Elexacaftor–tezacaftor–ivacaftor, lumacaftor–ivacaftor and tezacaftor–ivacaftor for treating cystic fibrosis [ID3834]

Final protocol

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1 Title of the project

Elexacaftor–tezacaftor–ivacaftor, lumacaftor–ivacaftor and tezacaftor–ivacaftor for treating cystic fibrosis.

2 Name of TAR team and 'lead'

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3 Plain English summary

Cystic fibrosis can cause a range of symptoms across the body, including in lungs, digestive system, skin and liver. Recently, a number of treatments for people with cystic fibrosis have been developed. These treatments help to correct the underlying cause of cystic fibrosis, a faulty protein in the body. Before these treatments were available, treatments for cystic fibrosis tried to make an individual's symptoms better, but they did not correct the cause of cystic fibrosis.

The aim of this project is to review the medical benefits, risks and costs of three treatments that correct the underlying cause of cystic fibrosis (elexacaftor/tezacaftor/ivacaftor, lumacaftor/ivacaftor

and tezacaftor/ivacaftor) in a multiple technology appraisal (MTA). The benefits, risks and costs of these treatments will be assessed for people who have a specific version of cystic fibrosis: those who have a specific faulty version of the cystic fibrosis transmembrane conductance regulator (CFTR*)* gene causing cystic fibrosis, called *F508del.*

The project will try to find all of the relevant evidence on how well each treatment works by performing a comprehensive search of published research papers, called a "systematic literature review". The medical benefits and risks associated with the three treatments will be assessed and compared with each other, and against the treatments used to treat the symptoms of cystic fibrosis. In addition, this project will assess whether elexacaftor/tezacaftor/ivacaftor, lumacaftor/ivacaftor and tezacaftor/ivacaftor are likely to be considered good value for money for the NHS.

4 Decision problem

4.1 Purpose

Cystic fibrosis (CF) is a genetic disease caused by loss-of-function mutations in the cystic fibrosis transmembrane conductance regulator (CFTR) gene. The *CFTR* gene codes for the CFTR protein, an anion transporter expressed across several body systems.[1] CFTR is primarily involved in chloride ion transportation, and CFTR dysregulation leads to the build-up of thick secretions that affect multiple organ systems, including the lungs, digestive system, skin and liver. While over 2,100 *CFTR* mutations have been identified,[2] only a minority are disease causing.[1] The most common mutation causing CF is a deletion of phenylalanine at residue 508 (*F508del* mutation). *F508del* leads to the misfolding and subsequent targeting for degradation of the CFTR protein, reducing CFTR expression at the plasma membrane of cells in the body.[3]

In the lungs, CFTR dysregulation leads to thick mucus obstructing the airways, causing difficulty breathing and leading to inflammation and chronic respiratory infections. Such respiratory infections are a primary cause of pulmonary exacerbations requiring hospitalisation in CF, with 18.7% of people with CF (pwCF) in the United Kingdom (UK) receiving hospital-based intravenous antibiotics in 2021.[4, 5] Lung disease is the primary cause of death for pwCF, and most pwCF experience progressive lung function loss over their lifetime, which can be measured using the percent predicted forced expiratory volume in one second (ppFEV$_1$). Decline in ppFEV$_1$ is, on average, 1.52% each year in pwCF who are pancreatic insufficient, and 0.55% in pwCF who are pancreatic sufficient.[6]

Pancreatic damage occurs early in life, with around 83% of adults with CF in the UK being pancreatic insufficient, i.e., requiring supplemental pancreatic enzyme therapy (PERT)[6-8]. Thick secretions in pancreatic ducts leads to clogging and irreversible damage to pancreatic cells,[8] including the loss of acinar cells and severe impairment to β-cell function,[9, 10] reducing enzyme and hormone availability in the intestines. This produces a host of gastrointestinal symptoms, including bloating, cramps and malnutrition.[11] Approximately 35% of adults with CF have CF-related diabetes.[5] In addition, infertility affects around 98% of men with CF, due to obstructive azoospermia caused by the blockage, atypical development, or absence of the vas deferens. In women with CF, fertility issues are less common, but can be caused by thicker vaginal mucus or due to CF-related illnesses.[12]

