CONSENSUS STATEMENT

Considerations for Endpoints in Lung Transplant Clinical Trials: An ISHLT Consensus Statement

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Abbreviations: ACR, acute cellular rejection; AKI, Acute kidney injury; ARDS, acute respiratory distress syndrome; ATS, American Thoracic Society; BAL, bronchoalveolar lavage; BLAD, baseline lung allograft dysfunction; CF, cystic fibrosis; CFTR, cystic fibrosis transmembrane conductance regulator; CKD, chronic kidney disease; CKD-EPI, Chronic Kidney Disease Epidemiology Collaboration; CLAD, chronic lung allograft dysfunction; CMV, cytomegalovirus; CTS, Canadian Thoracic Society; ddcfDNA, donor-derived cell-free DNA; DSA, donor-specific antibodies; ECLS, extracorporeal life support; ECMO, extracorporeal membrane oxygenation; eGFR, estimated glomerular filtration rate; eGFRcr, estimated glomerular filtration rate based on creatinine; eGFRcr-cys, estimated glomerular filtration rate based on creatinine and cystatin C; EMA, European Medicines Agency; FDA, United States Food and Drug Administration; FEV1, forced expiratory volume in 1-second; FFP, Fried Frailty Phenotype; FVC, forced vital capacity; HRQL, health-related quality of life; ISHLT, International Society for Heart and Lung Transplantation; KDIGO, Kidney Disease: Improving Global Outcomes; LASHA, lung allograft standardized histological analysis; LB, lymphocytic bronchiolitis; LT-FS, Lung Transplant Frailty Scale; LTOG, Lung Transplant Outcomes Group; OPTN, Organ Procurement and Transplantation Network; PFO, Physical Functioning Outcome; PGD, primary graft dysfunction; PRO, Patient Reported Outcome; PTLD, post-transplant lymphoproliferative disorder; SMWD, six-minute walk distance; SPPB, Short Physical Performance Battery; STAR, Sensitization in Transplantation Assessment of Risk

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Clinical trials in lung transplantation have been hindered by a lack of clarity on the formulation and significance of endpoints for evaluating therapeutic efficacy. To address this challenge, a multidisciplinary working group from the International Society for Heart and Lung Transplantation developed consensus recommendations on endpoints beyond mortality. These endpoints include primary graft dysfunction (PGD), chronic lung allograft dysfunction (CLAD), acute cellular rejection (ACR), antibody-mediated rejection (AMR), immunosuppression-related complications, patient-reported outcomes (PROs), and pediatric-specific considerations. For each endpoint, a subgroup reviewed measurement best practices, assessed links to clinical benefit, and evaluated the evidence supporting their utility in clinical trial settings. Consensus was established through a Delphi process involving three rounds of voting. This document provides practical guidance for operationalizing these endpoints and

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outlines their optimal use in clinical trials. By standardizing trial design, these recommendations aim to accelerate the development of urgently needed therapies to improve lung transplantation outcomes.
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1. INTRODUCTION

Long-term outcomes following lung transplantation remain limited: Primary graft dysfunction, antibody-mediated and acute cellular rejection, chronic lung allograft dysfunction (CLAD), and other complications can impact quality of life, physical function, and survival. CLAD, for example, affects up to 50% of lung transplant recipients by five years posttransplant, causes impairments in quality of life, and is the leading cause of death late post transplant.[1] New therapeutic approaches, such as novel immunosuppressive strategies, are needed to advance the field. Clinical trials are the cornerstone of an evidence-based approach to improve lung transplant outcomes. However, barriers to clinical trials in this field include a lack of clarity as to the value of specific clinical trial endpoints, the time needed to reach some endpoints, and complexities in how trials should be structured given the heterogeneity and small size of the lung transplantation population. The goal of this document is to describe consensus opinion on considerations for endpoints in interventional studies in lung transplantation.

The United States Food and Drug Administration (FDA) defines clinical benefit as the "positive effect on how an individual feels, functions, or survives".[2] A surrogate endpoint is a precisely defined variable that is expected to correlate with one of these established clinical benefit endpoints. Surrogate endpoints that are "validated" or "reasonably likely" may be used for approval of drugs or medical devices, depending on the context.[2] The European Medicines Agency (EMA) also supports the use of "reasonably likely" surrogate endpoints to accelerate clinical trials in small populations.[3] In solid organ transplantation, death and graft failure are fundamental endpoints that must be considered in any study, but other endpoints become necessary to provide comprehensive assessments in a reasonable timeframe.[4] Well-described and commonly used endpoints in lung transplantation include primary graft dysfunction (PGD), acute cellular rejection (ACR), infection and chronic kidney disease or other complications related to the use of immunosuppressive therapies, patient reported health-related quality of life, and CLAD.

Here we present consensus opinions on considerations and definitions for these endpoints, which may be targeted in clinical trials of novel interventions aimed at improving lung recipient outcomes. We describe measurement best practices and links between surrogate endpoints and clinical benefit, informed by the available literature and expert experience. In many cases these endpoints remain imperfect, and clinically meaningful changes are not well-established. While several DNA, RNA, and protein-based biomarkers could theoretically function as surrogate endpoints,[5] they have not yet been rigorously validated and are therefore beyond the scope of the current document. It is understood that optimal design for a given trial will be determined by the expected risks and benefits of the intervention under study. Some areas are actively evolving, such as the impact of CFTR modulators on pediatric transplant populations, and opinions may change as additional evidence accumulates.

Clinical trials in lung transplantation can be challenging because of limited numbers of eligible participants and heterogenous clinical presentations. Novel trial designs may help address these issues and increase efficiency: Adaptive designs can dynamically adjust interventions based on interim results, potentially utilizing Bayesian methods to integrate prior knowledge.[6] Platform trials can streamline the evaluation of multiple interventions within a shared infrastructure.[7] Synthetic controls can further minimize assignment to placebo arms.[8] Pragmatic trials can assess interventions within the context of routine clinical practice,[9] and real-world evidence studies can draw insights from the variability in transplant care across different centers.[10]

Clinical trials in lung transplantation should incorporate contemporary guidance on best trial practices, including randomization, blinding, and stopping rules monitored via an independent safety board, where possible.

