Division of Pulmonary, Critical Care & Sleep Medicine
University of Washington

Sponsor Protocol Title:	Preparation for lung transplant discussions and decisions among people with cystic fibrosis (1 R01 NR 020470-01A1)
Alternate Title:	Lung Transplant Resources for Education And Decision-making for Your CF 2 Study: A Multi-Site Randomized Controlled Clinical Trial
Alternate Short Title:	**LTx READY CF 2: A Multi-Site RCT**
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Abbreviations and Definitions of Terms

AE	**Adverse event**
AESI	**Adverse event of special interest**
APPs	**Advanced Practice Providers**
BMI	**Body mass index**
CF	**Cystic Fibrosis**
CFF	**Cystic Fibrosis Foundation**
CFFPR	**Cystic Fibrosis Foundation Patient Registry**
CFTR	**Cystic fibrosis transmembrane conductance regulator**
CIRG	**Clinical Informatics Research Group**
CTCAE	**National Cancer Institute's Common Terminology Criteria for Adverse Events**
DSMB	**Data safety monitoring board**
DSMP	**Data safety monitoring plan**
eCRF	**Electronic case report form**
EHR	**Electronic health record**
ETI	**Elexacaftor/Tezacaftor/Ivacaftor**
FEV_1	**Forced expiratory volume in 1 second**
HIPAA	**Health Insurance Portability and Accountability Act of 1996**
IPDAS	**International Patient Decision Aid Standards**
LTx	**Lung transplant**
MM	**Medical monitor**
PI	**Principal Investigator**
PrepDM	**Preparation for Decision Making Scale**
SAE	**Serious Adverse Event**
SD	**Standard deviation**
SES	**Socioeconomic status**
ToT	**Take on Transplant**
UNOS	**United Network for Organ Sharing**
UW	**University of Washington**

Statement of Compliance

The trial will be conducted in accordance with International Council on Harmonisation Good Clinical Practice (ICH GCP), applicable United States (US) Code of Federal Regulations (CFR), and the National Institute of Nursing Research (NINR) Terms and Conditions of Award. The Principal Investigator will assure that no deviation from, or changes to the protocol will take place without prior agreement from the funding agency and documented approval from the Institutional Review Board (IRB), except where necessary to eliminate an immediate hazard(s) to the trial participants. All personnel involved in the conduct of this study have completed Human Subjects Protection and ICH GCP Training.

The protocol, informed consent form(s), recruitment materials, and all participant materials will be submitted to the IRB for review and approval. Approval of both the protocol and the consent form(s) must be obtained before any participant is consented. Any amendment to the protocol will require review and approval by the IRB before the changes are implemented to the study. All changes to the consent form(s) will be IRB approved; a determination will be made regarding whether a new consent needs to be obtained from participants who provided consent, using a previously approved consent form.

Investigator's Signature

The signature below constitutes the approval of this protocol and provides the necessary assurances that this study will be conducted according to all stipulations of the protocol, including all statements regarding confidentiality, and according to local legal and regulatory requirements and applicable US federal regulations and ICH guidelines, as described in the 'Statement of Compliance' above.

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A Background

Cystic fibrosis (CF) is a genetic disease that leads to premature death, typically due to progressive respiratory failure (median age at death was 34 years in 2020).[1] Median predicted survival age is 65.6 years for people born in 2021, due in large part to the introduction of a new highly-effective CF therapeutic, elexacaftor/tezacaftor/ivacaftor (ETI), introduced in 2019.[1] The CF Foundation (CFF) lung transplant (LTx) referral guidelines recommend annual discussion of LTx for CF patients once their lung function falls to forced expiratory volume in one second (FEV_1) <50% of predicted[2], but there is no guidance for approaching the topic of LTx when it may be a decade or more away. Further, CF physicians may lack transplant-specific knowledge[3] or may feel ambivalent about discussing LTx given the beneficial impact of ETI. CF patients with low FEV_1 have high rates of anxiety and depression[4, 5]; anxiety may contribute to patients' avoidance of conversations about LTx. Mental health concerns are likely multifactorial, related to worsening medical acuity, adjustment-related concerns, including new social dynamics of needing assistance/caregivers, and a loss of control over the trajectory of their lung disease.[6] Patients with CF may also experience shame or stigma from the perceived association between progression of lung disease necessitating LTx and medical non-adherence[6]; these feelings may exacerbate avoidant behavioral tendencies, impeding LTx discussions and adversely impacting relationships with physicians and caregivers. CF physicians may avoid early LTx discussions because of the topic's emotional nature. Based on decreased access to transplant for people with low socioeconomic status (SES), non-White race or Hispanic ethnicity, implicit bias may hinder LTx discussions in some cases. Importantly, approximately 10% of patients with advanced CF die without LTx each year, while only 6-8% undergo LTx.[7] Deliberation is an iterative process in which patients explore what matters most to them, often requiring collaboration over time with health professionals and patients' social networks.[8] The decision to undergo LTx is complex and fraught with uncertainty about timing, which is worse in the setting of unclear benefits of LTx given the difficulty of predicting survival and quality of life without LTx in the setting of ETI. Prognostic uncertainty in advanced CF on ETI promotes decisional conflict and psychological discomfort[9], which may delay decision making about LTx, leading to missed opportunities for LTx.[7, 10] Data suggest LTx and death without LTx will occur despite ETI at half the rate of untreated individuals.[11, 12] Decreased rates of LTx may lead physicians to feel less equipped to provide LTx education and guidance.

Medicaid health insurance is used as a proxy for low SES; CF patients with lower SES have decreased referral for LTx and are less likely to undergo LTx after listing.[13, 14] CF patients in the US with public health insurance (Medicaid or Medicare) have worse survival compared to those on private health insurance in the US or to CF patients in other countries.[15, 16] While health insurance is frequently used as an SES proxy, a more nuanced set of SES markers, including insurance, race, education, and geography, showed a similar association of lower SES with decreased access to LTx.[17] Hispanic CF patients have a nearly 3-fold increased risk of death without LTx compared to non-Hispanics, adjusted for disease severity and health insurance.[18] Non-White race is associated with worsened survival in CF, regardless of country.[15, 16] The impact of lower SES, race, and ethnicity on lung transplant-related health disparities may be related to limited health literacy, among other factors.[19, 20] Limited health literacy is associated with decreased access to kidney transplant for people with chronic kidney disease.[21] For individuals who speak English as a second language, effects of lower health literacy on health outcomes may be amplified.[22] A systematic review and meta-analysis of shared decision making interventions found interventions targeting the needs of disadvantaged

groups were most effective and may benefit groups with lower health literacy more than those with higher SES and health literacy.[23]

Two decision aids exist for LTx in CF: the first, developed in Canada and Australia in 2006, reduced decisional conflict in an RCT and is publicly available but is no longer accurate[24]; the second, developed from interviews and focus groups with 24 CF patients hospitalized in the intensive care unit (2015-2016), addresses decisions around mechanical ventilation and LTx for end-stage CF[25]. This second decision aid targets a limited group of patients, is not publicly available and was not evaluated in an RCT.[25, 26] Our published findings[27] show CF patients favor learning about LTx in advance of when referral is medically necessary, and prefer to avoid LTx discussions during a crisis, consistent with the deliberation process[8]. For this reason, we developed Take on Transplant (ToT). ToT incorporates guidelines-based medical information (Resource Library), CF patient and caregiver experiences (CF Stories), and answers to common questions from the LTx journey (Frequently Asked Questions).[28] ToT tailors content recommendations based on the patient's disease severity (My CF Stage). Importantly, ToT was developed in partnership with CF patients of varied backgrounds, including those with non-White race and lower SES; diverse patients contributed personal narratives as "CF Stories" that serve as clinical vignettes (40% with Medicaid insurance).

For people with CF, premature death is a reality. Having LTx discussions with the CF care team is an important health behavior that can identify treatment options that contribute to avoiding premature death. We approached this work using the *Health Beliefs Model* theoretical framework (Table 1). Given the difficulty of determining optimal timing of LTx referral in the ETI era, and that patient preference often contributes to delayed referral[3, 10], arming CF patients with the information needed to help them to understand their *susceptibility* (likely need for LTx) and *severity* of end-stage CF, while helping to clarify *perceived benefits* and reduce *perceived barriers* to LTx discussion, is critical to prepare them for high-quality LTx discussions and help them make informed decisions. Moreover, ToT provides *cues to action* in the form of prompts to log in to the ToT website and to initiate a LTx discussion at their next clinic visit. Finally, the ToT components are designed to support *self-efficacy* by empowering patients to engage in proactive LTx discussions, as measured with the Preparation for Decision Making (PrepDM) Scale[29]. A patient's perceived self-efficacy correlates strongly with approach-oriented coping styles and mood function. It is key to measure the impact of ToT on mental health outcomes because patients and physicians may avoid LTx discussions due to the emotional nature of the conversation. ToT has the potential to help CF patients live long and fulfilling lives, and avoid premature death, by increasing understanding of

Table 1: The Health Beliefs Model (HBM) addresses whether, how, and why CF patients engage in LTx discussions and frames how ToT can impact discussions.

HBM Theoretical Constructs and RCT Measures
• *Perceived susceptibility:* patient perception of vulnerability to future end-stage CF and need for LTx • *Perceived severity:* patient perception of symptom burden and potential consequences of end-stage CF • *Perceived benefits:* patient perception of potential for LTx discussions to increase access to LTx • *Perceived barriers:* costs of LTx discussion (e.g. negative emotions, social impact, facing implicit bias) • *Cues to action:* exposure to factors prompting LTx discussion and decision-making processes • *Self-efficacy:* confidence in the ability, or feeling empowered, to have LTx discussion

LTx as a treatment option.[28]

A1 Prior Literature and Previous Studies

Initial Survey Assessment of Transplant Education Needs:
An online survey of individuals who were followed in the University of Washington (UW) Adult CF Center, distributed March-May 2020, had 159 responses (71% response rate): 87 (55%) male respondents; 44 (28%) Medicaid/Medicare health insurance; average FEV_1 68% predicted (SD 23%, range 24-112%). One hundred twenty-seven (80%) of the respondents reported using ETI. Most respondents (n=108, 68%) reported that highly effective CF medications are moderately likely or very likely to impact their need to ever have LTx. Only 56 (35%) respondents endorsed feeling moderately or very prepared to make decisions about LTx, while 113 (71%) reported that it is moderately or very important to feel prepared. The survey revealed knowledge gaps related to 1) low or high body mass index (BMI) as a potential barrier to LTx, 2) FEV_1 as an important component of the decision to refer for LTx, 3) survival benefit of LTx, and 4) improvements in health-related quality of life. More than 75% of respondents reported that a LTx decision support tool would be moderately or very useful and >75% would be moderately or very willing to use it once their FEV_1 is <50% of predicted. Despite high rates of ETI use, individuals with CF are interested in a LTx decision support tool.

Development of Take on Transplant:
Human-centered design is an iterative process comprised of four distinct phases to: 1) understand user needs and context, 2) specify user requirements, 3) generate design solutions, and 4) evaluate design against requirements. We recently published our process of development of ToT.[28] In Phase 1, we used interviews and surveys of CF patients (pre- and post-transplant) and surveys of CF physicians to understand user needs. In Phase 2, we analyzed these data to identify qualitative themes that specified key functionality that the web application must support (i.e., requirements) – including topics identified as important content for LTx education by patients. Pretransplant interviews highlighted the need to personalize the concept of LTx as a treatment option, the belief that one's CF physician should offer access to information about the process, and certain topics that could improve preparedness to discuss transplant with one's physician. Post-transplant CF patients reported connections with previous LTx recipients as a major component of preparing for LTx. CF LTx recipients identified their CF doctors, LTx team (doctors, social worker), and the Internet (e.g. unos.org) as sources for LTx information. In Phase 3 of the human-centered design approach, we produced possible design solutions as prototypes (example web interfaces), which we co-designed with CF patient focus groups. Each group included 4-7 individuals who met 6 times via teleconference. We iteratively refined the prototype, incorporating patient input on content and features. Next, we developed an interactive prototype. In Phase 4, evaluations focused on usability testing of the interactive prototype. In collaboration with the Clinical Informatics Research Group (CIRG), we developed a web-based implementation of the ToT intervention.

Feasibility Testing of Take on Transplant:
As a key step in creating ToT, we assessed the feasibility of the CF Stories embedded in ToT, which include narratives for individuals with a range of outcomes after LTx, consistent with International Patient Decision Aid Standards (IPDAS)[30, 31]. We enrolled 25 CF patients, from Dec 2020-Mar 2021, in a single-arm study with pre-/post-intervention design (no control arm). We utilized the CFF Community Voice (an organization of people with CF engaged in research

and advocacy) for participant recruitment to avoid depleting the available population of CF patients with low FEV_1 at the study sites for the proposed RCT. We assessed the effect of a 90-minute Zoom-based intervention using only the CF Stories portion of the ToT prototype web application. We approached 31 potential participants, 3 of whom did not respond and 3 declined to participate. Therefore, 25/31 (81%) participated in the feasibility testing. Participants had an average FEV_1 47% predicted (SD 15%, range 29-89%).

Participants read an average of 3.2 (SD 0.9) CF Stories during the 90-minute intervention. Feasibility testing showed improvements in multiple domains. Participants' Decisional Conflict Scale[32] decreased from a mean of 37.9 before vs 28.6 after, p=0.015 (lower is better), with an effect size of 0.52. Likert scale ratings of preparedness to discuss LTx improved ≥1 point for 74% of potential responders; 6 people were "very prepared" before vs. 13 people "very prepared" after intervention. Knowledge about LTx also improved (for example, % correct increased from 68% to 96% for survival benefit of LTx) after the 90-minute Zoom intervention. Qualitative data from interviews revealed high levels of satisfaction with 'CF Stories.' Participants voiced interest in didactic medical information to complement experiential learning from 'CF Stories'.

Pilot Randomized Controlled Trial (RCT) of Take on Transplant vs. Attention Control (unos.org): In December 2021, we began a recently completed pilot RCT of ToT compared to the United Network for Organ Sharing (UNOS) website (an attention control website that provides more general LTx information), clinicaltrials.gov identifier NCT05135156. We included CF patients who were referred from 15 CF Centers that advertised a screening survey collecting limited protected health information in accordance with UW IRB approval (target enrollment n=50). Referring centers pre-screened local CF registry data to identify eligible individuals with an FEV_1 <50% predicted and prioritized individuals from *communities of concern* (Medicaid insurance, non-White race, Hispanic ethnicity, or high school education or less). No clinical data was available from CF Centers or medical records for pilot RCT participants. Pilot RCT participants underwent 1:1 randomization stratified by patient-reported FEV_1 (<30% or 30-50% predicted) to either ToT or UNOS for 2 weeks, followed by 2 weeks of access to both websites. All participants in both arms of the pilot RCT received reminders to log in to the research website via email and/or text regardless of usage patterns. The Preparation for Decision Making (PrepDM) Scale[29] was administered at 2- and 4-weeks after randomization. Co-primary outcomes were feasibility of completion of the 2-week assessment and difference in 2-week PrepDM[29] in ToT vs UNOS arms. The pilot RCT was not powered to detect a difference in PrepDM between the two arms. Preliminary efficacy was planned for assessment via PrepDM.

Of 50 eligible patients surveyed who opted-in to being contacted for additional research opportunities on the screening survey, 37 (74%) agreed and enrolled in the pilot RCT. Fifteen patients were recruited from the University of Washington. Of the 52 enrolled, 2 participants were lost to follow up prior to starting the intervention (before the baseline study visit), but the remaining 50 people completed all study visits, yielding 4% attrition. Three (6%) participants were provided a hotspot for reliable Internet access (Franklin 4G LTE Mobile Hotspot from Straight Talk with 2GB/month data plan); no one requested a tablet or device. Of the 52 enrolled participants, median age was 38.9 years (SD 10.8) and 25 (48%) were women. Thirty-three participants (63%) are members of *communities of concern*, with 16 (31%) using Medicaid insurance, 3 (6%) are non-White, 3 (6%) with Hispanic ethnicity, and 11 (21%) with high school education or less. Low literacy was possibly (15%) or highly likely (5%) to be present for 20% of

participants, based on the Newest Vital Sign[33]. Preliminary usage data notes average time spent on the research website was 3.0 hours (SD 1.7 h) in the first 2 weeks and 2.0 h (SD 1.8 h) in the second 2 weeks (data pooled across both arms). The PrepDM Scale is a validated measure of preparedness for decision making with known variance and high internal consistency (α 0.92-0.96)[29], but it has not been studied in the CF population. At 2 weeks, the ToT arm had higher PrepDM scores (**71**, 95% CI 64-77 vs **57**, 95% CI 47-66), with a between-arm difference of 14 points, p=0.02. Participants in the pilot RCT reported that 2 hours was a reasonable minimum recommendation for research website use and 2 weeks was sufficient to explore content. During qualitative interviews, no one in the pilot RCT reported finding the content on either website to be emotionally distressing.

