ivacaftor, or triple-combination therapy (TCT) with elexacaftor/tezacaftor/ivacaftor were also recorded prospectively.

Results: In clinical practice, the CF-ABLE score performed substantially better than it did in its original derivation study and outperformed FEV_1 alone as a predictor of outcome. A CF-ABLE score of 5 or greater clearly distinguished PwCF who went on to poor outcomes from those who did not ($p < 0.001$). Approximately half of PwCF with a score of 5 or greater died or underwent lung transplantation within 4 years. In contrast, poor outcome at 4 years was observed in fewer than 5% of PwCF with a score less than 5. The score correlated with sputum neutrophil elastase activity; matrix metalloprotease activity; and interleukin (IL)-1β, IL-6, and IL-8 levels and inversely with IL-10 (all $p < 0.05$). For each mediator, the correlation with CF-ABLE score was stronger than with FEV_1 alone (all $p < 0.05$). In *F508del/F508del* PwCF, DCT did not result in better FEV_1 at 24 months than in matched controls not receiving DCT but significantly improved CF-ABLE score ($p = 0.002$), largely because of an effect on exacerbations. In contrast, TCT resulted in marked decreases in CF-ABLE score within 3 months ($p < 0.001$), enabling PwCF with baseline scores of 5 or greater to return to the low-risk range.

Conclusions: The CF-ABLE score robustly identifies PwCF at risk of poor outcome and correlates with airway inflammation better than FEV_1 alone. The score identifies a probable effect on mortality in response to CFTR modulators early in the treatment period – an endpoint that has proven elusive in prospective clinical trials and served as an obstacle in drug reimbursement negotiations with health care policymakers.

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157

A randomized controlled trial to determine the most sensitive outcome measure of airway clearance in cystic fibrosis

G. Stanford[1,2,3], D. Bilton[2,4], S. Charman[5], M. Jones[6], O. Usmani[3,7], J. Davies[3,8,9], N. Simmonds[1,2,3]. *[1]Department of Adult Cystic Fibrosis, Royal Brompton Hospital, Guys and St. Thomas's; [2]NHS Foundation Trust, London, UK; [3]National Heart and Lung Institute, Imperial College, London, UK; [4]Department of Adult Respiratory Medicine, Royal Brompton Hospital, Guys and St. Thomas's NHS Foundation Trust, London, UK; [5]Cystic Fibrosis Trust, London, UK; [6]Brunel University, London, UK; [7]Imperial College Respiratory Research Unit, St Mary's Hospital, London, UK; [8]Department of Paediatric Respiratory Medicine, Royal Brompton Hospital, Guys and St. Thomas's NHS Foundation Trust, London, UK; [9]Lung Clearance Index Core Facility, European Cystic Fibrosis Society, London, UK*

Background: The best outcome measure for airway clearance in cystic fibrosis (CF) is unknown. Our National Institute for Health and Care Research–funded randomized controlled trial compared five primary outcome measures—sputum weight, forced expiratory volume in 1 second (FEV_1), end expiratory lung impedance (ΔEELI) from electronic impedance tomography, lung clearance index (LCI) from multiple-breath washout (MBW), R5-R20 from impulse oscillometry (IOS))—to determine the most sensitive measure of a single airway clearance session.

Methods: Subjects performed the outcome measures of MBW, IOS, and spirometry and were randomized to a single session of supervised airway clearance or rest for 30 minutes, after which MBW, IOS, and spirometry were repeated. Electronic impedance tomography and sputum were collected during the rest or airway clearance period. At a subsequent visit, the outcome measures were completed with the other intervention. Primary endpoint was difference in change in outcome measures before and after airway clearance or rest. Secondary endpoints included within-group treatment effect and other physiological parameters. Target sample size was 64 to allow subgroup analysis of two groups stratified according to percentage predicted FEV_1 (FEV_1pp) (>60%, ≤60%).