The prevalence of CF in the UK is recorded by the UK Cystic Fibrosis Registry.[5] In 2021, 10,908 individuals were registered with the registry (pwCF with at least one annual review recorded in the last three years), representing over 99% of pwCF in the UK. Of these, 10,175 (93%) pwCF had an annual review in 2021. Genotyping was available for 99.0% of individuals reviewed, with 89.0% of pwCF having at least one *F508del* mutation: 47.7% of pwCF were homozygous for *F508del* and 41.3% were heterozygous for *F508del*. The median age was 21 years (with 61.9% of pwCF over 16 years of age), and the median age at diagnosis was 2 months. In 2020, 101 (1.0%) of the registered pwCF died, with a median age of death of 36 years. For people born with CF between 2017 and 2021, median predicted survival is 53.5 years, 10.0 years longer than the median predicted survival of individuals born 10 years earlier (43.5 years). Mean predicted survival is currently higher for men (55.3 years) than women (51.4 years).

Established clinical management for CF involves managing both CF symptoms and symptoms associated with CF treatments, rather than treating the underlying cause of the disease, i.e., CFTR protein function. The best supportive care therapies for managing CF symptoms and included in the NICE final scope are:[13]

- Inhaled mucolytics, such as dornase alfa, nebulised hypertonic saline and mannitol dry powder;
- Bronchodilators;
- Anti-inflammatory agents;
- Vitamin supplements and;
- Pancreatic enzymes.

NICE guidance exists for diagnosing and managing CF (NG78) and comments on the use of two of the classes of therapy included in the NICE final scope, recommending:[14]

- A mucoactive agent for people with CF who have clinical evidence of lung disease; and
- Oral pancreatic enzyme replacement therapy for people with exocrine pancreatic insufficiency.

NG78 makes several further recommendations for the treatment of CF symptoms, including:

- Use of physical airway clearance techniques;
- A range of eradication therapies, including oral, intravenous (IV) or inhaled antibiotics for treating pulmonary infections;
- Offering oral or IV fluids to ensure adequate hydration (and rehydration if needed) for people with distal intestinal obstruction syndrome, and further treatment if this is unsuccessful;
- Referring liver disease to a liver specialist and seeking specialist advice for people with a bone mineral density standard deviation below -2.0 (Z score);
- The off-label use of immunomodulators for people with CF and deteriorating lung function or repeated pulmonary exacerbations.

There are therapies for CF that have been approved for use by NICE, specifically:

- TA266: Mannitol dry powder for inhalation (DPI) is recommended, with conditions, as an option for treating CF in adults;[15]
- TA276: Tobramycin DPI and colistimethate sodium DPI are recommended, with conditions, as options for treating chronic pulmonary infection caused by *Pseudomonas aeruginosa* in people with CF.[16]

The 2021 UK Cystic Fibrosis Registry Annual Report provides details on the frequency of use of different established clinical management therapies by pwCF in the UK,[5] and these are provided in Table 1.

Table 1. Proportion of pwCF receiving non-CFTR treatments reported in the UK Cystic Fibrosis Registry 2021 Annual Report.[5]

Therapy[a]	Percentage of pwCF using each therapy in 2021 N=10,175
IV antibiotics	
Home	12.6
Hospital	18.7
Overall	24.3
Long-term azithromycin	40.9
Prophylactic flucloxacillin	19.3
Inhaled bronchodilators and corticosteroids	
Inhaled bronchodilators	60.2
Inhaled corticosteroids	18.6
Inhaled bronchodilators and inhaled corticosteroids combination	29.1
Mucoactive therapies	
DNase	69.2
Hypertonic saline	37.3
Mannitol	3.0
Non-invasive ventilation and oxygen use	
Non-invasive ventilation	1.4
Oxygen use	4.1
Physiotherapy	
Active cycle of breathing techniques	12.5
Autogenic drainage	17.7
Postural drainage	6.2
Any form of positive expiratory pressure	59.7
High-frequency chest wall oscillation	1.6
Exercise	59.9
Other	17.6
Feeding	
Any supplemental feeding	34.6
Gastrostomy tube/button	4.5

