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Association of Psychological Quality of Life Scores and Adverse Experiences in STOP2 Multi-center Clinical Trial

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THE HONORS PROGRAM

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Abstract

Background: Prior research has observed the relationship between psychological stressors and onset of chronic diseases as well as increased severity. This begs the question of whether psychometric qualities in Health-Related Quality of Life instruments can preliminarily predict participant risk of pathology or adverse events (AE) in clinical trials. Specifically, in studies of cystic fibrosis (CF), a genetic disease that primarily affects the lungs, pancreas, and other organs due to mucus accumulation.

Methods: The study design was an ancillary analysis of a clinical trial (STOP-2) examining duration of intravenous antimicrobial treatment for pulmonary exacerbations in CF (n = 908). Demographic characteristics, genotype, clinical comorbidities, microbiologic history, and lung function were included as potential confounders. The exposure of interest was psychological status at baseline, and the outcome of interest was the occurrence of AEs over the study (approximately 1 month). Patient reported measures were specific Cystic Fibrosis Respiratory Symptom Diary (CFRSD) and EuroQol-5 Dimension-5 Level (EQ-5D-DL) items deemed relevant indicators of psychological status. Each psychological status measure was assessed separately versus AEs. Spearman's rho assessed potential correlation between questionnaire items and the detection of any AEs over follow-up, as well as with AE incidence rates including multiple AEs. Poisson regression assessed whether predictors, adjusted in accordance with a causal framework, facilitated increased AE incidence.

Results: 11.6% of 908 persons experienced an AE during the course of treatment (n= 105). In the bivariable analyses, selected psychological items from EQ-5D-5L, which pertained to self-care, adherence to usual activities, and anxiety or depression within the current day lacked significance in both occurrence of AEs and AE incidence rates. However, items from CFRSD, which pertained to difficulty sleeping, worry about CF, feelings of crankiness, sadness and depression, and frustration within the past 24 hours were all associated with higher presence and incidence of AEs. Following multivariate adjustment, higher summary CFRSD scores were associated with 1.10 times higher risk for AE incidence (95% CI [1.06, 1.15], $p < 0.001$). Positive culture of B. *cepacia* complex at enrollment was associated with increased risk (aIRR = 3.69, 95% CI [0.76, 17.93], $p < 0.001$). In other clinical predictors, medical history of pancreatitis was associated with 3.03 times (95% CI [1.23, 7.46], $p = 0.003$) higher AE incidence. After adjustment, there were no significant associations between summary EQ-5D-5L scores and risk for AE incidence.

Conclusion: Psychological items in CFRSD at baseline were independently associated with AEs. Ultimately, psychological status represented by CFRSD interacted with physiological and clinical factors in prediction of AEs in STOP2 and may identify individuals at greater risk of experiencing adverse events.

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Glossary of Abbreviations

Abbreviation	Definition
AE(s)	Adverse Events
CF	Cystic fibrosis
CFF	Cystic Fibrosis Foundation
CFRQoL	Cystic fibrosis-related quality of life
CFRSD	Cystic Fibrosis Respiratory Symptom Diary
CRISS	Chronic Respiratory Infection Symptom Score
EQ-5D-5L	EuroQol-5 Dimension-5 Level
HRQoL	Health-related quality of life
pwCF	Persons with Cystic Fibrosis
STOP2	Standardized Treatment of Pulmonary Exacerbations II

Background

Cystic fibrosis (CF) is a genetic disease that affects over 30,000 persons in the US and over 70,000 worldwide (Endres & Konstan, 2022). It results from the presence of mutated variants of the CF transmembrane conductance regulator gene. In cases of CF, there is a deletion of phenylalanine 508 (F508del) in the gene and common genotypes include heterozygosity, homozygosity, and classes of mutations with varying severity (Rodman et al. 2005; "Deletion of phenylalanine 508 in the cystic fibrosis transmembrane conductance regulator reduces dimerization," 2015). This gene is primarily responsible for mobilization of electrolytes within the human body and dysfunction leads to limited ion and water distribution, rendering diagnosis possible through evaluation of increased chloride levels in sweat (Endres & Konstan, 2022). However, most patients are diagnosed by 2 years of age or prenatally through newborn screening programs (Ernst et al., 2010; McBennet et al., 2022). Limited ion transport leads to mucus accumulation throughout the body and primarily in the airways. This primary response plays a role in the development of comorbidities such as cystic fibrosis-related diabetes, lung infections, reduced fertility, and various metabolic complications like nutrient malabsorption (Endres & Konstan, 2022).

Due to the abovementioned implications of cystic fibrosis, it is a diagnosis that considerably influences the lifestyle of patients and their caregivers relative to non-affected families. Childhood and adolescence is filled with coordination and planning of treatments that provide additional burden above a patient's academic, social, and extracurricular commitments (Ernst et al., 2010). Due to poor prognosis, a typical adulthood involves eventual independence and autonomy related to these coordinations, but increased risk of severe symptoms such as pulmonary exacerbation, pancreatitis, and malnutrition (Ernst et al., 2010). Given the severity

and poor prognosis, there is no question why the mental welfare of affected individuals and biopsychosocial implications of the disease has grown as a topic of psychological research.

Thus far research surrounding psychopathology in persons with CF has been contradictory regarding the rates of relative risk for psychiatric disorders in each age group. However, some important findings include almost 60% of children in a 2009 study possessing a psychiatric disorder as defined by the Diagnostic and Statistical Manual of Mental Disorders (Ernst et al., 2010). High rates of depression among adolescents have also been observed in other studies, but anxiety is more prevalent of the two disorders and that is consistent across most literature (Ernst et al., 2010).

The intersection between psychology and physiology is not new and has been long studied in science. Prior research has observed the relationship between psychosocial stressors and onset of chronic diseases as well as increased severity. For one, a literature review of psychiatric and cardiological epidemiology by Kopp and Réthelyi (2003) found instances of the association of depression and anxiety with increased morbidity and mortality in coronary heart disease. The psychological mechanisms of negative emotions were also not only linked to the development of cardiovascular, but increased severity and symptomatology as well (Kopp and Réthelyi, 2003). Modern research regarding health-related quality of life (HRQoL) seeks to robustly analyze health outcomes while accounting for variables related to demographics, clinical characteristics, and perceived physical and mental well being in public health (Abbott et al., 2015). As the association is bidirectional, worsening psychological wellbeing and the resulting pathophysiological influence can dynamically increase symptom severity.

Analysis of psychology-specific items in longitudinal HRQoL surveillance can be utilized as a means of measuring psychological health status. Clinical variables such as decreased lung functioning and being listed for lung transplantation (indicating poor lung health)

are associated with decreased HRQoL in those with CF (Abbott et al., 2015). This relationship between physiology and psychology appears to be bidirectional as the same can be said for the association of HRQoL and poor clinical outcomes. This was observed by Abbott and colleagues (2008) who linked psychometric properties of the Cystic Fibrosis Quality of Life Questionnaire (CFRQoL) with medical records related to clinical visitations and mortality or time to death. It was found that portions of the CF-specific HRQoL instrument were predictive of survivability. Moreover, the association between deficits in HRQoL sections and depressive symptoms in persons with CF further substantiates the utility of HRQoL instruments in scientific inferences related to psychological status (Knudsen et al., 2016). Due to the preventative, therapeutic, and prognostic implications of HRQoL it became vital to employ it as an outcome measure in CF clinical trials, and a variety of instruments have been developed to do so (Abbott et al., 2011). This has been tested in the past, including a multicenter study by Bradley and colleagues (2013) that linked poor HRQoL domain scores to a worsening of pulmonary exacerbation status. Yet there exists a lack of investigative groundwork on how psychometric qualities in HRQoL instruments may predict outcomes of clinical trials in CF. More specifically, is it possible that the psychological status of participants as self-reported on qualitative measures is associated with physiological adverse experiences in CF clinical trials?

Introduction

Standardized Treatment of Pulmonary Exacerbations 2 (STOP2) is one of such trials that employs CF-specific HRQoL instruments. STOP2 is a multicenter randomized controlled clinical trial primarily investigating the effectiveness and safety of different durations of intravenous (IV) antibiotic treatments addressing acute worsening (i.e., exacerbation) of the underlying lung disease (Goss et al., 2021b). The three visit study recorded baseline physiology

such as dimensions, weight, ppFEV at visit 1, which took 1-3 days following initiation of IV antimicrobial treatment. In the second follow-up after administration or visit 2, which was 7-10 days after initiation of IV antimicrobial treatment, participants were either assigned into a respondent group that was dependent on improvements in ppFEV and Chronic Respiratory Infection Symptom Score (CRISS) metrics. Those who experienced improvement in those metrics by visit 2 were deemed early robust responders (ERR) and others were non-early robust responders (NERR) (Goss et al., 2021b). The psychological measure of interest within this particular clinical study were items from two qualitative instruments, Cystic Fibrosis Respiratory Symptom Diary and Chronic Respiratory Infection Symptom Score (CFRSD-CRISS) and EuroQol-5 Dimension- 5 Level (EQ-5D-5L), that assessed perceived symptomology and emotional state (Herdman et al., 2011).