In summary, we performed extensive multi-methods research and utilized human-centered design to create and demonstrate the usability, feasibility, and preliminary efficacy of ToT. We incorporated stakeholders from the CF Community in the design, development, and evaluation of ToT. This web-based resource is accurate, up-to-date, and informed by recent CFF guideline recommendations.[2, 34] CF patients have preparedness and knowledge gaps when considering LTx as a treatment. Evaluation of ToT is imperative to determine if it improves patients' preparedness for discussions about LTx, a treatment option underutilized by CF patients[7, 15], particularly among those from *communities of concern*[13, 14, 17]. Studying ToT use will provide insights about potential emotional or psychological benefits or harms of early LTx education in the setting of prognostic uncertainty due to ETI. Prior to implementation and widespread use of ToT, these factors must be assessed.

B Approach

The primary study objective is to determine whether "Take on Transplant" (ToT), a CF-specific LTx educational website, improves patient-reported preparedness for LTx discussions, as measured by the Preparation for Decision Making (PrepDM) Scale at 3 months after randomization, compared to an attention control transplant website (unos.org, UNOS).

B1 Aim 1 & Sub-Aim 1A [CF Patients]

Aim 1 – Test whether ToT improves patient preparedness for discussions about LTx compared to an attention control, assessed with the PrepDM Scale, using a multicenter single-blind RCT.

Hypothesis: ToT will increase preparedness for LTx discussions relative to unos.org, an attention control, as indicated by higher PrepDM Scale[29] ratings; effect sizes may be different in *communities of concern*.

Sub-Aim 1A – Explore the effect of the ToT intervention on psychosocial functioning.

Hypothesis: Serial measures of anxiety (GAD-7[35]), depression (PHQ-9[36]) and self-efficacy (General Self-Efficacy Scale[37]) will elucidate the beneficial or harmful psychological impacts of ToT or attention control.

1.a Rationale

Many patients with advanced CF will require LTx despite ETI and some will die without LTx; patients in *communities of concern* more often die without LTx than undergo the operation.[15, 16, 18] UNOS was selected as an attention control because it provides general transplant education, is publicly available, and is often recommended to patients seeking LTx information. ToT coaches CF patients for LTx discussions by exposing them to

CF-specific LTx education. Preparing patients for high-quality discussions could improve clinical outcomes for people with advanced CF by increasing engagement with the CF team and changing attitudes and choices related to LTx. ToT does not involve physician training, but this initial study could uncover a need to develop a physician component. The RCT incorporates a CF clinic visit to assess the physician's role.(Sub-Aim 1A) Behavioral and educational studies often assume that there will be positive psychological benefit. While this study may reduce anxiety by improving knowledge about LTx, nurturing the emotional capacity to consider LTx, and helping the sense of being more prepared for the future (i.e., reduce anxiety and/or depression), it is possible that ToT or the control condition (UNOS) may increase psychological distress (temporarily or longer-term) by increasing focus on one's own mortality or declining health. For this reason, we will assess anxiety (GAD-7[35]) and depressive symptoms (PHQ-9[36]) at each study visit (V1-V4).

B2 Aim 2 [CF Physicians/APPs]

Aim 2 – Assess perceptions of LTx education and observe LTx discussions through analysis of semi-structured interviews, website usage, and audio recordings of clinic visits in patient-physician dyads.

Anticipated findings: Content analysis of transcripts from clinic visits, patient interviews, and evaluation of website usage, will highlight deliberation, LTx education, and prognostic uncertainty.

2.a Rationale

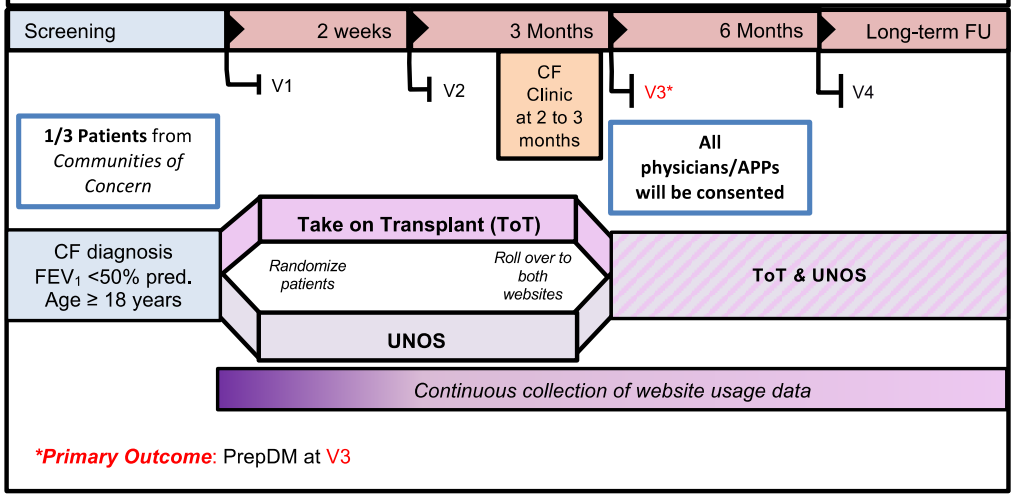
These data are critical to determine whether CF patients armed with LTx education raise the topic of LTx in their CF clinic visits, which questions they ask, and whether physicians or advanced practice providers (APPs) respond in a way that facilitates building trust and preparedness for LTx. If the RCT has a null result, these data may help to explain why. The lack of data regarding the timing of disease progression for advanced CF in the ETI era may result in physician ambivalence about discussing LTx. Physicians' implicit bias may prevent them from raising the topic of LTx in some cases. Patients' mental health or coping mechanisms may prevent conversations about LTx. The longstanding relationship between the patient and physician may facilitate exploration of difficult topics. Understanding barriers to LTx discussions and identifying markers of high-quality LTx discussions could improve our approach to this important treatment option during shared decision making.

C Study Design

C1 Study Design

This is a prospective, multicenter, randomized, controlled, single-blind, roll over study to investigate the effect of ToT, a CF-specific LTx educational website, versus an attention control website (unos.org, UNOS) on preparedness for LTx discussions among individuals with CF. (Figure 1)

Figure 1: Study schema for multicenter RCT evaluating effect of Take on Transplant (ToT) on patient preparedness for lung transplant discussions, with study visits at baseline (V1), 2 weeks (V2), 3 months (V3) and 6 months (V4) and CF Clinic visit at 2-3 months.



PrepDM: Preparation for Decision Making Scale [C. Bennett, et al. Validation of a preparation for decision making scale. *Patient Education and Counseling* 2010 Vol. 78 Issue 1 Pages 130-133]

CF patient participants in Aim 1 and Sub-Aim 1A will have 3 months of access to one of two websites (ToT or UNOS). CF patients from participating sites will be randomized 1:1 to ToT or UNOS. We will use REDCap to configure the randomization allocation constructed by the study statistician using a permuted block scheme with varying block sizes, stratified by CF Center, FEV_1% predicted (≥ or <30%) and member of *communities of concern* (yes/no). The 4 small centers (n=5 each) plus the medium center (n=10) will be pooled into one (n=30) for the purposes of randomization allocation to allow for varying block sizes within CF Center strata. Each study arm will have 66 participants.

Surveys will be collected from CF patient participants by study staff at the University of Washington during remote study sessions at baseline (V1), 2-weeks (V2), 3-months (V3), and 6-months (V4) to assess ToT efficacy and psychological endpoints. Between 2 and 3 months after randomization, a routine CF clinic visit will occur for all participants, separately from study visit V3. Participants and their CF physician or APP will complete online surveys after the clinic visit. After study visit V3, all participants will gain access to both ToT and UNOS for an additional 3 months (6 months total time in the study). Participants will be paired with their CF physician in dyads for in-depth qualitative data collection including audio-recording of their CF clinic visit. The UW Clinical Informatics Research Group (CIRG) will continuously capture identifiable, individual-level research website usage data (ToT and UNOS) for all participants throughout the RCT and during long-term follow up.

C2 Subject Selection

2.a Aim 1 & Sub-Aim 1A [CF Patients]

i Subject Population

Study participants will be volunteer CF patients aged 18 years or older with FEV_1 of less than 50% predicted and have not yet undergone LTx. In total, approximately 150 patients who give informed consent, meet eligibility criteria will be enrolled in the study.

ii Eligibility Criteria

The proposed study does not involve children (by NIH definition of age <18 years). Adult patients with CF who are greater than or equal to 18 years of age will be included in this study. All patient participants in the proposed research have a diagnosis of CF. We will not discriminate based on gender, race, or ethnicity. We will oversample CF patients with low socioeconomic status based on Medicaid insurance status. Research teams will also prioritize enrollment of CF patients with non-White race, Hispanic ethnicity, or high school education or less. English and Spanish-speakers will be included in this study. The Take on Transplant (ToT) intervention and all study documents will be available in Spanish. Study staff at the University of Washington will include a native Spanish-speaker who will be available for consent purposes and during all study procedures.

The composition of the cohort (with regard to gender and racial/ethnic groups) is largely based on the demographics of the CF patient population nationally. In 2020, the racial/ethnic composition in the CF Foundation Patient Registry was 93.4% White, 4.7% African American, and 3.9% other race; Hispanic ethnicity (any race) makes up 9.6% of the population.[1] The CF population nationally in 2020 was 48.2% females.[1] Our cohort of eligible patients, defined by severely impaired lung function (FEV_1 <50% predicted), will likely be composed of fewer racial minorities and fewer women, but this is not due to discrimination on the part of the investigators, and instead reflects the composition of the patient population with reduced lung function nationally[1, 7] and locally. We will oversample individuals with Medicaid health insurance, non-White race, and Hispanic ethnicity, as above, to increase their representation in the clinical trial. CF patients with Medicaid are more often non-White than CF patients with private health insurance. We will ensure a balanced recruitment of men and women and plan to evaluate usage of the research websites and clinical trial outcomes by gender.

Pregnant women will not be excluded from this study because the study poses low risk to participants and the research has the prospect of direct benefit to the pregnant woman by giving her access to resources that may increase her preparedness to consider LTx as a treatment option in the future.

Eligibility Criteria:

1. Adult, greater than or equal to 18 years of age
2. Documentation of a CF diagnosis as evidenced by one or more clinical features consistent with the CF phenotype and/or one or more of the following criteria:
    a. Sweat chloride ≥ 60 mEq/liter

   b. Two well-characterized mutations in the cystic fibrosis transmembrane conductance regulator (CFTR) gene
3. FEV_1 less than 50% of the predicted normal value
4. Informed consent obtained from subject, able to communicate with the Investigator and read (in English or Spanish) and comply with the requirements of the protocol
5. No prior LTx
6. No prior participation in pilot RCT testing of the "Take on Transplant" website

iii Third-Party Subjects

CF patient participants may be asked to provide contact information for third-party subjects for the purpose of informing them about additional research opportunities. Additionally, any third-party subjects who attend a clinic visit with CF patient participants must provide verbal approval to being recorded prior to when any audio recording occurs.

2.b Aim 2 [CF Physicians/APPs]

i Subject Population

CF physicians or advanced practice providers (APPs) at each of the research locations assisting with the recruitment of Aim 1 and Sub-Aim 1A participants and/or providing medical care during the routine CF Clinic visit at 2-3 months after participant's randomization will be consented for participation as subjects in the study. In total, approximately 50 CF physicians and APPs will be enrolled in the study.

ii Eligibility Criteria

All CF physicians and APPs practicing at recruiting research locations will be eligible to participate in Aim 2 study procedures.

Eligibility Criteria:

1. CF physician or APP at a participating site who assists in the recruitment of patients or provides CF care for potential participants in Aim 1 & Sub-Aim 1A study procedures.

C3 Compensation

Per CFF Therapeutics Development Network guidelines regarding patient compensation, our payment incentive meets the minimum of $30/hr. Payments are not exorbitant as to unintentionally coerce potential subjects. All compensation provided will be distributed in the form of a Tango gift card within 1-3 business days following each session.

Participants in Aim 1 & Sub-Aim 1A will receive compensation totaling approximately $170. Those who participate in a clinic visit audio recording will receive an additional $30. If participants complete all applicable study sessions and attend a CF clinic visit (see section 4.a), they will receive a completion bonus of $50. Compensation will be pro-rated for those who may become unable to complete all study procedures. Visit compensation is as follows:

- Baseline Session (30 min.): $15
- 2-Week Session (15 min. + 2 hr. website use regardless of actual usage): $70

- Clinic Visit Audio Recording (60 min.): $30 – if applicable
- Post-Clinic Visit Survey (15 min.): $10
- 3-Month Session (15 min. – primary endpoint survey completion): $10
- 6-Month Session (30 min.): $15
- Completion Bonus: $50

Participants in Aim 2 (Physicians and APPs) will receive $10 for the completion of each survey. No additional compensation will be provided if they participate in a clinic visit audio recording. Total compensation will vary depending on how many of their patients are enrolled in Aim 1 & Sub-Aim 1A study procedures.

Clinical team members (e.g. social worker, CF nurse, etc.) identified as local champions will be invited to take part in an information session to learn about the study. Local champions will not be enrolled as participants in the study and will only assist in recruitment efforts. Those who attend this information session will be eligible to receive a $20 Tango gift card as a courtesy for the reimbursement of their time.

A device and/or reliable internet connection (mobile Wi-Fi hotspot with pre-paid data) can be requested to make patient participation in this study possible. They may be used for the duration of the study, but must be returned to the study team at the University of Washington once active study involvement is completed.

C4 Data Sources & Variables

Local electronic health records (EHR) at research locations and/or PortCF (CF Foundation Patient Registry) may be used to access and obtain data for screening purposes and for the collection of relevant study data. Study staff at the University of Washington will obtain appropriate HIPAA Authorization consent, per local site requirements, from CF patient participants prior to research locations access and/or obtain study data. For screening and recruitment purposes, HIPAA Authorization will be waived for all research locations.

For screening purposes, research locations will obtain the following data to identify potential CF patient participants: Name, date of birth (DOB), clinic appointment dates, date of screening, lung function testing results, sex, race/ethnicity, insurance status, zip code, contact information, lung transplant referral status/history, pertinent information from recent clinic notes (i.e. documentation of exacerbations, prior metal health screening results), reason(s) for refusal to participate in the research, etc. All screening data will be retained and shared with the University of Washington, even if participants do not consent to enrolling in the study as a means to describe the demographics and clinical characteristics of individuals who decline to enroll. Additionally, these data will be kept for the purposes of future research study recruitment and follow-up purposes.

Research locations will require separate, active Cystic Fibrosis Foundation Patient Registry IRB approval to gain access to patient records via PortCF. Individuals with CF at care centers consent separately to having their information available to researchers for screening purposes. Information that may be accessed and/or obtained from PortCF includes: Name, CFF ID, date of birth (DOB), CFTR genotype, sweat test result, visit summaries, annual report, education level, insurance status, etc.

For enrolled CF patient participants, research locations will view their local EHR (i.e. EPIC) to access and/or obtain the following information: name, date of birth, medical record number, phone number(s), email address, complete address, pertinent clinic appointment dates and notes, lung function testing results, vital signs, BMI, demographic information, CFTR genotype, CFTR modulator status, 6-minute walk test distance, supplemental oxygen requirement, blood gas results, history of diabetes on insulin, documentation of pulmonary hypertension on echocardiogram or right heart catheterization, prescription of non-invasive mechanical ventilation (e.g. BiPAP), dates of hospitalizations (all causes), hospitalization diagnoses, dates of pulmonary exacerbations and treatments, insurance status, lung transplant referral history, PHQ-9 and GAD-7 scores, etc. Data may be retrospective or collected prospectively.

Additional data variables to be obtained from all participants via self-report and from the intervention website(s) will include: responses to survey assessments described in section D4, qualitative data obtained during clinic visits (if applicable), and user data collected from website analytics (e.g. session length, number of clicks, page views, IP address, etc.).

Study staff at the University of Washington will have access to and will obtain direct and indirect identifiers for all participants recruited from the University of Washington and from all research locations. Data Use Agreements will be established between the University of Washington and each research location prior to sharing of identifiable data.

All identifiers (or links between identifiers and data/specimens) and data that are part of the research records will not be destroyed until after the end of the applicable records retention requirements by Washington State.

C5 Risks and Benefits

5.a Potential Risks

This multicenter interventional clinical trial places human subjects at low risk. We plan to use a Data Safety Monitoring Board (DSMB), as described in the data safety monitoring plan (DSMP).

Overall Level of Risk
Participants may be exposed to low risk associated with the conduct of the study, whether they are in the ToT (intervention) or UNOS (attention control) group, related to the completion of questionnaires and accessing information about LTx online.