[a]Only therapies used by ≥1.0% of pwCF are reported. Therapies are not mutually exclusive.
Abbreviations: IV: intravenous
Source: UK Cystic Fibrosis Registry Annual Report 2021[5]

Recently, CFTR modulators have been presented as a novel therapeutic class for treating CF. Unlike previous established clinical management, CFTR modulators treat the underlying cause of CF by altering the form or function of the CFTR protein. CFTR modulators have five categories depending on their effect on the CFTR protein: correctors; potentiators; stabilisers; amplifiers; and read-though agents. One CFTR modulator monotherapy, and three CFTR modulator combination therapies, have received marketing authorisation in the UK:

- ivacaftor monotherapy;
- lumacaftor/ivacaftor combination therapy (LUM/IVA);
- tezacaftor/ivacaftor combination therapy (TEZ/IVA);
- elexacaftor/tezacaftor/ivacaftor combination therapy (ELX/TEZ/IVA).

Of these combinations, only LUM/IVA has been appraised by NICE. In TA398, LUM/IVA was not recommended within its marketing authorisation for treating cystic fibrosis in people 12 years and older who are homozygous for the *F508del* mutation in the *CFTR* gene.[17] However, all four CFTR modulator therapies are currently available on the NHS. Ivacaftor was made available to some pwCF in 2013, and an access agreement has been in place allowing access to the dual therapies LUM/IVA and TEZ/IVA since October 2019 and triple therapy ELX/TEZ/IVA since August 2020. Currently, most pwCF are receiving a CFTR modulator therapy. Of the 10,175 individuals registered and who had an annual review in 2021 in the UK Cystic Fibrosis Registry, 7,384 (72.6%) were taking a CFTR modulator by December 2021, including:

- 5,321 people (72.1% of individuals on a CFTR modulator) taking ELX/TEZ/IVA;
- 515 people (7.0%) taking TEZ/IVA;
- 942 people (12.8%) taking LUM/IVA and;
- 606 people (8.2%) taking ivacaftor monotherapy.

During 2021, the number of people receiving ELX/TEZ/IVA rose from 4,195 in January 2021 to 5,321 in December 2021, whereas the use of both other CFTR combination therapies declined over this period.

The purpose of this MTA is to assess the clinical and cost-effectiveness of LUM/IVA, TEZ/IVA and ELX/TEZ/IVA within their marketing authorisations for treating CF, compared with each other and established clinical management in England and Wales.

4.2 Interventions

LUM/IVA combination therapy (Orkambi®, Vertex Pharmaceuticals) is a systemic protein modulator, comprising of lumacaftor, a CFTR corrector, and ivacaftor, a CFTR potentiator. LUM/IVA is administered orally and has a marketing authorisation in the UK for treating, "cystic fibrosis (CF) in patients aged 6 years and older who are homozygous for the *F508del* mutation in the cystic fibrosis transmembrane conductance regulator (CFTR) gene".[18] For patients aged 6–11 years, two tablets of lumacaftor 100 mg/ivacaftor 125 mg are taken every 12 hours. For patients ≥12 years, two tablets of lumacaftor 200 mg/ivacaftor 125 mg are taken every 12 hours.[18] LUM/IVA granules also have a marketing authorisation for children with CF who are homozygous for *F508del* and who are aged 2–5 years. For children aged 2–5 years who weigh <14 kg, one sachet of lumacaftor 100 mg/ivacaftor 125 mg is taken every 12 hours.[19] For children aged 2–5 years who weigh ≥14 kg, one sachet of lumacaftor 150 mg/ivacaftor 188 mg is taken every 12 hours. The clinical effectiveness and safety of LUM/IVA has been studied in a Phase III clinical trial in children aged ≥1 year and <2 years.[20]