Results: Sixty-eight participants completed the study (42 male; mean age 41 ± 14.2; mean FEV_1pp 64.5 ± 23.9%). Sputum weight was significantly different after airway clearance (median change 4.4 g, interquartile range (IQR) 1.4–8.4 g) than after rest (median change 0 g, IQR 0–0.75 g) ($p < 0.05$). No other significant differences in primary outcome measures

Table 1 (abstract 157):
Change in primary outcome measures after airway clearance and rest for total study population and subgroups

Primary outcome measures	All participants (n = 68, except for LCI 2.5 where n = 62)			FEV1 > 60% Group (n = 33 for all OMs except LCI 2.5 where n = 31)			FEV1 ≤ 60% Group (n = 35 for all OMs except LCI2.5 where n =- 31)		
	Change after AC	Change after rest	Difference	Change after AC	Change after rest	Difference	Change after ACT	Change after rest	Difference
FEV_1 (litres) from spirometry			*p = 0.49*			*p = 0.79*			*p = 0.48*
Median	0	-0.01		0.01	0		0	0.01	
IQR	-0.05 - 0.04	-0.06 - 0.05		-0.04 – 0.05	-0.07 - 0.04		-0.03 – 0.03	-0.04 – 0.07	
95% CI	-0.02 – 0.02	-0.03 – 0.01		-0.03 – 0.05	-0.05 – 0.03		-0.02 – 0.02	-0.01 – 0.04	
FEV_1 %pred (%) from spirometry			*p = 0.17*			*p = 0.79*			*p = 0.22*
Median	0	0		-0.01	0		0	0	
IQR	-0.01 - 0.01	-0.02-0.01		-0.05 - 0.04	-0.04 - 0.07		-0.01 – 0.01	-0.02 – 0.01	
95% CI	0-0	-0.01 – 0		-0.05 – 0.03	-0.03 – 0.05		0 – 0.01	-0.01 - 0	
LCI 2.5 from MBW			*p = 0.53*			*p = 0.87*			*p = 0.34*
Median	-0.18	-0.12		-0.19	-0.11		-0.09	-0.12	
IQR	-0.81 - 0.68	-0.84 - 0.37		-0.55 – 0.36	-0.83 – 0.35		-0.91 – 0.88	-1.22 – 0.52	
95% CI	-0.4 – 0.4	-0.4 – 0.1		-0.36 – 0.31	-0.73 – 0.09		-0.76 – 0.77	-0.84 – 0.20	
R5-R20 (kPasL-1) from IOS			*p = 0.51*			*p = 0.17*			*p = 0.82*
Median	0	0		-0.01	0		0	-0.01	
IQR	-0.01 - 0.02	-0.02 - 0.02		-0.02 – 0	-0.02 – 0.01		-0.03 – 0.02	-0.03 - 0.02	
95% CI	0 – 0.01	0 – 0.01		-0.01 - 0	-0.01 – 0.01		-0.01 – 0.02	-0.02 – 0.01	
ΔEELI from EIT			*p = 0.21*			*p = 0.65*			*p = 0.19*
Median	933.04	55.93		-1857.8	-713.42		-652.82	742.35	
IQR	-1285.70 - 3611.41	-4255.4 - 1399.46		-12273 – 2066.31	-1823.7 – 5123		-2588.48 – 1056.18	-1139.91 – 3387.8	
95% CI	282.8 – 1873.7	-1198.8 – 724.9		-3298.6 - -87.9	-1403.1 – 1315.6		-1251.0 – 156.3	-455.0 – 1923.5	
Sputum Weight (grams)			*p <0.005 **			*p<0.005**			*p<0.005**
Median	4.4	0		3.9	0		5.8	0	
IQR	1.4 - 8.4	0 - 0.75		1.6 – 6.5	0 – 0.8		1.1 – 9.80	0 – 0.60	
95% CI	3.6 – 6.1	0 – 0.4		3.0 – 6.1	0 -0.7		2.6 – 8.4	0 – 0.4	

*** = Statistically significant difference.**
P-values calculated using Wilcoxen Signed Rank tests
95% CI's derived from medians

were observed (Table 1). In subgroup analysis, there were no additional differences in change in primary outcome measures after airway clearance therapy and rest according to FEV_1 severity (Table 1).