The primary HRQoL instrument employed was CFRSD-CRISS (Goss et al., 2021a). The instrument developed by Goss and colleagues asks patients to self-report different respiratory symptoms such as difficulty breathing as well as items corresponding to emotional and activity impacts and symptom severity from a likert-scale of 1 to 5, with 5 being the least favorable response (*CFRSD*, 2011). In analysis of the original STOP cohort, the increase of CFRSD-CRISS scores was higher for females relative to males at the conclusion of IV therapy indicating worse perceived symptoms at the time of exacerbation (Montemayor et al., 2021). This is significant as it identifies sex as a potential confounder in analysis of various CF outcomes. In similarity with the original STOP study, the EQ-5D-5L instrument was employed in STOP2 as well (Gold et al., 2019). Although the supplementary instrument is not specific to CF in comparison to CFRSD-CRISS, its items were found to have high correlation with the specific Cystic Fibrosis Questionnaire-Revised (Bradley et al., 2013). Additionally, it was generally validated for assessment of respiratory communities beyond CF (Bradley et al., 2013).

The physiological outcome of interest from STOP2 for this ancillary study was adverse events (AEs). In clinical trials, AEs are reported negative outcomes that occur to participants regardless of relation to study procedure. However, principal investigators may collect data pertaining to the cause of the outcome. In STOP2, classified AEs were blood and lymphatic system disorders, cardiac disorders, gastrointestinal disorders, general disorders, infections and infestations, musculoskeletal and connective tissue disorders, nervous system disorders, psychiatric disorders, and renal and urinary disorders. It was also determined whether said AEs were in relation to study drugs and procedures and whether they were considered serious adverse events (Goss et al., 2021a). The topic of AE and patient safety is of high priority to the Cystic Fibrosis Foundation especially in relation to clinical trials (*Patient safety is a priority*, 2023). Examples of AEs monitored in STOP2 that are of concern to the organization include but are not limited to: physiological disorders, infections, and pulmonary exacerbations (Goss et al., 2021a). No explorations thus far with STOP2 data prioritized investigation of HRQoL as an exposure of interest as it was a subsidiary measure and not a primary goal of the clinical study seeking to standardize antimicrobial treatment (Goss et al., 2021).

The main objective of this ancillary study was to fill a missing gap of knowledge by using data from a CF clinical trial containing physiological outcomes and psychology-related HRQoL instrument items. The primary outcome of interest is adverse experiences/events (AEs), which are vital in assessing the safety of clinical trials. The psychological exposure of interest was the responses to HRQoL instruments. It was hypothesized that there will be an association between psychological items and risk for AE incidence. Secondarily, psychological items will be correlated with dichotomous occurrence of AEs. These were assessed through correlational and predictive analyses.

Methods

The study design was a post-hoc evaluation of a clinical trial (STOP2), examining secondary aims of association between psychological well-being and AEs. Although the study was retrospective in that the clinical trial previously collected data for use, the assessment of this data was prospective in nature. The exposure of interest was psychological status at baseline with the outcome of interest, the AEs, following later.

Participants have been previously enrolled and studied. There was no further selection of participants and all persons with data were included in the ancillary study. The sourced STOP2 study ultimately included participants who met the following criteria: at least 18 years of age, possessed documentation of a CF diagnosis, enrolled in the Cystic Fibrosis Foundation National Patient Registry prior to enrollment, planned to initiate IV antibiotics for pulmonary exacerbation prior to the trial, performed spirometry in three visits, completed the CRISS questionnaire at Visit 1 and Visit 2 and the CFRSD questionnaire at Visit 3, willingness to adhere to specific treatment duration based on initial response to treatment and devised randomization, willingness to participate in Visit 3 follow up, and submission of written informed consent.

Enrollment and data collection for STOP2-IP-15 was completed under Seattle Children's Research Institute (SCRI) IRB ID# STUDY00000142 where informed consent allowed data to be used for future research. To fulfill the request of deidentified data, this study was approved by the SCRI IRB ID# STUDY00004586 and by the Gallaudet University IRB ID# IRB-FY23-181. Requested variables were related to categories of demographic characteristics, outcome of interest, patient reported measures, medical history, and clinical qualities.

Demographic characteristics allow aggregated overview and summary of the study participants. Linear visualization of incidence rates by age predictor variables (age at baseline and age at CF diagnosis) was used as a means of selecting parameterization to optimize the Poisson regression in regard to whether age was defined as continuous or subcategories of intervals. Sex was the dichotomous variable of whether participants were male or female, i.e., sex at birth, not to be confused with the term gender. Racial/ethnic categories were non-Hispanic white, non-Hispanic Black, Hispanic, and other or mixed. The three selected racial ethnicities make up the major prevalence of CF in the United States whereas other or mixed races were not expected or highly present in such a sample size. Given that they share a characteristic of underrepresentation, it was adequate to group others and mixed race together into one category from a biostatistical standpoint.

The outcome category pertaining to AEs was composed of multiple variables. First was the dichotomous status of AEs and whether they occurred to an individual in the duration of the study. Secondly, the start date of said AE if it occurred. Lastly, an included miscellaneous variable related to the methodology of STOPII was the assigned respondent group whether it was ERR or NERR and the treatment duration. These were useful for the determination of individual time at risk in analysis of AE incidence from the start date of IV antibiotic treatment to end of treatment.

Variables in the patient reported measure categories came from the questionnaires, specifically CRISS and EQ-E5-DL items deemed relevant indicators of psychological status. Selection of patient reported entries to include in analysis was based on similarity with items from the Patient Health Questionnaire-9 (PHQ-9), which is widely adopted for screening and estimating the severity of depression. Items from the EQ-E5-DL deemed relevant to psychological status based on correspondence to PHQ-9 themes concerned self-care, difficulty

with usual activities, and anxiety and depression. Items from CRISS deemed relevant to psychological status based on correspondence to PHQ-9 themes concerned difficulty sleeping, worry related to CF, crankiness, sadness or depression, and frustration. Accumulation of scores for each respective instrument was completed to observe them as exposures representative of mental health status in Poisson regression.

Possible long standing health issues were included as potential confounders in the analysis as they may be related to the outcome and/or patient reported measures, as follows. Medical history and clinical variables such as organ disease, modulator eligibility age at CF diagnosis were also included as potential confounders to be assessed alongside demographic characteristics. These are causes that can potentially influence both symptom scores and AE event rates which can complicate attribution of causal association.

Prior to regression and correlation analysis, for purposes of identifying patterns of association, incidence rates of AEs for each age grouping were calculated, a process called parameterization. Parameterization allowed researchers to observe rates of AEs by age and make determinations related to the classification and possible leveling of the age variable in the Poisson model based on the functional form of the bivariate relationship. This involved determination of the quotient of the number of AEs present and the time participants were at risk. This incidence rate was also assessed for association with the measures of psychological well-being. Spearman's correlation was regarded for its utility for leveled measures with ordinal ranking, which are commonplace in qualitative questionnaires.

Spearman's Rank Correlation Coefficient was employed to test potential correlation between questionnaire items pertaining to psychological status, occurrence of AEs, and individual-level incidence rates. This was selected among alternative correlational analyses as the nature of the psychological items is ordinal, lacks linear components, and Spearman's rho is

a statistical measure intended for such rank-ordered variables. In this instance, the data is more likely to depict monotonic relationships rather than true values of constant variance and their linear relationships. Responses to each item pertaining to psychological status in CRFSD and EQ-5D-5L were ranked from 1 to 5, with 1 being a favorable response. The secondary variables in the correlation analysis were the occurrence of an AE for each person and the individual-level incidence rate of any AEs over follow-up. The analysis, performed for AE occurrence and individual-level incidence rate, determined whether a monotonic correlation between items and the two respective variables was observable, the strength and direction of it if evident, and the presence of a statistical significance.

Prior to incidence analysis, a directed acyclic diagram was created with DAGitty.net to visualize assumed causal relationships between observed variables, exposures, and outcome of interest to explain statistical adjustments made with the analysis and infer causation of the outcome by the exposure. Pre-baseline exposures were demographic characteristics such as sex, age, race/ethnicity, and clinical characteristics of CFRD status as well as age at CF diagnosis and genotype, whereas medical history variables and comorbidities were those that developed over a lifetime, followed by measures taken at baseline, and finally the outcome or AE. In this model, the exposure of interest was psychological items which were representative of mental health status. These were ultimately assumed as predictive of adverse events through interaction with pre-baseline and intermediary variables.

Incidence analysis, in the form of Poisson regression, was employed for assessment of whether possible predictors, adjusted in accordance with the causal inference diagram, facilitated increased rates of incidence. The Poisson regression was adequate due to the nature of the data involving a count variable that is the occurrences of AE with count or nominal predictors. Poisson regression with the number of AEs as the outcome and offset being the log number of

days of accrued time at risk. Accrued time at risk for participants was days from actual start date of IV antibiotic treatment to the date of last reported data. Accounting time is vital in this model as some participants may either not have all the visits, or drop-out early, among other reasons. Returned coefficients were exponentiated for incidence rate ratios (IRR) and adjusted incidence rate ratios (aIRR) with robust standard-error based confidence intervals. All analyses were completed with R-programming statistical software.

Results

Table 1: Demographic Summary
This is a presentation of the demographic characteristics of the overall study population by independent responder treatment groups. Measures of central tendency are used for continuous age variables whereas percentages in nominal characteristics are out of sums at the first row of each respective column.

