Modulator Treatments for Cystic Fibrosis: Effectiveness and Value

Research Protocol

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Institute for Clinical and Economic Review

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Background, Objectives, and Research Questions

Background

Cystic fibrosis (CF) is an autosomal recessive condition caused by mutations in the cystic fibrosis transmembrane conductance regulator (*CFTR*) gene. Children born with CF inherit two pathogenic mutations, one from each parent. It is a relatively rare condition, occurring in approximately one in 2,500 to 3,000 live births, but it is the most common lethal genetic disease in Caucasian populations.[1-4] CF is a progressive disease that affects many organ systems, but most of its morbidity and mortality are associated with its impact on the respiratory system.

The life expectancy of patients with CF has increased substantially over the past 20 years, due in part to successes in the coordinated delivery of care and advances in CF management.[5] Until recently, treatment for CF focused on reducing symptoms and managing complications. New therapies target the abnormal proteins made by the mutated *CFTR* gene. More than 2,000 *CFTR* mutations have been identified that have different effects on the quantity and function of the CFTR protein (Table 1).[6] Mutations to the *CFTR* gene can affect the amount of CFTR protein that is produced, the amount of protein integrated into the cell membrane, or the CFTR protein's ability to regulate ion and water flow.[5] This leads to thick secretions that can block passages in the lungs, pancreas, and reproductive organs, which may result in frequent lung infections and reduced lung function, poor weight gain (due to gastrointestinal dysfunction), diabetes (due to pancreatic damage), and fertility problems.[7]

The focus of this review is on triple therapy that adds the novel agent elexacaftor to the combination of tezacaftor and ivacaftor (Trikafta™, Vertex Pharmaceuticals, Inc.), which was approved by the United States Food and Drug Administration (FDA) on October 21, 2019.[8] Elexacaftor is another corrector therapy like lumacaftor and tezacaftor. It helps to correct folding of the CFTR protein formed with an F508del mutation and its trafficking to the cell surface. In addition, we will update our prior review of ivacaftor (Kalydeco®, Vertex Pharmaceuticals, Inc.) and the combinations lumacaftor/ivacaftor (Orkambi®, Vertex Pharmaceuticals, Inc.) and tezacaftor/ivacaftor (Symdeko®, Vertex Pharmaceuticals, Inc.).

Table 1. Mutations Eligible for CFTR Modulator Treatment

Class / Mutations	Examples
Residual function mutations*	A1067T E193K A455E D110E
Minimal function mutations†	F508del N1303K Q2X 991del5
Mutations eligible for ivacaftor monotherapy (a subset of residual function mutations)	G551D G178R S549N S549 S549N D1152H

*Mutations that result in insufficient amounts of normal CFTR protein at the cell surface[9] Mutations that do not produce meaningful amounts CFTR protein[9]
†

The use of these agents has generated tremendous interest and hope on the part of clinicians, patients, and their families. The new triple therapy has the potential to improve the lives of patients with CF with mutations that are not effectively treated by the current generation of modulator therapies (patients who are heterozygous for the F508del mutation and a minimal function mutation). In addition, there may be new data with longer follow-up for patients treated with currently available therapies. All stakeholders will benefit from a comprehensive, updated review of the clinical evidence and potential economic impact of modulator treatments.

Objectives

The scope of this project was previously available for public comment and has been revised upon further discussions and input from stakeholders. In accordance with the revised scope, we will assess both the comparative clinical effectiveness and economic impacts of CFTR modulators for the treatment of cystic fibrosis. The assessment aims to systematically evaluate the existing evidence, taking uncertainty into account. To that aim, the assessment is informed by two research components: a systematic review of the existing evidence and an economic evaluation. This document presents the protocol for the systematic review of existing evidence (i.e., the clinical review). Details on the proposed methodology and model structure for the economic evaluation will be presented in a separate document (model analysis plan; expected publication December 16, 2019).