Conclusions: This study aimed to determine the most sensitive outcome measure for a single session of airway clearance. Of the five primary outcome measures (sputum weight, FEV_1, LCI2.5, ΔEELI, R5-R20), only sputum weight changed significantly more after airway clearance therapy than after rest, with minimal or no change in other outcome measures. Analysis of primary and secondary endpoints and their potential clinical significance with subgroup stratification are ongoing. For adults with CF, FEV_1, LCI 2.5, R5-R20, and ΔEELI may not be suitable outcome measures to assess the efficacy of a single airway clearance session. Although sputum weight changed significantly, this measure is limited in use to those who are productive of sputum. Further work is required to identify alternative outcome measures that are sensitive for short- and long-term assessment of airway clearance for the whole adult CF cohort.

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158

Validation of the Q-Life app: An individualized patient-reported outcome measure to assess quality of life

D. Muilwijk[1], T. van Paridon[1], V. Gulmans[2], H. Heijerman[3], C. van der Ent[4].
[1]Pediatric Pulmonology, University Medical Center Utrecht, Utrecht, the Netherlands; [2]Dutch Cystic Fibrosis Foundation, Baarn, the Netherlands; [3]Pulmonology, University Medical Center Utrecht, Utrecht, the Netherlands; [4]Pediatric Pulmonology, Wilhelmina Children's Hospital, Utrecht, the Netherlands

Background: Quality of life and prognosis of people with cystic fibrosis (PwCF) are drastically changing since the arrival of cystic fibrosis transmembrane conductance regulator (CFTR) modulators. Nevertheless, the variable impact of new therapies on individuals can be difficult to capture with standard questionnaires or physical outcome measures. To enable systematic assessment of the impact of care and treatment on important personal factors of quality of life, we developed and validated the Q-Life app as an individualized patient-reported outcome measure in PwCF.

Methods: The Q-Life app was developed in collaboration with PwCF and parents of children with CF. In the app, PwCF can describe and rank three to five factors that they find important for their personal quality of life. Factors can be labeled with an appropriate category and scored as to what extent the individual feels limited by CF on a 5-point Likert scale ranging from not limited to almost fully limited. Overall Q-Life score was calculated as percentage of the highest possible total score. An instructional video is available at https://youtu.be/3dNTdeI2TYE. Internal consistency and test-retest reliability of Q-Life scores were assessed in a cross-sectional study in PwCF aged 14 and older. Construct validity was evaluated by associations with Cystic fibrosis Questionnaire-Revised (CFQ-R) scores and percentage predicted forced expiratory volume in 1 second (FEV_1pp). Ee analyzed differences between groups with and without pulmonary exacerbations requiring intravenous (IV) antibiotics and between adolescents younger than 18 and adults aged 18 and older. Sensitivity to change is being assessed in a cohort of PwCF who initiated elexacaftor/tezacaftor/ivacaftor.

Results: Eighty-nine PwCF (median age 24 (interquartile range 17), 49% female) were enrolled. Participants described 340 individual Q-Life factors, which were most frequently labeled social activity (19%), physical exercise and sport (16%), work and education (13%), relaxation and rest (9%), and pulmonary symptoms (8%). High internal consistency (Cronbach alpha = 0.80) and test-retest reliability (intraclass correlation coefficient = 0.90, $p < 0.001$) demonstrated reliability of Q-Life scores. Q-Life scores were also correlated with overall CFQ-R scores (Spearman's rho (r) = 0.58, $p < 0.001$), CFQ-R respiratory domain scores (r = 0.39, $p < 0.001$), and FEV1pp (r = 0.58, $p < 0.001$), supporting construct validity. Higher Q-Life scores reflected better quality of life in PwCF without IV-treated pulmonary exacerbations in the last 12 months compared to PwCF with at least 1 IV-treated pulmonary exacerbations (median 85.0% (IQR 27.7%) vs 67.7% (IQR 28.7%), $p < 0.001$). Q-Life scores were also higher in adolescents (median 91.7% (IQR 33.7%) than adults (75.0% (IQR: 26.7%), $p = 0.01$).