Characteristic	Responder Treatment Group		
	Overall	**ERR**	**NERR**
	Total: 908	258 (28.4%)	650 (71.6%)
Age			
Mean (SD)	30.31 (9.7)	26.70 (7.6)	31.75 (10.1)
Median	28.0	24.8	29.5
Min, Max	18.0, 77.9	18.0, 70.8	18.0, 77.9
Age at CF Diagnosis			
Mean (SD)	7.36 (11.66)	5.38 (9.3)	8.15 (12.4)
Median	1.1	0.8	1.4
Min, Max	0, 72.1	0, 62.2	0, 72.1
Sex, n (%)			
Male	448 (49.3%)	136 (52.7%)	312 (48.0%)

Female	460 (50.7%)	122 (47.3%)	338 (52.0%)
Ethnicity, n (%)			
Hispanic	61 (6.7%)	18 (7.0%)	43 (6.6%)
Non-Hispanic White	796 (87.7%)	224 (87.8%)	572 (88.0%)
Non-Hispanic Black	31 (3.4%)	10 (3.9%)	21 (3.2%)
Other/Multi-racial	20 (2.2%)	6 (2.3%)	14 (2.2%)
Race, n (%)			
White	843 (92.8%)	237 (91.9%)	606 (93.2%)
Black or African American	33 (3.6%)	11 (4.3%)	22 (3.4%)
Asian	3 (0.3%)	0 (0.0%)	3 (0.5%)
American Indian or Alaska Native	3 (0.3%)	0 (0.0%)	3 (0.5%)
Other/Multi-racial	26 (2.9%)	10 (3.9%)	16 (2.5%)

Figures 1: Adverse Event Incidence Rates by Age Predictors

Figures 1a and 1b are graphic representations of AE incidence rates by each age variable grouping with 5-year intervals. Incidence rates are cases in each grouping over the sum of time at risk for all individuals at risk transformed to 1,000 people-day at risk. Linear trends support a case for fitting in regression by specified 5-year intervals rather than as a continuous variable.

Figure 1a: Adverse Event Incidence by Age at Baseline

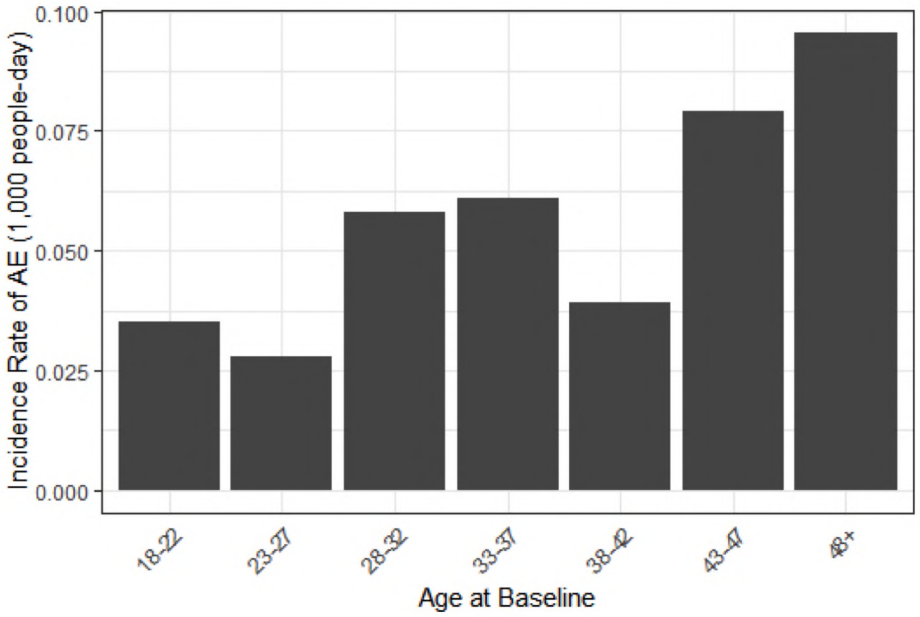

Figure 1b: Adverse Events Incidence by Age at CF Diagnosis

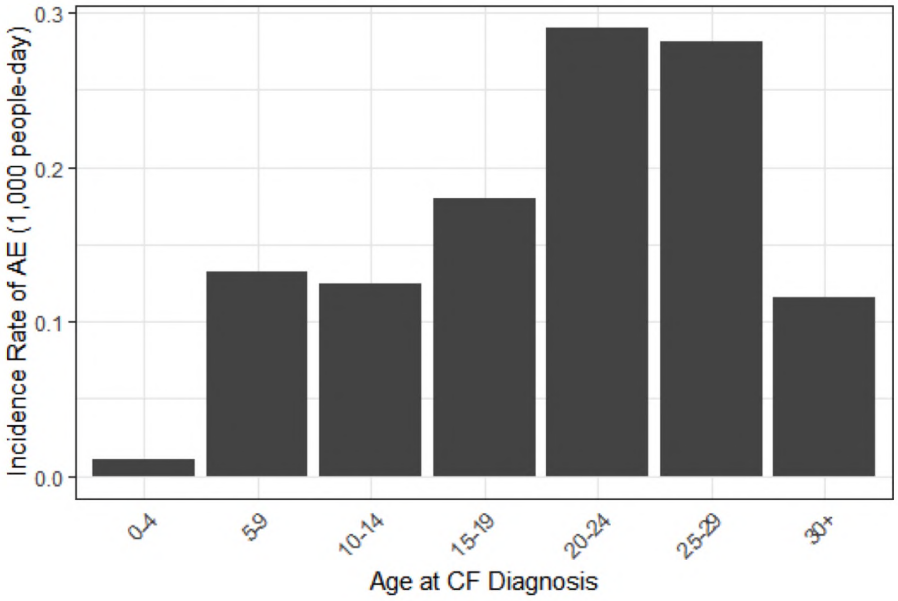

Table 2: Tabular Presentation of Prevalence and Incidence Rates by Age Variables

Tabulated presentation of Figures 1 with the incidence rates calculated for each graphical column. Prevalence is unrelated to study analyses and is the proportion in each 5-year interval grouping with any cases. While irrelevant to incidence analysis, it was calculated to observe any trends that are similar with incidence.

Characteristic	Overall, N (# of cases)	Prevalence, (proportion)	Incidence, (1000 people-day)
Age at Baseline			
18-22	246 (32)	0.130	0.035
23-27	241 (25)	0.104	0.028
28-32	162 (25)	0.154	0.058
33-37	113 (13)	0.115	0.061
38-42	55 (2)	0.036	0.039
43-47	27 (1)	0.037	0.079
48+	64 (7)	0.109	0.096
Age at CF Diagnosis			
0-4	619 (65)	0.105	0.011
5-9	52 (6)	0.115	0.132
10-14	55 (6)	0.109	0.125
15-19	53 (8)	0.151	0.180
20-24	45 (10)	0.222	0.290
25-29	29 (4)	0.206	0.281
30+	55 (6)	0.110	0.115

Table 3: Stratified Summary of Adverse Events and Demographic Characteristics
Tabulated summary of the occurrence of any AEs over the course of the clinical trial. Percentages in each characteristic are out of the group sums at the first row in each column. To consider disproportion in the occurrence of any AEs, percentages will have to be calculated out of the number of persons in the subcategory, the number in the first column, involved in the study relative to those in the similar category who also had any adverse events.

Characteristic	Occurrence of Any Adverse Events		
	Overall, N = 908	**No,** N = 803	**Yes,** N = 105
Sex			
Male	448 (49.3%)	396 (49.3%)	52 (49.5%)
Female	460 (50.7%)	407 (50.7%)	53 (50.5%)
Race/Ethnicity			
Hispanic	61 (6.7%)	54 (6.7%)	7 (6.7%)
Non-Hispanic White	796 (87.7%)	704 (87.7%)	92 (87.6%)
Non-Hispanic Black	31 (3.4%)	28 (3.5%)	3 (2.9%)
Other/Multi-racial	20 (2.2%)	17 (2.1%)	3 (2.9%)
Age at Baseline			
18-32 Years of Age	608 (66.9%)	530 (66%)	78 (74.3%)
33-47 Years of Age	241 (26.5%)	221 (27.5%)	20 (19%)
48+ Years of Age	59 (6.6%)	52 (6.5%)	7 (6.7%)
Age at CF Diagnosis			
0-14 Years of Age	712 (78.4%)	636 (79.2%)	76 (72.4%)
15-29 Years of Age	144 (15.9%)	120 (14.9%)	24 (22.8%)
30+ Years of Age	52 (5.7%)	47 (5.9%)	5 (4.8%)
Treatment Duration			
ERR	258 (28.4%)	230 (28.6%)	28 (26.7%)
NERR	650 (71.6%)	573 (71.4%)	77 (73.3%)

Body Mass Index			
Underweight	136 (15.0%)	126 (15.7%)	10 (9.5%)
Healthy Weight	601 (66.3%)	531 (66.2%)	70 (66.7%)
Overweight	132 (14.5%)	133 (14.1%)	19 (18.1%)
Obese	38 (4.2%)	32 (4.0%)	6 (5.7%)
Genotype			
Delta F508 Homozygous	441 (48.6%)	398 (49.6%)	43 (41.0%)
Delta F508 Heterozygous	343 (37.8%)	292 (36.4%)	51 (48.6%)
Other	94 (10.4%)	83 (10.3%)	11 (10.5%)
Unidentified/Unavailable	30 (3.3%)	30 (3.7%)	0 (0.0%)
Percent Predicted Forced Expiratory Volume in 1s			
Optimal	10 (1.1%)	8 (1.0%)	2 (2.0%)
Moderate	112 (12.3%)	96 (12.0%)	16 (15.2%)
Critical	492 (54.2%)	438 (54.5%)	54 (51.4%)
Severe	294 (32.4%)	261 (32.5%)	33 (31.4%)
Other Clinical/Medical History *			
Cystic Fibrosis-Related Diabetes	344 (37.9%)	309 (38.5%)	35 (33.3%)
Any Positive Microbiology Culture	659 (72.6%)	582 (72.5%)	77 (73.3%)
Liver Disease	55 (6.1%)	51 (6.4%)	4 (3.8%)
Pancreatic Insufficiency	809 (89.1%)	715 (89.0%)	94 (89.5%)
Pancreatitis	34 (3.7%)	26 (3.2%)	8 (7.6%)

Non-Tuberculous Mycobacteria	96 (10.6%)	84 (10.5%)	12 (11.4%)
Highly Effective Modulator Use	284 (33.6%)	257 (34.3%)	27 (11.4%)
Conventional Medical Therapy	89 (9.8%)	81 (10.1%)	8 (7.6%)

*Overall denominator for this category is out of the entirety of the study sample, indicating some individuals may be counted in more than one clinical or medical history characteristic. AE status quotient is of those with the clinical characteristic out of those with the adverse event status (yes/no).