Psychological risks:
Questionnaires: There are no physical risks associated with the study surveys. The risks to participants completing surveys are minimal and consist mainly of perceived or real invasion of privacy or psychological impacts related to surveys about symptoms of anxiety or depression. To minimize concerns about invasion of privacy, we will make it clear that surveys are confidential; however, results from surveys regarding psychological symptoms (GAD-7 and PHQ-9 scores) will be shared with a patient's CF clinician(s) regardless of results. If they meet diagnostic thresholds for anxiety or depression or if there is report of possible suicidality, the patient's care team will be notified with urgency (described in

DSMP). Participants may choose not to answer select questions in the surveys if they are uncomfortable providing responses.

Accessing information about LTx: There are no physical risks associated with accessing websites about LTx. The potential risks to participants are low and are primarily psychological, including the potential for increasing anxiety, depression, or distress. The level of psychological impact of the LTx educational resources (the "Take on Transplant" website or the UNOS website) depends on many factors, including whether the patient has previously considered LTx as a treatment option, has been denied from LTx in the setting of a contraindication, has experience with others who underwent LTx, the amount of information they know about LTx (and whether that information is correct), and how sick they are.

In a study of 153 University of Washington adult CF patients in 2015, there was a surprisingly high rate of report of suicidality with 7 (5%) of clinically stable patients who reported suicidality on routine PHQ-9 screening questionnaires.[39] Of the 7 patients with suicidal ideation, 2 had co-morbid clinically-significant depression (PHQ-9 >10) and anxiety symptoms (GAD-7 >10), 1 patient had clinically-significant anxiety symptoms alone (GAD-7 >10), and the remaining 4 did not have clinically-significant depression or anxiety symptoms but had elevated PHQ-9 scores between 5 and 10 corresponding to mild depression symptoms. Only FEV_1 % predicted was independently associated with the presence of diagnostic PHQ-9 depression scores[39], raising the concern for risk of depression for people with severe CF in the proposed RCT. A separate study of CF patients in the United Kingdom found that 10% of patients reported suicidality on routine screening PHQ-9 surveys.[40] We are enrolling patients with a large range of lung function with many who will be "too well" for LTx. While initially learning about LTx may be distressing, over the longer term it may be beneficial to one's mental health to have a better understanding of the context for LTx. Qualitative data will be important for understanding the psychological implications (potential harms and benefits) of LTx education in this population. Understanding background rates of depression, anxiety and suicidality in the CF population inform the interpretation of the psychological risks of study participation.

Risks to confidentiality:
Access to private medical records: One risk of this study involves the access to private medical documents and patient level data that is not anonymous. We will take precautions to ensure the confidentiality of patient specific data. All researchers who participate in the study will sign a confidentiality statement. Identifying information will be kept separate from survey results and clinic transcripts in a password-protected computer to which only study staff will have access as noted below.

Individual-level web usage analytics: There are no physical risks associated with tracking individual-level web usage analytics, and most people have this type of data collection occurring in their daily lives. Patients will be informed of usage tracking on the research website. There is the potential for perceived or real invasion of privacy because the web analytics can track location precisely. We will take precautions to ensure the confidentiality of patient-specific data. All researchers who participate in the study will sign a confidentiality statement.

Recording of CF clinic visit: There are no physical risks associated with recording a CF clinic visit, but it is possible for patients to have a perceived or real invasion of privacy because the recording may contain sensitive health information unrelated to LTx considerations. We will take precautions to ensure the confidentiality of patient-specific data. Additionally, physicians or APPs may have a perceived or real invasion of privacy as their conversation with the patient may contain sensitive information related or unrelated to LTx. We will de-identify the physician, APP, and CF center in clinic visit transcripts to avoid ascribing conversation(s) to a specific physician, APP, or center. All researchers who participate in review of the audio recordings will sign a confidentiality statement. Identifying information will be kept separate from the audio recordings. Audio recordings will be transmitted from collaborating sites to the University of Washington research team using secure transfer method within 5 days and recording devices will be cleared of original files immediately after transfer.

There are no research procedures that may have risks that are currently unforeseeable. Additionally, it is unlikely that significant new safety findings will be discovered as this study is minimal in risk and there were no significant new findings in the pilot RCT study.

Alternatives
Participation will be voluntary. Patients that choose not to participate in the study will continue to receive clinical care at their local CF center.

5.b Potential Benefits to the Subjects

Preliminary testing of ToT suggests research participants may experience improvement in key outcomes like preparedness for LTx discussions, LTx knowledge, decisional conflict about LTx, and others. Based on feedback from CF patients who have pilot tested ToT, we hypothesize that the proposed intervention will be well-received and will lead research participants to have an improved understanding of the questions they have about LTx for their own CF doctor. Further, the current study will yield important feedback to refine ToT for future users with low SES and/or low health literacy. This study may also inform the future implementation of ToT, with respect to the timing and context of LTx discussions in CF clinic.

5.c Protections Against Risk

Psychological risks: Given the sensitive nature of LTx as a treatment option for CF, it is possible that patients may experience psychological distress from reading about LTx, especially in cases where CF patients have died after LTx. We have worked to mitigate this risk by allowing participants to moderate the amount of information they read about particular patient stories or ‘Resource Library’ content. Specifically, we have applied “story highlights” to ‘CF Stories,’ which describe an overview of the content and are visible prior to entering the story. We also give an overview of ‘Resource Library’ content prior to entering the topic. More than 100 CF patients (pre- and post-transplant) have reviewed the content and provided feedback on the content and presentation of sensitive information. Additionally, most CF clinics have a mental health coordinator embedded in the clinic. Screening for depression and anxiety is the standard of care at CFF accredited care centers. We have the contact information for the CF providers, including social workers and mental health coordinators, at all participating sites in case we need to contact them

acutely about a participant. Further, we are collecting robust measures of mental health outcomes, including the PHQ-9 and GAD-7, which will be monitored closely for evidence of harm to study participants. We will administer the PHQ-9, and GAD-7 at baseline (V1), 2-weeks (V2), 3-months (V3), and 6 months (V4). The UW research facilitator will review all PHQ-9 and GAD-7 results immediately to identify new onset of psychologic symptoms worsening to diagnostic level (PHQ-9 ≥10 or GAD-7 ≥10) or evidence of possible suicidality (an affirmative response to #9 on the PHQ-9) and will consider any of these an adverse event. The Data Safety Monitoring Plan outlines in detail how abnormal mental health outcomes will be addressed as adverse events of special interest and how a Data Safety Monitoring Board will monitor for risks to human subjects.

Herein, we will describe our approach to an affirmative response to question #9 on the PHQ-9 ("Over the last 2 weeks, how often have you been bothered by: Thoughts that you would be better off dead or of hurting yourself in some way"). It is important to note that an affirmative response to this question does not necessarily indicate that a person is suicidal. Given the severity of the symptom burden in end-stage CF, some people may have thoughts that they may be better off dead without actually wanting to die or kill themselves. It is important to assess individuals for evidence of suicidality in this setting. First, all study sessions for completion of surveys in REDCap (i.e. PHQ-9) are scheduled to ensure availability of a physician to contact a participant in the event of the report of an affirmative response to #9 on the PHQ-9. Dr. Ramos and the UW research facilitator receive an instantaneous automatic email alert from REDCap in the setting of an affirmative response to #9 on the PHQ-9. The UW research facilitator will notify the participant during the Zoom-based study session to expect a call from Dr. Ramos or another study physician. The study physician will call the patient within 4 hours of the result, perform the Columbia-Suicide Severity Rating Scale triage for primary care[41], provide information for the national suicide and crisis hotline (9-8-8), and establish a safety contract with the patient in the interim, as indicated. Additionally, the study physician will notify the participant's CF clinician directly via secure communication within 4 hours of the result. All episodes of reported suicidality documented on PHQ-9 administered during study sessions will be reported to the medical monitor within 24 hours, to the DSMB within 2 working days, and to the central IRB in accordance with the standard operating procedures and policies of the IRB. If Dr. Ramos is unavailable, Dr. Goss (co-I) or Dr. Kapnadak (co-I) will perform these duties.

Risks to Confidentiality: As with any research study, there is a potential risk of breach of confidentiality. Study personnel will enter personally identifiable data into a protocol-specific electronic Case Report Form (eCRF), managed through REDCap. We will take precautions to ensure the confidentiality of patient specific data. Further, audio recordings of CF clinic visits may contain sensitive health information that is beyond the scope of the current research project. Research staff who perform the role of observer to rate the quality of shared decision making will have HIPAA training and will access the audio recordings via a secure web interface. Study participants will not be identified by name in the study database or on any data capture screens but will be identified by a subject identification number unique to this study. Participants will have different identification numbers in Aims 1 and 2 to limit the potential for accidental unblinding by comparing numbers across the projects within the study. Only authorized individuals will be able to link the study ID to the participant's name. All investigators and staff involved in the proposed research will have

completed human subject protection training, have HIPAA training, and will be bound by the agreement of confidentiality. All study databases at the UW will be maintained on password protected computers and routinely backed up to an encoded password protected file. All procedures for the handling and analysis of data will be conducted using GCP, meeting FDA guidelines for the handling and analysis of data for clinical trials. Data presentations will include only group data and will be presented in a way that ensures individual participants and institutions cannot be identified. If respondents may be identified by a specific subgroup (e.g., male minority CF patients), these subgroup data will not be presented in any format.

In addition to the issues discussed above, participants will be informed that involvement in the study is voluntary and that refusing to participate will not be associated with any loss of rights or benefits to which they are otherwise entitled. To minimize perception of coercion, we will make it clear that subjects may withdraw from the study at any time without penalty by notifying study staff. If participants choose to withdraw, they will be given the choice of having their data kept as part of the dataset, as identifiable or de-identified, or removed.

D Study Procedures

D1 Screening for Eligibility

Potential subjects involved in Aim 1 and Sub-Aim 1A procedures will be largely, if not exclusively, known to the investigators at research locations as patients are followed at the CF Care Center. Study Staff (i.e. research coordinators/assistants, research nurse, etc.) and/or the lead researcher at each site will use local access to the CFF Patient Registry data (PortCF) and/or local EHR (i.e. EPIC) to screen and identify patients who meet eligibility criteria. Additionally, potential participants may be screened by viewing the CF clinic schedule in the EHR. To determine if a patient is eligible, study staff and/or the site-PI at each research location will review the screening variables described in section C4. We aim to over-enroll participants with disadvantaged backgrounds (from *communities of concern* – Medicaid insurance, non-White race, Hispanic ethnicity, or high school education or less). We will close enrollment to individuals outside *communities of concern* after 85 participants not meeting these criteria, balancing across sites, to achieve a sufficient sample to target at least 1/3 (n=40) from *communities of concern*. Participants meeting eligibility criteria will be recruited for participation.

For Aim 2 participants, there will be no formal screening procedure. Study staff at each site will provide the University of Washington with a physician/APP roster which includes contact information for recruitment purposes.

D2 Recruitment Methods

Once an eligible CF patient is identified, designated study staff at each recruiting research location will contact the patient to provide information about the study. Study staff can contact potential participants in person, by phone and/or email using IRB-approved phone call script or email templates. Research locations will use their best-practices depending on local guidelines.

Some CF clinics maintain a list of email addresses for patients interested in notifications about relevant clinical research, and these email addresses may be used to send IRB-approved

email templates to describe the study and provide study contact information. Alternatively, patients may be approached in-person during a CF clinic visit and provided with an IRB-approved informational handout. In clinic, the patient's CF physician or local champion (described below) may introduce the study prior to an approach by study staff to increase the likelihood of participation.

Our recruitment efforts will oversample difficult to engage patients, including people from *communities of concern* (Medicaid insurance, non-White race, Hispanic ethnicity, or high school education or less); study staff and local champions for the project will make a coordinated effort to recruit individuals from *communities of concern* to fill at least 1/3 of the study population. The University of Washington will track demographics of the enrolled participants as the study progresses to assess whether we are achieving the desired demographics. Sites will be asked to keep an updated screening log (via REDCap), including a record of individuals who are approached and decline enrollment. If we are not reaching enrollment targets, we will engage with individual sites to identify reasons for not enrolling from the patient groups of interest, to see what changes, if any, could be made to improve recruitment. Additionally, patients who state refusal to participate or are unable to be contacted after multiple attempts may be re-screened and re-approached for participation after approximately three months elapse, as a change in health status may prompt their interest in participating. Participants who state refusal to participate, will be asked to share their reason(s) for refusal which will be obtained as part of the study data.

Once an interested individual has been identified, study staff may provide the potential participant with a copy of consent documents to review and a link to schedule a study session or information session with study staff at the University of Washington. To schedule their visit, participants will be asked to provide their name, contact information, and mailing address if a device and/or Wi-Fi hotspot is requested. Alternatively, study staff at research locations may share the potential participant's contact information with study staff at the University of Washington (via email and/or REDCap), if the patient provides verbal permission for sharing this information. Study staff at the University of Washington will then contact the participant for scheduling of the baseline session where electronic documentation of informed consent will be obtained.

For CF physicians and APPs recruited for enrollment into Aim 2 study procedures, study staff at participating sites will be asked to provide the University of Washington with a physician/APP roster which will include names, phone numbers, and emails. Study staff from the University of Washington will contact all physicians and APPs via email with information about the research study using an IRB-approved email template. Study staff from the University of Washington will be available in person or via Zoom or phone to describe the study in detail to the CF clinical teams at participating research locations. This will allow for the identification of local champions (e.g. social worker, CF nurse) who can identify individuals from disadvantaged backgrounds who are eligible for participation in the RCT. Clinical team members (i.e. social worker, CF nurse, etc.) identified as local champions will not be enrolled as participants in this study. They will only assist in the recruitment efforts of participants.

CF patient participants enrolled into Aim 1 and Sub-Aim 1A will be asked to provide contact information for third-party subjects. Study staff at the University of Washington may contact

these individuals by phone and/or email using IRB-approved phone call script and/or email template, covered under separate study protocols and IRB(s).

D3 Informed Consent

Informed consent will be obtained electronically for all participants by study staff at the University of Washington using a University of Washington installation of REDCap. It is unlikely that documentation of consent will not be able to be obtained electronically as internet access is a requirement to participating in this study and can be provided to participants if necessary.

Aim 1 and Sub-Aim 1A [CF Patients]:
Eligible participants will join the baseline session remotely via Zoom where they will first review electronic consent documents with University of Washington study staff. Participants will be given ample time to review the consent form between when they were notified of the study and the scheduled baseline session. They will also be given the opportunity to have all questions answered to their satisfaction before providing an electronic signature and continuing with baseline session study procedures. All participants will be informed that involvement in the study is voluntary and that deciding not to participate will not be associated with any loss of rights or benefits to which they are otherwise entitled. To minimize perceptions of coercion, we will make it clear that participants may withdraw from the study at any time without penalty by notifying study staff. All participants will receive a PDF copy of their signed consent documents to keep for their records and will be encouraged to contact study staff if any questions arise.

Additionally, at the start of all sessions study staff will review an agenda of study procedures to be completed with participants. Participants will be allowed to ask the study staff any questions prior to proceeding and University of Washington study staff will provide clarifications if necessary.

Aim 2 [CF Physicians/APPs]:
Study staff from the University of Washington will be available via Zoom, email, or phone to describe the study in detail to the CF clinical teams, including the physicians and APPs, at participating research locations. Study staff at the University of Washington will provide all CF physicians and APPs with a link via email where they will be able to review consent documents. Consent documents will provide sufficient information, and providers will be encouraged to contact the University of Washington study staff if there are any questions prior to providing an electronic signature.

D4 Description of Study Procedures

Aim 1 & Sub-Aim 1A [CF Patients]:
Survey Assessments: Participants will be asked to complete surveys during each session. Surveys will take approximately 15-30 minutes to complete. For individuals with CF, surveys may include questions from the following measures: demographics, shortened test of functional health literacy in adults (S-TOFHLA), assessment of health numeracy (Newest Vital Sign), Assessment of digital health care literacy, Preparation for Decision Making (PrepDM) Scale, investigator-designed lung transplant knowledge assessment, Decisional Conflict Scale, Likert rating of preparedness to discuss lung transplant, Patient Health Questionnaire (PHQ-9), Generalized Anxiety Disorder scale (GAD-7), General Self-Efficacy Scale, Perceived Social Support Scale, Shared Decision Making Questionnaire (SDM-Q-9), patient report of

discrimination during medical care, Big Five Inventory (BFI), etc. (Table 2, next page) Additional questions may be asked to confirm medical record information (i.e. occurrence of lung transplant conversations, adverse events, etc.) and/or information pertaining to website usage (i.e. barriers to use, future website implementation, access outside of the research website, etc.). Additionally, all participants will be asked at the baseline visit to share their reason(s) for choosing to participate in the research study.