Research Questions

To inform our review of the clinical evidence, we have developed the following research questions with input from clinical experts, patients and patient groups:

- In patients with cystic fibrosis who carry mutations included in the **FDA-approved indications for ivacaftor**, what is the comparative efficacy, safety, and effectiveness of ivacaftor plus best supportive care **versus best supportive care alone** in terms of lung function, hospitalization, changes in weight and body mass index (BMI), health-related quality of life, adverse events, and other key outcomes?
- In patients with cystic fibrosis who are **homozygous for the F508del mutation**, what is the comparative efficacy, safety, and effectiveness of tezacaftor/ivacaftor, lumacaftor/ivacaftor, and elexacaftor/tezacaftor/ivacaftor (each in combination with best supportive care) **versus each other** in terms of lung function, hospitalization, changes in weight and BMI, health-related quality of life, adverse events, and other key outcomes?
- In patients with cystic fibrosis who are **homozygous for the F508del mutation**, what is the comparative efficacy, safety, and effectiveness of tezacaftor/ivacaftor, lumacaftor/ivacaftor, and elexacaftor/tezacaftor/ivacaftor (each in combination with best supportive care) **versus best supportive care alone** in terms of lung function, hospitalization, changes in weight and BMI, health-related quality of life, adverse events, and other key outcomes?
- In patients with cystic fibrosis who are **heterozygous for the F508del mutation and a residual function mutation**, what is the comparative efficacy, safety, and effectiveness of tezacaftor/ivacaftor, ivacaftor, and elexacaftor/tezacaftor/ivacaftor (each in combination with best supportive care) **versus each other** in terms of lung function, hospitalization, changes in weight and BMI, health-related quality of life, adverse events, and other key outcomes?
- In patients with cystic fibrosis who are **heterozygous for the F508del mutation and a residual function mutation**, what is the comparative efficacy, safety, and effectiveness of tezacaftor/ivacaftor, ivacaftor, and elexacaftor/tezacaftor/ivacaftor (each in combination with best supportive care) **versus best supportive care alone** in terms of lung function, hospitalization, changes in weight and BMI, health-related quality of life, adverse events, and other key outcomes?
- In patients with cystic fibrosis who are **heterozygous for the F508del mutation and a minimal function mutation**, what is the comparative efficacy, safety, and effectiveness of elexacaftor/tezacaftor/ivacaftor plus best supportive care **versus best supportive care alone** in terms of lung function, hospitalization, changes in weight and BMI, health-related quality of life, adverse events, and other key outcomes?

PICOTS Criteria

In line with the above research questions, the following specific criteria have been defined utilizing PICOTS (Population, Interventions, Comparisons, Outcomes, Timing, Setting and Study Design) elements.

Population

We will review CFTR modulator therapies in four distinct populations across all ages based on current FDA labeling and the clinical trial populations.

1. Individuals with CF who carry mutations included in the FDA-approved indications for ivacaftor.
2. Individuals with CF who are homozygous for the F508del mutation.
3. Individuals with CF who are heterozygous for the F508del mutation with a residual function mutation.
4. Individuals with CF who are heterozygous for the F508del mutation with a minimal function mutation.

Within these populations, subgroups of interest are defined according to presence of advanced nonreversible lung disease (e.g., patients with or without bronchiectasis; who have predicted FEV_1 below 40%, 40-<70%, 70-90%, or above 90%) and age (groups as defined in each study). Predicted FEV_1 is a measure of lung function defined as forced expiratory volume during the first second of expiration, adjusted for age, height, sex, and race. Other subgroups of interest are people with advanced non-pulmonary disease, such as recurrent pancreatitis, liver transplantation, poor growth, and infertility.

We will include studies of individuals of any age, regardless of their past medical history, comorbidities, or the severity of their CF.

Interventions

<u>Population 1</u>

- Ivacaftor plus best supportive care

<u>Population 2: Homozygous for F508del</u>

- Lumacaftor/ivacaftor plus best supportive care
- Tezacaftor/ivacaftor plus best supportive care
- Elexacaftor/tezacaftor/ivacaftor plus best supportive care

Population 3: Heterozygous F508del and a residual function mutation

- Ivacaftor plus best supportive care
- Tezacaftor/ivacaftor plus best supportive care
- Elexacaftor/tezacaftor/ivacaftor plus best supportive care

Population 4: Heterozygous F508del and a minimal function mutation

- Elexacaftor/tezacaftor/ivacaftor plus best supportive care

Comparators

The comparator for each population will be best supportive care and, where applicable, the other Interventions for that population.