Conclusions: High internal consistency, test-retest reliability, and construct validity of Q-Life scores validated the Q-Life app as an individualized patient-reported outcome measure.

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159

Qualitative examination of participation in the SIMPLIFY treatment withdrawal trial

J. Maggs[1], C. Bacon[2], E. McWilliams[3], D. Yablon[4], G. Sawicki[3,5], K. Riekert[6].
[1]Success with Therapies Research Consortium Community Member, Cystic Fibrosis Foundation, Bethesda, MD; [2]Division of Respiratory Diseases, Boston Children's Hospital, Boston, MA; [3]Boston Children's Hospital, Boston, MA; [4]Johns Hopkins University, Baltimore, MD; [5]Harvard Medical School, Boston, MA; [6]Pulmonary and Critical Care Medicine, School of Medicine, Johns Hopkins University, Baltimore, MD

Background: In the era of effective modulator therapy, several clinical trials evaluating the impact of withdrawal of other daily cystic fibrosis (CF) therapies have been initiated. We sought to understand why people with CF (PwCF) and their caregivers enrolled in a randomized treatment withdrawal study and to explore their experiences of study participation.

Methods: The Qualitative Understanding of Experiences in the SIMPLIFY Trial (QUEST) Study is an ongoing qualitative interview study enrolling participants after they complete participation in the Cystic Fibrosis Foundation (CFF)-sponsored SIMPLIFY Trial, a randomized controlled trial evaluating short-term withdrawal of hypertonic saline or dornase alfa therapy in individuals on a stable modulator therapy regimen. QUEST participants were recruited from 39 SIMPLIFY sites and included adults and teenagers with CF and caregivers of the teenage participants. Two interviews were conducted remotely via Zoom (audio only) or telephone, with the first interview within 4 months of completion of SIMPLIFY trial participation. The interviews were recorded and transcribed. Transcripts were analyzed using codes that the research team developed inductively. Two coders coded independently. This analysis focuses on interview 1, which explored reasons for participation in SIMPLIFY.

Results: One hundred six participants completed interview 1 (64 adults, 21 teens, 21 caregivers). Median age of participants with CF was 24.8, and 53% were female. Participants talked about joining SIMPLIFY out of curiosity or a desire to help others or to advance scientific knowledge, in addition to finding out if they personally could stop a therapy. Some joined for the compensation, to reduce the burden on their family and friends, or because their care team suggested they join. Caregivers also noted fostering responsibility in their adolescent child as a reason for study participation. Adult participants made the decision to participate in SIMPLIFY independently, but many noted that they consulted family or their care team. When specifically considering experiences during SIMPLIFY, all QUEST participants accepted their randomized assignment. Those who expressed disappointment in their study arm assignment were most often assigned to maintain therapy. When asked about joining future withdrawal studies, participants expressed a willingness to do so but noted that they would need to be "healthy" and not feel that they were putting their health at risk. Several PwCF were emphatic that they would not join a study about withdrawing modulator therapy. Overall, participants expressed hope and optimism about the possibility of withdrawing other therapies in the future.

Conclusions: Personal and community-minded factors drove participation by PwCF in the SIMPLIFY treatment withdrawal study, often in the context of optimism for the future. Future withdrawal studies in CF should consider highlighting these factors to foster research participation from PwCF.

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