Research Website Access: Participants will be introduced to the research website during the Baseline Session via a pre-recorded video housed on the research website. The research website will contain two interventions including a CF-specific LTx education website ("Take on Transplant") and an attention control (UNOS.org). Before accessing the research website during the baseline session, participants will be randomized 1:1 to either the CF-specific website ("Take on Transplant") or the attention control (UNOS.org). Participants will be given unlimited access to the website from their study arm assignment for 2 weeks. After the 2-week session, participants will have ongoing access to the website to which they were randomized for 3 months. At the 3-month session, access to the opposite arm assignment will be unlocked and participants will have unlimited access to both the CF-specific website ("Take on Transplant") and the attention control (UNOS.org). All participants will receive up to weekly text message and/or email reminders to log into the research website for the first 3 months of the study, regardless of study arm assignment.

Clinic Visit Audio Recording (if applicable): Participants will be asked to have their next routinely-scheduled CF clinic visit audio recorded. No recordings will occur without expressed verbal permission from CF patients, the CF provider, and third-party subjects (if applicable). By recording these visits, we will assess the dyadic relationships between patients and their CF providers and their role in decision making about LTx as a potential treatment option. Study staff at the University of Washington will evaluate the recordings for duration of visit, duration spent discussing LTx, rating the quality of shared decision making using the Observing Patient Involvement in Decision Making (OPTION) score, and content analysis. If participants do not have a routine CF clinic visit scheduled during the specified window (at least 6 weeks after enrollment and before the 3-month study visit), they may be approached to have a clinic visit recorded after their 3-month study visit but before their 6-month study visit (if a routine clinic visit occurs).

Medical Record Review: Study staff at each research location will access and obtain all data variables described in section C4 for all participants. At approximately 6-12 months after study completion, local study staff will assess the clinical impact of the study via assessment for documentation of LTx discussion and/or LTx referral in local EHR records. Study staff will list dates of all CF clinic visits (including telemedicine), changes in disease severity (e.g. exacerbations, FEV_1, BMI), and dates of clinic notes that document LTx discussion or LTx referral. Additionally, long-term follow-up data will be captured from local EHR records annually for up to 4 years following study termination. Information collected may include variables listed in section C4.

Table 2: Assessment schedule for Aim 1 and Sub-Aim 1A CF patient participants at baseline (V1), 2-weeks (V2), 3-months (V3), 6-months (V4) and during a routine CF Clinic visit (2-3 months after randomization).	
Key survey assessments (collected via REDCap)	**Assessment Schedule**

	V1	V2	CF Clinic	V3	V4
Demographics survey (e.g. highest education level attained, annual household income, race/ethnicity, languages spoken in the home)	x				
Shortened Test of Functional Health Literacy in Adults (S-TOFHLA)[42]	x				
Assessment of health numeracy (Newest Vital Sign)[33]	x				
Assessment of digital health care literacy[43]	x				
Efficacy measures: Preparation for Decision Making (**PrepDM)** Scale[29]		**x**		**Primary patient outcome**	x
Investigator-designed lung transplant (LTx) knowledge assessment and patient's Likert rating of preparedness to discuss LTx	x	x		x	x
Decisional Conflict Scale[32]	x	x		x	x
Psychological and social support measures: Patient Health Questionnaire (PHQ-9)[36]	x	x		x	x
Generalized Anxiety Disorder 7-item scale (GAD-7)[35]	x	x		x	x
General Self-Efficacy Scale[37]	x	x		x	x
Perceived Social Support Scale[46]	x	x		x	x
CF clinic measures Patient's Likert rating of satisfaction with LTx discussion			x		
Shared Decision Making Questionnaire (SDM-Q-9)[48]			x		
Patient report of discrimination during medical care[49]			x		

Aim 2 [CF Physicians/APPs]:
Survey Assessments: CF physicians and APPs will be asked to complete a survey after one CF clinic visit per patient for all patients who are enrolled in this study. The CF clinic visit should occur 2 to 3 months after the patient is randomized, but surveys will be collected even if the visit occurs after this window as long as it occurs before study visit 4 (6 months). The survey will take approximately 15 minutes to complete. The survey may include the following measures: demographics, Shared Decision Making Questionnaire – physician version (SMD-Q-Doc), Likert rating of provider's satisfaction with LTx discussion during the visit, Likert rating of patient preparation for LTx discussion, Likert rating of patient's knowledge about LTx during the visit, etc. (Table 3)

Clinic Visit Recording (if applicable): CF physicians and APPs will be asked to have their CF clinic visits audio recorded. No recordings will occur without expressed verbal permission from CF patients, CF providers, and third-party subjects (if applicable). By recording these visits, we will assess the dyadic relationships between patients and their CF providers and their role in decision making about LTx as a potential treatment option. Study staff at the University of Washington will evaluate the recordings for duration of visit, duration spent discussing LTx, rating the quality of shared decision making using the Observing Patient Involvement in Decision Making (OPTION) score, and content analysis.

Table 3: Assessment schedule Aim 2 CF provider/APP participants, occurs only after a routine CF Clinic visit.	
Physicians and advanced practice providers (APPs) survey measures	**Assessment Schedule**

	V1	V2	CF Clinic	V3	V4
Demographics (e.g. age, gender, race, ethnicity, years in practice, clinical practice specialties) – Once per MD/APP			x		
Shared Decision Making Questionnaire–physician version (SDM-Q-Doc)[50]			x		
Provider's Likert rating of satisfaction with LTx discussion			x		
Provider's Likert rating of patient preparation for LTx discussion and patient's LTx knowledge			x		

4.a Schedule: Aim 1 & Sub-Aim 1A [CF Patients]

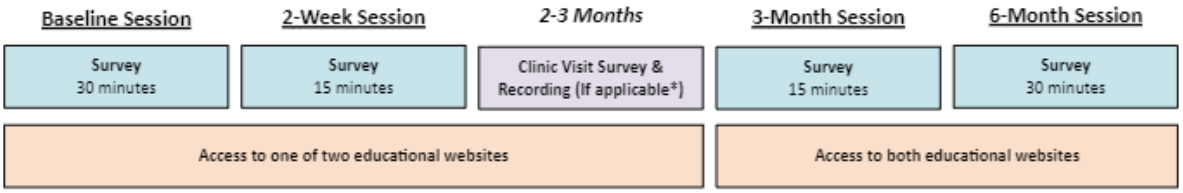
All study visits, apart from any in-person routine CF clinic visits, will occur remotely via Zoom videoconferencing with study staff at the University of Washington. To ensure patient privacy, individual meeting links will be sent to participant's confirmed email addresses. The waiting room setting will be enabled so that only the research participant will be able to join the call. Additionally, participants will not be required to enable their video if they prefer not to.

Study staff may communicate with participants throughout their involvement in the study via email, text, and/or phone for reminders pertaining to study visits, website usage, or to address any questions.

Unless approved by study staff at the University of Washington, study windows should be scheduled as follows:

2-Week Session (V2): -3 / +3 days
2 to 3-Month CF clinic visit: at least 6 weeks after randomization/until 3-Month Session (V3)*
3-Month Session (V3): -7 / +7 days
6-Month Session (V4): -7 / +7 days

*If participants do not have a routine CF clinic visit scheduled during the specified window (at least 6 weeks after enrollment and before the 3-month study visit), they may be approached to have a clinic visit recorded after their 3-month study visit but before their 6-month study visit (if a routine clinic visit occurs).



No recordings will occur without expressed verbal permission from CF patients, CF providers, and thrid-party subjects (if applicable).

i Baseline Session (V1)

- Survey – 30 minutes
- Gain access to Website #1

ii 2-Week Session (V2)

- Survey – 15 minutes
- Continued access to Website #1

iii 2-3 Months after Baseline

- Routine CF clinic visit
- Post-Clinic visit survey – 15 minutes
- *Clinic visit audio recording*
- Continued access to Website #1

iv 3-Month Session (V3)

- Survey – 15 minutes
- Gain access to Website #2 (in addition to Website #1)

v 6-Month Session (V4)

- Survey – 30 minutes
- End of active study participation and start of long-term follow up

D5 Data Collection Procedures

All study data will be collected and maintained using a University of Washington installation of REDCap. Research locations will have limited access with permissions set to only view data from their site. Only authorized study staff at the University of Washington will be able to view all data from each research location. To protect patient data, each research location will require a Data Use Agreement with the University of Washington prior to sharing any identifiable data.

Study staff at the University of Washington will conduct all study sessions remotely via Zoom videoconferencing. Study staff at each research location assisting with the recruitment of participants will be responsible for collecting and sharing EHR data for screening and enrollment purposes and facilitating and transmitting clinic audio recordings.

E Data Safety Monitoring Plan

Brief synopsis of the project: The overall research objective is to test the efficacy of an investigator-designed lung transplant education website, Take on Transplant, compared to an attention control website in a multicenter randomized controlled trial. The project incorporates mixed methods to assess preparedness for lung transplant discussions among cystic fibrosis patients with severe obstructive lung disease (FEV_1 <50% predicted). Study procedures include surveys performed electronically and interviews conducted via Zoom videoconferencing. The University of Washington study staff will perform these study procedures, while all study sites will participate in recruitment of participants and conduct of the protocolled 3-month clinic visit (routine cystic fibrosis care). We will oversample from *communities of concern* – people with low socioeconomic status, Hispanic ethnicity, or non-White race – to inform improvements in a process that disadvantages these patients and leads to health disparities. We aim to empower patients to discuss lung transplant. This study will explore the impact of lung transplant education on patients' psychosocial functioning and assess patients' and physicians'

perceptions and use of lung transplant education. Lung transplant is a sensitive topic, raising concerns about mortality, health complications, and financial stress. There is a risk that exposure to lung transplant educational content could increase anxiety, depression, or emotional distress. Additionally, we will evaluate patient-physician dynamics, including implicit bias and experience of discrimination, which may also produce an emotional response for participants. For these reasons, it is warranted to form a Data Safety Monitoring Board (DSMB) to longitudinally assess mental health outcomes, including report of possible suicidality via the PHQ-9, for participants in the clinical trial.

Table 5: Overview of Data Safety Monitoring Plan	
Section	Description and location within this document
Monitoring Entity: Data Safety Monitoring Board	A Data Safety Monitoring Board (DSMB) will be established with the relevant expertise to oversee mental health risks to clinical trial participants. An independent medical monitor will review adverse events. Responsibilities of the DSMB are outlined, including addressing conflicts of interest. (Section E1)
Monitoring for Compliance	Dr. Kathleen Ramos (PI) will oversee the monitoring schedule and procedures for ensuring compliance with IRB requirements, minimizing research-associated risk, and verification of informed consent source documents. (Section E2)
Data Management Practices and Quality Control	Data management and quality control will be provided by the University of Washington research team (Section E3)
Identifying, managing, and reporting adverse events and unanticipated problems	Potential risks and benefits to participants are discussed. Frequency and mechanism of monitoring for adverse events, along with management and reporting of adverse events are outlined. (Section E4)
Monitoring plan for multiple sites	The University of Washington research team will ensure compliance with the monitoring plan and reporting requirements across all study sites (Section E5)
Assessment of external factors that may impact participant safety	The PI and co-Investigators will remain up-to-date with relevant developments in the literature that could have implications for the ethics of the study. (Section E6)
Plans for interim safety analysis	The DSMB will review an interim analysis to ensure the safety of participants in the trial. (Section E7)
Communication plan and mechanisms for reporting to the DSMB, IRB and NINR	This section describes communication plan details and an overview of responsible persons who report to the DSMB, IRB, and NINR in the setting of AE/SAEs, unanticipated problems, AEs of special interest (e.g. suicidality), IRB actions, or protocol changes. (Section E8)

E1 Monitoring Entity: Data Safety Monitoring Board

An independent Medical Monitor will review individual serious adverse events (SAEs) throughout the study as they occur (see Section 1d for details related to identification, management, and reporting of adverse events). An external Data Monitoring Board (DSMB) will be created to function as an independent group of experts who will advise the study's investigators with respect to participant safety and monitoring study progress and conduct.

The Medical Monitor is Engi Attia, a pulmonologist (MD) from the University of Washington who has been trained to perform medical monitoring for Cystic Fibrosis Foundation Therapeutics Development Network (TDN) studies and on the current protocol and study procedures. This Medical Monitor will review and assess SAE reports and make the preliminary assessment of seriousness, expectedness, and causality with assessment for need of expedited reporting. The Medical Monitor will also determine if follow-up information is required and write an SAE narrative for each SAE. The Medical Monitor will review all adverse events, SAEs, and medical coding for DSMB reporting purposes and communicate safety concerns to the DSMB at least every 6 months.

DSMB Membership

The members of the DSMB will serve in an individual capacity and provide their expertise and recommendations. The DSMB will be composed of at least 4 members, including an experienced statistician. One of these members will have experience in clinical trial conduct and experience in adult CF clinical care, and another will have expertise in clinical psychology. There will be an Executive Secretary who will ensure that the members will not be co-investigators of the study and will have no undisclosed conflicts of interest. The Executive Secretary will take notes during meetings to facilitate draft minutes for chair approval. The DSMB will develop and approve a Charter that will outline the roles and responsibilities of DSMB members, including the specifics related to participant protection oversight, monitoring of study operations, and ensuring data integrity.

DSMB Meetings

Prior to enrolling human subjects, the DSMB will meet to approve the Charter, review the IRB-approved study protocol, and review the IRB-approved informed consent form. The DSMB will approve reporting templates that will be used at DSMB meetings. The DSMB will review immediately reportable events (i.e., report of possible suicidality based on an affirmative response to question #9 of the PHQ-9) and establish an approved mechanism for communication within 48 hours of the event. The statistician will review the planned interim safety analysis (see section E7 below) and approve or recommend modification to the proposed plan. During this first meeting, the DSMB will review a summary of existing literature and make recommendations about whether the trial should proceed as planned or be changed based on new findings.

Every 6 months while participants are enrolling, or more often if requested by the DSMB chair, DSMB meetings will occur via teleconference. The DSMB will contribute to the protection of participants by review of adverse event data and other safety data, and will assure the integrity of the study by reviewing quality and completeness of study data, and enrollment data at each meeting.

Data safety monitoring for the intervention will focus on evaluating mental health concerns raised during participation in the trial and will monitor all complaints about the study. We will administer the PHQ-9, and GAD-7 at baseline (V1), 2-week (V2), 3-month (V3), and 6-month (V4) study visits. Concern for diagnosis of depression and anxiety is defined when PHQ-9 is ≥10 and GAD-7 is ≥10, respectively. Evidence of possible suicidality (an affirmative response to #9 on the PHQ-9) is an immediately reportable adverse event (described in detail in section E4 below). The DSMB will also be charged with reviewing any complaints from patients, family members, and clinicians about any aspect of the study including recruitment procedures and study implementation. All potential participants will be provided contact information to register complaints, if they experience coercion or other problems. The DSMB will make recommendations to modify or stop the study if any such complaints represent a legitimate concern about the study procedures or methods.

The DSMB will review quarterly data safety monitoring reports and enrollment reports, prepared and submitted by the PI, as long as participants are being enrolled or evaluated. There will be one planned interim safety analysis (described in section E7 below). The DSMB will review the following activities associated with the intervention's evaluation: 1) participants' PHQ-9 and GAD-7 scores; 2) episodes of reported possible suicidality (an affirmative response to #9 on the PHQ-9); and 3) SAEs. The DSMB will monitor for rates of suicidality and the new onset of PHQ-9 or GAD-7 scores consistent with depression or anxiety, respectively, in both arms of the RCT. In order to do this effectively in a trial, the DSMB is expected to review the data in an unmasked fashion in closed session, separate from the open session attended by the PI and other study team members. Blinding will be maintained during the open session. Unmasking will occur during the closed session. Voting members of the DSMB will attend an executive session to determine whether the safety data warrant changes to the protocol or terminate the study. The DSMB will also evaluate data on participant enrollment, site visits, study procedures, forms completion, data quality, losses to follow-up, and other measures of adherence to the protocol. At the conclusion of the sessions, the DSMB chair may provide a summary of the preliminary recommendations to the lead investigators to provide an opportunity for study investigators to ask questions to clarify the recommendations. The meeting is then adjourned.

DSMB communication (see also Section E8)
The Executive Secretary will take minutes at each DSMB meeting. The DSMB chair will be responsible for generating a summary report after each meeting of the DSMB. Reports of DSMB deliberations will be delivered as formal minutes within 14 days of each meeting or call.
Minutes will document whether there is conflict of interest on the part of Board members and will summarize the key points of the discussion and debate, requests for additional information, response of the investigators to previous recommendations, and the recommendations from the current meeting. The summary report will not contain any unmasked safety or efficacy data by treatment arm. The summary report will be provided to the central IRB (Advarra) and to NINR.