Outcomes

Key Outcomes

- Lung function and decline in lung function over time
- Pulmonary exacerbations
- Lung transplant
- Hospitalizations
- Mortality
- Health-related quality of life
- Mental health including depression and anxiety
- Weight, body mass index (BMI), and growth
- CF-related diabetes

Other Outcomes

- Time lost from school or work
- Pill burden and correlation to adherence with medication regimen
- Worry, stress, and anxiety about the disease or its financial impact
- Ability to participate in athletic activity and social functions
- Financial insecurity
- Caregiver burden
- Acute pancreatitis
- Fertility
- Liver transplant
- Hemoptysis

- Pneumothorax
- Gall stones
- Kidney stones
- Sinus / nasal polyp surgeries
- Fertility in women

Intermediate Outcomes

- FEV_1 (predicted), including rate of FEV_1 decline
- Sweat chloride
- Vital capacity
- Lung clearance index
- Pseudomonas colonization
- Fasting glucose and related measures of glucose control

Adverse Events

- Chest discomfort
- Increased blood pressure
- Liver function / injury
- Cataracts
- Adverse events (AEs) leading to treatment discontinuation
- Serious adverse events (SAEs)

Timing

Studies of all follow-up durations are eligible. Our focus will be on studies in which patients are prescribed a course of treatment.

Setting

All settings will be considered. Studies conducted in any country will be considered. However, the primary interest is in outpatient settings in the United States.

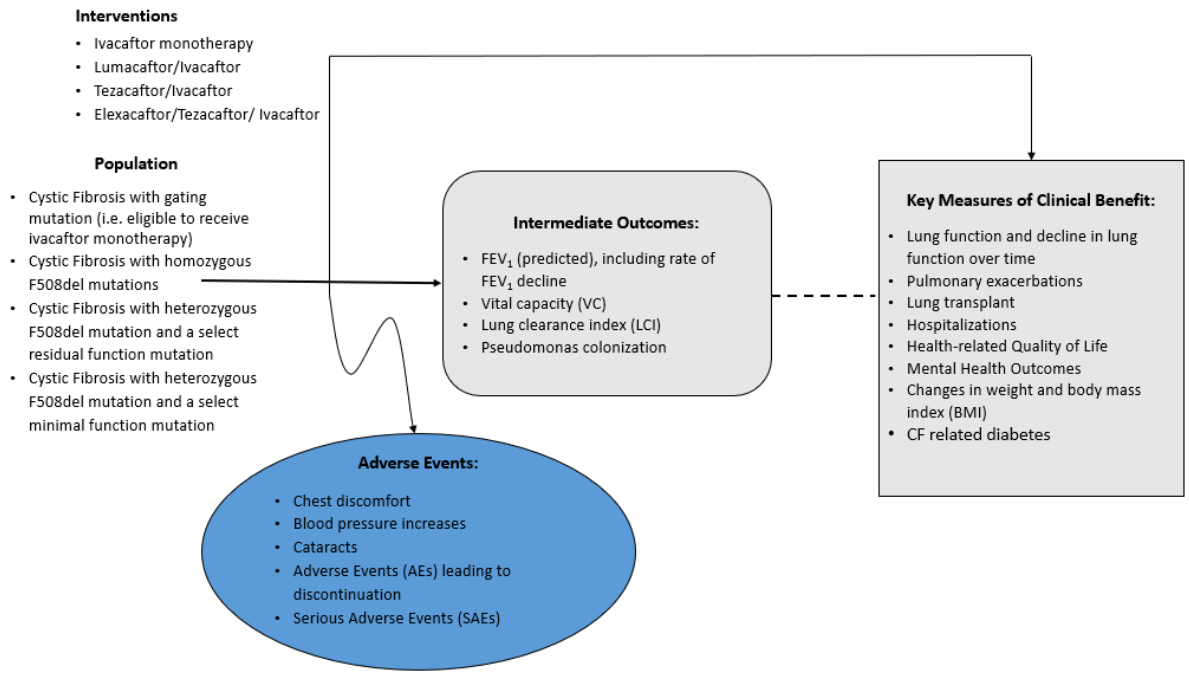
Study design

Randomized controlled trials and non-randomized controlled trials with any sample size will be included. Comparative observational studies with any sample size and single-group (noncomparative) studies with ≥100 participants and at least one month of follow-up will also be