Table 4: Types of Adverse Events and Relation to Study Treatment and Procedure
Overview of AE classifications coded in the clinical trial and their relation to. This table is for descriptive, exploratory purposes and no analyses accounted for the classification or relation to treatment due to collinearity with the outcome of interest.

	Relation to Study Treatment or Procedure			
System Organ Class Code	**Unrelated,** N = 74	**Possibly,** N = 16	**Probably,** N = 12	**Definitely,** N = 3
Blood & Lymphatic System Disorders	1 (1.4%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Ear & Labyrinth Disorders	0 (0.0%)	0 (0.0%)	1 (8.3%)	0 (0.0%)
Eye Disorders	0 (0.0%)	1 (6.3%)	0 (0.0%)	0 (0.0%)
Gastrointestinal Disorders	1 (1.4%)	2 (12.5%)	0 (0.0%)	0 (0.0%)
General Disorders & Admin Site Conditions	5 (6.8%)	1 (6.3%)	0 (0.0%)	0 (0.0%)
Infections Infestations	32 (43.2%)	7 (43.8%)	9 (75.0%)	1 (33.3%)
Investigations	4 (5.4%)	0 (0.0%)	0 (0.0%)	1 (33.3%)

Metabolism & Nutrition Disorders	1 (1.4%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Musculoskeletal & Connective Tissue Disorders	1 (1.4%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Nervous System Disorders	3 (4.1%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Product Issues	2 (2.7%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Renal & Urinary Disorders	8 (10.8%)	0 (0.0%)	1 (8.3%)	1 (33.3%)
Respiratory, Thoracic, & Mediastinal Disorders	14 (18.9%)	3 (18.8%)	0 (0.0%)	0 (0.0%)
Skin & Subcutaneous Tissue Disorders	1 (1.4%)	1 (6.3%)	1 (8.3%)	0 (0.0%)
Vascular Disorders	1 (1.4%)	1 (6.3%)	0 (0.0%)	0 (0.0%)

Table 5: Correlation of Psychological Items and Occurrence of Any Adverse Events
Spearman's ranked correlation coefficient analysis of the occurrence of any adverse events and scored responses to each instrument's select psychological items. The two-level analysis was any occurrence (yes/no or 0/1) versus ranked response (1-5). With higher response scores being operationally defined as worse psychological status, a statistically significant positive rho indicates worse psychological status is correlated with occurrence of any adverse events and vice versa if negative.

	Spearman's Rank Correlation	
Psychological Items	ρ (rho)	P-value
EQ-5D-5L		
Do I have problems washing or dressing myself today?	-0.006	0.854
Do I have problems doing my usual activities today?	-0.015	0.648

Am I anxious or depressed today?	0.004	0.898
CFRSD		
During the last 24 hours, how difficult was it to sleep?	0.100	0.003
During the last 24 hours, how worried were you about your cystic fibrosis?	0.145	<0.001
During the last 24 hours, how cranky did you feel?	0.141	<0.001
During the last 24 hours, how sad or depressed did you feel?	0.076	0.022
During the last 24 hours, how frustrated did you feel?	0.158	<0.001

Table 6: Correlation of Psychological Items and Adverse Event Incidence Rates

In contrast with Table 5, Table 6 assesses ranked responses to each psychological item versus incidence rates for each individual calculated as all AE occurrences in the duration of study over the individual's time at risk.

	Spearman's Rank Correlation	
Psychological Items	ρ (rho)	P-value
EQ-5D-5L		
Do I have problems washing or dressing myself today?	-0.007	0.833
Do I have problems doing my usual activities today?	-0.014	0.663
Am I anxious or depressed today?	0.001	0.970
CFRSD		
During the last 24 hours, how difficult was it to sleep?	0.097	0.003
During the last 24 hours, how worried were you about your cystic fibrosis?	0.142	<0.001
During the last 24 hours, how cranky did you feel?	0.137	<0.001
During the last 24 hours, how sad or depressed did you feel?	0.072	0.030
During the last 24 hours, how frustrated did you feel?	0.156	<0.001

Figures 2: Incidence of Adverse Events by Total Instrument Scores

Graphic representation of AE incidence rates by groupings of instrument summary scores. Instrument scores of both psychological items were aggregated into a sum for each individual and visualized with 3-year intervals starting from the lowest value. Incidence rates were calculated using subpopulations who scored within each summary score groupings and their respective sum of times at risk. Note that higher summary scores are indicative of worse psychological status.

Figure 2a: Adverse Event Incidence Rates by Total CFRSD Score

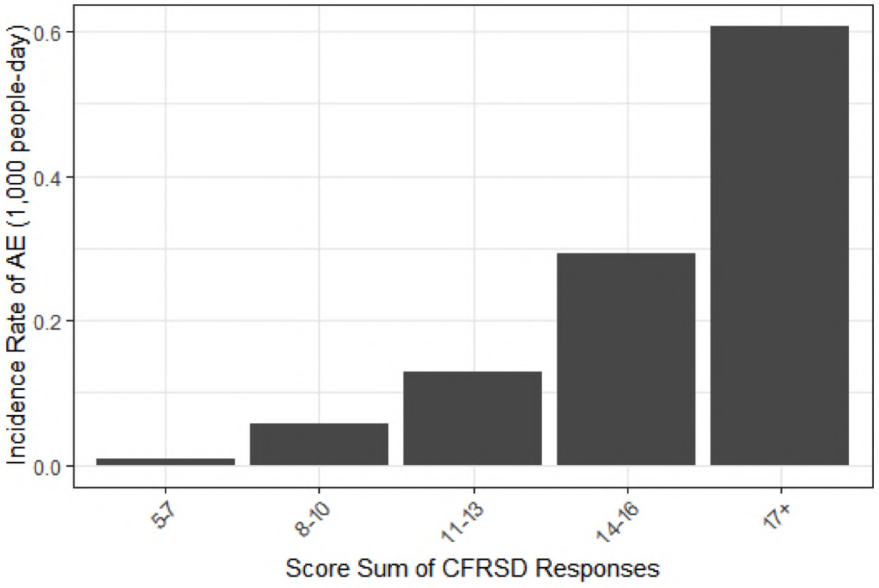

Figure 2b: Adverse Event Incidence Rates by Total EQ-5D-5L Score

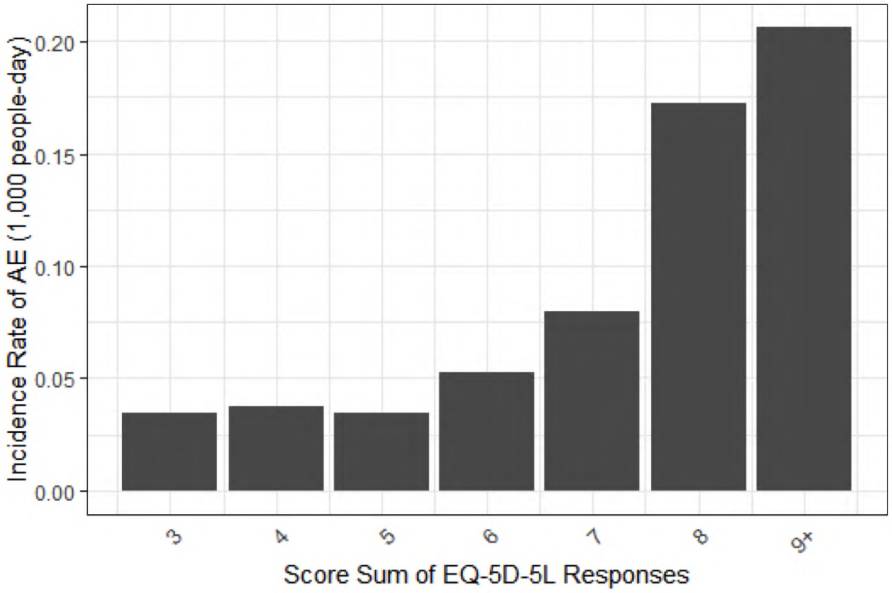

Table 7: Tabular Presentation of Prevalence and Incidence Rates by Instrument Scores
Tabulated version of Figures 2 with values of incidence rates for each graphic column. Prevalence is calculated as proportion in each summary score grouping with any cases of adverse events. This proportion is not utilized for any further analysis but rather descriptive and for consideration of possible parallels with incidence rates.