2. METHODS

The detailed methods used for the creation of this document are presented in Section A of the Supplemental Material, available online at www.jhltonline.org. Briefly, an international workgroup of 47 specialists in lung transplantation, including lung transplant pulmonologists and experts in related allied fields, was created and divided into 7 subgroups each covering a specific content area. The subgroup content areas included primary graft dysfunction, chronic lung allograft dysfunction, antibody mediated rejection, acute cellular rejection, quality of life and physical functioning, complications of immunosuppression and pediatrics. Given the nature of the document discussing clinical trial endpoints, two experts from statistics also participated in the document review and voting but were not part of specific content area subgroup (49 total). The subgroups were charged with performing a focused literature review relevant to their content area (Supplement), discussing shared expertise, and drafting proposed statements to represent consensus recommendations based on available literature and, where literature is lacking, expert experience. All statements were subjected to voting by all workgroup members according to the Delphi method. Specifically, three rounds of voting were conducted. The first round of voting was focused on the completeness of each content area and comprehensiveness of the proposed statements. The second and third round of voting were to evaluate the level of agreement of each working group member with each proposed statement. Revisions to the document and statements were made after the first round of voting. Additional revisions to the discussion (but not voting statements) were made after rounds 2 and 3 were complete. The voters rated each statement on a scale of −3 (strongly disagree) to +3 (strongly agree) using a 7-point Likert scale. For each statement, a space was available to suggest revisions. The level of consensus was defined as the percent of responders who voted within 1 integer of the median. Agreement was calculated as the percent of responders who voted "slightly agree" (1) or more on the 7-point Likert scale. Members were also permitted to abstain. Abstentions were removed from the vote count such that percent agreement and percent concordance are calculated from among the number of non-abstaining votes. For each statement, the median of votes, level of consensus and agreement, and number of abstaining members is also shown.

3. PRIMARY GRAFT DYSFUNCTION

Primary graft dysfunction (PGD) is a frequent and serious early outcome after lung transplantation, occurring in 14–38% of all recipients.[11,12] Severe PGD, defined by the 2016 International Society for Heart and Lung Transplantation (ISHLT) consensus as grade 3 PGD at either 48 or 72 h after transplant (PGD3),[11] is validated and approved by the FDA as a primary clinical trial endpoint.[13,14] PGD3 at 48 h or 72 h has been associated with increased risk of death, increased acute cellular rejection (ACR), lower peak lung function, and CLAD.[11,15–18] PGD3 is also associated with worse health-related quality of life (HRQL) and more frequent hospitalizations.[19,20] In the pediatric population, PGD3 is associated with shorter CLAD-free survival.[21] Therefore, PGD3 at 48 or 72 h is an early posttransplant outcome that informs important clinical benefit endpoints. The minimum change in the incidence of PGD3 at 48 or 72 h that represents a clinically meaningful improvement is not well established. Further, it is uncertain whether an absolute change or relative change in the rate of PGD3 would be viewed as more clinically meaningful. One example of PGD as a study endpoint was used in the INSPIRE trial, which assessed PGD as an outcome in recipients of lungs undergoing ex-vivo lung perfusion. This trial considered an absolute change in grade 2 or 3 PGD at 72 h of 7.5% as a secondary non-inferiority endpoint to determine study power.[22] This subgroup assessed one possible absolute change and one possible relative change in PGD to be considered for clinical trial endpoints, with the specific values being selected by the group. It is important to note that secondary endpoints like time to extubation[23] or time to liberation from ventilatory support may be important adjunct outcomes in a clinical trial studying PGD.

Although the definition of PGD requires assessment of chest radiographs for opacities consistent with allograft edema, this criterion is potentially limited by high variability in x-ray interpretation.[24] To account for this variability and general complexities of PGD assessment, some multi-center studies such as the Lung Transplant Outcomes Group (LTOG) have employed centralized PGD adjudication. In contrast, other groups have had each participating center report PGD grading as determined by local adjudication of radiographs and oxygenation. Central adjudication of PGD grading is time-intensive and may contribute to logistical challenges in future trial execution. This has led to the question of whether PGD can be graded without assessment of chest radiographs, a topic that should be addressed in any future revisions of PGD definitions.

Additionally, increasing use of mechanical circulatory support (extracorporeal life support [ECLS] or extracorporeal membrane oxygenation [ECMO]) in the post-operative setting adds complexity to the assessment of PGD in certain

patients. Currently, patients requiring post-operative ECLS are categorized as PGD3 if ECLS is used for hypoxemic respiratory failure, and otherwise are considered ungradable if ECLS is being used for hemodynamic support, particularly in patients with pulmonary hypertension.[11] Future clinical trials will need to specify whether these patients will be included in PGD endpoints for the specific intervention being tested. In general, intra-operative ECLS use that does not extend into post-operative care is not considered in PGD grading. As indications for ECLS expand, there will be greater complexity in postoperative care that may complicate assessment of PGD in these patients and alter the validity of PGD grading. This is another area for consideration in future iterations of PGD definitions.

In summary, grade 3 PGD at 48 or 72 h is an early posttransplant outcome that correlates with clinical benefit as defined by regulatory bodies and identifies adult lung transplant recipients at risk of poor patient-centered outcomes. Notably, recent data suggest that there may be biological heterogeneity within severe PGD that may differentially affect outcomes,[25] however it is not currently understood what mechanisms underlie these differences and how these endotypic features should be accounted for in considering PGD as an endpoint.

Delphi Statements.

1. Severe PGD (PGD3) is defined as a PaO_2:FiO_2 ratio of < 200 at 48 or 72 h (with a window of +/- 6 h) after reperfusion.
   Median: 3 (Strongly agree), 98% concordance, 98% agreement, 8 abstentions.
2. Table 1 should be used to grade PGD in the setting of ECLS:
   Median: 2 (Agree), 76% concordance, 76% agreement, 11 abstentions.
3. When PGD is the primary study endpoint, PGD grading should require central adjudication of radiographs.
   Median: 2 (Agree), 83% concordance, 83% agreement, 7 abstentions.
4. When PGD is the primary study endpoint, PGD grading should require central adjudication of oxygenation information.
   Median: 0 (Neither Agree nor Disagree), 41% concordance, 43% agreement, 5 abstentions.
5. When PGD is included as a study endpoint, radiographic images should be collected centrally to allow for use in future studies.
   Median: 1 (Somewhat agree), 77% concordance, 82% agreement, 5 abstentions.
6. A 7.5% absolute change in the rate of severe PGD (PGD3) would be clinically meaningful.
   Median: 1 (Somewhat agree), 81% concordance, 83% agreement, 7 abstentions.
7. A 10% relative change in the rate of severe PGD (PGD3) would be clinically meaningful.
   Median: 2 (Agree), 93% concordance, 93% agreement, 7 abstentions.
8. Consensus on PGD as a clinical trial endpoint from adult lung recipients can be extrapolated to pediatric lung transplant recipients.
   Median: 2 (Agree), 89% concordance, 89% agreement, 12 abstentions.