included. Furthermore, we will include all observational, open-label extensions of included RCTs, regardless of sample size or follow-up duration.

Analytic Framework

The proposed analytic framework for this project is depicted below:



The diagram begins with the population of interest on the left. Actions, such as treatment, are depicted with solid arrows which link the population to outcomes. For example, a treatment may be associated with specific clinical or health outcomes. Outcomes are listed in the shaded boxes: those within the rounded boxes are intermediate outcomes (e.g., change in predicted FEV_1), and those within the squared-off boxes are key measures of clinical benefit (e.g., health-related quality of life). The key measures of clinical benefit are linked to intermediate outcomes via a dashed line, as the relationship between these two types of outcomes may not always be validated. Curved arrows lead to the adverse events of an action (typically treatment), which are listed within the blue ellipsis.

Evidence Review Methods

Search Methods and Data Sources

Procedures for the systematic literature review assessing the evidence on CFTR Modulators for cystic fibrosis will follow established best methods. [10,11]The review will be conducted in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines.[12] The PRISMA guidelines include a list of 27 checklist items, which are described further in Appendix A.

We will search MEDLINE, EMBASE, and Cochrane Central Register of Controlled Trials for relevant studies. Each search will be limited to English language studies of human subjects and will exclude articles indexed as guidelines, letters, editorials, narrative reviews, case reports, or news items. We will include abstracts from conference proceedings identified from the systematic literature search if they provide any additional data not available in previously published literature. All search strategies will be generated utilizing the Population, Intervention, Comparator, and Study Design elements described above. The proposed search strategies include a combination of indexing terms (MeSH terms in MEDLINE and EMTREE terms in EMBASE), as well as free-text terms, and are presented in Tables 1-4 below.

To supplement the database searches, we will perform a manual check of the reference lists of included trials and reviews and invite key stakeholders to share references germane to the scope of this project. We will also supplement our review of published studies with data from conference proceedings, regulatory documents, information submitted by manufacturers, and other grey literature when the evidence meets ICER standards (for more information, see http://icer-review.org/methodology/icers-methods/icer-value-assessment-framework/grey-literature-policy/).

Search Strategy of MEDLINE(R) Epub Ahead of Print, In-Process & Other Non-Indexed Citations, Ovid MEDLINE(R) Daily, Ovid MEDLINE and Versions(R) 1946 to Present and Cochrane Register of Controlled Trials via Ovid:

Table 1. Elexacaftor/tezacaftor/ivacaftor

#	Search Terms
1	Exp cystic fibrosis/ OR cystic fibrosis.ti,ab.
2	(deltaF508-CFTR OR deltaF508-CFTR protein OR f508del).mp.
3	Exp cystic fibrosis transmembrane conductance regulator/ OR (cystic fibrosis transmembrane conductance regulator OR CFTR).ti,ab.
4	(cystic fibrosis transmembrane conductance regulator potentiator OR CFTR potentiator).ti,ab.
5	(cystic fibrosis transmembrane conductance regulator corrector OR CFTR corrector).ti,ab.
6	(cystic fibrosis transmembrane conductance regulator modulator OR CFTR modulator).ti,ab.
7	OR/1-6
8	(Elexacaftor OR VX 445 OR VX-445 OR VX445 OR Trikafta).mp.
9	7 AND 8
10	(animals not (humans and animals)).sh.
11	9 NOT 10
12	Limit 11 to English Language

Table 2. Updated Search for ivacaftor, lumacaftor/ivacaftor, and tezacaftor/ivacaftor