- If the DSMB does not identify any safety or other protocol-related concerns, the Summary Report will state that:
    - A review of adverse event data, and information relating to study performance (e.g., data timeliness, completeness, and quality) across all centers took place on a given date;
    - the observed frequency of adverse events did not exceed what was expected and indicated in the informed consent;

    - a review of recent literature relevant to the research took place, and;
    - the DSMB recommended that the study continue without modification of the protocol or informed consent
- If the DSMB does identify concerns, the UW staff will distribute, as soon as feasible, and within 7 calendar days of the DSMB meeting, the Summary Report as outlined above, outlining the concerns and the basis for any recommendations that the DSMB has made in response to the concerns.
- Dr. Ramos will ensure timely delivery of the report to study investigators and co-investigators.

Dr. Kathleen Ramos (PI) will be responsible for ensuring that the DSMB summary report is shared with the central IRB (Advarra) and the NIH/NINR, along with any action plan or response to the summary report, within 7 days of receiving the final report from the DSMB chair. Dr. Ramos will also be responsible for timely reporting to NINR: unanticipated problems or unexpected SAEs that may be related to study participation; IRB-approved changes to the study protocol that could impact the risk to participants; notice of any actions taken by the IRB related to the research. Dr. Ramos will communicate the results of the DSMB meeting to all participating clinical sites and they may share the summary report with their local IRB if indicated.

E2 Monitoring for Compliance

Dr. Ramos (PI) will lead the research team and provide oversight of the entire research program, development and implementation of all policies, procedures, and processes. (Figure 2) She will be responsible for the implementation of the scientific agenda and will ensure that systems are in place to guarantee institutional compliance with US laws, DHHS and NIH policies. Dr. Ramos will oversee Mrs. Lauren Bartlett (research facilitator and data manager). Mrs. Bartlett will be responsible for training of collaborating site personnel and will oversee patient recruitment and enrollment. All participants will undergo the informed consent process

with trained University of Washington (UW) staff. Dr. Ramos will oversee the informed consent procedures, the training of study staff, and manage the resultant follow-up. She will also provide medical oversight for the randomized controlled trial (RCT). Monitoring visits to clinical sites participating in the RCT is covered in Section E5, below. Table 6 provides an overview of tasks and responsibilities of the UW research team and collaborating sites, including reference to collection of regulatory documents (e.g., 1572 forms, curricula vitae, Good Clinical Practice [GCP] certifications, etc.), management of participant data, and delegation of informed consent to the UW research team.

Figure 2: Overall Structure of the Study Team

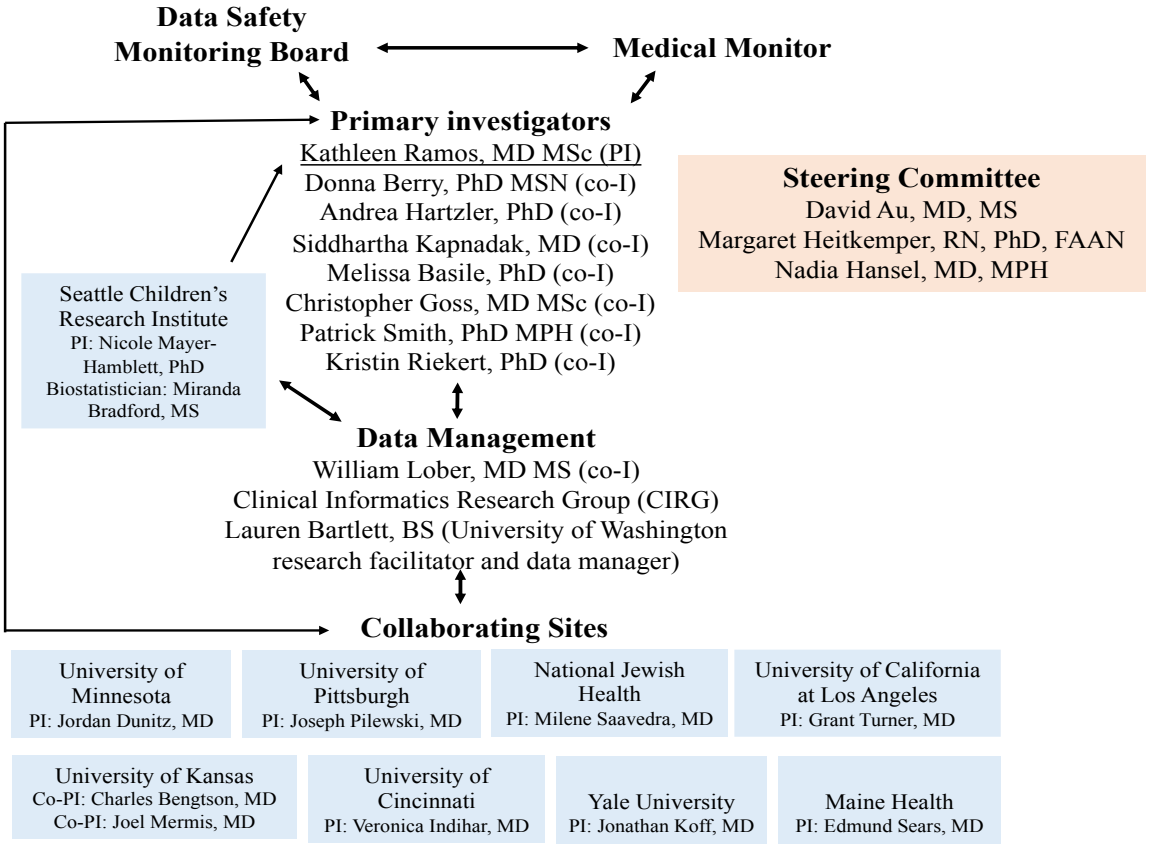


	Table 6: Overview of tasks and responsibilities during the Award *Recurring tasks as noted in gray	
TASK/RESPONSIBILITY*	**PI and UW research team**	**Collaborating sites/research locations**
Prepare and maintain study timeline	X	
Ensure final IRB approvals are in place at all sites	X	X
Review, negotiate, track site budgets and contracts	X	X
Oversee study visit supplies (e.g. audio recorder, printed materials), shipping to sites	X	
Collect all regulatory documents from sites (1572 forms, curricula vitae, Good Clinical Practice [GCP] certifications, etc.)	X	X
Obtain informed consent for participation in the trial from all CF physicians at all sites	X	
Investigator meeting for site training (site initiation)	X	X
Develop publication plan	X	X

Develop data transfer plans and test data transfers	X	X
Submit screening and recruitment logs	review	X
Enter electronic health record data for participants	review	X
Obtain informed consent for participation in the trial for all CF patients from all sites	X	
Manage receipt of REDCap eCRF data transfers; perform data cleaning	X	
Generate data management reports	X	
Day-to-day site management activities	X	X
Administer and track site payments	X	
Perform medical monitoring including review and reporting of all serious adverse events	X	
Perform medical coding (coding of adverse events)	X	
Review informed consent records for all participants monthly	X	
Track patient enrollment and retention and develop additional recruitment plans as needed	review	X
Regular investigator and research coordinator teleconferences	X	X
Prepare NIH status reports	X	
Generate quarterly SAE summaries for DSMB and arrange meetings every 6 months	X	
Oversee IRB renewals and updates of other regulatory documents	X	
Data base lock	X	
Seattle Children's Research Institute: - Generate analysis datasets - Statistical programming, analyses, and validation for final stat report - Generate final statistical report - Provide statistical support for primary endpoint manuscript - Generate data sharing datasets for NIH	X	
Perform study close out activities; archive study data and documents	X	
Perform site close out activities		X
Coordinate the communication of the trial results to the investigators, patients and public, including posting of results to ClinicalTrials.gov	X	X
Publication of the primary manuscript	X	X

Monitoring study safety

As described above, the DSMB will receive quarterly safety reports and meet via teleconferencing every 6 months to review all safety data from the ongoing RCT (Section E1). Remote site monitoring visits will occur quarterly (Section E5) and will include audits of investigator compliance with IRB regulations and the study protocol, and verification of source documents. To minimize research-associated risk, additional monitoring will occur every month at the UW clinical and data coordinating center to include review of documentation of informed

consent for all participants, audit of one in every 10 participants to ensure compliance with IRB requirements, and review of data security over the prior month.

E3 Data Management Practices and Quality Control

All data management and quality control will be provided by the UW research team. This group will function as the Data Coordinating Center for the trial. This project requires the creation, maintenance, and analysis of data from multiple sources, including multiple questionnaires, audio recordings, and individual-level web usage data. Recognizing that the success of the proposed study critically depends on the quality of the data collected, systematic data collection, quality control, and data management procedures will be implemented. These methods include: 1) specification and use of concise protocols and standardized data entry forms; 2) rigorous training of study staff; 3) use of electronic data capture system (REDCap); 4) validation and verification of all data collected with range checks, assessment of missing data, secondary verification of extreme data points; and 5) regular meetings between the research teams to discuss issues related to study implementation and conduct. Up-to-date screening logs for recruitment will be provided to the UW study team and will be reviewed quarterly. Study staff at UW will generate a report on the first of each month, which will include site enrollment and milestone payments to date and targets. Case report forms and any applicable monitoring queries are required to be complete prior to any milestone payments. Quarterly remote monitoring visits with each site will provide opportunities for communication about difficulties with recruitment, retention, study protocols, or other aspects of the clinical trial (see Section E5, below).

Collaborating site PIs will have the primary responsibility of overseeing screening and recruitment of participants at their local site. The UW research team will provide benchmarks and feedback for enrollment targets. The UW research team will facilitate all study visits via Zoom and conduct all informed consent procedures via Zoom. The collaborating sites will schedule the CF clinic visit. If indicated, the collaborating site will be responsible for audio-recording the CF clinic visit and securely transferring the audio file to UW. The collaborating sites will be responsible for data entry from participants' local electronic health records (EHR). Once electronic case report forms (eCRFs) are completed, the process of milestone payments for participant enrollment will be managed by UW research staff.

Dr. Ramos will work with Mrs. Bartlett (research facilitator and data manager) to refine their well-established data management infrastructure. Dr. Ramos will work with Mrs. Bartlett and have oversight in regard to the development and implementation of a study database, study forms (case report forms for the electronic data base) and mechanisms for data collection. She will meet regularly with Mrs. Bartlett to review data quality and completion. They will review protocol adherence every month, with attention to completion of study visits, completion of survey data during study visits, and recording of CF clinic visits as planned. Our study statistician, Miranda Bradford, will have primary responsibility for preparing data for interim and final analyses. Analyses will be performed by Ms. Bradford under the guidance of the PI and Dr. Nicole Mayer-Hamblett (co-investigator). Ms. Bradford will remain blinded to study arm assignment during the RCT; only the DSMB statistician and other members of the DSMB will have access to study arm assignment during the RCT. Once the final participant finishes the final visit, sites will have 60 days until the database will be locked for entry of clinical data from the EHR.

Dr. William Lober (co-investigator) will be primarily responsible for overseeing the Clinical Informatics Research Group (CIRG). This team will maintain the web interface for the research intervention and attention control, ensure its operation on secure, actively monitored and maintained clinical-quality servers for the duration of the project period. CIRG will provide weekly summaries of usage data to the research team.

Survey Data

All survey instruments will be completed directly by participants via UW REDCap. Patient participants will complete surveys during study visits hosted remotely (via Zoom) by UW study staff. UW study staff will review the surveys in real-time to ensure no surveys were missed and to determine whether the PHQ-9 indicates potential suicidality (see Section E4 for identification, management, and reporting of suicidality). Patients will not have access to surveys outside of scheduled study visits. Physician participants will complete surveys independently via UW REDCap after CF clinic visits and responses will be reviewed for completeness within 48 hours of survey completion. Physicians will be prompted to complete surveys up to 3 times within the 14 days following a CF clinic visit.

Electronic Health Records Data

The participating sites will enter clinical information from the EHR and local Cystic Fibrosis Foundation Registry data into a UW REDCap eCRF. Research coordinators performing EHR data abstraction will be blinded to a participant's study arm. These EHR data will include baseline demographics and markers of CF severity; documentation of LTx discussion and/or LTx referral in the EHR; dates of all CF clinic visits (including telemedicine); changes in disease severity (e.g. exacerbations, FEV_1, BMI); and dates of clinic notes that document LTx discussion or LTx referral. Data will be reviewed with range checks, assessment of missing data, and secondary verification of extreme data points within 7 days of data entry. Queries will be returned to sites within 7 days of data entry. Co-investigators and research coordinators will participate in monthly investigator calls to discuss issues with data entry. Completeness and accuracy of data entry will be reviewed during quarterly monitoring visits with each site.

CF Clinic Visit Recording

There will be one CF clinic visit (in person or via telemedicine) at 2-3 months after randomization. Each site will have audio recorders to record clinic visits for participants in Aim 2. Recorded files will be transferred securely to the UW study team within 5 days of the clinic visit. Recording devices will be erased immediately after files are transferred. Recordings may be professionally transcribed, and transcripts will be deidentified. Recordings will be preserved on a UW HIPAA compliant cloud until all analyses are complete and manuscripts are published.

Interview and Focus Group Recording

Interviews and focus groups will be conducted via Zoom and recorded. Recordings will be professionally transcribed, and transcripts will be deidentified. Recordings will be preserved on a UW HIPAA compliant cloud until all analyses are complete and manuscripts are published.

Confidentiality and Security

All study documents will be kept in a secured locked office or on a password-protected computer. Study participants will not be identified by name in the study database, but will be identified by a subject identification number unique to this study. Only authorized individuals will be able to link the study ID to the subject's name. All investigators and staff involved in the proposed research will have completed human subjects' protection training, have HIPAA training, and be bound by the agreement of confidentiality. Study data from all sites will be captured using a UW REDCap installation maintained on a secure server. All study databases will be maintained at the UW on password protected computers and backed up to an encoded password protected file in the UW cloud. All procedures for the handling and analysis of data will be conducted using good clinical practices meeting FDA guidelines for the handling and analysis of data for clinical trials. There will be no deletion of entered data and any corrections to erroneous data will be tracked with date, time, and the person responsible for the change. Further, all participants will be protected by the NIH Certificate of Confidentiality, which provides additional privacy protections.

E4 Identifying, managing, and reporting adverse events and unanticipated problems

Potential risks and benefits to participants

Participants may be exposed to low risk associated with the conduct of the study, whether they are in the intervention (Take on Transplant) or attention control (UNOS) group, related to the completion of questionnaires and accessing information about lung transplant. Anxiety and depression are more common in people with CF than the general public and increase in prevalence with increasing CF-related lung disease severity. This study will explore the impact of lung transplant education on patients' psychosocial functioning and assess patients' and physicians' perceptions and use of lung transplant education. Lung transplant is a sensitive topic, raising concerns about mortality, health complications, and financial stress. There is a risk that exposure to lung transplant educational content could increase anxiety, depression, or emotional distress. Additionally, we will evaluate patient-physician dynamics, including implicit bias and experience of discrimination, which may also produce an emotional response for some participants. However, preliminary testing suggests research participants may experience improvement in key outcomes like preparedness for lung transplant discussions, transplant knowledge, and decisional conflict about lung transplant. Our recently completed pilot RCT (NCT05135156) included 50 people with CF who were enrolled for a 4-week study, and only 3 (6%) of participants experienced an AE of special interest (AESI) –suicidality. Of the 3 participants with an affirmative response to #9 on the PHQ-9, one person reported this twice (at V1 prior to randomization and at the 2-week session after using UNOS) and the other two people only reported this at baseline (V1). The abnormal PHQ-9 was deemed unrelated to study participation in all cases, as depression was an active medical issue under treatment and symptoms preceded enrollment in the study. Therefore, while we remain vigilant for potential negative effects of participation on mental health, we are encouraged that participants will experience low risk during the study and may personally experience benefit from lung transplant education.

Identification of Adverse Events and Grading Scale

<u>Assessment of Adverse Events</u>

An adverse event (AE) is any untoward medical occurrence in a clinical investigation of a

patient administered a pharmaceutical product or undergoing an investigational procedure that does not necessarily have a causal relationship with the treatment or procedure. An AE is therefore any unfavorable and unintended sign (including an abnormal laboratory finding), symptom or disease temporally associated with the administration of an investigational product or procedure, whether or not related to that investigational product. An unexpected AE is one of a type not identified in nature, severity, or frequency in the currently accepted risk profile for the treatment or procedure.

The UW research staff will probe, via discussion with the participant, for the occurrence of AEs during each study visit (baseline, 2-weeks, 3-months, and 6-months) and record the information in the study's records. AEs will be described by duration (start and stop dates and times), severity, outcome, treatment, and relation to study procedure, or if unrelated, the cause.