Characteristic	Overall, N (# of cases)	Prevalence, (proportion)	Incidence, (1000 people-day)
CFRSD Scores			
5-7	620 (56)	0.090	0.009
8-10	148 (20)	0.135	0.058
11-13	75 (12)	0.160	0.129
14-16	32 (6)	0.182	0.293
17+	32 (11)	0.344	0.607
EQ-5D-5L Scores			
3	222 (26)	0.117	0.035
4	212 (28)	0.132	0.038
5	176 (17)	0.097	0.034
6	133 (15)	0.113	0.052
7	87 (10)	0.115	0.080
8	40 (4)	0.100	0.172
9+	38 (4)	0.132	0.207

Figure 3: Adverse Event Incidence Rates by Responses to CFRSD Items

Each theme on CFRSD has a respective grayscale column representing AE incidence rate for populations scoring at each degree of severity (1-5). Note the trend in incidence rates as the chart progresses to those with more severe responses to each item theme.

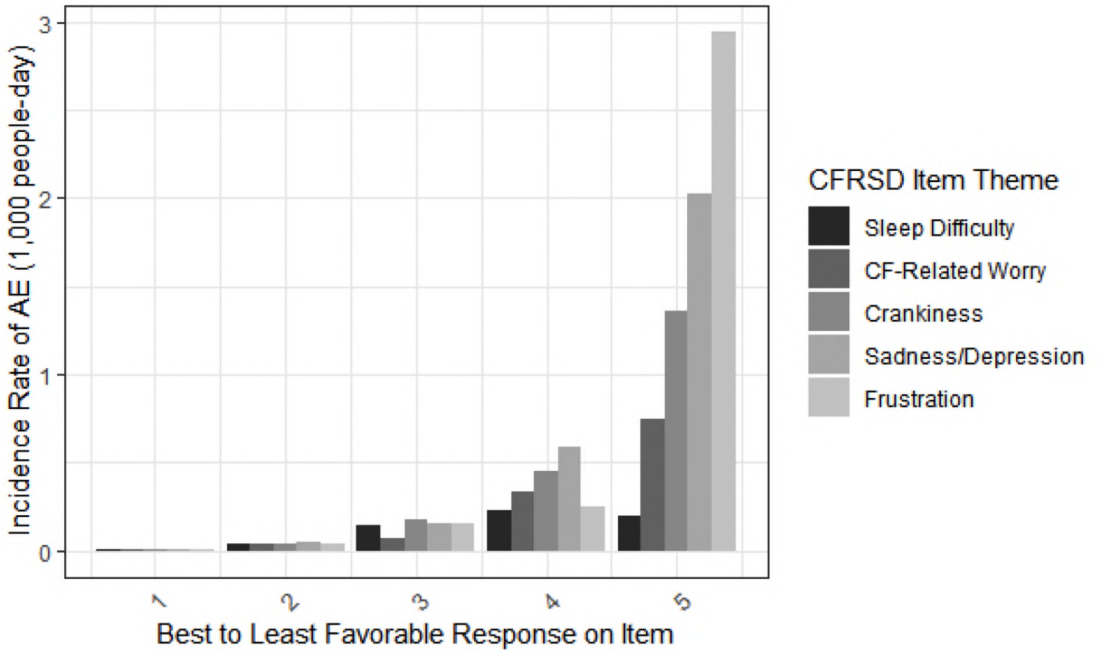

Figure 4: Directed Acyclic Graph Model of Causal Relationships

Visual framework of key facilitators in AE incidence. See Table 8 below for justification.

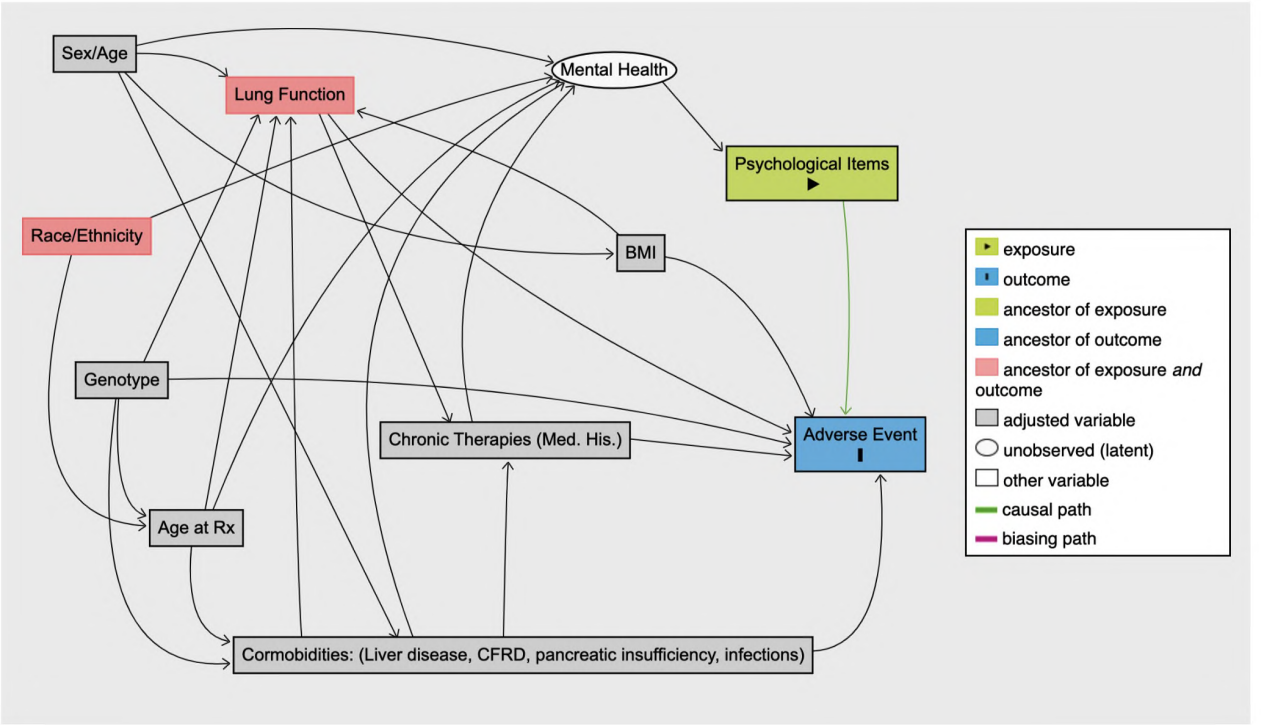

Table 8: Literature Review Justification of Causal Interaction

An eclectic approach to validation of causal relationships between key facilitators involved in dynamics related to AE incidence. Arrows left to right are indicative of each respective literature's concluded direction of association. A comma separated list implies the variable on the left end of the arrow is influential toward the multiple listed instances. The effect of this influence, as in its degree and whether it is protective or harmful, is not recorded.

Synthesized from Literature	Assumptions
Liou (2019) Provides a base causal inference diagram of the cystic fibrosis clinical disease and related manifestations.	Genotype → Lung Function, Pancreatic Sufficiency Lung Function → Chronic Therapies, Infection Pancreatic Sufficiency → BMI, CFRD Chronic Therapies → Infections, BMI, Sex/Age BMI → Lung Function, CFRD Sex/Age → Lung Function
Debray et al. (2011) Increased incidence of liver disease during the first decade of life. Liver disease is associated with poor protein retention and fat absorption.	Age → Liver Disease Liver Disease → BMI

Hutchins et al. (2022)	
Depression, anxiety, fear, and anger is more likely to be expressed by racial/ethnic minorities in qualitative items. Minority females are more likely to express lower understanding of CF and feel less represented.	Race → Mental Health Sex → Mental Health
McGarry et al. (2023)	
Detection rates of CFTR variants are lower in racial/ethnic minority groups. Racial/ethnic minorities overrepresented in false negative newborn screening and delayed diagnosis.	Race → Age at Diagnosis Age at Diagnosis → Chronic Therapies, Mental Health
Nagy et al. (2022)	
Higher BMI is protective of CFRD, pancreatic insufficiency, and microbial colonization. Normal weight, overweight, and obese associated with better pulmonary function.	BMI → Lung Function, CFRD, Pancreatic Insufficiency, Infections
Rodman et al. (2005)	
Genotype severity is associated with late/early diagnosis status.	Genotype → Age at Diagnosis

Table 9: Univariate Incidence Analysis of Adverse Events
The univariate Poisson regression assessed the independent influence of each variable on the outcome of interest, the count of AEs. In statistically significant cases ($P \leq 0.05$), the effect size is an exponentiation and is a multiplier of a characteristic's influence relative to its reference or for each increase in a unit in cases where the characteristic is continuous. In a hypothetical instance, an IRR of 1.30 indicates that the characteristic is associated with 30% increased risk of AE incidence relative to the reference characteristic in that category. However, in the case of another discrete variable like age, which is coded with 5-year intervals it would mean advancement to the next 5-year interval is associated with 30% higher risk. In continuous variables such as summary scores of psychological items, each unit of increase is associated with 30% higher risk of AE incidence. Theoretically, if a population is the reference group and they have an AE incidence of 10 per 1000 people-day, the higher risk group relative to reference (IRR = 1.30) would have one of 13 per 1000 people-day. Subsequently, an IRR of 1 indicates no effect and below 1 indicates a protective effect, or decreased risk.