#	Search Terms
1	Exp cystic fibrosis/ OR cystic fibrosis.ti,ab.
2	Exp cystic fibrosis transmembrane conductance regulator/ OR (cystic fibrosis transmembrane conductance regulator OR CFTR).ti,ab.
3	(cystic fibrosis transmembrane conductance regulator potentiator OR CFTR potentiator).ti,ab.
4	(cystic fibrosis transmembrane conductance regulator corrector OR CFTR corrector).ti,ab.
5	(cystic fibrosis transmembrane conductance regulator modulator OR CFTR modulator).ti,ab.
6	OR/1-5
7	(Ivacaftor OR Kalydeco OR VX-770 OR VX 770 OR VX770).ti,ab.
8	(Lumacaftor OR Orkambi OR VX-809 OR VX 809 OR VX809).ti,ab.
9	(Tezacaftor OR Symdeko OR VX-661 OR VX 661 OR VX661).ti,ab.
10	OR/7-9
11	6 AND 10
12	(addresses or autobiography or bibliography or biography or clinical trial, phase I or comment or congresses or consensus development conference or duplicate publication or editorial or guideline or in vitro or interview or lecture or legal cases or legislation or letter or news or newspaper article or patient education handout or periodical index or personal narratives or portraits or practice guideline or review or video audio media).pt.
13	11 NOT 12
14	(animals not (humans and animals)).sh.
15	13 NOT 14
16	Limit 15 to yr=2017-Current
17	Remove duplicates from 16

Search strategy of EMBASE

Table 3. Elexacaftor/tezacaftor/ivacaftor

#	Search Terms
#1	'cystic fibrosis'/exp OR 'cystic fibrosis':ti,ab
#2	(deltaF508-CFTR OR deltaF508-CFTR protein OR f508del):ti,ab
#3	'cystic fibrosis transmembrane conductance regulator'/exp OR ('cystic fibrosis transmembrane conductance regulator' OR 'CFTR'):ti,ab
#4	'cystic fibrosis transmembrane conductance regulator potentiator':ti,ab OR 'CFTR potentiator':ti,ab
#5	'cystic fibrosis transmembrane conductance regulator corrector':ti,ab OR 'CFTR corrector':ti,ab
#6	'cystic fibrosis transmembrane conductance regulator modulator':ti,ab OR 'CFTR modulator':ti,ab
#7	#1 OR #2 OR #3 OR #4 OR #5 OR #6
#8	'elexacaftor'/exp OR "elexacaftor plus ivacaftor plus tezacaftor'/exp OR ('elexacaftor' OR 'vx-445' OR 'vx 445' OR 'vx445' OR 'trikafta'):ti,ab OR ('elexacaftor' AND 'ivacaftor' AND 'tezacaftor'):ti,ab
#9	#7 AND #8
#10	'animal'/exp or 'nonhuman'/exp or 'animal experiment'/exp NOT 'human'/exp
#11	#9 NOT #10
#12	#11 AND [English]/lim

Table 4. Updated Search for ivacaftor, lumacaftor/ivacaftor, and tezacaftor/ivacaftor

#	Search Terms
#1	'cystic fibrosis'/exp OR 'cystic fibrosis':ti,ab
#2	'cystic fibrosis transmembrane conductance regulator'/exp OR ('cystic fibrosis transmembrane conductance regulator' OR 'CFTR'):ti,ab
#3	('cystic fibrosis transmembrane conductance regulator potentiator' OR 'CFTR potentiator'):ti,ab
#4	('cystic fibrosis transmembrane conductance regulator corrector' OR 'CFTR corrector'):ti,ab
#5	('cystic fibrosis transmembrane conductance regulator modulator' OR 'CFTR modulator'):ti,ab
#6	#1 OR #2 OR #3 OR #4 OR #5
#7	'ivacaftor'/exp OR ('ivacaftor' OR 'VX-770' OR 'VX770' OR 'VX 770' OR 'Kalydeco'):ti,ab
#8	'lumacaftor'/exp OR 'ivacaftor plus lumacaftor'/exp ('lumacaftor' OR 'ivacaftor plus lumacaftor' OR 'VX-809' OR 'VX 809' OR 'VX809' OR 'Orkambi'):ti,ab
#9	'tezacaftor'/exp OR 'ivacaftor plus tezacaftor'/exp OR ('tezacaftor' OR 'ivacaftor plus tezacaftor' OR 'VX-661' OR 'VX 661' OR 'VX661' OR 'Symdeko'):ti,ab
#10	#7 OR #8 OR #9
#11	#6 AND #10
#12	'animal'/exp or 'nonhuman'/exp or 'animal experiment'/exp NOT 'human'/exp
#13	#11 not #12
#14	#13 NOT ('case report'/de OR 'human tissue'/de OR 'nonhuman'/de OR 'practice guideline'/de OR 'questionnaire'/de OR 'chapter'/it OR 'conference review'/it OR 'editorial'/it OR 'letter'/it OR 'note'/it OR 'review'/it OR 'short survey'/it)
#15	#14 AND (2017:py OR 2018:py OR 2019:py)
#16	#15 AND [English]/lim