4. ACUTE CELLULAR REJECTION

Consensus on the diagnostic requisites and pathologic grading of biopsy-proven ACR has been previously published.[26] Numerous studies have reported ACR as a strong risk factor for the development of CLAD,[27–30] with more frequent and severe episodes of ACR conferring increased CLAD risk. This supports ACR as a plausible surrogate endpoint in lung transplant studies examining the impact of interventions, including for CLAD. It is important to note that although ACR meets some of the epidemiological criteria for a surrogate endpoint, its

Table 1 PGD Grading in the Setting of Extracorporeal Life Support (ECLS)

Chest X-ray	ECLS for Post-operative Hypoxemic Respiratory Failure	ECLS for Only Non-respiratory Indications
CXR with diffuse alveolar opacities	PGD 3	ungradable
CXR normal	PGD 0	PGD 0
CXR unavailable	ungradable	ungradable

association with CLAD or death has not been consistently validated in prospective studies.[27,28,31–33] ACR has been used as a primary endpoint in clinical trials, however the way in which the ACR endpoint was defined varied. Some trials have defined the incidence of biopsy-proven grade A2 or greater ACR,[34] while other trials use alternative methods such as histological grade A1 or greater ACR,[35] the cumulative A grade score or cumulative B grade score within a specified time period in an effort to reflect overall burden of ACR,[36] or presumed ACR with clinical signs of graft dysfunction (spirometric decline, hypoxemia, radiographic opacities) in the absence of infection that responds to augmented immunosuppressive therapy.[37] Others have considered ACR as part of a composite endpoint reflecting important complications. For example, the ScanCLAD study used a composite endpoint of treated ACR, CLAD, graft loss, or death.[38] When considering a composite endpoint that includes ACR, inclusion of additional markers associated with ACR and/or subsequent CLAD, such as BAL immune cell proportions, may strengthen classification for trial purposes.[39,40]

There are several considerations identified by our consensus group regarding the use of ACR as a clinical trial endpoint. We recommend the use of ≥A2 grade ACR *or* spirometrically-significant (defined as a 10% or greater decline in FEV1 from prior) ≥A1 grade ACR as an endpoint when considering ACR. Episodes of such severity and spirometric significance are almost uniformly treated by transplant centers and are consistently correlated with CLAD.[27,28,31,33,41] This contrasts with asymptomatic grade A1 ACR which is variably treated by transplant centers and inconsistently associated with CLAD.[32–34,36,42] Published data and clinical experience do not support the use of lymphocytic bronchiolitis (LB, or B-grade rejection) as a clinical trial endpoint. This is in part due to the difficulty in attributing the histopathological presence of LB to ACR in the setting of concomitant infection and the variable presence of bronchioles in transbronchial biopsy samples which often precludes ability to diagnose and grade LB.[26] Our consensus group recognizes the value of clinical, non-histopathological correlates of ACR such as symptoms, spirometry, radiology, inflammation on BAL, exclusion of infection, treatment initiation, details of treatment given, and/or treatment response. In this context, collection of granular clinical information enables subsequent detailed interpretation of trial data as required. However, clinically-presumed ACR without biopsy may reflect overlapping pathologies that could impact trial endpoints.

It is important to note that while pathologic grading of ACR has been defined by the ISHLT,[26] inter-rater variability amongst lung transplant pathologists is often cited as an obstacle to standardization of trial endpoint assessment with a range of reported kappa values in the literature showing poor to modest agreement.[43–45] For this reason, we support prospective discussion amongst center pathologists to foster better concordance of histologic grading across sites prior to trial initiation. The optimal method when considering this aspect of trial design may be to perform a centralized pre-trial "harmonization" session between all participating center pathologists to agree on histopathologic grading approach of ACR in advance of study initiation.[46] The study should then continue with center-level pathology review of transbronchial biopsy specimens, ideally followed by blinded central review to ensure standardization in reporting throughout the study. A digital slide repository would allow multiple pathologists to review histology of biopsy specimens and promote standardization across study sites.

As with PGD, the term ACR represents a spectrum of disease that encompasses a vastly heterogeneous group of histological, physiological, and clinical entities with potentially unique biological underpinnings. Parallel analyses of not only lung histology but also established and emerging biological measures such as cellular components and proteins in the bronchoalveolar lavage fluid, circulating donor-derived cell-free DNA, and molecular analyses of biopsies or airway brushings are needed to inform and refine ACR as an endpoint in the future.[47]

Delphi Statements:

1. In the context of a clinical trial where long-term endpoints such as CLAD or death cannot be readily measured, e.g. due to sample size requirements or follow-up time, ACR may be an appropriate secondary endpoint, although care should be taken to articulate that ACR is a less clinically meaningful endpoint than CLAD in trial design.
   Median: 2 (Agree), 96% concordance, 96% agreement, 3 abstentions.
2. Prior to study initiation, pathological considerations of ACR should be discussed and agreed upon by pathologists across participating centers, through a consensus-style conference.
   Median: 3 (Strongly agree), 98% concordance, 100% agreement, 3 abstentions.
3. ISHLT Grade ≥A2; *or* ISHLT Grade ≥A1 with *either* a decline in FEV_1 of at least 10% from recent baseline, *or* other clinical evidence of graft injury; such as new breathlessness, ground glass opacification on HRCT or new oxygen requirement, are appropriate clinical endpoints.
   Median: 2 (Agree), 98% concordance, 98% agreement, 4 abstentions.

4. Clinician decision to treat ACR may be a reasonable endpoint, independent of pathology. Clear documentation of clinical indication is mandatory for cross-site comparison purposes.
   Median: 1 (Somewhat agree), 80% concordance, 84% agreement, 4 abstentions.
5. Non-pathological qualifiers of ACR are important to consider in clinical management and should be reported in future lung transplant studies. These include the following: symptoms, spirometry, radiology, inflammation on BAL, exclusion of infection, treatment initiation, details of treatment given, and/or treatment response.
   Median: 2 (Agree), 98% concordance, 98% agreement, 5 abstentions.
6. Parallel analyses of emerging biomarkers (such as BAL cellular components and proteins, plasma ddcfDNA, molecular analysis of biopsies or airway brushings, and others) are urgently needed to allow for clinical utilization.
   Median: 3 (Strongly agree), 93% concordance, 100% agreement, 3 abstentions.
7. Standardization of clinical trial frameworks with defined timepoints for data/sample collection are critical for ongoing validation of emerging biomarkers of ACR.
   Median: 3 (Strongly agree), 96% concordance, 100% agreement, 3 abstentions.

5. ANTIBODY MEDIATED REJECTION

Pulmonary antibody mediated rejection (AMR) is associated with increased risk for CLAD and can lead to profound functional decline and even death. However, the complexities and diagnostic uncertainties of AMR make it a challenging endpoint for interventional clinical studies. Prior to the 2016 ISHLT consensus statement,[48] which provided a framework for AMR diagnosis, AMR was rarely included in interventional trials. Despite the introduction of the 2016 criteria, the diagnosis of AMR remains challenging, limiting its use as a primary or secondary trial endpoint. [49–52] The majority of the data on AMR as a marker of post lung transplant outcomes comes from observational or retrospective studies.[53] The definitions proposed here represent the best current guidance for use of AMR as primary or secondary endpoint. While further validation is needed to strengthen its role as a clinical trial endpoint, (as stated in statement 7), this should not be interpreted as a discouragement of trials investigating AMR.