	Univariate Unadjusted
Characteristic	IRR (95% CI) P-value
Sex	
Male	1.26 (0.83, 1.93) 0.161
Female	Reference
Race/Ethnicity	
Hispanic	0.81 (0.37, 1.77) 0.561
Non-Hispanic White	Reference
Non-Hispanic Black	0.80 (0.24, 2.67) 0.653
Other/Multi-racial	1.23 (0.37, 4.1) 0.679
Age Predictors*	
Age at Baseline	1.01 (0.99, 1.03) 0.444
Age at CF Diagnosis	1.01 (0.99, 1.02) 0.442
Age at CF Diagnosis (x^2)	1.00 (1.00, 1.00) 0.502

Psychological Items	
EQ-5D-5L Score	0.96 (0.86, 1.07) 0.436
CFRSD Score	1.11 (1.07, 1.15) <0.001
Body Mass Index	
Underweight	Reference
Healthy Weight	2.10 (1.06, 4.15) 0.020
Overweight	2.44 (1.13, 5.25) 0.013
Obese	1.95 (0.73, 5.20) 0.187
Genotype	
Delta F508 Homozygous	Reference
Delta F508 Heterozygous	1.74 (1.11, 2.75) 0.002
Other	1.09 (5.55, 2.14) 0.782
Unidentified/Unavailable	0.00 (0.00, 0.00) 0.981
Microbiology Culture	
P. aeruginosa	0.96 (0.62, 1.47) 0.783
S. aureus	0.79 (0.51, 1.22) 0.163
Methicillin-resistant S. aureus	0.73 (0.42, 1.30) 0.181
B. cepacia	3.13 (0.75, 13.07) <0.001
Any positive	1.19 (0.74, 1.91) 0.376
Percent Predicted Forced Expiratory Volume in 1s	
Optimal	Reference

Moderate	0.47 (0.108, 2.03) 0.165
Critical	0.40 (0.10, 1.65) 0.075
Severe	0.35 (0.08, 1.45) 0.044
Other Clinical	
Cystic Fibrosis-Related Diabetes	0.76 (0.49, 1.20) 0.127
Medical History at Baseline	
Liver Disease	0.55 (0.19, 1.58) 0.194
Pancreatic Insufficiency	1.15 (0.60, 2.18) 0.630
Pancreatitis	2.32 (1.14, 4.70) 0.005
Non-Tuberculous Mycobacteria	0.98 (0.49, 1.95) 0.929
Highly Effective Modulator Use	0.78 (0.47, 1.27) 0.183
Conventional Medical Therapy	0.54 (0.27, 1.09) 0.088
Number of Treated PEx in the Past Year	1.49 (0.94, 2.36) 0.024

* 5-year increments

Table 10: Multivariate Incidence Analysis of Adverse Events

In contrast with Table 9, predictors are no longer assessed independently and are included in a multivariate analysis that can introduce interaction. This is when the relationships of multiple variables may change the effect of another on the outcome (AE). The first glance should be at the predictors of interest for determination of whether they are significant otherwise the effect of variables in their respective columns are negligible as there is no effect to be explained from that variable of interest or psychological item toward the outcome of interest. In the case that the predictor of interest is significant, particular attention should be paid to other notable factors as they may explain its influence.

Characteristic	Adjusted with CFRSD aIRR (95% CI) P-value	Adjusted with EQ-5D aIRR (95% CI) P-value
Sex		
Male	1.27 (0.81, 1.99) 0.195	1.26 (0.79, 1.99) 0.220
Female	Reference	Reference
Age Predictors*		
Age at Baseline	1.00 (0.98, 1.03) 0.982	1.00 (0.98, 1.03) 0.613
Age at CF Diagnosis (x^2)	1.00 (1.00, 1.00) 0.183	1.00 (1.00, 1.00) 0.117
Psychological Items		
EQ-5D-5L Score		0.96 (0.85, 1.09) 0.472
CFRSD Score	1.10 (1.06, 1.15) <0.001	
Body Mass Index		
Underweight	Reference	Reference
Healthy Weight	2.19 (1.01, 4.75) 0.016	2.34 (1.04, 5.27) 0.009
Overweight	2.16 (0.93, 5.04) 0.039	2.35 (1.00, 5.54) 0.023
Obese	2.54 (0.88, 7.35) 0.076	2.63 (0.88, 7.89) 0.065

Genotype		
Delta F508 Homozygous	Reference	Reference
Delta F508 Heterozygous	1.79 (1.02, 3.13) 0.018	1.70 (0.97, 2.98) 0.033
Other	1.29 (0.61, 2.71) 0.479	1.33 (0.64, 2.78) 0.424
Unidentified/Unavailable	0.00 (0.00, 0.00) 0.981	0.00 (0.00, 0.00) 0.981
Microbiology Culture		
P. aeruginosa	0.99 (0.62, 1.57) 0.943	0.96 (0.60, 1.52) 0.812
S. aureus	0.63 (0.34, 1.17) 0.045	0.63 (0.34, 1.16) 0.040
Methicillin-resistant S. aureus	0.93 (0.44, 1.97) 0.805	0.96 (0.44, 2.08) 0.888
B. cepacia	3.69 (0.76, 17.93) <0.001	3.57 (0.74, 17.28) <0.001
Other Clinical		
Cystic Fibrosis-Related Diabetes	0.78 (0.45, 1.36) 0.197	0.81 (0.48, 1.37) 0.266
Medical History at Baseline		
Liver Disease	0.62 (0.21, 1.80) 0.296	0.63 (0.22, 1.81) 0.308
Pancreatic Insufficiency	2.02 (0.95, 4.29) 0.056	1.90 (0.93, 3.89) 0.080
Pancreatitis	3.03 (1.23, 7.46) 0.003	3.06 (1.33, 7.02) 0.003
Non-Tuberculous Mycobacteria	0.98 (0.47, 2.06) 0.944	0.97 (0.45, 2.10) 0.924
Highly Effective Modulator Use	1.16 (0.64, 2.10) 0.570	1.09 (0.59, 2.01) 0.751
Conventional Medical Therapy	0.51 (0.23, 1.14) 0.089	0.50 (0.23, 1.10) 0.080
Number of Treated PEx in the Past Year	1.33 (0.80, 2.24) 0.121	1.44 (0.86, 2.40) 0.053

* 5-year increments

Discussion

As shown in Table 1, the majority of participants were in the NERR treatment group whereas the ERR made up 28.4% of the population. The NERR was relatively older (M = 31.75, SD = 10.1) v. (M = 26.70, SD = 7.6) and had later ages at CF diagnosis (M = 8.15, SD = 12.4) v. (M = 5.38, SD = 9.3) compared to the ERR group. The overall study population and each responder treatment group had approximately even proportions (~50%) of both male and females. Participants were predominantly Non-Hispanic White (~88%), followed by Hispanic (~7%), Non-Hispanic Black (~3.5%), and Other/Multiracial (~2.2%). Racial/ethnic proportions of the overall study was consistent within both responder treatment groups.

In descriptive statistics shown in Table 3, proportions of AEs at any time during follow-up by demographic characteristics were noted. Generally, 11.6% of participants experienced an AE during the course of IV antibiotic treatment. Proportions of AEs did not differ drastically between male and female as they had AE prevalence of 11.6% and 11.5%, respectively. This was in contrast with Somayaji and colleagues (2023) who observed greater AE frequency among females and inferred it to sex-related physiological differences in pharmacokinetics. The same literature also observes significant association of age with the odds of AE attribution which aligns with observable trends of increased prevalence and incidence of AE individuals who were older at baseline. With regards to race and ethnicity, the Non-Hispanic Black group exhibited the lowest prevalence of AEs during follow-up 9.7% followed by Hispanic, Non-Hispanic White, Other/Multiracial with AE proportions of 11.5%, 11.6%, and 15.0%, respectively. At 11.9%, proportions of those with AEs in NERR were not much higher than those in ERR (10.9%). Assigned treatment duration and actual treatment duration varied among enrolled participants and thus should not be interpreted as an implication of increased risk or

vulnerability. Moreover, proportions are not intended to be conclusive of causal relationships, but rather provide an overview of concentration of AE occurrences within each stratification.

As above-mentioned, parameterization of age variables in Figures 1 and Table 2 revealed positive linear relationships between both age at baseline and age at CF diagnosis by incidence rates of AEs, which substantiated assessment of age as continuous. However, in the case of age at CF diagnosis, a quadratic definition for fit in the Poisson regression was warranted by decrease of incidence rates at 30 years of age or later, after grouping such participations within the 30+ definition, due to low numbers of people in each respective 5-year age interval after 30 years of age at CF diagnosis. By allowing the consideration of various functional forms and relationship of the outcome with age variables, regularization led to flexibility, improved interpretability, and enhanced statistical power in detection of associations involving age at baseline, age at CF diagnosis, and the outcome of interest. However, this approach is subject to statistical bias in the statistical assumptions made regarding functional forms that can lead to interpretation challenges or a degree of overfitting resulting from increased complexity of selected age range subcategories or operational definitions.

Spearman's Rank Correlation Coefficient, as shown in Tables 5 and 6, examined the degree of correlation between psychological items, dichotomous occurrence of AE for each person, and individual-level AE incidence rates. Selected psychological items from EQ-5D-5L, which pertained to self-care, adherence to usual activities, and anxiety or depression within the current day lacked significance in both occurrence of AEs and individual-level incidence rates. However, selected psychological items from CFRSD, which pertained to difficulty sleeping, worry about CF, feelings of crankiness, sadness and depression, and frustration within the past 24 hours all exhibited statistical significance in the direction of least favorable responses. This was consistent with both occurrence of AE and individual-level AE incidence rates. Assessment

of AE incidence rates and response to each CFRSD item revealed a curvilinear increase as responses scored higher or least favorable responses were made (Figure 3). They were highest in participants who responded with a score of 5 on frustration, sadness/depression, crankiness, and CF-related worry. However, for sleep difficulty, rates increased after response scores of 1 and 2, but remained similar for responses 3 to 5. In another instance by Gifford et al. (2021), CFRSD-CRISS was used as a repeated measure of symptom burden and frequently examined for associations with changes in physiologic indices during PEx treatment. Similarly, associations and trends were observed between the HRQoL instrument, lung functioning, and physiological responses to PEx treatment. Upon summation of item scores, both CFRSD and EQ-5D-5L summary scores demonstrated a curvilinear increase in incidence rates of AEs by the sum of scored responses. Trends were similar with regards to prevalence as proportions of persons with AEs increased with summed score increments for each respective instrument (Table 7).