Selection of Eligible Studies

Subsequent to the literature search and removal of duplicate citations using both online and local software tools, study selection will be accomplished through two levels of screening, at the abstract and full-text level. Two reviewers will independently screen the titles and abstracts of all publications identified using DistillerSR (Evidence Partners, Ottawa, Canada); a third reviewer will work with the initial two reviewers to resolve any issues of disagreement through consensus. No study will be excluded at abstract level screening due to insufficient information. For example, an abstract that does not report an outcome of interest in the abstract would be accepted for further review in full text.

Citations accepted during abstract-level screening will be retrieved in full text for review. Reasons for exclusion will be categorized according to the PICOTS elements during both title/abstract and full-text review.

Data Extraction Strategy

Data will be extracted into evidence tables. The basic design and elements of the extraction forms will follow those used for other ICER reports. Elements include a description of patient populations, sample size, duration of follow-up, study design features, interventions (agent, dosage, frequency, schedules), outcome assessments, results, and quality assessment for each study.

The data extraction will be performed in the following steps:

1. One reviewer will extract information from the full articles, and a second reviewer will validate the extracted data.
2. Extracted data will be reviewed for logic, and a random proportion of data will be validated by a third investigator for additional quality assurance.

Quality Assessment Criteria

We will use criteria published by the US Preventive Services Task Force (USPSTF) to assess the quality of clinical trials and cohort studies, using the categories "good," "fair," or "poor."[13]

Good: Meets all criteria: Comparable groups are assembled initially and maintained throughout the study; reliable and valid measurement instruments are used and applied equally to the groups; interventions are spelled out clearly; all important outcomes are considered; and appropriate attention paid to confounders in analysis. In addition, intention to treat analysis is used for RCTs.

Fair: Any or all of the following problems occur, without the fatal flaws noted in the "poor" category below: Generally comparable groups are assembled initially but some question remains whether some (although not major) differences occurred with follow-up; measurement instruments are

acceptable (although not the best) and generally applied equally; some but not all-important outcomes are considered; and some but not all potential confounders are addressed. Intention to treat analysis is done for RCTs.

Poor: Any of the following fatal flaws exists: groups assembled initially are not close to being comparable or maintained throughout the study; unreliable or invalid measurement instruments are used or not applied equally among groups (including not masking outcome assessment); and key confounders are given little or no attention. For RCTs, intention to treat or modified intention to treat (e.g., randomized and received at least one dose of study drug) analysis is lacking.

Publication Bias Assessment

Given the emerging nature of the evidence base for these newer treatments, we will scan the ClinicalTrials.gov site to identify studies completed more than two years ago. Search terms include "elexecaftor", "ivacaftor", "lumacaftor", "tezacaftor". Alternative drug names will also be used as search terms. We will select studies which would have met our inclusion criteria, and for which no findings have been published. We will provide qualitative analysis of the objectives and methods of these studies to ascertain whether there may be a biased representation of study results in the published literature.

Evidence Synthesis

The purpose of the evidence synthesis is to estimate the clinical effectiveness of the interventions being compared. The analysis will be based on the data from all relevant studies identified from the systematic review. This section contains two components: 1) a summary of the evidence base and 2) a synthesis of outcome results.