TEZ/IVA combination therapy (Symkevi®, Vertex Pharmaceuticals) is a systemic protein modulator, comprising of tezacaftor, a CFTR corrector, and ivacaftor. TEZ/IVA is administered orally and has a marketing authorisation in the UK, "in a combination regimen with ivacaftor tablets for the treatment of patients with cystic fibrosis (CF) aged 6 years and older who are homozygous for the *F508del* mutation or who are heterozygous for the *F508del* mutation and have one of the following mutations in the cystic fibrosis transmembrane conductance regulator (CFTR) gene: P67L, R117C, L206W, R352Q, A455E, D579G, 711+3A→G, S945L, S977F, R1070W, D1152H, 2789+5G→A, 3272-26A→G, and 3849+10kbC→T".[21] Dosing for TEZ/IVA is age and weight dependent, and is presented in Table 2.[21]

Table 2. Dosing recommendations for TEZ/IVA patients aged 6 years and older.[21]

Age and weight	Morning dose	Evening dose
6 to <12 years, <30 kg	One tablet containing tezacaftor 50 mg/ivacaftor 75 mg	One tablet containing ivacaftor 75 mg

6 to <12 years, ≥30 kg	One tablet containing tezacaftor 100 mg/ivacaftor 150 mg	One tablet containing ivacaftor 150 mg
≥12 years	One tablet containing tezacaftor 100 mg/ivacaftor 150 mg	One tablet containing ivacaftor 150 mg
Abbreviations: kg: kilograms; mg: milligrams		

ELX/TEZ/IVA combination therapy (Kaftrio®, Vertex Pharmaceuticals) is a systemic protein modulator, comprising of elexacaftor, a CFTR corrector, tezacaftor and ivacaftor. ELX/TEZ/IVA is administered orally and has a marketing authorisation in the UK, "in a combination regimen with ivacaftor for the treatment of cystic fibrosis (CF) in patients aged 6 years and older who have at least one *F508del* mutation in the cystic fibrosis transmembrane conductance regulator (CFTR) gene".[22] Dosing for ELX/TEZ/IVA is age and weight dependent, and is presented in Table 3.[22] The clinical effectiveness and safety of ELX/TEZ/IVA has also been studied in a Phase III clinical trial in children aged ≥2 years.[23]

Table 3. Dosing recommendations for ELX/TEZ/IVA patients aged 6 years and older.[22]

Age and weight	Morning dose	Evening dose
6 to <12 years, <30 kg	Two tablets, each containing ivacaftor 37.5 mg/tezacaftor 25 mg/elexacaftor 50 mg	One tablet containing ivacaftor 75 mg
6 to <12 years, ≥30 kg	Two tablets, each containing ivacaftor 75 mg/tezacaftor 50 mg/elexacaftor 100 mg	One tablet containing ivacaftor 150 mg
≥12 years	Two tablets, each containing ivacaftor 75 mg/tezacaftor 50 mg/elexacaftor 100 mg	One tablet containing ivacaftor 150 mg
Abbreviations: kg: kilograms; mg: milligrams		

4.3 Place of the interventions in the treatment pathway

As CFTR modulators treat the underlying cause of CF, CFTR modulator combination therapy is the preferred treatment for pwCF aged ≥6 years. For children aged 2–5 years, LUM/IVA is the only combination therapy with a marketing authorisation in the UK, and the EAG's clinical experts stated that they would recommend all eligible children to receive LUM/IVA. At 6 years, the EAG's clinical experts advised that ELX/TEZ/IVA combination therapy is the preferred CFTR combination therapy

for a child, due to clinical trial evidence and clinical experience indicating that the triple combination therapy has a substantially greater clinical effectiveness than TEZ/IVA and LUM/IVA. The EAG's clinical experts advised that they would recommend that all children aged 2–5 who are currently treated with LUM/IVA should switch to ELX/TEZ/IVA once they reach 6 years old. If a child were unsuccessful, intolerant of, or experienced adverse events after initiation of ELX/TEZ/IVA from 6 years old, TEZ/IVA or LUM/IVA may be considered. The EAG's clinical experts noted that, when ELX/TEZ/IVA became more widely available, many people transitioned to the triple combination therapy from TEZ/IVA and LUM/IVA to ELX/TEZ/IVA.

