Patient Preference and Adherence

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PERSPECTIVES

Patient Involvement in the Design of an Innovative Clinical Study to Compare the Palatability of Anti-Hyperkalemia Medications

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Abstract: The inclusion of patient representatives as study consultants brings diverse perspectives, insights, and experiences to clinical trial design and execution, and their role in the clinical trial development process is being increasingly recognized and valued. The APPETIZE study evaluated the palatability of, and preference for, three potassium binders for treating hyperkalemia in patients with chronic kidney disease. A core aspect of the development of this study was the inclusion of a patient representative during the design stage. Here, I describe the process of patient involvement in the APPETIZE study design (ClinicalTrials.gov Identifier: NCT04566653), the resultant positive impacts, and key learnings. A patient with chronic kidney disease was invited to be a member of the APPETIZE trial design team. This patient representative attended study team meetings and provided invaluable input into protocol development, questionnaire selection, design of patient information sheets and consent forms, and primary manuscript structure. These critical insights resulted in an enhanced trial design and generation of high-quality, patient-relevant data. APPETIZE provides an excellent example of a patient preference study that relied on input from multiple stakeholder groups, including, most notably, the patients themselves. This approach may serve as a model for early and deep patient engagement in the design and interpretation of clinical trials.

Keywords: clinical trials, patient representation, chronic kidney disease, hyperkalemia

Introduction

Patient participation in and contribution to the drug development cycle has historically been restricted to post-approval disease education.[1] Traditional approaches to clinical trial design considered the disease symptoms of a patient in isolation from the patient as an individual, with the primary role of the patient to adhere to prescribed treatment.[2,3] Recent changes have seen an evolution of the medical field from a "paternalistic" medical model towards a more "patient-centric" one.[2–4] Once patients are thought of as individuals rather than as a collection of clinical symptoms or laboratory values, the patient voice becomes more relevant and it becomes essential to involve patients as consultants in the design of clinical studies.

Patient centricity has been defined, during consultation with key stakeholders, patients, and carers, as "putting the patient first in an open and sustained engagement of the patient to respectfully and compassionately achieve the best experience and outcome for that person and their family".[1] Patient centricity does not need to be confined solely to the healthcare setting; patient involvement and engagement can and should also be incorporated into research and all aspects of the clinical trial lifecycle (Figure 1).[5,6] The value of experience provided by patients is highlighted by the Patient-Centered Outcomes Research Institute (PCORI), who recommend that "meaningful involvement" of patients, caregivers, and clinicians should occur in the planning and conduct of clinical trials.[7]

In this paper, I introduce the importance of patient centricity in clinical trial design before summarizing the process, key changes, and lessons learned from involvement of a patient representative in the design of the APPETIZE clinical trial.