Summary of Evidence Base

The studies will be summarized in the text and in evidence tables of the Evidence Report. This summary is key to understanding the evidence base pertaining to the topic. Evidence table shells are presented in Appendix B. Relevant data include those listed in the data extraction section. Any key differences between the studies in terms of the study design, patient characteristics, interventions (including dosing and frequency), outcomes (including definitions and methods of assessments), and study quality will be noted in the text of the report.

Synthesis of Results

The results of the studies will be synthesized for each outcome and described narratively in the report. Analyses to be conducted will reflect the nature and quality of the evidence base (see below). Key considerations for interpreting the results will be specified and described in the Evidence Report.

In addition, for each outcome of interest, we will evaluate the feasibility of quantitatively synthesizing the evidence by exploring the differences in study populations, study design, analytic methods, and outcome assessments in the available clinical data. We will seek to update the analyses presented in ICER's 2018 review of CFTR modulators with the most current evidence as well as generate de novo analyses where no analysis was previously feasible due to data limitations. If at least two studies comparing the same two interventions are sufficiently similar, we will conduct restricted maximum likelihood random effect pairwise meta-analyses. A pairwise meta-analysis quantitatively synthesizes results from multiple studies of the same two treatments.[14] Odds ratios will be chosen as the metric to analyze binary outcomes (e.g., occurrence of pulmonary exacerbations). In the analysis of rare outcomes (i.e., occurring in less than 1% of the population), we will use Peto's odds ratios. Results in terms of a point estimate and 95% confidence intervals will be summarized graphically in forest plots.

We also will assess the feasibility of updating the 2018 review's network meta-analyses (NMA) and conducting any novel NMAs. An NMA extends pairwise meta-analyses by simultaneously combining both the direct estimates (i.e., estimates obtained from head-to-head comparisons) and indirect estimates (i.e., estimates obtained from common comparator(s)).[15,16]For continuous outcomes (e.g., weight change, rate of pulmonary exacerbations), the NMA model corresponds to a generalized linear model with identity link. For binary outcomes (e.g., count of individuals who experienced a pulmonary exacerbation), the NMA model corresponds to a generalized linear model with a logit link. For all analyses, we will include random effects on the treatment parameters, and the amount of between-study variance (i.e., heterogeneity) will be assumed constant across all treatment comparisons.

Furthermore, for any network where there are "loops" in evidence, we will empirically compare the direct and indirect estimates to assess if the NMA consistency assumption is violated.[17] If there is evidence of inconsistency, the results will be presented for the direct and indirect evidence separately. If there is no evidence of inconsistency, we will present the pooled results.

All NMAs will be conducted using JAGS via R using the R2jags package. Results for all pairwise comparisons will be presented tabularly in terms of a point estimate and 95% confidence intervals.

To explore heterogeneity across studies, we will examine if there are differences in the distribution of key characteristics across studies. For this project, key characteristics include types of CFTR

mutations, age, sex, and prior use of CFTR modulator therapies. If studies differ with respect to these characteristics, subgroup analyses or meta-regressions may be performed where sufficient data exist.

References

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Appendix A. PRISMA Checklist

The checklist below is drawn from Moher et al. 2009.[12] Additional explanation of each item can be found in Liberati et al. 2009.[18]