Current best practice for diagnosing AMR requires a high index of suspicion and a comprehensive assessment of multiple diagnostic criteria including histologic findings, circulating donor-specific antibodies (DSA), evidence of complement binding, and clinical correlates.[48] Antibodies with high-risk characteristics—such as high titer, C1q-binding, or DQ subtypes[44–48]—along with histologic features like neutrophilic capillaritis, organizing pneumonia, or diffuse alveolar damage,[54] have been independently linked to worse outcomes. This has led to recent studies associating AMR with poor prognosis, including the development of CLAD and increased mortality.[50,51] However, these same studies have highlighted significant gaps in the recognition and standardization of AMR-related changes. Challenges in adjudicating AMR arise from the lack of specificity in histopathologic features, variability in DSA assays and reporting, and the limited sensitivity of current methods for detecting complement deposition. Two recent additions to the literature have begun to address these limitations. The lung allograft standardized histological analysis (LASHA) collaboration[55] introduced a standardized framework for assessing histologic findings, while the Sensitization in Transplantation Assessment of Risk (STAR) consensus statement[53] provided guidance on post-transplant DSA evaluation and its clinical application. The ISHLT recently convened a working group of experts to revise the 2016 AMR consensus report. While the 2016 criteria framed AMR within a probabilistic framework—categorizing diagnostic certainty as possible, probable, or definite—the proposed 2025 revision shifts toward a more descriptive approach, emphasizing clinical, histological, and immunological features. However, neither framework defines disease severity or provides a specific definition of graft dysfunction. Recognizing the need for simple and reproducible AMR classifications for the clinical trial endpoints, we propose categorizing AMR as subclinical or clinical, based on the presence of graft dysfunction. The 2025 proposed AMR definition acknowledges that ACR or infection may coexist with AMR, however excluding other causes would improve the specificity as a trial endpoint.[56] This raises ongoing debate on how to approach co-existing diagnoses, as seen in Statement 5. The optimal approach will depend on the specific trial design and should be detailed in the trial methodology.

Delphi Statements:

1. AMR is associated with CLAD and decreased graft and patient survival, making it an important unmet clinical need.
   Median: 3 (Strongly agree), 100% concordance, 100% agreement, 3 abstentions.

2. A subclinical AMR (without graft dysfunction) endpoint can be defined by evidence of humoral activation, specifically: *de novo* DSA, evidence of complement binding, and/or histologic changes consistent with AMR.
   Median: 2 (Agree), 95% concordance, 95% agreement, 5 abstentions.
3. Clinical AMR as an endpoint requires both meeting criteria for subclinical AMR and having evidence of graft dysfunction.
   Median: 3 (Strongly agree), 98% concordance, 100% agreement, 4 abstentions.
4. In the context of using AMR as a trial endpoint, graft dysfunction can be defined as a ≥10% decline in FEV1 within 6 months, a new or increase in oxygen requirement, or new or worsening abnormalities on chest imaging without an alternative diagnosis.
   Median: 2 (Agree), 98% concordance, 98% agreement, 5 abstentions.
5. We recommend excluding patients with coexisting diagnoses, such as ACR or infection, from this definition of AMR-associated graft dysfunction.
   Median: 0 (Neither Agree nor Disagree), 58% concordance, 49% agreement, 6 abstentions.
6. The reliability and performance of AMR definitions have yet to be demonstrated.
   Median: 2 (Agree), 91% concordance, 91% agreement, 3 abstentions.
7. The diagnosis of AMR should be better validated before it can be used as a primary endpoint in clinical trials.
   Median: 2 (Agree), 80% concordance, 80% agreement, 5 abstentions.
8. The relative clinical significance of AMR diagnostic subcomponents is yet to be determined.
   Median: 2 (Agree), 98% concordance, 98% agreement, 4 abstentions.

6. CHRONIC LUNG ALLOGRAFT DYSFUNCTION

CLAD is a clinical syndrome of persistent loss of lung allograft function from established baseline after lung transplantation, not explained by other conditions.[1,57] CLAD diagnosis is probabilistic, with *possible* (< 3 weeks), *probable* (3 weeks – 3 months), and *definite* (> 3months) phases established in the 2019 ISHLT consensus document on CLAD.[1] Possible CLAD may spontaneously resolve, so we recommend probable or definite CLAD as rigorous endpoints. FEV1 should be measured per ATS/ERS standards in a pulmonary function lab, as home spirometry may not be as reliable.[58,59] Greater than 10% FEV1 decline in the 6-months after CLAD onset can be considered rapidly progressive and is associated with worse outcomes.[60] Similarly, CLAD onset early post-transplant may have a more aggressive course, leading to bias if time post-transplant if not considered in the study design. Four potential phenotypes of CLAD have been described including bronchiolitis obliterans syndrome, restrictive allograft syndrome, mixed, and undefined which may associate with differential survival.[1,57] We agree with the 2019 consensus statement recommendation for calculating baseline lung function but note emerging data that baseline lung allograft dysfunction (BLAD) may be associated with worse outcomes, as addressed in statement 6. Current treatment options are limited, and clinical trials in CLAD prevention and treatment constitute an urgent unmet clinical need.[61] The most relevant endpoints for clinical trials in CLAD have not been well-defined. As such, we summarize here clinical and surrogate endpoints with regards to CLAD prevention and treatment trials, aiming to develop recommendations for future clinical trial design strategies and novel clinical trial approaches in CLAD. CLAD onset is a reliable diagnosis that has been shown to have good interobserver reproducibility both in terms of its presence and timing of onset.[62] CLAD has been shown to be associated with reduced quality of life, poorer performance status, and increased risk of death. Hence, therapies which delay the onset or progression of CLAD are likely to delay these risks as well.[63,64]

With regard to CLAD prevention trials, we suggest the primary endpoint of time from initiation of study intervention to probable CLAD onset, with death and retransplant included in a composite endpoint or considered as competing risks.[38] Alternate endpoints of acute lung allograft dysfunction (> 10% decline in FEV1 without a requirement for persistence) might improve study efficiency but have not yet been sufficiently validated. Based on available evidence and previous trials, for CLAD treatment studies we suggest the primary endpoint of time from treatment assignment to CLAD progression, with death and retransplant included in a composite endpoint or as competing risks.[60,65–67] Cause of death – particularly CLAD/respiratory versus other – should be recorded and accounted for in analyses. The use of composite endpoints can help improve study power and better reflects real world risk, but additional analyses should evaluate individual components (Table 2).[68]

Therapeutic trials could consider including patients in the *possible* and *probable* phases of the CLAD diagnostic algorithm as well as patients with FEV_1 decline between 10–19% from baseline, as these phases may

