The Role of Patient-reported Outcomes and Medication Adherence Assessment in Patient-focused Drug Development for Solid Organ Transplantation

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INTRODUCTION

On September 27–28, 2018, the US Food and Drug Administration (FDA) and the Critical Path Institute's Transplant Therapeutics Consortium convened a public workshop to address drug development in the field of transplantation, titled "Evidence-based Treatment Decisions in Transplantation: The Right Dose & Regimen for the Right Patient/Individualized Treatment." The workshop occurred over 2 days focusing on biomarker use in transplantation and the incorporation of the patient's voice into the drug development process[1] represented in this report.

Drug development of immunosuppressive therapies (ISTs) for use in transplantation has historically focused on morbidity and mortality as the primary clinical outcomes of interest, with patient experiences often being an afterthought. Drug development programs that aim to include patients' experiences through various methodologies, including patient-reported outcome (PRO) measures, help ensuring novel therapies meet the most pressing needs felt by patients. Patient-focused drug development (PFDD) is defined by the FDA as a "systematic approach to help ensure that patients' experiences, perspectives, needs, and priorities are captured and meaningfully incorporated into drug development and evaluation." PFDD considers patients to be the experts in living with their condition, uniquely qualifying them to inform drug development and evaluation. PFDD is a major FDA priority, as codified in the 21st Century Cures Act (Cures Act) and the sixth reauthorization of the Prescription Drug User Fee Act (PDUFA VI).[2]

This report aims to capture discussion on the impact of PRO measures and medication adherence on PFDD for transplantation by exploring:

1. Challenges for individuals living with a transplant and managing complex treatment regimens and treatment-related side effects.
2. Need to establish a validated set of PRO measures in transplantation to better reflect patient preferences when evaluating the risk-benefit profile of novel therapies in product development and regulatory decision making.
3. Strategies to develop PRO measures for symptom assessment in transplantation through previously established tools or by adapting PRO measures from other therapeutic areas.
4. Challenges with medication adherence in solid organ transplantation and strategies to improve medication adherence

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in clinical trials to improve the validity and interpretability of study results.

SYMPTOMS, TRANSPLANT REGIMEN COMPLEXITY, AND ADHERENCE FROM THE PATIENT PERSPECTIVE

Solid organ transplantation saves and improves the quality of life for patients with end-stage organ disease; however, it also brings significant lifelong challenges. Transplant recipients are placed on IST for life to maintain the health of their transplanted organs. Adherence to IST is a considerable challenge for these patients, given the complex nature of IST regimens and their short-term and long-term adverse effects. The combined impact of these factors, alongside transplant-related symptoms, has profound implications for overall daily life.

This public workshop provided FDA and stakeholders an opportunity to hear patients discuss their experiences managing posttransplant treatment regimens.

The expert panel comprised 3 kidney and 2 lung transplant recipients who provided insights regarding the intersection of chronic care management, disease-related symptoms, medication-related side effects, and medication adherence. While patients understood the benefits of their transplant, they also highlighted the complexities of posttransplant life. Several common themes emerged, including the complexity and burden of managing and coordinating their care (eg, issues with medication cost or insurance; loss of medication coverage; employment and associated financial stress; high pill burden; and the need for coordination of care between pharmacy, insurance, and physician to reconcile refill dates), the ability to differentiate between a medication's side effect and disease complications, the desire for care to be continually provided by the transplant team and difficulties finding other clinicians with transplant expertise to provide care, improved use of technology in care, and incentives to improve medication adherence. They expressed desires to stop taking medications they had associated with adverse events, such as prednisone. Additionally, the panelists recounted specific signs and symptoms they found to be most bothersome, including acid reflux, difficulty clearing infections, hair loss, itching, reduced sensation during sexual activity, insomnia, deterioration in eyesight, bone degeneration, skin cancer, muscle weakness, cognitive impairment, numbness and tingling in hands and feet, pain, hyperglycemia, low white blood cell counts, swelling in face and abdomen, cognitive impairment, skin cancers, increased appetite, and uncontrollable cravings. These patient experiences mirror those reported elsewhere, further underscoring the need to improve safety and efficacy profiles of novel transplant therapeutics.[3]

The panelists also described their strategies to maintain medication adherence. These included phone alarms, pillboxes, family support, automatic refills, bringing medications when they leave the house, and taking medications at the same time every day. Panelists described how feeling healthy keeps them adherent. They also brought to light areas of concern, such as inadequate education about how to handle missed doses, how to adjust their medication schedule while traveling to different time zones, and a dislike of blister packs.