Received: 25 October 2023
Accepted: 8 May 2024
Published: 31 May 2024

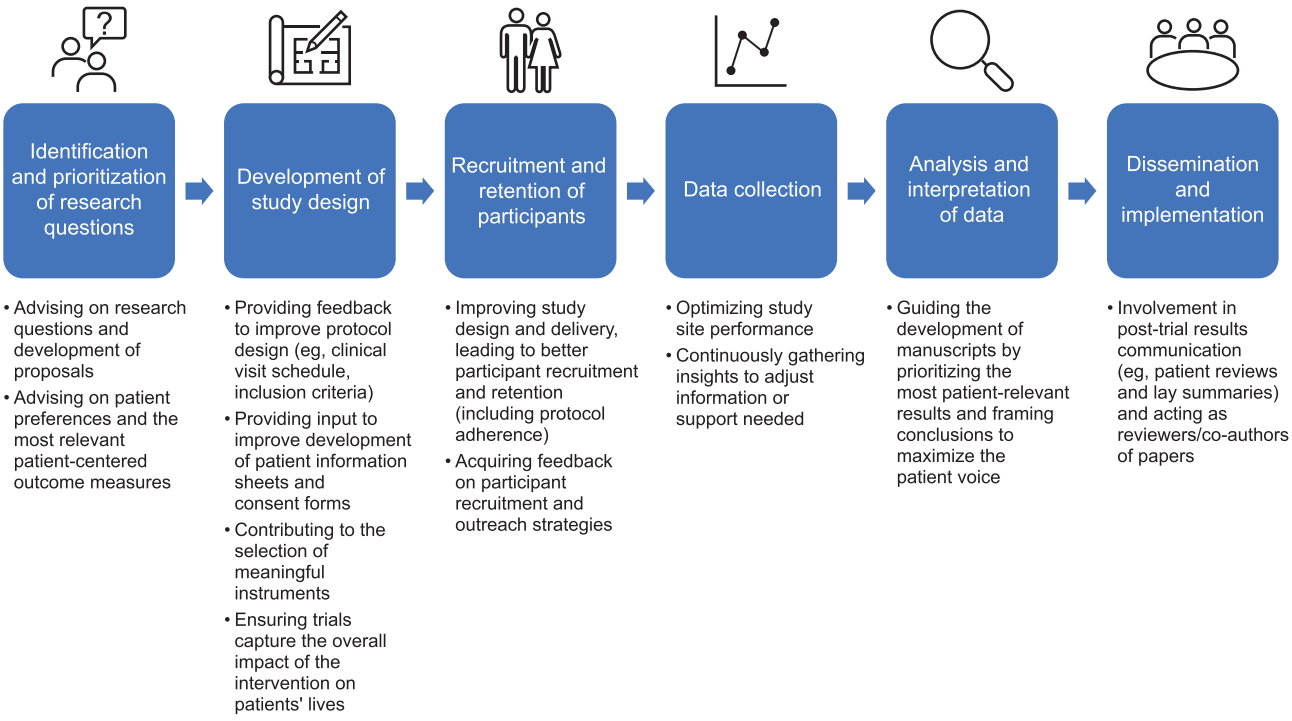

Figure 1 Patient involvement across the clinical trial lifecycle.

Why is Patient Involvement in Clinical Trial Design Important?

Patient centricity and engagement in the context of clinical trials confers a number of benefits to different stakeholders (Figure 2).[8,9] Benefits to patients include enhanced engagement, because patient inclusion as consultants in clinical trial development offers a sense of empowerment, resulting in a more positive trial experience.[9,10] There can also be a reduced burden and improved convenience with respect to study assessments, such as flexible appointment schedules, remote monitoring options, and decreased travel requirements.[11] Patient involvement in the development of trial communication