Table 2 Proposed Endpoints in CLAD Clinical Trials

Endpoint	Objective	Endpoint Type	Primary vs. Secondary	Notes
CLAD Prevention Trials				
CLAD onset (preferred)	CLAD development	Single	Primary	CLAD as the event; death or retransplant are competing outcomes
CLAD onset or death	CLAD-free survival	Composite	Primary	
CLAD onset or death or retransplantation	CLAD-free allograft survival	Composite	Primary	
Death	Overall survival	Single	Secondary	
Death or retransplantation	Allograft survival	Composite	Secondary	
CLAD Treatment Trials				
FEV_1 decline (preferred)	CLAD progression	Single	Primary	Analyzed from enrollment as an >=10% decline threshold (preferred) or continuously
FVC decline	CLAD progression	Single	Primary	Analyzed together with FEV_1 decline (preferred)
CLAD progression or death or retransplantation	CLAD progression-free allograft survival	Composite	Primary	
Death	Overall survival	Single	Secondary	
Death or retransplantation	Allograft survival	Composite	Secondary	

be more modifiable by early intervention. Trial design and/or analyses should account for CLAD phenotypes. The optimal duration of treatment and prevention trials as well as timing of endpoint assessments is not clear, but we propose assessments at 1, 3-, 6-, 9-, and 12-months for treatment trials and 6-, 12-, 18-, 24-, and 36-months in prevention trials, based on current knowledge regarding CLAD prevalence and progression over time. Careful modeling including the projected impact on rate of FEV_1 decline may however allow for shorter trials. The role of CLAD biomarkers remains exploratory, and these are not felt to be ready for deployment as surrogate endpoints.[5,69] However, clinical trials for CLAD prevention and treatment should routinely evaluate and report comprehensive endpoints, such as lung physiology, imaging, patient-reported outcome measures, and hypothesis-driven biomarkers with the goal of facilitating discovery of surrogate markers for future CLAD research, surveillance, and prognostication.

Delphi Statements:

General:

1. Clinical trials for CLAD prevention and treatment are an unmet clinical need.
   Median: 3 (Strongly agree), 100% concordance, 100% agreement, 3 abstentions.
2. Interventions that delay time to CLAD onset or progression are expected to improve survival, health-related quality of life, and functional status.
   Median: 3 (Strongly agree), 98% concordance, 100% agreement, 3 abstentions.
3. CLAD should be diagnosed according to the ISHLT 2019 consensus statement.[1]
   Median: 3 (Strongly agree), 98% concordance, 100% agreement, 4 abstentions.
4. CLAD diagnosis adjudication should be blinded to study intervention.
   Median: 3 (Strongly agree), 91% concordance, 100% agreement, 4 abstentions.
5. Endpoint assessments should be measured, at minimum, at 1-, 3-, 6-, 9-, and 12-months post-study intervention assignment.
   Median: 2 (Agree), 100% concordance, 100% agreement, 4 abstentions.
6. Clinical trials for CLAD prevention and treatment should account for the patient's best level of post-transplant lung function (baseline lung allograft function).
   Median: 3 (Strongly agree), 93% concordance, 98% agreement, 5 abstentions.

7. Clinical trials for CLAD prevention and treatment should routinely evaluate and report comprehensive endpoints, such as lung physiology, imaging, patient-reported outcome measures, and hypothesis-driven biomarkers with the goal of facilitating discovery of surrogate markers for CLAD research, surveillance, and prognostication.
   Median: 2 (Agree), 100% concordance, 100% agreement, 3 abstentions.
   CLAD prevention trials:
8. CLAD prevention trials should use time from initiation of study intervention to CLAD onset as the primary endpoint, with death and retransplant reported and analyzed as competing risks for CLAD or in a composite endpoint with CLAD onset.
   Median: 3 (Strongly agree), 95% concordance, 98% agreement, 5 abstentions.
9. CLAD prevention trials that enroll patients at varying times post-lung transplantation should account for these differences via study design and/or analysis.
   Median: 3 (Strongly agree), 98% concordance, 98% agreement, 5 abstentions.
   CLAD treatment trials:
10. CLAD treatment trials should use time from treatment assignment to CLAD progression (defined by FEV1 ± FVC decline of > 10%) as the primary endpoint, with death and retransplant reported and analyzed as competing risks or in a composite endpoint with CLAD progression.
    Median: 2 (Agree), 96% concordance, 96% agreement, 3 abstentions.
11. CLAD treatment trials should account for CLAD phenotypes.[57]
    Median: 3 (Strongly agree), 89% concordance, 96% agreement, 3 abstentions.
12. To increase the likelihood of including patients with actively declining CLAD, CLAD treatment trials could consider enrolling patients with probable CLAD (i.e, FEV1 ± FVC decline to < 80% of baseline for 3 weeks-3 months), possible CLAD (i.e, FEV1 ± FVC decline to < 80% of baseline for < 3 weeks), and patients with persistent (> 3 weeks) FEV1 ± FVC decline between 10-19% from baseline consistent with early CLAD.
    Median: 2 (Agree), 89% concordance, 89% agreement, 5 abstentions.
13. CLAD treatment trials that enroll patients at varying times after CLAD development (i.e., the first date on which lung function definitively declines to < 80% of baseline) should account for these differences via study design and/or analysis.
    Median: 3 (Strongly agree), 93% concordance, 100% agreement, 4 abstentions.

7. QUALITY OF LIFE

7.1. Health-Related Quality of Life (HRQL) and Other Patient Reported Outcomes (PROs)

Lung transplantation aims to improve survival, physical functioning, symptom burden, and HRQL for patients suffering from advanced lung disease.[70] The latter two aims are generally solicited directly from patients through survey-based methods called patient-reported outcomes (PROs). PROs directly reflect patients' health related experience and yield information that cannot be derived from any other source. Since clinically, lung transplant is deemed successful if patients experience both improved survival and HRQL, PROs are important outcomes to all stakeholders. For this reason, where feasible, clinical trials should include at least one PRO. Measures of physical function/performance are not substitutes for PROs, as they do not directly measure patients' psychosocial, 'lived' experiences, which may differ from their physical function. Some transplant recipients may continue to engage in routine physical activity even in the presence of poor HRQL, for example.

PROs selected for clinical trials should be fit-for-purpose and meet generally accepted validity standards.[71–73] They should capture conceptual health domains deemed important and relevant to lung transplant patients. PROs should be reliable, discriminative, and plausibly responsive to the direct and indirect effects of the intervention on how patients feel and function. Validated PROs designed to query outcome domains relevant to lung transplant recipients are uniquely calibrated to capture the heterogeneous, multidomain changes in functioning and symptomatology often experienced by lung transplant recipients. While generic measures may be effective for capturing broad changes, they may fail to capture other health domains highly valued by, and often impaired among, lung transplant recipients (e.g., treatment burden, worries about future health, sexual health, cognitive functioning, etc.).[74]

Thus, in general, a lung transplant-specific or respiratory-specific PRO along with a generic PRO may better quantify important health domains for a clinical trial in the lung transplant population than a single PRO alone.