DEVELOPING PATIENT-REPORTED OUTCOMES TO UNDERSTAND THE PATIENT'S PERSPECTIVE IN DRUG DEVELOPMENT

PFDD includes techniques to minimize the burden of patient participation in clinical trials, capture patient preference, and use patient and caregiver input to inform drug development. One approach to collecting this information is through the use of clinical outcome assessment (COA), defined by FDA as a drug development tool that helps interpret how a patient feels, functions, or survives. Specifically, Section 507 of the FD&C Act defines drug development tools as including biomarkers, COAs, and any other method, material, or measure that FDA determines aids drug development and regulatory review (FD&C Act section 507(e)(5)). PRO measures, defined as "any report of the status of a patient's health condition that comes directly from the patient, without interpretation of the patient's response by a clinician or anyone else," are one type of COA. PRO measures inform drug development by directly capturing patient self-assessment, providing crucial information on clinical IST safety and efficacy. Implementation of PRO measures in clinical trials is greatly facilitated through validation or endorsement of FDA, which requires well-defined and reliable assessments of specified concepts of interest. Tools must be systematically and scientifically developed to ensure the relevant and desired information is captured.

PRO measures are critical components to incorporating patient perspective into more complete evaluations of medical interventions.[3] Transplant recipients have previously emphasized the importance of PRO measures being included as part of clinical trial outcome evaluations.[4] Most PRO measures incorporated in transplant clinical trials assess health-related quality of life, with few trials utilizing PRO measures for symptom assessment. The PRO measures frequently used to capture health-related quality of life have been the Medical Outcomes Study Short-form 36-item health survey and the EuroQol-5 Dimension. Despite being the most used measures in transplant trials, none have been endorsed by regulatory agencies for use in this setting.

Use of symptom assessment measures would be greatly encouraged through a validated core set of PRO measures that capture patients' voice in evaluating disease-related symptoms and treatment-related side effects. Development of a validated core set of PRO measures for symptom assessment can improve the drug development process by incorporating the patient perspective further to characterize the risk-benefit profile of novel agents in transplantation. The Cures Act and PDUFA VI have led to a new series of 4 guidance documents that detail current FDA recommendations to enhance the incorporation of the patient's voice into product development. The first guidance, available as a final guidance document, covers collecting comprehensive and representative input. The second guidance covers methods to identify what is important to patients and is available now in draft form. The third and fourth guidance documents will cover approaches to select, develop, and modify fit-for-purpose COAs and incorporate COAs as endpoints to support regulatory decision making. Guidance documents 3 and 4 are currently under development.

FDA's COA Qualification Program, formalized as part of the Cures Act, established a process for regulatory review of COAs to facilitate their use in clinical studies. Regulatory qualification is "a conclusion that within the stated context of use, results of the assessment can be relied upon to measure a specific concept and have a specific interpretation and application in drug development and regulatory decision making." While qualification is not required to use a COA to support drug labeling claims, qualified tools reduce uncertainty and increase confidence in the incorporation of a tool into a clinical trial. The overall process of developing and seeking COA qualification through the COA Qualification Program is outlined in Figure 1.

PATIENT-REPORTED OUTCOME MEASURES THAT COULD BE ADAPTED FOR USE IN DRUG DEVELOPMENT FOR SOLID ORGAN TRANSPLANTATION

The time and resources required to develop novel PRO measures are substantial. To streamline this process, existing validated PRO measures may be adapted for transplantation. Specifically, the Patient-Reported Outcome-Common Terminology Criteria for Adverse Events (PRO-CTCAE), developed by the National Cancer Institute, may represent an efficient path to develop and seek qualification of a novel tool for use in transplant clinical studies.

The PRO-CTCAE Measurement System is designed to capture 78 symptomatic adverse events drawn from the CTCAE. PRO-CTCAE items were created to evaluate frequency, severity, amount, or presence/absence of drug-related adverse events and their interference with usual activity. For any given adverse event, 1–3 symptom attributes are evaluated. The PRO-CTCAE item library includes 124 items and displays validity, reliability, and responsiveness in a large heterogeneous sample of patients undergoing cancer treatment.[5] More information about PRO-CTCAE is available at https://healthcaredelivery.cancer.gov/pro-ctcae.