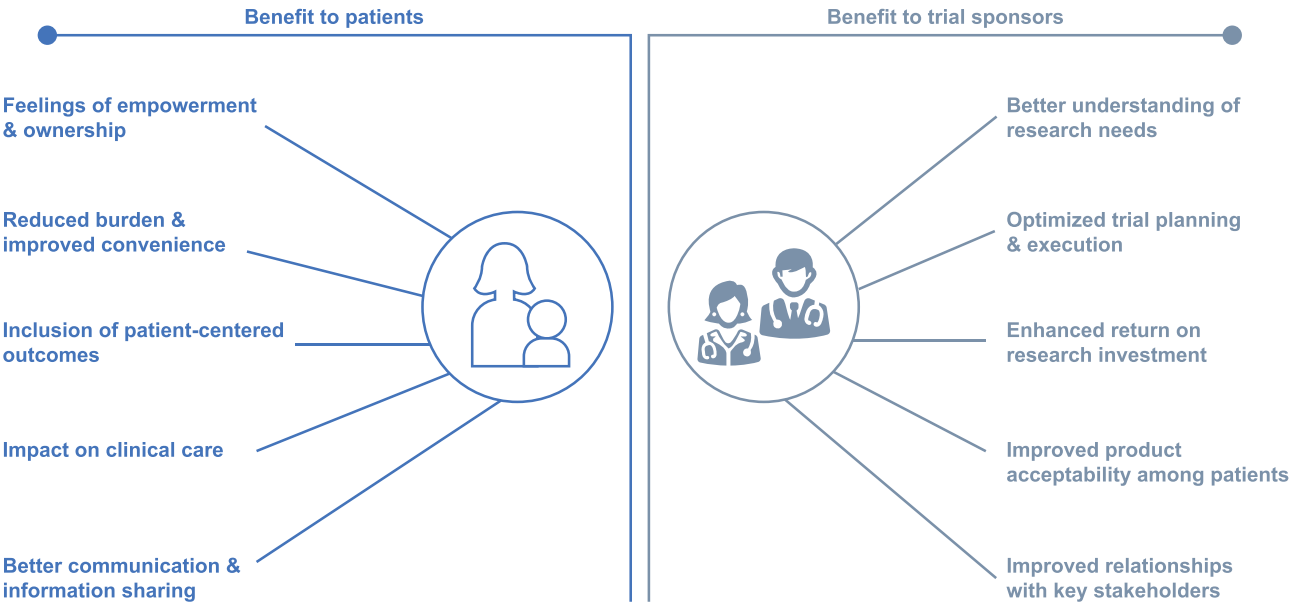

Figure 2 Stakeholder benefits from patient involvement in clinical trial design.

materials allows for the inclusion of more relevant information from lived patient experiences, and facilitates improved patient understanding through the use of plain language.[6,12,13] Patient representatives are well-positioned to advise on the most relevant patient-centered outcome measures, which can include improvements in health-related quality of life, symptom relief, mental health, and functional capacity, and can help ensure that trials are better able to capture the overall impact of the intervention on patients' lives.[9,12,13] Data on patient experiences, treatment effectiveness, and safety profiles from well-designed patient-centric clinical trials can also inform future clinical practice and guideline development resulting in benefits not only to trial participants but also the broader patient population.

Patient-centric trials also offer benefits to trial sponsors (Figure 2) through enhanced understanding of disease burden and unmet research needs.[14] Trial protocol development and execution is optimized through more efficient trial planning and institutional review board approval, reduced likelihood of future protocol amendments, and better access to patients for study recruitment and retention.[6,9,12,15–17] There is also evidence that the benefits of patient engagement in clinical trials can result in more efficient use of scarce resources such as dedicated personnel time and cost.[16] Patient engagement may also help with the design of pragmatic clinical trials, whereby trial assessments are included in routine clinical care to minimize trial procedures and data collection requirements to reflect real-world settings.[18] Furthermore, drugs developed using a patient-centric design are 19% more likely to progress to regulatory approval when compared with drugs developed without patient-centric trial design.[19] Improved trial adherence among patients can also be observed due to improved drug acceptability via the implementation of patient support programs or the improvement of drug packaging and dosing strategies.[20,21] Patient-centric trial design can also result in improved relationships between sponsors and regulators,[22–24] payers,[25] clinicians,[26] and patients.[3]

Below, a case study is presented demonstrating the process, impact, and lessons learned from patient involvement in the design of a study evaluating the palatability of, and patient preference for, three currently available potassium (K^+) binders for the treatment of hyperkalemia (HK).

The APPETIZE Trial

Why Was This Study Important?

Patients with chronic kidney disease (CKD) are at high risk of HK (defined as increased serum K^+ concentration levels [> 5.0 or > 5.5 mEq/L]), which is associated with risks of adverse events and mortality.[27–29] Traditional K^+ binders such as sodium and calcium polystyrene sulphonate (S/CPS) can be used to manage HK,[28] but are associated with being unpalatable,[30,31] and are also associated with the increased incidence of side effects such as hospitalization and gastrointestinal complications.[32,33] The lack of palatability and tolerability of K^+ binders impacts treatment adherence,[34] and prior to the APPETIZE study, the palatability of two newer K^+ binders, sodium zirconium cyclosilicate (SZC) and calcium patiromer sorbitex (patiromer), had not yet been tested. The APPETIZE study (ClinicalTrials.gov Identifier: NCT04566653) was a non-interventional, Phase IV study that measured the palatability and preference of SZC versus patiromer versus S/CPS in patients with dialysis and non-dialysis CKD and HK. The primary aim of the study was to evaluate an outcome that was closely linked with patient preference; it was therefore essential to ensure that the patient perspective was a prominent consideration of the trial design process.