Unanticipated Problems

According to the Office of Human Research Protections (OHRP), unanticipated problems are: 1. Unexpected in the nature, severity or frequency of the event given the research protocol, IRB-approved informed consent form, and the population under study; 2. Related to participation or there is at least a reasonable possibility that the incident, experience, or outcome may have been caused by the research procedure; and 3. Suggestive that the research places participants at greater risk of harm than was previously recognized or anticipated. Assessment for unanticipated problems will occur in the same manner as evaluation for AEs, via research staff probing at all study visits, and review of AEs by the study's Medical Monitor. The Medical Monitor review will occur at least quarterly in preparation of safety reports for the DSMB (described further in Section E1). If unanticipated problems are identified, corrective actions to protect the safety of participants may include changing the study protocol, changing inclusion/exclusion criteria, additional monitoring of participants for early detection of problems, suspension of research activities, modification of the informed consent form, and/or providing information about newly recognized risks to people who previously enrolled in the study.

Assessment of AE Severity and Relationship to Treatment

The National Cancer Institute's Common Terminology Criteria for Adverse Events (CTCAE) Version 4.03, as modified for CF, will be used to assess and grade AE severity. If the experience is not covered in the modified criteria, the guidelines shown in Table 7 below will be used to grade severity. It should be pointed out that the term "severe" is a measure of intensity and that a severe AE is not necessarily serious.

Table 7: Adverse Event Severity Grading	
Severity (Toxicity Grade)	Description
Mild (1)	Transient or mild discomfort; no limitation in activity; no medical intervention or therapy required. The subject may be aware of the sign or symptom but tolerates it reasonably well. (e.g. fatigue after completing a study visit or reading the website for a long time)
Moderate (2)	Mild to moderate limitation in activity, no or minimal medical intervention/therapy required. (e.g. lightheadedness brought on by mild anxiety after reading the website about lung transplant)

Severe (3)	Marked limitation in activity, medical intervention/therapy required, hospitalization possible. (e.g. significant desaturation brought on by severe anxiety/panic after reading the website about lung transplant)
Life-threatening (4)	The subject is at risk of death due to the adverse experience as it occurred. This does not refer to an experience that hypothetically might have caused death if it were more severe. (e.g. suicide attempt brought on by severe depression after reading the website about lung transplant)

The relationship of an AE to the study procedure should be assessed using the following guidelines (Table 8):

Table 8: Adverse Event Relationship to Study Procedure	
Relationship to Study Procedure	Comment
Definitely	Previously known risk of procedure (e.g. reading the website or participating in a study visit); or an event that follows a reasonable temporal sequence from performance of the procedure/testing; that follows a known or expected physiologic response to the procedure; that is confirmed by stopping or reducing the intensity of the procedure; and that is not explained by any other reasonable hypothesis.
Probably	An event that follows a reasonable temporal sequence from performance of the procedure; that follows a known or expected physiologic response to the procedure; that is confirmed by stopping or reducing the intensity of the procedure; and that is unlikely to be explained by the known characteristics of the participant's clinical state or by other interventions.
Possibly	An event that follows a reasonable temporal sequence from performance of the procedure; that follows a known or expected physiologic response to the procedure; but that could readily have been produced by a number of other factors.
Unrelated	An event that can be determined with certainty to have no relationship to the study procedure.

<u>Immediately Reportable Adverse Events</u>
Definition of Serious Adverse Events (SAE): An SAE is defined as any untoward medical occurrence that at any level of procedural intensity:

- Results in death
- Is considered life threatening (i.e., in the view of the Investigator the adverse experience places the patient or subject at immediate risk of death from the response, as it occurred; it does not include a reaction that, had it occurred in a more severe form, might have caused death)

- Requires hospital admission or prolongation of an existing hospitalization
- Results in persistent or significant disability/incapacity (i.e., a substantial disruption of a person's ability to conduct normal life functions)
- Is an important medical event (i.e., when based upon appropriate medical judgment, the adverse experience may jeopardize the patient or subject and may require medical or surgical intervention to prevent one of the above listed outcomes)

For the purposes of this study, participant report of an affirmative response to #9 on the PHQ-9 is an immediately reportable AE of special interest, even if it is not an SAE. An alternative approach would be to utilize the PHQ-8 (which excludes the question about suicide), but it is important to understand whether there is a risk of increasing suicidality through the introduction of lung transplant education in this patient population. Avoiding the question in our study will not prevent the thoughts/feelings from occurring and we determined that it is in the interest of patient safety to include the question about suicidality and have a plan in place for responding in the case of this AE.

Management of Adverse Events of Special Interest (Suicidality)
All study visits that include completion of surveys in REDCap (i.e. PHQ-9) are scheduled to ensure the availability of a physician to contact a participant in the event of the report of an affirmative response to #9 on the PHQ-9. Dr. Ramos and the UW research facilitator receive an instantaneous automatic email alert from REDCap in the setting of an affirmative response to #9 on the PHQ-9. The UW research facilitator will notify the participant during the Zoom-based study session to expect a call from Dr. Ramos or another qualified study physician (Dr. Goss or Dr. Kapnadak, if Dr. Ramos is unavailable). The study physician will call the patient within 4 hours of the result, perform the Columbia-Suicide Severity Rating Scale triage for primary care, provide information for the national suicide and crisis hotline (9-8-8), probe for information about the cause of mental health symptoms, and establish a safety contract with the patient in the interim, as indicated. Drs. Ramos, Goss and Kapnadak have undergone training by a mental health expert with expertise in CF and were given specific questions to ask and responses to provide to participants with an affirmative response to #9 on the PHQ-9. Additionally, Dr. Ramos or the study physician will notify the participant's CF clinician directly via secure communication within 4 hours of the result.

Reporting of SAEs, Unanticipated Problems, and Adverse Events of Special Interest (Suicidality)
All SAEs that occur after a participant signs informed consent until the end of the study (whether procedure related or not) that occur within 48 hours of a study visit will be documented. SAEs that occur in the interval between study visits will be captured through questioning at subsequent study visits (i.e. 2-week, 3-month, and 6-month visits). All SAEs will be sent to the Medical Monitor within 24 hours of the identification of the event. All SAE and AEs of special interest (suicidality) will be reported to the central IRB in accordance with the standard operating procedures and policies of the IRB. Adequate documentation will be reviewed by the Medical Monitor to ensure that the IRB was properly notified of SAEs. SAEs that are expected (e.g. hospitalization for a CF pulmonary exacerbation) will be reported in quarterly safety reports to the DSMB. SAEs that are unexpected and at least possibly related to study procedures will be reported to the DSMB and IRB within 7 days (SAEs that are unexpected but unrelated to study participation will be included in quarterly safety reports to

the DSMB). All unanticipated problems will be reported within 7 days of identification. All episodes of reported possible suicidality documented on PHQ-9 (an affirmative response to #9 on the PHQ-9) administered during study visits, regardless of relatedness to study participation, will be reported to the Medical Monitor within 24 hours, to the DSMB within 2 working days, and to the central IRB within 2 working days. Additionally, the patient's CF clinician will be contacted directly immediately via secure communication, by the PI (Dr. Ramos), and a safety contract established with the patient by phone in the interim. If Dr. Ramos is unavailable, Dr. Goss (co-I) or Dr. Kapnadak (co-I) will perform these duties. The DSMB Chair will review the SAE, unanticipated problem, or AE of special interest (suicidality) and determine if a review by the full committee is warranted. Additional information or data summaries may also be requested by the DSMB at this time. In the event of an unanticipated problem, the PI will notify all participating clinical sites within 14 days, allowing time for review by the DSMB and IRB. All other SAEs and all other non-serious adverse events will be summarized as specified in the comprehensive quarterly safety reports to the DSMB. The results of DSMB and IRB reviews will be communicated to NINR within 7 days of the summary report or IRB action (Section E8).

E5 Monitoring of multi-site study

Monitoring schedule
The UW research team will conduct a site initiation visit prior to recruitment of participants and will conduct quarterly remote monitoring visits during the active recruitment and enrollment phases of the trial. All investigators and research staff (e.g. research coordinators) will attend a monthly investigator call via videoconferencing (e.g. Zoom).

Site initiation
The site initiation visit will occur in person or virtually prior to recruitment of participants from each clinical site. This meeting will include the rationale for the proposed RCT, an overview of the protocol, and a description of the plan to oversample patients from *communities of concern*. All members of the CF clinical team will be invited to attend. The clinical team will contribute ideas to engaging difficult to reach patients who may benefit the most from the proposed intervention. Local champions for the study will be identified during the site initiation meeting. Review of regulatory documents and milestones will occur with the site PI and research staff. We will ensure all study supplies have been delivered (e.g. audio recorder, printed materials). All CF physicians will be consented for participation in advance of the site initiation visit. We will review screening log templates and eCRFs. We will review communication plans in the event of an AE of special interest (suicidality) including email addresses and cell phone numbers for relevant clinical staff.

Monthly investigator calls
Monthly investigator calls will occur via Zoom and will be recorded. The recording will be distributed to all sites within 2 business days of the meeting. The monthly investigator calls will focus on study operations, including updates on recruitment, retention, and targets for enrollment. We will highlight the number of participants from *communities of concern* and provide strategies for engaging this population. Local champions will also be invited to join the calls. We will also highlight issues with data entry and provide feedback to all sites to aid in complete and accurate data entry from the EHR. We will provide updates after DSMB meetings or whenever changes to the protocol are under consideration.

Quarterly monitoring visits
Quarterly monitoring visits provide opportunities for communication about difficulties with recruitment, retention, study protocols, or other aspects of the clinical trial. Sites will provide up-to-date screening logs for recruitment. Local champions will be invited to join when we review recruitment and enrollment numbers. The monitoring visit will include an audit of investigator compliance with IRB regulations and the study protocol. Completeness and accuracy of data entry will be reviewed during quarterly monitoring visits with each site. We will verify source documents for completed eCRFs. We will review CF clinic visit recording transmissions and ensure that recording devices have been promptly erased. Milestones will be reviewed and payments will be confirmed. At the end of the visit, Dr. Ramos (PI) will meet one-on-one with the site PI to discuss any additional issues related to trial conduct and review action items from the monitoring visit.

E6 Assessment of external factors impacting participant safety

Dr. Ramos (PI) will review the literature every 6 months to ensure there are no new reports or studies that would impact the safety of participants or the ethics of continuing the study. Additionally, Dr. Ramos serves as an ad hoc reviewer for multiple prominent journals in the field (e.g. *Journal of Cystic Fibrosis, Journal of Heart and Lung Transplantation, American Journal of Respiratory and Critical Care Medicine, CHEST*) and is often asked to review manuscripts that address advanced CF lung disease and lung transplantation, which keeps her informed of the newest findings. Co-investigators will also notify Dr. Ramos if they become aware of new data relevant to this project. Dr. Ramos will summarize the literature for the progress report to the DSMB every 6 months.

E7 Interim analysis

There will be one planned interim safety analysis. The DSMB will review the following activities associated with the intervention's evaluation: 1) participants' PHQ-9 and GAD-7 scores; and 2) episodes of reported possible suicidality (an affirmative response to #9 on the PHQ-9). The DSMB will monitor for rates of suicidality and the new onset of PHQ-9 or GAD-7 scores consistent with depression or anxiety, respectively, in both arms of the RCT.

The DSMB will be provided the following formal stopping rules involving the safety endpoint of the rate of suicidality (an affirmative response to #9 on the PHQ-9), an AE of special interest. This stopping rule was constructed to permit early detection of a higher than anticipated AE rate in study participants and has known operating characteristics. While the DSMB is an independent body whose recommendations are not bound by these rules, it is anticipated that deviations from this stopping rule will be well-founded and explained in DSMB documentation. The stopping rule is subject to discussion and change during the first meeting of the DSMB when the Charter is formed, prior to the enrollment of any patients in the RCT.

We plan to stop our study early if the observed AE of special interest (suicidality) rate among all who are enrolled, or among the Take on Transplant arm, exceeds 30% (>3X that observed in observational studies of outpatient CF patients), which may signal excessive harm from study participation. Specifically, we will use Fleming stopping rules to detect a high rate of AE of special interest during an interim analysis. With 35 persons enrolled, we have 93% power to identify an event rate of at least 30% versus the expected rate of only 10%. We will recommend

stopping for harm after 35 persons are enrolled if there are >10 participants with AE of special interest events (regardless of study arm). Additionally, the DSMB will compare AE of special interest rates in the two trial arms. These rules provide a low (<6%) probability of erroneously stopping the trial early if study participation is not associated with increased risk of suicidality. Ongoing monitoring of rates of suicidality, in addition to PHQ-9 and GAD-7 scores, will continue via quarterly safety reports and formal DSMB meetings every 6 months while patients are participating in the RCT. Of note, as described above, the pilot RCT of this intervention included 50 people with CF who were enrolled for a 4-week study, and only 3 (6%) participants experienced this AE of special interest.

There will be no interim statistical analyses to assess for futility of efficacy as this population will be eligible for other CF trials concurrently with this non-pharmacological intervention.

E8 Communication plan

The study team includes Clinical Coordination/Study Management by the PI, Dr. Ramos, and the UW research team. UW will serve as the clinical and data coordinating center for the clinical trial. This study organization will ensure subject and data safety, timely and accurate data collection, appropriate interpretation and dissemination of positive or negative study findings, and timely communication with relevant stakeholders. The organizational chart is shown in Figure 2 (above).

In the development of this proposal Drs. Ramos, Berry, Hartzler, Kapnadak, Basile, and Mrs. Bartlett had weekly Zoom meetings with email communications interspersed between the calls for 6 months as part of their planning efforts to prepare for this proposed clinical trial. Drs. Smith, Goss, Lober, and Riekert had individual calls with Dr. Ramos over the same timeframe and contributed to the study design via calls and email correspondence. All collaborating site PIs met with Dr. Ramos via Zoom on at least 4 occasions over the past 10 months to discuss the Approach and feasibility of this RCT. All collaborating site PIs reviewed the entire research strategy multiple times and contributed to the final product. Dr. Ramos and the UW research team value the input of collaborators and will continue to meet as a group of primary investigators 1-2 times per week throughout the study. Additionally, Dr. Ramos will participate in monthly clinical study conference calls with all trial operations staff (described below). Dr. Ramos will also lead study orientation meetings as part of the study initiation and annual update meetings for the CF clinical teams. Additionally, meetings may be arranged by the study manager or site PIs if any concerns arise with data quality or protocol adherence for the duration of the study. Our plan for managing conflicts includes clear communication and expectation setting, along with utilizing the experienced mentorship in multicenter RCT management of the co-Is. Additionally, we will leverage input from our Steering Committee every 6 months and as needed if conflict arises.

Communication Plan Details

I. Dr. Ramos will meet weekly with UW research staff focused on trial operations throughout the study. The meetings will focus on:
    - Recruitment, with a focus on participants with lower socioeconomic status, non-White race, or Hispanic ethnicity (“*communities of concern*”)
    - Retention

- Assessment of all site protocol implementation performance
- Status of case report form [and monitoring query] completion
- Payments to sites
- Monthly review of data security, informed consent documentation, and audits for IRB compliance

These meetings with the UW research staff are in addition to project-specific meetings with co-investigators.

II. Once per month a meeting with trial operations staff from all collaborating sites will include all aspects of study operations.

At a minimum this will include:

- Kathleen Ramos (PI)
- Joseph Pilewski (site PI)
- Jordan Dunitz (site PI)
- Milene Saavedra (site PI)
- Charles Bengtson (site PI)
- Joel Mermis (site PI)
- Jonathan Koff (site PI)
- Veronica Indihar (site PI)
- Edmund (Ted) Sears (site PI)
- Grant Turner (site PI)
- Donna Berry (co-I)
- Christopher Goss (co-I)
- Siddhartha Kapnadak (co-I)
- Andrea Hartzler (co-I)
- Melissa Basile (co-I)
- Nicole Mayer-Hamblett (co-I)
- Kristin Riekert (co-I)
- Patrick Smith (co-I)
- Lauren Bartlett (UW Research facilitator, data manager)
- Research staff from each collaborating site

Dr. Ramos will closely oversee the study operations with additional electronic, phone, or in-person meetings on an as-needed basis. Dr. Ramos and the site PIs will plan on a bi-monthly phone meeting during the early phases of the study to discuss progress and milestone management. This meeting may be replaced by an email every 2 weeks as the trial progresses and the needs shift, but at a minimum a monthly call will remain in place throughout the study.

III. Dr. Ramos will conduct a site initiation visit (in person or remotely) with each collaborating site (Section E5).

IV. The UW research team will conduct quarterly remote monitoring visits during the active recruitment and enrollment phases of the trial (Section E5).

V. Annual CF clinical team updates will provide updates about enrollment, changes to

the protocol, and initial findings (as applicable). These annual updates will be via Zoom and recorded.