With CTCAE, clinicians integrate severity, frequency, and level of interference into a single severity grade for the adverse event. In the PRO-CTCAE, patients are asked separately to rate the frequency, severity, and level of interference regarding the adverse event on a Likert-type scale. The PRO-CTCAE score(s) are not the same as the CTCAE grade, and the 2 reports provide complementary information. Using clinician-graded assessments with patient reports of similar events may provide an improved means to identify tolerable treatment regimens.[6]

Adaptation of PRO-CTCAE for solid organ transplantation to capture the symptomatic adverse effects of ISTs could expand our understanding of toxicity profiles. However, the content validity of PRO-CTCAE for this purpose has yet to be established, as many adverse events related to ISTs are not currently included in the PRO-CTCAE item library. Thus, concept elicitation studies that reflect the patient experience concerning immunosuppressive-associated adverse effects, followed by item development and psychometric testing of new PRO-CTCAE items, would be required. Modifying PRO-CTCAE may represent

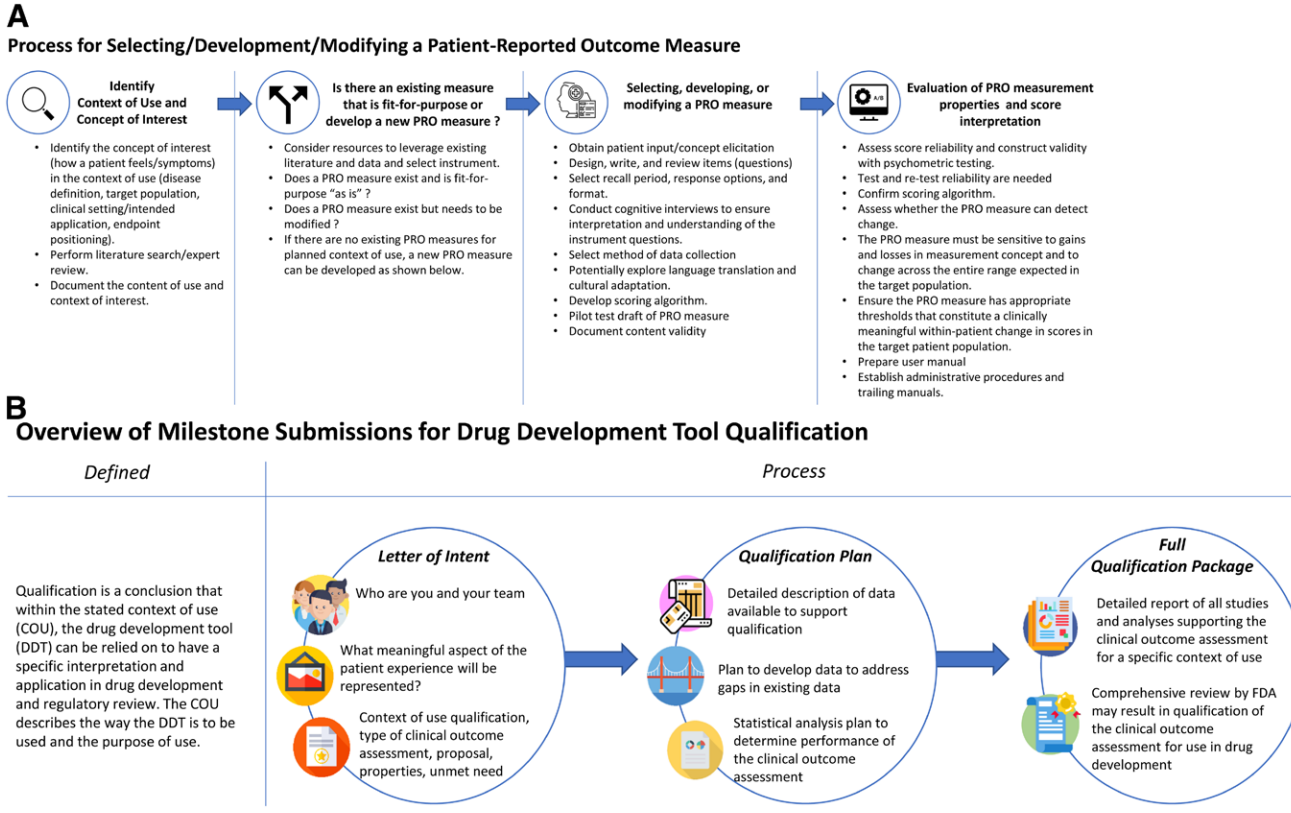

FIGURE 1. The PRO selection, development, and qualification processes. Panel A outlines the process for selecting a measure, developing, or modifying an existing measure, and evaluating a PRO measure is outlined, beginning with identifying the needs of the patients. Once a measure is developed and validated, it can be submitted to obtain a fit-for-purpose regulatory status or (as outlined in panel B) it can move along the path to qualification as a drug development tool. PRO, patient-reported outcome.

an expedited pathway to include the patient voice into drug labeling for transplant therapeutics. Another potential pathway would be to refine one of the existing PRO measures of side effects of immunosuppression that have been used in studies of solid organ transplantation. While these measures offer the benefit of demonstrated content validity for this patient population, most have had only limited evaluation of their measurement properties and a few of the measures are quite long.

IMPACT OF MEDICATION NONADHERENCE ON DRUG DEVELOPMENT IN SOLID ORGAN TRANSPLANTATION

Medication nonadherence in transplantation is strongly associated with transplant failure.[3] Thus, identifying and improving medication adherence during clinical trials can enrich outcomes. Unaccounted for medication nonadherence may lead to increased uncertainty in trial results and potentially lead to erroneous conclusions regarding safety and efficacy of novel agents. Medication nonadherence negatively impacts the validity and accuracy of clinical studies by lowering the overall study power, increasing variance, and decreasing the magnitude of visible treatment effects.[7]