When selecting PRO(s) for a trial, the following are important considerations: patient response burden; impact of cultural differences on interpretation; native language spoken; trial duration and frequency of survey sampling; and administration methods. For trials involving children and adolescents, selecting PROs requires unique considerations. Unique considerations include potential developmental and age differences across the pediatric lifespan, proxy versus self-report, vocabulary, recall period, pictorial versus text representations, and cross-cultural factors (see Pediatric Considerations section below for further discussion).[75] Thus, in line with FDA/EMA guidance, trialists should engage subject matter experts when deciding on final PRO measures for a given trial and in defining clinically meaningful changes.[71,72] In line with FDA guidance, trialists should also consider engaging patients throughout the development and intervention process.[72] PROs also lend themselves to remote collection, which presents advantages for trials that plan to leverage remote data collection. Table 3 provides a curated list of validated and accepted PROs used in lung transplantation. As PRO science evolves, other measures may emerge that meet key principles; therefore, the PROs in Table 3 should not be considered exhaustive.

7.2. Physical Functioning Outcomes (PFOs)

Physical functioning is a central contributor to functional independence and quality of life in lung transplantation. Declines in physical functioning often parallel illness progression and declines in overall health. Similarly, improvements in physical functioning provide important prognostic information that can inform clinical responsivity following cardiopulmonary rehabilitation, transplant recovery, and even behavioral coping interventions. Objective markers of physical function may therefore serve as a pragmatic behavioral biomarker and have even been proposed as an additional 'vital sign'.[76] Physical functioning measures may also augment the interpretation of PROs and traditional clinical biomarkers[77] and are now routinely integrated within remote intervention paradigms among lung transplant recipients.[78–80]

Several objective measures of physical functioning are accepted in lung transplantation. They differ widely in their sensitivity to systemic physical change, portability, and their reflection of broad versus increasingly specific quantification of physical function. In order from broad to specific, they include measures of physical activity (e.g. actigraphy), physical capacity/endurance (e.g. six-minute walk distance [SMWD]), physical frailty (e.g. Short Physical Performance Battery [SPPB], Fried Frailty Phenotype [FFP],[81] or the Lung Transplant Frailty Scale [LT-FS][82]), and cardiopulmonary fitness (e.g. exercise testing). Actigraphy[83–85] and SMWD[86,87] are widely used and are sensitive to targeted interventions.[86,88–90] Physical frailty can be improved[80,91] and is itself predictive of clinical outcomes.[92] While the literature is nascent, the LT-FS appears to have the strongest construct and predictive validity in lung transplantation.[82] Notably, physical frailty is a narrower construct than broader concepts of frailty that also include cognitive and social domains. If frailty, as a broader concept, is considered as an intervention target or ancillary outcome, other frailty measures including cumulative deficit measures might also be considered.[93,94] Finally, a select group of studies have examined changes in cardiopulmonary exercise testing markers in lung transplant recipients.[95]

Despite their widespread acceptance as surrogates for important lung transplant outcomes, each of the measures noted here has methodological and interpretive complexities. First, they may not be practical in some clinical contexts.[96,97] Second, the relationships between commonly used objective measures of physical functioning, such as the SPPB, SMWD, and actigraphy do not track uniformly in pulmonary,[98] community-dwelling,[99] or older adult samples.[100] Similarly, they inconsistently predict clinical outcomes after lung transplant and correlate only moderately with PROs.[98] For this reason, recent reviews have advocated for their distinction from PROs and 'patient-important' lung transplant outcomes.[101] Thus, while serving as important ancillary surrogates, for pivotal trials targeting factors other than physical functioning, physical functioning measures should not serve as the sole primary outcome. As with PROs, some measures of physical functioning can be collected remotely provided that methodological and interpretative considerations are anticipated and addressed in the study design phase.

Delphi Statements:

1. When feasible, clinical trials of interventions expected to impact how patients ultimately function or feel should include at least one lung transplant- or respiratory-specific PRO measure and, ideally, a generic PRO measure.
   Median: 3 (Strongly agree), 100% concordance, 100% agreement, 5 abstentions.

Table 3 Patient-reported Outcome measures that meet key validity criteria for use in clinical trials in lung transplantation*

Instrument	Domains Measured	Evidence for Face, Construct, and Discriminative Validity** +++ = Robust ++ = Moderate + = Modest	Evidence for Responsiveness to Transplant, CLAD, non-CLAD Transplant Complications	Estimated Time Needed to Complete in Minutes (Number of Items)	Available in Languages Other Than English
Generic HRQL/Utility					
SF–36[178]	• General Health Perceptions • Physical functioning • Mental health • Vitality • Bodily pain • Physical role functioning, • Emotional role functioning • Social role functioning	• Face: +++ • Construct: +++ • Discriminative for general health: +++ • Discriminative for lung transplant health: ++	• Transplant: Yes • CLAD: Yes • Non-CLAD complications: Yes	10–15 (n=36)	Yes
SF–12[179]	Same as SF–36	• Face: +++ • Construct: +++ • Discriminative for general health: +++ • Discriminative for lung transplant health: ++	• Transplant: Yes • CLAD: Yes • Non-CLAD complications: Yes	5–7 (n=12)	Yes
EQ–5D[180]	Health utility. Allows for cost-utility analysis	• Face: +++ • Construct: ++ • Discriminative for general health: ++ • Discriminative for lung transplant health: +	• Transplant: Yes • CLAD: Yes • Non-CLAD complications: Yes	2 (n=5)	Yes
Lung Transplant Specific HRQL and Symptoms					
LT-QOL[181]	• General quality of life • Respiratory symptoms • GI symptoms • Neuromuscular symptoms • Cognitive limitations • Sexual problems • Worry about future health • Treatment burden • Depression • Anxiety • Health distress	• Face: +++ • Construct: +++ • Discriminative for general health: ++ • Discriminative for lung transplant health: +++	• Transplant: Yes • CLAD: Yes • Non-CLAD complications: Yes	18–20 (n=60)	Yes
TSI[182]	• 64 symptoms spanning multiple organs and psychological domains relevant in lung transplant	• Face: +++ • Construct: ++ • Discriminative for general health: ++ • Discriminative for lung transplant health: ++	• Transplant: Yes • CLAD: No • Non-CLAD complications: No	18–20 (n=64)	No
Respiratory Specific HRQL					
SGRQ[183]	• Respiratory Symptoms • Respiratory impact on physical activity • Respiratory impact on psychosocial functioning	• Face: +++ • Construct: +++ • Discriminative for general health: ++ • Discriminative for lung transplant health: ++	• Transplant: Yes • CLAD: Yes • Non-CLAD complications: Yes	10–15 (n=50)	Yes

Continued

Table 3 Patient-reported Outcome measures that meet key validity criteria for use in clinical trials in lung transplantation*