Communication with the DSMB, IRB, and NINR

Dr. Ramos (PI) is responsible for overseeing and ensuring timely communication with the *DSMB*, IRB, and NINR (Table 9). The Medical Monitor will communicate directly to the *DSMB* during *DSMB* meetings every 6 months or more often if there is a concern for participant safety. The PI will report to the *DSMB*in quarterly safety reports and every 6 months with a summary of the status of the RCT, AEs, problems encountered, site performance, and any proposed changes to the protocol. The PI will communicate at least annually with NINR via a progress report describing the research activities and results of DSMB meetings. The PI will communication to all collaborating sites, the IRB and NINR if the DSMB recommends changes to the protocol.

Table 9: Communication with the DSMB, IRB, and NINR

Event	Communication From	Communication To	Timeline
All AEs, SAEs, Unanticipated Problems	UW research team	Medical Monitor	Within 24 hours of identification of event
All non-serious AEs, Expected SAEs or Unexpected SAEs unrelated to study participation	Medical Monitor and Dr. Ramos (PI)	DSMB	With quarterly safety report prior to DSMB meeting
Unexpected SAE at least possibly related to study participation	Medical Monitor and Dr. Ramos (PI)	DSMB, IRB, NINR	Within 7 days of identification of event
Unanticipated problem	Dr. Ramos (PI)	DSMB, IRB, NINR	Within 7 days of identification of event
Unanticipated problem	Dr. Ramos (PI)	All collaborating sites	Within 14 days of identification of event
AE of special interest – suicidality at least possibly related to study participation	Dr. Ramos (PI)	DSMB, IRB, NINR	Within 2 business days of event
AE of special interest – suicidality unrelated to study participation	Dr. Ramos (PI)	DSMB, IRB	Within 2 business days of event
Final DSMB summary report	DSMB Chair	Dr. Ramos (PI)	Within 14 days of DSMB meeting

Final DSMB summary report and any action plan or response to the summary report	Dr. Ramos (PI)	IRB, NINR	Within 7 days of receiving the final report from the DMC chair
IRB actions	Dr. Ramos (PI)	NINR, DSMB	Within 7 days of notification
Changes or amendments to protocol or consent form	Dr. Ramos (PI)	NINR, DSMB	Prior to making changes and within 7 days of completion of changes
Changes or amendments to protocol or consent form	Dr. Ramos (PI)	All collaborating sites	Within 7 days of completion of changes
AE: adverse event; SAE: serious adverse event; DSMB: Data Safety Monitoring Board; IRB: central IRB (Advarra); NINR: National Institute of Nursing Research			

F Statistical Plan

F1 Sample Size Determination and Power

Aim 1:
Assuming 6% attrition from 132, a total sample size of 125 yields 80% power to detect a PrepDM score difference between UNOS and ToT means of 8.9 with a SD of 18.8, equivalent to an effect size of 0.48, using a test with 2-sided alpha = 0.05 obtained from a mixed model fit without treatment-by-center interaction and assuming the intraclass correlation for site is 0.1 (Table 10).[54] This is a reasonable expectation based on preliminary results of the pilot RCT.

Table 10: Standardized effect sizes and (in parentheses) detectable between-arm mean score differences for PrepDM score at 3 months (primary endpoint)

		Total N including both arms		
Power	SD*	100	125	150
80%	18.8	0.53 (10.0)	0.48 (8.9)	0.43 (8.2
90%	18.8	0.62 (11.6)	0.55 (10.3)	0.50 (9.4)
*Standard deviation of PrepDM score in pilot RCT				

Aim 1 secondary endpoints
There is no minimally clinically important change in Decisional Conflict Scale, though scores lower than 25 are associated with implementing decisions and scores exceeding 37.5 are associated with decision delay or feeling unsure about implementation.[55] For PHQ-9, minimally clinically important difference is 5.

For secondary change outcomes from baseline to 3 months, we will have 80% power to detect between-arm differences:

- Patient-reported preparedness for LTx discussions on a Likert scale of 1-4: change of 0.6 (SD 1.2)

- Decisional Conflict Score: change of 12.4 (SD 26)
- LTx knowledge (percent correct out of 14 questions): change of 9 percentage points (SD 19)
- For PHQ-9 scores: change of 2.0 (SD 4.2)

The SDM-Q-9 has been used widely in international populations and has a Cronbach's α coefficient of 0.88; a change in SDM-Q-9 of 12 to 15 has been considered clinically meaningful. A sample size of 125 yields 80% power to detect a difference between UNOS and ToT means:

- SDM-Q-9 score difference between UNOS and ToT means of 12.4 with a SD of 26, equivalent to an effect size of 0.48, using a test with 2-sided alpha = 0.05 obtained from a mixed model fit without treatment-by-center interaction and assuming the intraclass correlation for site is 0.1.
- For SDM-Q-doc scores, a between-arm detectable difference in means of 10.5 (SD 22)
- For OPTION scores, a between-arm detectable difference in means of 7.1 (SD 8.3)

Aim 2:
For qualitative studies, sample size is determined by achieving theoretical saturation (i.e., when no new themes emerge). For Aim 2, we plan to record all clinic visits. It is unknown how often clinic visits will contain discussions of LTx. Qualitative analyses will continue simultaneously with recruitment of participants. We aim to record visits until we reach a number sufficient to identify markers of high-quality LTx discussions, learn more about what it takes to empower a patient to raise the topic of LTx, and understand if/how we could intervene to get CF physicians ready for LTx conversations. Our analyses will also involve assessment for implicit bias in the recordings (e.g. speech rate, verbal dominance) and whether the topic of LTx is raised with different frequency among participants from *communities of concern*. If saturation is achieved in these qualitative analyses, we may stop recording clinic visits.

F2 Analysis Plan

Aim 1:
The primary statistical analyses will be intention-to-treat to avoid confounding by non-random participant attrition. Demographics, clinical characteristics, and survey responses will be summarized at each time-point using descriptive statistics: frequencies and proportions for categorical variables, means and standard deviations for continuous variables, or median and interquartile range if the distribution is markedly skewed. Analyses will be adjusted for randomization strata CF Center, FEV_1% predicted, and *communities of concern* status, as well as baseline characteristics clearly imbalanced between groups.

> *Primary outcome:* The primary outcome is PrepDM[29] at 3 months (V3) and the primary analysis will compare mean PrepDM score between the ToT and UNOS arms using linear mixed models.
>
> *Secondary outcomes*: Key secondary outcomes include change in Decisional Conflict Scale[32], change in Likert scale rating of preparedness to discuss LTx, change in LTx knowledge, and change in PHQ-9[36], GAD-7[35], General Self-Efficacy Scale[37], and Perceived Social Support Scale[46] from baseline to 3 months (V3). Secondary analyses will compare mean change between ToT and UNOS using linear mixed models.

Because amount of change depends on the initial score at baseline, we will control for baseline score as a covariate in the regression. Other secondary analyses will include between-arm comparisons of SDM-Q-9, SDM-Q-doc, documentation of LTx discussions or LTx referral, and ratings of satisfaction with the LTx discussion. Analyses will account for the presence/absence and timing of a CF clinic visit.

Sensitivity analyses: We will compare results of the full RCT to those of the pilot RCT by assessing outcomes at 2 weeks (V2). We will describe baseline values and changes in the primary and key secondary outcomes between patients from smaller vs larger CF Centers, CF Centers located with a LTx Program versus without a LTx Program, those with higher versus lower FEV_1% predicted (≥ or <30%), those with Medicaid versus non-Medicaid insurance, and those who report a prior LTx discussion with their CF physician at V1 versus those who have not discussed LTx. For explanatory purposes, we will consider models to test for a potential dose-response relationship by estimating the association between change in PrepDM from V2 to V3 and the predictor: time spent using ToT or UNOS. The dose-response relationship will also be tested for the outcome of Decisional Conflict Scale change between pre-intervention baseline (V1) and V2 and V3. For participants in the UNOS arm (gain access to both websites after 3 months), changes in 3-month to 6-month outcome measures within patient, from pre- to post-ToT, will be measured. We will evaluate for response to the intervention by gender in the primary and key secondary outcomes and explore usage patterns by gender, given that women and men may approach LTx education differently.

Communities of concern and low health literacy: The largest potential impact may be among *communities of concern*. We will compare baseline knowledge, preparedness, and decisional conflict among those from *communities of concern* to the rest of the cohort. We will use graphical methods and descriptive statistics to evaluate differences in usage and outcomes across subsets of the cohort with different SES (insurance status, education level, race/ethnicity, income) and health literacy (S-TOFHLA, Newest Vital Sign, digital literacy).

Aim 2:
Analysis of clinic transcripts: Audio recordings may be listened to and/or be transcribed and will be read in parallel with the data collection process toward achieving data saturation. Recordings will be listened to by at least two members of the study team for assessment or implicit bias (e.g. speech rate, verbal dominance) and whether the topic of LTx is raised with different frequency among participants from *communities of concern*. Initial transcripts will be read by at least 2 members of the study team using a deductive approach based on a provisional coding frame developed from: a) our earlier qualitative research, b) domains of the Health Beliefs Model constructs c) whether and how LTx was discussed in clinic and d) our a priori interest in assessing TOT and UNOS.[57] Using the Observing Patient Involvement in Decision Making (OPTION) Scale[58] for observer rating of shared decision making and an objective analysis of what occurred during the visit, researchers will evaluate the LTx discussion (audio and/or transcript). After coding the first transcript, the coders and the PI will discuss coding discrepancies and reach agreement on code application before proceeding to the next transcript. At each stage, categories will be analyzed independently and compared and contrasted across the data to confirm/identify themes by consensus.[59] This approach will continue until we have reconciled codes for at least six transcripts.[60] The coding frames will be iteratively revised based on how the initial codes and definitions have evolved, including new codes generated inductively. In developing the codebook, the study team will select appropriate

excerpts from transcripts and identify exemplar quotes that reflect themes. A final codebook (i.e. coding manual) with categories and subcategories, exemplar quotes, inclusion and exclusion criteria will be provided to coders and then all transcripts will be re-coded using the final codebook. All transcripts will be coded by two coders.[61] Transcripts will be coded in Atlas.ti, a qualitative analysis program with which our team has experience. We will calculate intercoder reliability for each dataset at intervals of 5, 10 and 20 “batches” of transcripts and a final coding comparison will be competed after all transcripts have been coded.[62]

G Data Handling and Record Keeping

G1 Confidentiality and Security

All study documents will be kept in a secured locked office or on a password-protected computer. Study participants will not be identified by name in the study database, but will be identified by a subject identification number unique to this study. Only authorized individuals will be able to link the study ID to the subject’s name. All investigators and staff involved in the proposed research will have completed human subjects’ protection training, have HIPAA training, and be bound by the agreement of confidentiality. Study data from all sites will be captured using a University of Washington REDCap installation maintained on a secure server. All study databases will be maintained at the UW on password protected computers and backed up to an encoded password protected file. All procedures for the handling and analysis of data will be conducted using good clinical practices meeting FDA guidelines for the handling and analysis of data for clinical trials.

G2 Data Sharing and Possible Secondary Use

Results of analyses of these data will be made available publicly, but access to the data will be limited to individuals approved by the investigators and the Institutional Review Board at UW.

All data obtained and collected for this study may be de-identified and used for future research not described in this protocol and/or shared with other researchers if appropriate IRB approval is obtained and data use agreements are established. Dr. Ramos will oversee and manage the sharing of this data. Data may be used for research regarding CF populations, recruitment of diverse clinical research participants, and/or lung transplant.

H Study Administration

H1 Organization and Participating Centers

Lead/Coordinating Site	Personnel/Role	
University of Washington* *UWMC – Montlake* *1959 NE Pacific Street* *Seattle, WA 98195*	Kathleen Ramos, MD MSc	Lead PI
	Donna Berry, PhD MSN	Co-I
	Christopher Goss, MD MSc	Co-I

	Siddhartha Kapnadak, MD	Co-I
	Andrea Hartzler, PhD	Co-I
	William Lober, MD MS	Co-I
	Clinical Informatics Research Group (CIRG)	Data Management
Non-Recruiting Research Locations	Personnel/Role	
Northwell Health**	Melissa Basile, PhD	Co-I
Seattle Children's Hospital+ *Seattle Children's Research Institute* *1920 Terry Ave* *Seattle, WA 98101*	Nicole Mayer-Hamblett, PhD	Co-I
	Miranda Bradford, MS	Biostatistician
University of North Carolina at Chapel Hill**	Patrick Smith, PhD MPH	Co-I
Johns Hopkins University**	Kristin Reikert, PhD	Co-I
Research Locations*	Personnel/Role	
University of Minnesota *MHealth Clinics and Surgery Center* *909 Fulton Street SE* *Minneapolis, MN 55455* *MN Cystic Fibrosis Center,* *420 Delaware Street SE, MMC 742* *Minneapolis, MN, 55455*	Jordan Dunitz, MD	Site PI
University of Pittsburgh *UPMC Children's Hospital of Pittsburgh* *4401 Penn Avenue* *Pittsburgh, PA 15224*	Joseph Pilewski, MD	Site PI
National Jewish Health *1400 Jackson Street* *Denver, CO 80206*	Milene Saavedra, MD	Site PI
University of Kansas *University of Kansas Medical Center* *3901 Rainbow Blvd* *Kansas City, KS 66160*	Charles Bengtson, MD	Co-Site PI
	Joel Mermis, MD	Co-Site PI
Yale University *6 Devine Street* *North Haven, CT 06473*	Jonathan Koff, MD	Site PI
University of Cincinnati *UC Health Holmes* *200 Albert Sabin Way* *Cincinnati, OH 45220*	Veronica Indihar, MD	Site PI
Maine Health *Maine Medical Center* *22 Bramhall Street*	Edmund (Ted) Sears, MD	Site PI

Portland, ME 04102		
University of California, Los Angeles *UCLA Health* *200 Medical Plaza* *Los Angeles, CA 90095*	Grant Turner, MD MHA FACP	Site PI
**All research locations involved in recruiting and engaged in study procedures will designate a study staff team of research coordinators, research nurses, research assistants, etc. All study responsibilities will be recorded in a study delegation log.* ***Indicated non-recruiting research locations will only participate in the analysis of de-identified data, study interpretation, manuscript preparation, etc.* *+Indicated non-recruiting research location will only participate in the analysis of identifiable data, study interpretation, manuscript preparation, etc.*		

H2 Study Timetable

Study timelines below reflect approximations. Timelines will be used as a guideline for study sites and may change as necessary. Enrollment numbers do not reflect participants who may be lost to follow-up.

Study Timeline								
	Year 1		**Year 2**		**Year 3**		**Year 4**	**Year 5**
Month	1-6	6-12	1-6	6-12	1-6	6-12	1-12	1-12
Start-up Activities:								
Regulatory approvals	x							
Site orientation, annual meetings	x		x		x			
Data Safety Monitoring Board (initiate and form charter; meet every 6 months while patients are enrolled in Aim 1)	x	x	x	x	x	x		
Specific Aim 1:								
Trial enrollment (# of patients)		35	33	32	32			
Data preparation and interpretation					x	x	x	x
Manuscripts: write, submit					x	x	x	x
Follow up with cystic fibrosis clinic for clinical outcomes							x	x
CIRG data collection ongoing		x	x	x	x	x		
Specific Aim 2:								
Clinic visits recorded (# of visits)		35	33	32	32			
Data preparation, analysis, and interpretation		x	x	x	x	x	x	x
Manuscripts: write, submit						x	x	x
Refine Take on Transplant for *communities of concern*								x
Close-out Activities:								
Regulatory close out								x

Site Enrollment Timeline				
Research Location	**Year 1**	**Year 2**	**Year 3**	**Total***
University of Washington	7	12	8	27
University of Pittsburgh	7	12	6	25
University of Minnesota	7	12	6	25
National Jewish Health	7	12	6	25
University of Kansas	3	5	2	10
University of California at Los Angeles (UCLA)	1	3	1	5
Yale University	1	3	1	5
University of Cincinnati	1	3	1	5
Maine Medical Center	1	3	1	5
CF Patient Participant Total*	35	65	32	132

* Totals may exceed the number of participants needed for analysis due to attrition.

I Dissemination & Publication

I1 Plans for publications

After completion of all study procedures and analyses, results will be interpreted with the help of all participating site PIs. All manuscripts will be submitted to a peer-reviewed journal for publication. This publication will be available through PubMed, the free resource developed and maintained by the National Center for Biotechnology information, at the U.S. National Library of Medicine, located at the National Institutes of Health. Results of analyses will be made available publicly, but access to the data will be limited to individuals approved by the investigators and applicable Institutional Review Boards.

I2 Dissemination Plan

The proposed multicenter randomized clinical trial will be registered on ClinicalTrials.gov and results will be submitted according to policy. Dr. Ramos (PI) will be responsible for ensuring all regulatory requirements are met, including registering and updating the study on ClinicalTrials.gov. Key time points for registration and submission of results will be adhered to, including registration on ClinicalTrials.gov not later than 21 calendar days after the enrollment of the first participant. Results from this trial will be submitted not later than one year after the trial's primary completion date. The informed consent document will contain a statement relating to posting clinical trial information at ClinicalTrials.gov.