Section/Topic	#	Checklist Item	Reported on Page #
TITLE			
Title	1	Identify the report as a systematic review, meta-analysis, or both.	
ABSTRACT			
Structured summary	2	Provide a structured summary including, as applicable: background; objectives; data sources; study eligibility criteria, participants, and interventions; study appraisal and synthesis methods; results; limitations; conclusions and implications of key findings; systematic review registration number.	
INTRODUCTION			
Rationale	3	Describe the rationale for the review in the context of what is already known.	
Objectives	4	Provide an explicit statement of questions being addressed with reference to participants, interventions, comparisons, outcomes, and study design (PICOS).	
METHODS			
Protocol and registration	5	Indicate if a review protocol exists, if and where it can be accessed (e.g., Web address), and, if available, provide registration information including registration number.	
Eligibility criteria	6	Specify study characteristics (e.g., PICOS, length of follow-up) and report characteristics (e.g., years considered, language, publication status) used as criteria for eligibility, giving rationale.	
Information sources	7	Describe all information sources (e.g., databases with dates of coverage, contact with study authors to identify additional studies) in the search and date last searched.	
Search	8	Present full electronic search strategy for at least one database, including any limits used, such that it could be repeated.	
Study selection	9	State the process for selecting studies (i.e., screening, eligibility, included in systematic review, and, if applicable, included in the meta-analysis).	
Data collection process	10	Describe method of data extraction from reports (e.g., piloted forms, independently, in duplicate) and any processes for obtaining and confirming data from investigators.	
Data items	11	List and define all variables for which data were sought (e.g., PICOS, funding sources) and any assumptions and simplifications made.	
Risk of bias in individual studies	12	Describe methods used for assessing risk of bias of individual studies (including specification of whether this was done at the study or outcome level), and how this information is to be used in any data synthesis.	
Summary measures	13	State the principal summary measures (e.g., risk ratio, difference in means).	
Synthesis of results	14	Describe the methods of handling data and combining results of studies, if done, including measures of consistency (e.g., I^2) for each meta-analysis.	
Risk of bias across studies	15	Specify any assessment of risk of bias that may affect the cumulative evidence (e.g., publication bias, selective reporting within studies).	
Additional analyses	16	Describe methods of additional analyses (e.g., sensitivity or subgroup analyses, meta-regression), if done, indicating which were pre-specified.	
RESULTS			
Study selection	17	Give numbers of studies screened, assessed for eligibility, and included in the review, with reasons for exclusions at each stage, ideally with a flow diagram.	
Study characteristics	18	For each study, present characteristics for which data were extracted (e.g., study size, PICOS, follow-up period) and provide the citations.	
Risk of bias within studies	19	Present data on risk of bias of each study and, if available, any outcome-level assessment (see Item 12).	
Results of individual studies	20	For all outcomes considered (benefits or harms), present, for each study: (a) simple summary data for each intervention group and (b) effect estimates and confidence intervals, ideally with a forest plot.	
Synthesis of results	21	Present results of each meta-analysis done, including confidence intervals and measures of consistency.	
Risk of bias across studies	22	Present results of any assessment of risk of bias across studies (see Item 15).	
Additional analysis	23	Give results of additional analyses, if done (e.g., sensitivity or subgroup analyses, meta-regression [see Item 16]).	
DISCUSSION			
Summary of evidence	24	Summarize the main findings including the strength of evidence for each main outcome; consider their relevance to key groups (e.g., health care providers, users, and policy makers).	
Limitations	25	Discuss limitations at study and outcome level (e.g., risk of bias), and at review level (e.g., incomplete retrieval of identified research, reporting bias).	
Conclusions	26	Provide a general interpretation of the results in the context of other evidence, and implications for future research.	
FUNDING			
Funding	27	Describe sources of funding for the systematic review and other support (e.g., supply of data); role of funders for the systematic review.	

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Appendix B. Data Extraction Summary Table Shells

Table B1. Study Design

Author & Year of Publication (Trial)	Study Design & Duration of Follow-Up	Interventions and Dosing Schedule	Inclusion Criteria	Exclusion Criteria

Table B2. Baseline Characteristics

Author & Year of Publication (Trial)	Study Arms	N	Sex	Age	ppFEV$_1$	BMI	Sweat Chloride Concentration	CFQ-R Respiratory Domain Score

Table B3. Efficacy Outcomes

Author & Year of Publication (Trial)	Study Arms	N	Change in ppFEV$_1$	Change in Sweat Chloride	Pulmonary Excacerbations	Change in Weight / BMI	Change in CFQ-R Respiratory Domain Score

Table B4. Harms

Author & Year of Publication (Trial)	Study Arms	N	Any Adverse Events, n (%)	Serious Adverse Events, n (%)	Adverse Events Leading to Discontinuation, n (%)	Other Adverse Events, n (%)