astrazeneca, GSK, Novartis, Chinook, Roche, Reate, Nestle, Otsuka, Gilead Science, Bayer, and Vifor Fresenius. Hiddo J. L. Heerspink reports funding to conduct clinical trials from AstraZeneca, Bayer, Boehringer Ingelheim, Janssen and Novo Nordisk (payments to his institution, the University of Groningen); consulting fees from AstraZeneca, Alexion, Alnylam, Bayer, Boehringer Ingelheim, BioCity Biopharma, Dimerix, Eli Lilly, Gilead, Idorsia, Janssen, Novartis, Novo Nordisk, Roche and Travere Therapeutics (payments to his institution, the University of Groningen); honoraria for lectures from AstraZeneca, Bayer and Novo Nordisk; and support for traveling to and attending the American Diabetes Association meeting and the American Society of Nephrology meeting from AstraZeneca and Eli Lilly (payment to his institution, the University of Groningen). Lesley A. Inker reports funding to Tufts Medical Center from National Institutes of Health (NIH), National Kidney Foundation (NKF), Chinook, R3R, Otsuka Pharmaceutical, Alexion Pharmaceuticals, and Novartis; consulting agreements to Tufts Medical Center from Alexion Pharmaceuticals and AstraZeneca; and consulting agreements from Diamerix. Juan Jose Garcia Sanchez, Dustin J. Little, Marvin Sinsakul, and You-Seon Nam are employees of AstraZeneca. Rod S. Taylor reports research grant from UK Medical Research Council (MRC) funding for the SPIRIT/CONSORT-Surrogate extension development (grant reference MR/V038400/1).

Ethical Approval. This article is based on previously conducted studies and does not contain any new studies with human participants or animals performed by any of the authors.

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