For example, the recent MAGIC Trial determined that methods associating medication adherence with established daily routines and environmental cues significantly improve medication adherence and outcomes in adult kidney transplant recipients. The act of setting phone alarms or having medications located near routine activities (eg, coffeemakers, T.V. remotes, toothbrushes) was found to augment adherence rates by maximizing expediency and is consistent with strategies described by the patient panel in this workshop. The learnings from this study and others serve as a template for adherence interventions in clinical practice and could improve adherence rates in clinical trials. Further work is needed to evaluate how these methods could improve clinical trials.[8]

DESIGNING DRUG REGIMENS TO IMPROVE ADHERENCE IN TRANSPLANT CLINICAL TRIALS AND PRACTICE

The impact of medication nonadherence is an important consideration when designing clinical trials in transplantation. Clinical trial simulation (CTS) tools are models that describe disease progression, expected drug effects, placebo effects, dropout rates, and trial design effects.[9,10] CTS tools, when appropriately validated, can predict efficient study designs that reduce the trial size and duration while maintaining an adequate study power to characterize drug effects.[9] When CTS tools consider medication nonadherence data, the trial design is further informed. A study by Mallayasamy et al assessed the effect of different adherence patterns using a CTS tool. They concluded that as rates of medication nonadherence increase, the calculated number needed to treat (and therefore required trial size) also increases. This study also found drugs with shorter half-lives (~12 h) and delayed onsets of action-required trials with larger sample sizes due to lower adherence rates. Tools like these provide a powerful mechanism to improve the design of clinical trials and should encourage to develop novel agents that provide consistent drug levels while reducing the dosing burden, either through once daily dosing or monthly injections.[10] In addition to improving clinical trial designs, these considerations are consistent with patients' desires for medications with a lower burden of use and could facilitate improved medication adherence in the clinical care setting.

CONCLUSION

While advancements have been made since the 2018 workshop, there remains a clear need to incorporate the patient's voice into transplant drug development, which can be achieved through a multifaceted approach. Developing new or modifying existing PRO measures and seeking regulatory endorsement for an appropriate context of use should be an essential component of PFDD in transplantation. Increasing the use of PRO measures to provide a better understanding of the patient experience across multiple organ transplant types may lead to more informed clinical trial designs. Additionally, accounting for medication adherence in clinical trials may streamline clinical trial design and reduce uncertainty in trial results. By systematically incorporating the patient voice into transplant drug development, the process of developing safer and more efficacious therapies can be significantly optimized.

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