CONSENSUS PERSPECTIVE

Considerations for Endpoints in Lung Transplant Clinical Trials: Perspective on the ISHLT Consensus Statement

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Abbreviations: ACR, acute cellular rejection; AMR, antibody-mediated rejection; CLAD, chronic lung allograft dysfunction; ISHLT, International Society for Heart and Lung Transplantation; PFO, physical functioning outcome; PGD, primary graft dysfunction; PRO, patient-reported outcome

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KEYWORDS:
Lung transplantation; Clinical trial endpoints; Primary graft dysfunction; Chronic lung allograft dysfunction (CLAD); Antibody-mediated rejection (AMR); Patient-reported outcomes (PROs)

1. INTRODUCTION

New therapies are required to enhance survival rates and quality of life following lung transplantation.[1] Developing clinical trials in this field presents with specific challenges due to a limited number of potential participants and the need for extended follow-up periods for certain outcomes. Regulatory agencies evaluate clinical benefit based on changes in how participants feel, function, or survive.[2] Several shorter-term clinical endpoints are relevant for lung transplant recipients, but there remains uncertainty about their association with clinical benefit. Additionally, best practices for operationalizing and measuring these endpoints within a clinical trial framework, as well as their prioritization, have not been firmly established.

A multidisciplinary working group comprising 49 experts from the International Society for Heart and Lung Transplantation (ISHLT) was convened to develop consensus recommendations on lung transplant clinical trial endpoints beyond mortality. The resulting document is intended as a reference for stakeholders across the lung transplant clinical trial spectrum. It addresses endpoints including primary graft dysfunction (PGD), chronic lung allograft dysfunction (CLAD), acute cellular rejection (ACR), antibody mediated rejection (AMR), complications related to immunosuppression, and patient-reported outcomes (PROs). For each endpoint, the document describes the relationship of the endpoint to mortality or other clinically meaningful longer-term outcomes and gives recommendations on the approach to measure, operationalize, and, if applicable, adjudicate these conditions when used as trial endpoints. Simplified definitions are provided for some endpoints to enable their operationalization within the context of an interventional trial.

The Delphi method was used to facilitate and evaluate consensus around recommendation statements, identifying areas of strong agreement, and illuminating areas of less strong agreement where further research would be helpful to strengthen the evidence base. Below, we highlight some of the questions and areas of uncertainty addressed by the expert recommendations for each lung transplant interventional trial endpoint.

2. KEY TAKEAWAYS

1. The document proposes an optimal grade and timepoint of PGD assessment for a trial endpoint, clarifies PGD grading in participants on extracorporeal life support, and addresses whether central adjudication of radiographs and oxygenation information are required when PGD is used as a trial endpoint. The document also proposes a threshold for absolute or relative change in the rate of severe PGD that may be considered clinically meaningful based on available data and expert opinion.

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2. The document provides a strong rationale for using probable CLAD as a primary endpoint. For CLAD treatment trials, consensus is reported on clinically meaningful lung function outcomes, analytic strategies to account for the competing risks of death or retransplant, and the lung function decline parameters needed to optimize the target population. Other important variables to collect and consider, such as baseline lung allograft function and time posttransplant, are discussed and the value of blinded CLAD adjudication is addressed.
3. ACR and AMR are important endpoints. Given challenges seen using variable ACR trial endpoint definitions, the document proposes a robust and operationalizable ACR endpoint, supported by available literature and expert opinion, and endorses practices to standardize ACR pathological interpretation across participating centers. With regard to AMR, it is acknowledged that the definition of AMR as originally reported in the ISHLT 2016 consensus document and revisited in a recent ISHLT working group[3] is challenging to operationalize in the clinical trial framework. Thus, the document considers the strength of the evidence supporting AMR as a clinical trial endpoint and proposes a simplified and reproducible approach to define AMR when used as a clinical trial endpoint.
4. Endpoints such as PGD, CLAD, ACR, and AMR do not capture all of what is important to patients. Measuring the impact of investigational therapies on how patients feel and function is important to stakeholders across the clinical trial spectrum including patients, physicians, and regulatory bodies. The document provides a detailed synthesis of patient-reported outcome (PRO) measures and physical function outcome (PFO) measures to guide selection for trials. There are both generic and lung transplant-specific PRO and PFO instruments that meet key validity criteria for use in clinical trials in lung transplantation, but the domains measured, responsiveness to transplant, and time needed to complete vary across the instruments.
5. The document considers points regarding the evaluation of complications of immunosuppression during trial conduct, with detailed guidance on assessment of infection and renal impairment. Additionally, specific considerations relevant to clinical trials in the pediatric lung transplant population are given, including ensuring robust plans to extrapolate data from adult trials to children given declining numbers of pediatric recipients limit trials exclusively in this population.

3. CONCLUSION

This statement provides guidance on endpoints for clinical trials in lung transplantation, describing their relative merit and offering direction on robust measurement. Emerging concepts in the lung transplant field, such as acute lung allograft dysfunction and baseline lung allograft dysfunction,[4] may be relevant to future lung transplant clinical trials, but were not explored in detail because their definitions and construct validity are still being established. We also acknowledge that various biological measures, such as circulating donor-derived cell-free DNA and transcriptomic or cellular profiling, may have an emerging role in targeting therapies to high-risk individuals or individuals with specific endotypic features,[5] yet detailed discussion of surrogate biomarker endpoints were beyond the scope of the current document.

There is a substantial unmet need for clinical trials in lung transplantation. Such trials are necessary to establish a strong foundation of evidence for current and future therapies. We trust this document will facilitate and accelerate innovative and effective trials in this critical area and illuminate evidence gaps for future research.

References

1. Swaminathan AC, Todd JL, Palmer SM. Advances in human lung transplantation. Annu Rev Med 2021;72:135-49.

2 FDA-NIH Biomarker Working Group. BEST (Biomarkers, EndpointS, and other Tools) Resource [Internet]. Silver Spring (MD): Food and Drug Administration (US); 2016-. Reasonably Likely Surrogate Endpoint. 2017 Sep 25 [Updated 2020 Sep 23].

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3. Levine DJ, Glanville AR, Aboyoun C, et al. Antibody-mediated rejection of the lung: a consensus report of the International Society for Heart and Lung Transplantation. J Heart Lung Transpl 2016;35:397-406.

4. Verleden GM, Bos S. The ABC of transplant: ALAD, BLAD, and CLAD: definition and significance. Curr Opin Pulm Med 2025.

5. Verleden SE, Hendriks JMH, Lauwers P, Yogeswaran SK, Verplancke V, Kwakkel-Van-Erp JM. Biomarkers for chronic lung allograft dysfunction: ready for prime time? Transplantation 2023;107:341-50.

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