Instrument	Domains Measured	Evidence for Face, Construct, and Discriminative Validity** +++ = Robust ++ = Moderate + = Modest	Evidence for Responsiveness to Transplant, CLAD, non-CLAD Transplant Complications	Estimated Time Needed to Complete in Minutes (Number of Items)	Available in Languages Other Than English
PQLS[184]	• Respiratory impact on • Physical functioning • Psychological/emotional status • Functional status/activities of daily living • Social activities • Intimacy/relationships/sexuality • Occupational functioning • View of self	• Face: +++ • Construct: +++ • Discriminative for general health: ++ • Discriminative for lung transplant health: ++	• Transplant: Yes • CLAD: No • Non-CLAD complications: Yes	10–12 (n=25)	No
AQ20-R[185]	• Respiratory impact on • Physical functioning • Psychological/emotional status • Functional status/activities of daily living	• Face: +++ • Construct: +++ • Discriminative for general health: ++ • Discriminative for lung transplant health: ++	• Transplant: Yes • CLAD: No • Non-CLAD complications: No	5–10 (n=20)	Unknown
Patient Reported Measures of physical functioning					
LT-VLA[186]	Functional capacity/disability in activities of daily living, activities required for life roles, and discretionary activities	• Face: +++ • Construct: +++ • Discriminative for general health: ++ • Discriminative for lung transplant health: ++	• Transplant: Yes • CLAD: No • Non-CLAD complications: No	3–5(n=15)	Yes
DASI[187]	Functional capacity, VO2 Max, metabolic equivalent of tasks	• Face: +++ • Construct: +++ • Discriminative for general health: ++ • Discriminative for lung transplant health: ++	• Transplant: Yes • CLAD: No • Non-CLAD complications: No	3–5(n=12)	Unknown

*As PRO science in lung transplant evolves, other measures may emerge that meet key validity criteria that are not represented in this Table. Also, for interventions targeting conditions not specific to lung transplant patients (e.g., diabetes, chronic kidney disease, depression/anxiety), PROs specific for those conditions may be appropriate to include. Thus, this Table should not be considered exhaustive nor permanent.

**Criteria applied for PRO inclusion in this Table: Has been used in contemporary multicenter studies; acceptable face, construct, criterion, and predictive validity thresholds for HRQL domains deemed important by lung transplant patients; evidence for responsiveness to at least one major transplant event (transplant surgery, CLAD, or important non-CLAD complications after transplant; were multidimensional (i.e., did not include unidimensional measures such as shortness of breath, depression, pain measures); deemed broadly scientifically and clinically acceptable by this consensus group to support their ongoing use in future studies.

SF-36= Medical Outcomes Study Short Form-36; SF-12 = Medical Outcomes Study Short Form-12; EQ-5D = EuroQol 5D; LT-QOL = Lung Transplant Quality of Life; TSI = Transplant Symptom Inventory; SGRQ = St. George's Respiratory Questionnaire; PQLS = Pulmonary Specific Quality of Life Scale; AQ20-R = Airways Questionnaire-20 Revised; LT-VLA = Lung Transplant Valued Life Activities scale; DASI = Duke Activity Status Index.

2. PRO measures selected for an intervention should have evidence supporting their validity in lung transplant populations.
   Median: 2 (Agree), 100% concordance, 100% agreement, 6 abstentions.
3. PRO measures selected for an intervention should be expected to be responsive to the intervention's potential treatment benefit as well as risks.
   Median: 3 (Strongly agree), 100% concordance, 100% agreement, 5 abstentions.
4. PRO measures should be administered at time intervals that reflect the anticipated efficacy timeframe of the intervention under study, producing longitudinal data across the clinical trial.
   Median: 3 (Strongly agree), 100% concordance, 100% agreement, 5 abstentions.

8. COMPLICATIONS OF IMMUNOSUPPRESSION

Infectious complications are an inherent side effect of all immunosuppressive therapies and are the most common cause of death in the first five years following lung transplantation.[102] Most interventional trials of immunosuppressive drugs in lung transplant recipients have included infectious complications as safety or secondary endpoints, but the criteria for adjudicating infections have been highly variable.[103–118] The ISHLT,[119] AST,[120–129] ATS,[188130] CTS,[131] CMV Drug Development Forum,[132] and Transplantation Society[133] have all published consensus guidelines or workshop recommendations on how to diagnose various infections in solid organ transplant recipients (Supplemental Tables 1–4). Definitions of infectious endpoints in clinical trials should be informed by these existing guidelines and will be highly-dependent on the research question and study design. However, we strongly recommend that infectious endpoints are defined prospectively and that protocols to adjudicate infections are standardized for any interventional trial given the heterogeneity of how infections are classified in lung transplant recipients.

Impaired kidney function is a frequent complication of many drugs, but especially calcineurin inhibitors.[134,135] Acute kidney injury (AKI) may predispose to subsequent chronic kidney disease (CKD), which itself is associated with mortality, frailty, and end-stage kidney disease.[136–141] Many interventional trials of immunosuppression in lung transplant recipients have used changes in estimated glomerular filtration rate (eGFR) as primary, secondary, and safety endpoints.[107,113,116,117,142–147] While outcomes data specific to lung transplant recipients are limited, we recommend defining kidney impairment thresholds using those associated with increased risk of CKD progression and/or mortality in large non-transplant cohorts.[148] We support KDIGO kidney function staging criteria, which include longitudinal urine albumin, serum creatinine, and when possible, serum cystatin C measurements.[147,149] We recommend using the 2021 CKD-EPI equations for estimating GFR. We favor incorporating both creatinine-cystatin C when possible (eGFRcr-cys preferred over eGFRcr) and not adjusting for race.[149–151]

There are many additional long-term complications of immunosuppression with high incidence rates compared with the general population, but whose overall prevalence following transplantation is relatively low.[152] Non-skin *de novo* malignancies[153] occur in 4.6% of lung transplant recipients by 3-years post-transplant.[154] The incidence of skin squamous cell carcinoma has been estimated to be 3.6% and 26.5% at 3- and 10-years post-transplant, respectively, with a metastatic rate of approximately 8%.[155–157] The cumulative incidence of PTLD in lung transplant recipients is 1.1% at 1-year post-transplant.[158] Neurologic outcomes such as seizures, stroke, encephalopathy, and delirium are very common in the peri-transplant period,[159–162] yet are reported at much lower rates in the years following transplant.[163,164] Osteoporosis related to pre-transplant morbidity and post-transplant corticosteroid use is very common in lung transplant recipients. The overall prevalence of fractures ranges from 18–37% but has been reported as low as 8% in well-managed cohorts.[165,166] The reported rates of coronary revascularization and stroke following lung transplant are relatively low (~1–5%).[167] Although the incidence rates for these longer-term complications of immunosuppression are too low to make well-powered conclusions in most interventional trials, we recommend that the incidence of these complications be collected and reported in some manner for studies with longer-term follow-up given how clinically meaningful these complications are to lung transplant recipients.

Delphi Statements:

1. The definitions for infectious endpoints in clinical trials should be informed by existing consensus guidelines (Supplemental Tables 1–4) depending on the research question and study design.
   Median: 2 (Agree), 100% concordance, 100% agreement, 4 abstentions.
2. Infectious endpoints for all clinical trials should be prospectively defined and have standardized protocols for adjudication that are implemented prior to study enrollment.
   Median: 3 (Strongly agree), 98% concordance, 100% agreement, 4 abstentions.