We will also present our results at national meetings (e.g. the North American Cystic Fibrosis Conference, the American Thoracic Society Annual Conference, the International Society for Heart and Lung Transplantation Annual Meeting).

All participants will be informed about the results of the study via a letter to their Cystic Fibrosis Center after the results of the study are publicly presented. Additionally, results will be shared with the CF community via the Cystic Fibrosis Foundation's Community Voice. Community Voice is an empowering volunteer opportunity for people with CF to share their experiences, perspectives, and knowledge, bringing their insights and priorities to the forefront of CF research, care, and programs. The Community Voice has a monthly newsletter that highlights research that is relevant to individuals with CF and their caregivers. We leveraged Community Voice participation in the pilot testing of Take on Transplant and we share project updates with them regularly (including grants, manuscripts, and new projects). We will disseminate results of the clinical trial via the Community Voice newsletter.

J References

1. **Cystic Fibrosis Foundation Patient Registry Annual Data Report 2020** [https://www.cff.org/sites/default/files/2021-11/Patient-Registry-Annual-Data-Report.pdf]
2. Ramos KJ, Smith PJ, McKone EF, Pilewski JM, Lucy A, Hempstead SE, Tallarico E, Faro A, Rosenbluth DB, Gray AL: **Lung transplant referral for individuals with cystic fibrosis: Cystic Fibrosis Foundation consensus guidelines**. *Journal of Cystic Fibrosis* 2019.

3. Ramos KJ, Somayaji R, Lease ED, Goss CH, Aitken ML: **Cystic fibrosis physicians' perspectives on the timing of referral for lung transplant evaluation: a survey of physicians in the United States**. *BMC Pulm Med* 2017, **17**(1):21.
4. Yohannes AM, Willgoss TG, Fatoye FA, Dip MD, Webb K: **Relationship between anxiety, depression, and quality of life in adult patients with cystic fibrosis**. *Respiratory care* 2012, **57**(4):550-556.
5. Fidika A, Herle M, Goldbeck L: **Symptoms of depression impact the course of lung function in adolescents and adults with cystic fibrosis**. *BMC Pulm Med* 2014, **14**:205.
6. Smith PJ, Dunitz JM, Lucy A, Hempstead SE, Tallarico E, Faro A, Pilewski JM, Ramos KJ: **Incorporating patient and caregiver feedback into lung transplant referral guidelines for individuals with cystic fibrosis—Preliminary findings from a novel paradigm**. *Clinical Transplantation* 2020, **34**(10):e14038.
7. Ramos KJ, Quon BS, Heltshe SL, Mayer-Hamblett N, Lease ED, Aitken ML, Weiss NS, Goss CH: **Heterogeneity in Survival in Adult Patients With Cystic Fibrosis With FEV1 < 30% of Predicted in the United States**. *Chest* 2017, **151**(6):1320-1328.
8. Elwyn G, Frosch D, Thomson R, Joseph-Williams N, Lloyd A, Kinnersley P, Cording E, Tomson D, Dodd C, Rollnick S: **Shared decision making: a model for clinical practice**. *Journal of general internal medicine* 2012, **27**(10):1361-1367.
9. Van Harreveld F, Rutjens BT, Rotteveel M, Nordgren LF, Van Der Pligt J: **Ambivalence and decisional conflict as a cause of psychological discomfort: Feeling tense before jumping off the fence**. *Journal of Experimental Social Psychology* 2009, **45**(1):167-173.
10. Martin C, Hamard C, Kanaan R, Boussaud V, Grenet D, Abely M, Hubert D, Munck A, Lemonnier L, Burgel PR: **Causes of death in French cystic fibrosis patients: The need for improvement in transplantation referral strategies!** *J Cyst Fibros* 2016, **15**(2):204-212.
11. Volkova N, Moy K, Evans J, Campbell D, Tian S, Simard C, Higgins M, Konstan MW, Sawicki GS, Elbert A: **Disease progression in patients with cystic fibrosis treated with ivacaftor: data from national US and UK registries**. *Journal of Cystic Fibrosis* 2020, **19**(1):68-79.
12. Ramos KJ, Wai TH, Stephenson AL, Sykes J, Stanojevic S, Rodriguez PJ, Bansal A, Mayer-Hamblett N, Goss CH, Kapnadak SG: **Development and internal validation of a prognostic model of 2-year death or lung transplant for cystic fibrosis**. *Chest* 2022.
13. Quon BS, Psoter K, Mayer-Hamblett N, Aitken ML, Li CI, Goss CH: **Disparities in access to lung transplantation for patients with cystic fibrosis by socioeconomic status**. *Am J Respir Crit Care Med* 2012, **186**(10):1008-1013.
14. Ramos KJ, Quon BS, Psoter KJ, Lease ED, Mayer-Hamblett N, Aitken ML, Goss CH: **Predictors of non-referral of patients with cystic fibrosisfor lung transplant evaluation in the United States**. *Journal of Cystic Fibrosis* 2016, **15**(2):196-203.
15. Ramos KJ, Sykes J, Stanojevic S, Ma X, Ostrenga JS, Fink A, Quon BS, Marshall BC, Faro A, Petren K *et al*: **Survival and Lung Transplant Outcomes for Individuals With Advanced Cystic Fibrosis Lung Disease Living in the United States and Canada: An Analysis of National Registries**. *Chest* 2021.
16. Stephenson AL, Sykes J, Stanojevic S, Quon BS, Marshall BC, Petren K, Ostrenga J, Fink AK, Elbert A, Goss CH: **Survival comparison of patients with cystic fibrosis in**

Canada and the United States: a population-based cohort study. *Annals of internal medicine* 2017, **166**(8):537-546.
17. Lehr CJ, Fink AK, Skeans M, Faro A, Fernandez G, Dasenbrook E, Valapour M: **Impact of Socioeconomic Position on Access to the US Lung Transplant Waiting List in a Matched Cystic Fibrosis Cohort**. *Annals of the American Thoracic Society* 2020(ja).
18. Buu MC, Sanders LM, Mayo JA, Milla CE, Wise PH: **Assessing differences in mortality rates and risk factors between Hispanic and non-Hispanic patients with cystic fibrosis in California**. *Chest* 2016, **149**(2):380-389.
19. Stormacq C, Van den Broucke S, Wosinski J: **Does health literacy mediate the relationship between socioeconomic status and health disparities? Integrative review**. *Health promotion international* 2019, **34**(5):e1-e17.
20. Svendsen MT, Bak CK, Sørensen K, Pelikan J, Riddersholm SJ, Skals RK, Mortensen RN, Maindal HT, Bøggild H, Nielsen G: **Associations of health literacy with socioeconomic position, health risk behavior, and health status: a large national population-based survey among Danish adults**. *BMC Public Health* 2020, **20**:1-12.
21. Taylor DM, Bradley JA, Bradley C, Draper H, Dudley C, Fogarty D, Fraser S, Johnson R, Leydon GM, Metcalfe W: **Limited health literacy is associated with reduced access to kidney transplantation**. *Kidney International* 2019, **95**(5):1244-1252.
22. Sentell T, Braun KL: **Low health literacy, limited English proficiency, and health status in Asians, Latinos, and other racial/ethnic groups in California**. *Journal of health communication* 2012, **17**(sup3):82-99.
23. Durand M-A, Carpenter L, Dolan H, Bravo P, Mann M, Bunn F, Elwyn G: **Do interventions designed to support shared decision-making reduce health inequalities? A systematic review and meta-analysis**. *PloS one* 2014, **9**(4):e94670.
24. Vandemheen KL, O'Connor A, Bell SC, Freitag A, Bye P, Jeanneret A, Berthiaume Y, Brown N, Wilcox P, Ryan G: **Randomized trial of a decision aid for patients with cystic fibrosis considering lung transplantation**. *American journal of respiratory and critical care medicine* 2009, **180**(8):761-768.
25. Basile M, Andrews J, Wang J, Hadjiliadis D, Henthorne K, Fields S, Kozikowski A, Huamantla J, Hajizadeh N: **Using qualitative methods to inform the design of a decision aid for people with advanced cystic fibrosis: The InformedChoices CF patient decision aid**. *Patient education and counseling* 2019, **102**(11):1985-1990.
26. Dauber-Decker KL, Basile M, Polo J, Calise K, Khan S, Solomon J, Dunne D, Hajizadeh N: **Developing a Decision Aid to Facilitate Informed Decision Making About Invasive Mechanical Ventilation and Lung Transplantation Among Adults With Cystic Fibrosis: Usability Testing**. *JMIR Human Factors* 2021, **8**(2):e21270.
27. Ramos KJ, Hobler MR, Engelberg RA, Curtis JR, Zander MI, Howard SS, Goss CH, Aitken ML: **Addressing lung transplant with adults with cystic fibrosis: A qualitative analysis of patients' perspectives and experiences**. *Journal of Cystic Fibrosis* 2019, **18**(3):416-419.
28. Hartzler AL, Bartlett LE, Hobler MR, Reid N, Pryor JB, Kapnadak SG, Berry DL, Lober WB, Goss CH, Ramos KJ: **Take on transplant: human-centered design of a patient education tool to facilitate informed discussions about lung transplant among people with cystic fibrosis**. *Journal of the American Medical Informatics Association* 2022.
29. Bennett C, Graham ID, Kristjansson E, Kearing SA, Clay KF, O'Connor AM: **Validation of a preparation for decision making scale**. *Patient education and counseling* 2010, **78**(1):130-133.

30. O'Connor A, Llewellyn-Thomas H, Stacey D: **IPDAS Collaboration Background Document. International Patient Decision Aid Standards (IPDAS) Collaboration, 2005**. *IPDAS_Background pdf* 2005.
31. Elwyn G, O'Connor A, Stacey D, Volk R, Edwards AG, Coulter A, Thomas R, Barratt A, Barry M, Bernstein S: **International Patient Decision Aids Standards (IPDAS) Collaboration. Developing a quality criteria framework for patient decision aid: online international Delphi consensus process**. *British Medical Journal* 2006, **333**(7565):417-419.
32. O'Connor AM: **Validation of a decisional conflict scale**. *Medical decision making* 1995, **15**(1):25-30.
33. Weiss BD, Mays MZ, Martz W, Castro KM, DeWalt DA, Pignone MP, Mockbee J, Hale FA: **Quick assessment of literacy in primary care: the newest vital sign**. *The Annals of Family Medicine* 2005, **3**(6):514-522.
34. Kapnadak SG, Dimango E, Hadjiliadis D, Hempstead SE, Tallarico E, Pilewski JM, Faro A, Albright J, Benden C, Blair S: **Cystic Fibrosis Foundation consensus guidelines for the care of individuals with advanced cystic fibrosis lung disease**. *Journal of Cystic Fibrosis* 2020.
35. Spitzer RL, Kroenke K, Williams JB, Löwe B: **A brief measure for assessing generalized anxiety disorder: the GAD-7**. *Archives of internal medicine* 2006, **166**(10):1092-1097.
36. Kroenke K, Spitzer RL, Williams JB: **The PHQ-9: validity of a brief depression severity measure**. *Journal of general internal medicine* 2001, **16**(9):606-613.
37. Chen G, Gully SM, Eden D: **Validation of a new general self-efficacy scale**. *Organizational research methods* 2001, **4**(1):62-83.
38. Glajchen M, Kornblith A, Homel P, Fraidin L, Mauskop A, Portenoy RK: **Development of a brief assessment scale for caregivers of the medically ill**. *Journal of pain and symptom management* 2005, **29**(3):245-254.
39. Quon BS, Bentham WD, Unutzer J, Chan Y-F, Goss CH, Aitken ML: **Prevalence of symptoms of depression and anxiety in adults with cystic fibrosis based on the PHQ-9 and GAD-7 screening questionnaires**. *Psychosomatics* 2015, **56**(4):345-353.
40. Latchford G, Duff AJ: **Screening for depression in a single CF centre**. *Journal of Cystic Fibrosis* 2013, **12**(6):794-796.
41. Guidance D: **Guidance for Industry: Suicidal Ideation and Behavior: Prospective Assessment of Occurrence in Clinical Trials**. *Center for Drug Evaluation and Research (CDER)* 2012.
42. Parker RM, Baker DW, Williams MV, Nurss JR: **The test of functional health literacy in adults**. *Journal of general internal medicine* 1995, **10**(10):537-541.
43. Nelson LA, Pennings JS, Sommer EC, Popescu F, Barkin SL: **A 3-Item Measure of Digital Health Care Literacy: Development and Validation Study**. *JMIR Formative Research* 2022, **6**(4):e36043.
44. Bangor A, Kortum PT, Miller JT: **An empirical evaluation of the system usability scale**. *Intl Journal of Human–Computer Interaction* 2008, **24**(6):574-594.
45. Bjelland I, Dahl AA, Haug TT, Neckelmann D: **The validity of the Hospital Anxiety and Depression Scale: an updated literature review**. *Journal of psychosomatic research* 2002, **52**(2):69-77.
46. Zimet GD, Dahlem NW, Zimet SG, Farley GK: **The multidimensional scale of perceived social support**. *Journal of personality assessment* 1988, **52**(1):30-41.

47. John OP, Donahue EM, Kentle RL: **Big five inventory**. *Journal of Personality and Social Psychology* 1991.
48. Kriston L, Scholl I, Hölzel L, Simon D, Loh A, Härter M: **The 9-item Shared Decision Making Questionnaire (SDM-Q-9). Development and psychometric properties in a primary care sample**. *Patient education and counseling* 2010, **80**(1):94-99.
49. Nong P, Raj M, Creary M, Kardia SLR, Platt JE: **Patient-Reported Experiences of Discrimination in the US Health Care System**. *JAMA Network Open* 2020, **3**(12):e2029650-e2029650.
50. Scholl I, Kriston L, Dirmaier J, Buchholz A, Härter M: **Development and psychometric properties of the Shared Decision Making Questionnaire–physician version (SDM-Q-Doc)**. *Patient education and counseling* 2012, **88**(2):284-290.
51. Cohen S, Doyle WJ, Skoner DP, Rabin BS, Gwaltney JM: **Social ties and susceptibility to the common cold**. *Jama* 1997, **277**(24):1940-1944.
52. Rini C, Redd WH, Austin J, Mosher CE, Meschian YM, Isola L, Scigliano E, Moskowitz CH, Papadopoulos E, Labay LE: **Effectiveness of partner social support predicts enduring psychological distress after hematopoietic stem cell transplantation**. *Journal of Consulting and Clinical Psychology* 2011, **79**(1):64.
53. Mitchell PH, Powell L, Blumenthal J, Norten J, Ironson G, Pitula CR, Froelicher ES, Czajkowski S, Youngblood M, Huber M: **A short social support measure for patients recovering from myocardial infarction: the ENRICHD Social Support Inventory**. *Journal of Cardiopulmonary Rehabilitation and Prevention* 2003, **23**(6):398-403.
54. Vierron E, Giraudeau B: **Sample size calculation for multicenter randomized trial: taking the center effect into account**. *Contemporary clinical trials* 2007, **28**(4):451-458.
55. **User Manual - Decisional Conflict Scale** [https://decisionaid.ohri.ca/docs/develop/User_Manuals/UM_Decisional_Conflict.pdf]
56. Morse JM: **Determining sample size**. In.: Sage Publications Sage CA: Thousand Oaks, CA; 2000.
57. Cho JY, Lee E-H: **Reducing confusion about grounded theory and qualitative content analysis: Similarities and differences**. *Qualitative Report* 2014, **19**(32).
58. Elwyn G, Hutchings H, Edwards A, Rapport F, Wensing M, Cheung WY, Grol R: **The OPTION scale: measuring the extent that clinicians involve patients in decision-making tasks**. *Health Expect* 2005, **8**(1):34-42.
59. Ayres L, Kavanaugh K, Knafl KA: **Within-case and across-case approaches to qualitative data analysis**. *Qualitative health research* 2003, **13**(6):871-883.
60. MacPhail C, Khoza N, Abler L, Ranganathan M: **Process guidelines for establishing intercoder reliability in qualitative studies**. *Qualitative research* 2016, **16**(2):198-212.
61. Saldaña J: **Codes and coding. The coding manual for qualitative researchers**. Los Angeles: Sage; 2009.
62. O'Connor C, Joffe H: **Intercoder reliability in qualitative research: debates and practical guidelines**. *International Journal of Qualitative Methods* 2020, **19**:1609406919899220.
63. Adelman RD, Tmanova LL, Delgado D, Dion S, Lachs MS: **Caregiver burden: a clinical review**. *Jama* 2014, **311**(10):1052-1060.