How Were Patients Involved in the Design of This Trial?

A patient advisory board held by the sponsor in 2019 identified that taste, texture, smell, and mouthfeel were particularly important to patient adherence to long-term K^+ binder treatment. These essential elements as prioritized by patients were used to guide the choice of palatability attributes used in the APPETIZE trial.

In addition, a patient representative was invited to participate in the design of the APPETIZE study at the protocol development stage. At the time of invitation, the patient representative had collaborated with AstraZeneca on CKD studies for over 5 years. This individual was presented with the study protocol for review and input, involving several rounds of review and revision before protocol finalization. Following protocol development, the patient representative was invited to all trial meetings and advisory boards, was regarded as an equal partner in all decisions, and received the same information as the other members of the study team.

What Was the Impact of Patient Involvement on This Trial?

Involving a patient representative in the development of the APPETIZE study protocol allowed them to provide input and direction into the study design at an early stage, which resulted in changes to the wording of the APPETIZE questionnaires to improve understanding of the patients' priorities for HK treatment and how to focus questions to generate relevant data. In particular, the patient representative highlighted how chronic dialysis impacts patients' sense of taste and smell, and how this should be addressed in the trial. Questions were included to assess the palatability of treatments, and these questions were refined and prioritized to make them more relevant to patients with CKD. In addition, review of the protocol by the patient representative contributed to the inclusion of an ideal washout period between tastings, a tolerable duration of time for a single-visit taste test, and recommendations on what should be avoided and for how long prior to assessment, such as caffeine. Insights gathered from the patient representative were also instrumental in shaping questions related to CKD stage, dialysis status, and medication burden. These critical insights also led to the development of high-quality and more accessible patient information sheets and consent forms. In addition, the patient representative helped guide the study team in the development of the primary manuscript by prioritizing the most patient-relevant results and framing the conclusion to maximize the patient voice.

The inclusion of a patient living with CKD in the APPETIZE study provided unique, first-hand knowledge of the challenges that are presented by CKD; this contributed to the addition and refinement of questions to be more relevant to patients with CKD, as well as amendments to the protocol.

What are the Key Learnings from This Experience?

Experience from the APPETIZE study confirms that patient involvement results in clear improvements in the clinical trial design process and the overall quality of the trial design.

Aspects that contributed to the success of the APPETIZE trial included involvement of the patient representative in decisions about outcome measures—resulting in the inclusion of highly specific, patient-relevant outcomes—and their input into the development of materials. The patient representative also provided key insights that guided primary manuscript development, and their presence may also have influenced the communication style of the study team to promote greater understanding by all stakeholders.

Ensuring the inclusion of patient representation, particularly in certain disease areas, remains challenging. A patient's health condition may sometimes cause them to miss meetings or limit their ability to provide timely feedback. A potential solution is to include two or more patient representatives in the process, which would increase the likelihood that at least one patient will be available at each stage of the trial development process. Furthermore, inclusion of more than one patient representative may enrich the input received if the representatives themselves are able to discuss aspects of the trial and provide increased patient diversity.

Conclusion

APPETIZE is an excellent example of a patient preference study that relied on input from multiple stakeholder groups, including healthcare professionals, scientists, caregivers, and foremost, the patients who stand to benefit from the findings. This approach may serve as a model for early and deep patient engagement in the design and interpretation of clinical trials.

Acknowledgments

Medical writing support was provided by David McMinn, PhD, and Matty Stone, MRes, and editorial support by Jess Galbraith, BSc, of Core (a division of Prime, London, UK), supported by AstraZeneca according to Good Publication Practice guidelines (https://www.acpjournals.org/doi/10.7326/M22-1460). Eric Wittbrodt, of AstraZeneca provided input into the sections "How were patients involved in the design of this trial?" and "What was the impact of patient involvement on this trial?".

Funding

The APPETIZE study was funded by AstraZeneca.

Disclosure

HS reports no conflicts of interest in this work.

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