3. Clinically important thresholds for kidney impairment that should be reported when studying CKD as an adverse event related to immunosuppressive therapies in lung transplant recipients include: 1) eGFR < 60 ml/min/1.73 m2 (KDIGO category G3) for longer than 3 months; 2) urine albumin-creatinine ratio ≥ 30 mg/g (KDIGO category A2); and 3) need for chronic kidney replacement therapy or kidney transplantation.
   Median: 2 (Agree), 98% concordance, 98% agreement, 7 abstentions.
4. Alternative measures of CKD that may be considered include: 1) reporting eGFR change over time, particularly in studies including participants with eGFR < 60 ml/min/1.73 m2 at enrollment as in the approach described by the National Kidney Foundation/FDA statement,[168] and 2) when feasible, reporting measured GFR < 60 ml/min/1.73 m2 or change over time.
   Median: 2 (Agree), 98% concordance, 98% agreement, 8 abstentions.
5. Both AKI (KDIGO Stage 1 or worse) and referral to a kidney specialist may be clinically relevant outcomes to report in studies of immunosuppressive therapies depending on study design, drug, and population.
   Median: 1 (Somewhat agree), 83% concordance, 80% agreement, 8 abstentions.
6. Long-term complications of immunosuppression including *de novo* malignancies, neurologic abnormalities, cardiovascular disease, hematologic dysfunction, and bone metabolism should be reported in trials of novel immunosuppressive therapies despite their relatively low overall prevalence. Other complications of immunosuppression not listed should also be reported depending on study design, drug, and population.
   Median: 3 (Strongly agree), 100% concordance, 100% agreement, 6 abstentions.

9. PEDIATRIC CONSIDERATIONS

The introduction of highly effective CFTR modulator therapy has significantly reduced the frequency of lung transplantation for cystic fibrosis (CF) in the United States and Europe.[169,170] Because historically CF has been the indication performed for transplant in ~50% of pediatric lung recipients, the number of pediatric lung transplants in the US has dropped to less than half of previous volumes (18 transplants reported to the OPTN in 2022). Moreover, increased use of the Potts shunt as a treatment for pulmonary hypertension has impacted lung transplantation in that population.[171] Although at least one randomized clinical trial has been performed previously in pediatric lung transplant recipients, these diminishing numbers will make future studies exclusively involving pediatric patients extremely challenging.[172] For these reasons, and consistent with both FDA and EMA guidance, clinical trials involving adult lung transplant recipients should include plans to study pediatric lung transplant recipients, at a minimum for the purposes of obtaining pharmacokinetic and safety data. Such data, coupled with evidence that adult data is extrapolatable to children will be critical to ensure that pediatric recipients will be able to benefit from new therapies.

In that light, when surrogate endpoints are being considered, it will be important to ensure that tests/tools used to construct these endpoints are not impacted by developmental or psychosocial factors inherent in children (else alternative endpoints are developed). For example, obtaining reproducible spirometry in children under 6 years of age is challenging; most pediatric pulmonary function laboratories do not attempt spirometry in children under 4–5 years of age.[173] And even if pulmonary function testing is performed in this young age group, results may be limited due to age-related deficiencies in test performance. Moreover, to mitigate the impact of growth, z-scores or percent of predicted values rather than absolute values should be used when comparing populations and/or measuring change in lung function from patient baseline. Alternatively, passive lung function testing methods such as multiple breath washout or impulse oscillometry should be considered for pediatric patients.[174,175] In addition, younger children may have difficulty with compliance on 6-minute walk tests and may similarly have difficulty with inspiratory/expiratory CT views so accommodations for such differences may be needed. Assessment of PRO and QOL / functional outcome in children should be adapted to account for level of development by using validated pediatric PROs/QOL-questionnaires. Finally, many laboratory tests used in transplantation have age-dependent normal values which should be considered when designing studies and assessing results.

Given that the power to assess pediatric lung recipients in any study will be limited, it will be important for the pediatric lung transplant community to catalog and where possible minimize variability in clinical protocols to reduce the potential that modifiable confounders will reduce the power to detect the impact of interventions. For example, in previously reported pediatric lung transplant clinical trials, investigators agreed in advance on immunosuppression protocols (including the use of induction agents), prophylactic antibiotic strategies and

definitions and treatment strategies for rejection.[172,176] For this reason, any clinical trial involving children should address potential biases resulting from pediatric patients transplanted in an adult center or transitioning into adult care during follow-up.

Delphi Statements:

1. Given recent improvements in the care of patients with CF and pulmonary hypertension, the volume of pediatric lung transplants for the foreseeable future will make conducting controlled efficacy trials exclusively involving pediatric lung transplant recipients extremely challenging.
   Median: 3 (Strongly agree), 97% concordance, 100% agreement, 10 abstentions.
2. Future trials of therapies to improve outcomes in lung transplantation should include robust plans for extrapolation of results to children and should enroll children at a minimum to obtain the necessary pharmacokinetic and safety assessments.
   Median: 2 (Agree), 95% concordance, 95% agreement, 11 abstentions.
3. Given the impact of growth and development in children on many clinical assessments (including spirometry, other measures of end organ function like creatinine and ability to assess QOL), potential clinical endpoints and surrogate markers should include methods for adjustment to ensure that growth and/or development of the child does not affect interpretation of the result.
   Median: 3 (Strongly agree), 97% concordance, 100% agreement, 12 abstentions.
4. FEV_1 z-scores predicted based on age and height apply well to the pediatric population.[173]
   Median: 2 (Agree), 91% concordance, 91% agreement, 26 abstentions.
5. The PedsQL quality of life score applies well to the pediatric population.[177]
   Median: 2 (Agree), 95% concordance, 95% agreement, 28 abstentions.
6. Pediatric lung transplant programs should take steps to catalog the variability in treatment protocols and where possible harmonize them to minimize potential outcome confounders for pediatric patients participating in interventional trials.'
   Median: 3 (Strongly agree), 97% concordance, 100% agreement, 12 abstentions.

10. SUMMARY AND CONCLUSIONS

There is an acute need for novel therapies to improve outcomes following adult and pediatric lung transplantation. The selection of appropriate endpoints depends on several factors, as detailed above. For example, PGD is a key early endpoint that can be leveraged in short trials, which may have applicability to ARDS. Acute cellular rejection or antibody mediated rejection may be important intermediate endpoints. CLAD as an endpoint requires greater study follow up but may be best linked to long-term survival after transplant. Consideration of medication complications and patient quality of life and functional status will be key in any study. The lung transplant community strongly supports clinical trial research. While some therapeutic trials are underway, it is hoped that this document can help accelerate research in this field.

APPENDIX A. SUPPORTING INFORMATION

Supplemental data associated with this article can be found in the online version at doi:10.1016/j.healun.2025.09.017.

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