The base model of the causal inference diagram was derived from review of the clinical biology of CF and associated manifestations by Liou (2019). However, the overall diagram of causal interaction was eclectic as evidenced in Table 8. Structurally, baseline physiologic and clinical characteristics, though having their respective influence on the exposure of interest, interacted with intermediary exposures to facilitate mental health or psychological status. The unobserved variable of mental health, indicating the exposure of interest (psychological status) and represented by psychological items, was assumed to be causative of the outcome of interest, AEs, through interaction with said facilitators. Evaluation of the causal structure permitted identification of minimal sufficient adjustment to assess attribution of total effect of AE incidence to psychological status. Biasing paths were avoided via adjustment of sex/age, age at CF diagnosis, BMI, genotype, comorbidities, and chronic therapies in a multivariate model (Figure 4). Though directed acyclic diagrams facilitate informed visualization of causal

structures they are limited by knowledge and remain a simplification that does not fully capture the entirety of complex dynamic systems and phenomena.

Incidence analysis of AEs and potential predictors yielded notable findings. As shown in Table 10, following multivariate adjustment, summary scores of psychological items from one of the instruments were significantly associated with AE incidence. Whereas higher summary CFRSD scores were associated with 1.10 times higher risk for AE incidence (95% CI [1.06, 1.15], $p < 0.001$), summary EQ-5D-5L scores lacked significance both in univariate and multivariate models (Table 9).

Although various literature such as Nagy and colleagues (2022) observed increased BMI to be protective of CF comorbidities, overweight and healthy weight BMI classifications were significantly associated with increased risk for AE incidence by 2.16 times (95% CI [0.93, 5.04], $p = 0.039$) and 2.19 times (95% CI [1.01, 4.75], $p = 0.016$) relative to underweight, respectively. Moreover, significance and direction of association was consistent univariately for the BMI classifications. Possessing the heterozygous genotype of delta F508 was significantly associated with 79% increased risk of AE incidence (95% CI [1.02, 3.13], $p = 0.018$) relative to homozygosity and this was also observable univariately (IRR = 1.74, 95% CI [1.11, 2.75], $p = 0.002$). The harmful effect of heterozygosity within the multivariate model aligns with Polgreen and Comellas (2022) findings of heterzygote's increased susceptibility to the same comorbidities as their homozygous counterparts regardless of possessing only one allele.

The positive microbiology culture linked with increased risk of AE incidence was *B. cepacia* complex (aIRR = 3.69, 95% CI [0.76, 17.93], $p < 0.001$) whereas *S. aureus* was associated with 0.63 times (95% CI [0.34, 1.17], $p = 0.045$) lower risk. Only the trend of *B. cepacia* was influential univariately (IRR = 3.13, 95% CI [0.75, 13.07], $p < 0.001$). In other

clinical predictors, medical history of pancreatitis was associated with 3.03 times (95% CI [1.23, 7.46], p = 0.003) higher AE incidence.

Conclusion

Observations in this ancillary study ultimately enforced the pair of alternate hypotheses as statistically significant trends were evident between AEs and psychological status indicators in both correlational and predictive respects. Psychological items in CFRSD specifically held trends in correlational, univariate, and multivariate analyses whereas significance for EQ-5D-5L was not observable until inclusion in the multivariate model. This implies the presence of complex, multifactorial dynamics explaining the causal path between the instrument and occurrence of AEs. In the case of CFRSD, the effect was already sufficiently revealed and accounting for these dynamics supported further attribution of it toward the outcome. Moreover, it was discovered that psychological status, indicated by the instruments, interacted with physiological and clinical factors in prediction of AEs.

These primary findings are clinically significant as they support consideration of these predictors at initiation of clinical trials and may aid with identification of participant risk levels and equipment of appropriate professionals with the knowledge to determine subpopulations who may require increased or specialized monitoring. Although the trends of some predictors such as microbiology culture and medical history were in line with previous literature that linked them to worse outcomes in pwCF or specific comorbidities, it is important to note that the clinical trial environment has limited generalizability or external validity. For instance, higher body mass index categories relative to underweight and normal/healthy weight are typically protective of comorbidities in pwCF that would have been flagged as an AE in the context of this study (Nagy et al., 2022). However, in actuality they are harmful in this context.

With contrast between the clinical trial and general population there are implications for the context in which research is considered translational. In the perspectives of clinicians this signals the importance of withholding bias or expectations derived from known trends in the general CF population as clinical trials are a small subset that is not precisely representative. From a patient viewpoint, the clinical trial experience likely introduces a new set of stressors associated with participation that include, but are not limited to transportation or logistics, visits and time commitments, and unpredictability. These stressors may likely be accounted for through socioeconomic factors, which was also a limitation in the ancillary study's methodology and causal network as precedent observed their interaction with psychological status and various mentioned CF manifestations.

This study was also limited by the potential confounding between AEs and symptoms. Any common causes that influence both symptom scores and AE event rates, rendered it difficult to attribute a causal association between them. For instance, there could've been older common causes, like long-standing infections with a bacteria, or decline due to organ disease. The direction of determined associations can still be unclear as bidirectionality is also a rational conclusion. Additionally, there was the actual relation of AEs to study procedures. This is vital to interpretations because investigators would need to practice caution in attributing their occurrence to the clinical trial simply because they were in its duration. 70.5% of primary AE incidence was deemed unrelated to study medication or procedures. In retrospect, consideration of socioeconomic and demographic factors would have allowed contemplations of the baggage participants carried with them to study initiation that potentially influence the outcome outside of physiological and clinical factors. Future interventional research should seek methods allowing modernization and individualized approaches to treatment trials without major sacrifice of

clinical validity. This would allow adaptation of practices that may benefit specific subgroups but would otherwise be harmful to those with psychological and physiological circumstances.

The researcher completing this capstone has been involved in cystic fibrosis research for two summers at Seattle Children's Research Institute as a part of the Summer Scholars Program. His initial project involved the intersection of cystic fibrosis-related diabetes and race. It particularly investigated the prevalence and incidence of cystic fibrosis-related diabetes with regards to race after adjustment for clinical, treatment, and socioeconomic confounders determined through directed acyclic graphs. A preliminary presentation of the project was given to the foundation's equity, diversity, and inclusion representatives and the project as a whole is currently undergoing abstract presentation with a manuscript being prepared for publication.

In the duration of the second summer interning (2022), the researcher suggested a research project for a University Honors Capstone at Gallaudet University, Washington, DC. Given his areas of study in biology, psychology, and mathematics, He was especially interested in developing a research question related to a topic of psychology in cystic fibrosis using retrospectively collected data. Discussions and exchanges occurred with the director of biostatistics, Sonya Heltshe, the co-executive director of the Cystic Fibrosis Therapeutics Development Network Coordinating Center, Nicole Hamblett, and the principal investigator Amalia Magaret. It was concluded that using qualitative items from the STOP2 clinical trial and other clinical outcomes would be ideal for the researcher's interests. The researcher's role was synthesizing background content related to the research topic, outlining rationale behind the exploration, post-hoc analysis of provided data in alignment with decided research questions, producing and communicating results as well as inferences with relevance to missions of the foundation. In addition to abstract submission to conferences, the project will also likely be ultimately inherited by a postdoctoral fellow that will extend the content into a publication level

composition. The researcher was mentored by Amalia Magaret, PhD and David Nichols, MD in collaboration with Derek Braun, PhD and Regina Nuzzo, PhD (statistical consulting) at Gallaudet University who specialize in the sciences or mathematics. Project support was also provided by Sonya Heltshe, PhD and Nicole Hamblett, PhD.

The researcher is a double major in biology and psychology with a minor in mathematics. His major career goal is to become a physician-scientist. After shadowing medical doctors and being involved in academic medicine research, He developed a liking for both clinical and academic components of a physician-scientist's responsibilities. In chronic diseases like cystic fibrosis, there is a high demand for physician-scientists that support therapeutic development for the people behind all the numbers. This is especially true in the field of psychology that proves flexible for evidence-based practice and translational medicine. Immersion in this capstone project supported the mission of the foundation provided necessary exposure that honed research foundation and skills in the scientific method, literature review, data analysis, scientific writing, and presentation.

Remarks

It has been a pleasure to undertake the Honors Program curriculum. Beyond all the requirements, credits, and assignments, I am honored to have crossed paths with various other scholars that value academic excellence in their respective disciplines of interest. Moreover, to have been surrounded by supportive faculty, staff, and possess all the resources at our disposal that allowed my fellow scholars and me to succeed. I can't thank Drs. Nelson, VanGilder, and Miller enough for supporting me in making this research a reality and welcoming external collaborators. I also thank Drs. Lundberg and Braun for delaying the submission of a composition that was not my best. I still remember my remote freshman year during COVID-19 vividly. I met with the Honors director at the time, Dr. Myers, regarding the A- she assigned me

for a social justice paper that I felt was beautifully written and deserving of an A+. When I joined the zoom meeting and I explained why I was upset, we both laughed and had a small talk regarding perfectionism. I knew I was in good hands. All the feedback, criticism, discourse, and disagreements the past four years – is why we succeeded.

References

Abbott, J., Hart, A., Havermans, T., Matossian, A., Goldbeck, L., Barreto, C., Bergsten-Brucefors, A., Besier, T., Catastini, P., Lupi, F., & Staab, D. (2011). Measuring health-related quality of life in clinical trials in cystic fibrosis. Journal of Cystic Fibrosis: Official Journal of the European Cystic Fibrosis Society, 10, S82–S85. https://doi.org/10.1016/s1569-1993(11)60013-1

Abbott, J., Morton, A. M., Hurley, M. A., & Conway, S. P. (2015). Longitudinal impact of demographic and clinical variables on health-related quality of life in cystic fibrosis. BMJ Open, 5(5), e007418–e007418. https://doi.org/10.1136/bmjopen-2014-007418

Abbott, Janice, Hart, A., Morton, A. M., Dey, P., Conway, S. P., & Webb, A. K. (2009). Can health-related quality of life predict survival in adults with cystic fibrosis? American Journal of Respiratory and Critical Care Medicine, 179(1), 54–58. https://doi.org/10.1164/rccm.200802-220oc

Bradley, J. M., Blume, S. W., Balp, M.-M., Honeybourne, D., & Elborn, J. S. (2013). Quality of life and healthcare utilisation in cystic fibrosis: a multicentre study. The European Respiratory Journal: Official Journal of the European Society for Clinical Respiratory Physiology, 41(3), 571–577. https://doi.org/10.1183/09031936.00224911

Cystic fibrosis respiratory symptom diary (CFRSD) and chronic respiratory infection symptom score (CRISS©). (n.d.). Washington.edu. Retrieved March 30, 2024, from https://depts.washington.edu/seaqol/CFRSD-CRISS

Debray, D., Kelly, D., Houwen, R., Strandvik, B., & Colombo, C. (2011). Best practice guidance for the diagnosis and management of cystic fibrosis-associated liver disease. Journal of Cystic Fibrosis:

Official Journal of the European Cystic Fibrosis Society, 10 Suppl 2, S29-36. https://doi.org/10.1016/S1569-1993(11)60006-4

Deletion of phenylalanine 508 in the cystic fibrosis transmembrane conductance regulator reduces dimerization. (2015). The Journal of Biological Chemistry, 290(38), 22879. https://doi.org/10.1074/jbc.p115.641134

Endres, T. M., & Konstan, M. W. (2022). What is cystic fibrosis? JAMA: The Journal of the American Medical Association, 327(2), 191. https://doi.org/10.1001/jama.2021.23280

Ernst, M. M., Johnson, M. C., & Stark, L. J. (2010). Developmental and psychosocial issues in cystic fibrosis. Child and Adolescent Psychiatric Clinics of North America, 19(2), 263–283. https://doi.org/10.1016/j.chc.2010.01.004

Gifford, A. H., Polineni, D., He, J., D'Amico, J. L., Dorman, D. B., Williams, M. A., Nymon, A. B., Balwan, A., Budden, T., & Zuckerman, J. B. (2021). A pilot study of cystic fibrosis exacerbation response phenotypes reveals contrasting serum and sputum iron trends. Scientific Reports, 11(1). https://doi.org/10.1038/s41598-021-84041-y

Gold, L. S., Patrick, D. L., Hansen, R. N., Beckett, V., Goss, C. H., & Kessler, L. (2019). Correspondence between symptoms and preference-based health status measures in the STOP study. Journal of Cystic Fibrosis: Official Journal of the European Cystic Fibrosis Society, 18(2), 251–264. https://doi.org/10.1016/j.jcf.2018.08.001

Goss, C.H., Flume, P., Heltshe, S.L. (2021a). *Standardized Treatment of Pulmonary Exacerbations II (STOP2)*. Identifier NCT02781610. https://clinicaltrials.gov/ct2/show/NCT02781610

Goss, C. H., Heltshe, S. L., West, N. E., Skalland, M., Sanders, D. B., Jain, R., Barto, T. L., Fogarty, B., Marshall, B. C., VanDevanter, D. R., Flume, P. A., Omlor, G., Bourne, B., Roberts, D., Roberts, V., Nasr, S., Kruse, D., Linnemann, R., Hailemichael, T., … Longtine, K. (2021b). A randomized clinical trial of antimicrobial duration for cystic fibrosis pulmonary exacerbation treatment. American Journal of Respiratory and Critical Care Medicine, 204(11), 1295–1305. https://doi.org/10.1164/rccm.202102-0461oc

Herdman, M., Gudex, C., Lloyd, A., Janssen, M. F., Kind, P., Parkin, D., Bonsel, G., & Badia, X. (2011). Development and preliminary testing of the new five-level version of EQ-5D (EQ-5D-5L). Quality of Life Research: An International Journal of Quality of Life Aspects of Treatment, Care and Rehabilitation, 20(10), 1727–1736. https://doi.org/10.1007/s11136-011-9903-x

Herzig, M. P. (2009). Understanding the motivation of deaf adolescent Latino struggling readers. UC San Diego.

Hutchins, K., Barr, E., Bellcross, C., Ali, N., & Hunt, W. R. (2022). Evaluating differences in the disease experiences of minority adults with cystic fibrosis. Journal of Patient Experience, 9, 237437352211126. https://doi.org/10.1177/23743735221112629

Knudsen, K. B., Pressler, T., Mortensen, L. H., Jarden, M., Skov, M., Quittner, A. L., Katzenstein, T., & Boisen, K. A. (2016). Associations between adherence, depressive symptoms and health-related quality of life in young adults with cystic fibrosis. SpringerPlus, 5(1). https://doi.org/10.1186/s40064-016-2862-5

Kopp, M. S., & Réthelyi, J. (2004). Where psychology meets physiology: chronic stress and premature mortality—the Central-Eastern European health paradox. Brain Research Bulletin, 62(5), 351–367. https://doi.org/10.1016/j.brainresbull.2003.12.001

Liou, T. G. (2019). The clinical biology of cystic fibrosis transmembrane regulator protein. Chest, 155(3), 605–616. https://doi.org/10.1016/j.chest.2018.10.006

McBennett, K. A., Davis, P. B., & Konstan, M. W. (2022). Increasing life expectancy in cystic fibrosis: Advances and challenges. Pediatric Pulmonology, 57(S1). https://doi.org/10.1002/ppul.25733

McGarry, M. E., Ren, C. L., Wu, R., Farrell, P. M., & McColley, S. A. (2023). Detection of disease-causing CFTR variants in state newborn screening programs. Pediatric Pulmonology, 58(2), 465–474. https://doi.org/10.1002/ppul.26209

Montemayor, K., Psoter, K. J., Lechtzin, N., Carson, S. W., Merlo, C. A., Dezube, R. H., Riekert, K. A., Allgood, S., Toporek, A., Jennings, M. T., & West, N. E. (2021). Sex differences in treatment patterns in cystic fibrosis pulmonary exacerbations. Journal of Cystic Fibrosis: Official Journal of the European Cystic Fibrosis Society, 20(6), 920–925. https://doi.org/10.1016/j.jcf.2021.05.012

Nagy, R., Gede, N., Ocskay, K., Dobai, B.-M., Abada, A., Vereczkei, Z., Pázmány, P., Kató, D., Hegyi, P., & Párniczky, A. (2022). Association of body mass index with clinical outcomes in patients with cystic fibrosis: A systematic review and meta-analysis. JAMA Network Open, 5(3), e220740. https://doi.org/10.1001/jamanetworkopen.2022.0740

Patient safety is a priority. (2023). Cystic Fibrosis Foundation. https://www.cff.org/research-clinical-trials/patient-safety-priority

Polgreen, P. M., & Comellas, A. P. (2022). Clinical phenotypes of cystic fibrosis carriers. Annual Review of Medicine, 73(1), 563–574. https://doi.org/10.1146/annurev-med-042120-020148

Rodman, D. M., Polis, J. M., Heltshe, S. L., Sontag, M. K., Chacon, C., Rodman, R. V., Brayshaw, S. J., Huitt, G. A., Iseman, M. D., Saavedra, M. T., Taussig, L. M., Wagener, J. S., Accurso, F. J., & Nick, J. A. (2005). Late diagnosis defines a unique population of long-term survivors of cystic fibrosis. American Journal of Respiratory and Critical Care Medicine, 171(6), 621–626. https://doi.org/10.1164/rccm.200403-404oc

Somayaji, R., Wessels, M. E., Milinic, T., Ramos, K. J., Mayer-Hamblett, N., Ramsey, B. W., Heltshe, S., Khan, U., & Goss, C. H. (2023). Potential implicit bias in attribution of adverse events in randomized controlled trials in cystic fibrosis. Journal of Cystic Fibrosis: Official Journal of the European Cystic Fibrosis Society, 22(4), 669–673. https://doi.org/10.1016/j.jcf.2023.05.014

Stone-MacDonald, A., & Department of Curriculum and Instruction, University of Massachusetts Boston, 100 Morrissey Blvd., Boston, MA 02125, USA. (2019). Coming to America for the good of a deaf child: The case of Joy. African Educational Research Journal, 7(4), 201–211. https://doi.org/10.30918/aerj.74.18.031