The EAG's clinical experts also noted that pwCF on a CFTR modulator treatment would be expected to receive all other elements of established clinical management, should their symptoms require it. However, the EAG's clinical experts noted that the need for certain therapies, such as inhaled mucolytics, may reduce following successful CFTR modulator treatment.

4.4 Relevant comparators

The comparators of interest listed in the NICE final scope are:[13]

- Each of the interventions under consideration in the MTA:
    - LUM/IVA;
    - TEZ/IVA;
    - ELX/TEZ/IVA.
- Established clinical management, including:
    - Best supportive care;
    - Mannitol DPI;
    - Inhaled mucolytics;
    - Nebulised hypertonic saline;
    - Anti-inflammatory agents;
    - Bronchodilators;
    - Vitamin supplements;
    - Pancreatic enzymes.

Of the listed established clinical management therapies, only mannitol DPI (Bronchitol®, Pharmaxis Europe Limited) has been approved by NICE (TA266[15]). The use of mannitol DPI is restricted to adults who cannot use rhDNase because of ineligibility, intolerance or inadequate response to rhDNase,

and whose lung function is rapidly declining and for whom other osmotic agents are not considered appropriate. The EAG considers that inhaled mucolytics, of which mannitol DPI and nebulised hypertonic saline are examples, are therapies that individuals receiving a CFTR modulator would still be eligible for, and would still receive, should their symptoms require. Moreover, the EAG considers the population eligible for mannitol DPI to be small, and considers it unlikely that there will be sufficient evidence from CFTR modulator trials to conduct a comparison between CFTR modulator and mannitol DPI within the population eligible for mannitol DPI. Based on discussion with its clinical experts, the EAG considers it likely that established clinical management without CFTR modulator therapy, including mannitol DPI if required, will have been adequately captured by the control arms of CFTR modulator RCTs. Overall, the EAG considers the comparators listed in the NICE final scope to be appropriate, but notes that best supportive care also includes some therapies, procedures, and lifestyle changes not explicitly mentioned, such as physiotherapy, supplemental feeding, and exercise, as outlined in Table 1. The EAG also notes that the availability of some established clinical management therapies varies with age. For example, rhDNase is only indicated for people with CF who are over 5 years of age and who have a $ppFEV_1$ >40%, and mannitol DPI is indicated for the treatment of CF in adults aged 18 and over.

Although not a relevant comparator in the NICE final scope, the EAG notes that a number of pwCF (606) were receiving ivacaftor monotherapy in the CF Trust Register, as of December 2021. Ivacaftor monotherapy is indicated for pwCF aged 4 months and above who have an *R117H CFTR* mutation or one of the following gating (class III) mutations in the *CFTR* gene: G551D, G1244E, G1349D, G178R, G551S, S1251N, S1255P, S549N or S549R. Such individuals may be heterozygous for *F508del*, and as such may be eligible for ELX/TEZ/IVA when they reach 6 years. As such, the EAG notes that ivacaftor monotherapy may form part of a connected evidence network with ELX/TEZ/IVA and best supportive care in pwCF with an *F508del* mutation and a gating mutation in the *CFTR* gene.

4.5 Population and relevant subgroups

The population relevant to this MTA is pwCF with at least one *F508del* mutation. Relevant subgroups are based on the genotype eligibility criteria specified in the marketing authorisation for each CFTR modulator combination therapy. Only individuals homozygous for the *F508del* mutation are eligible for LUM/IVA, whereas individuals with at least one copy of the *F508del* mutation are eligible for ELX/TEZ/IVA. To be eligible for TEZ/IVA, an individual must either be homozygous for the *F508del* mutation, or have one copy of the *F508del* mutation and one of the following residual function

mutations: P67L, R117C, L206W, R352Q, A455E, D579G, 711+3A→G, S945L, S977F, R1070W, D1152H, 2789+5G→A, 3272-26A→G, and 3849+10kbC→T.

Hence, the relevant subgroups for this appraisal are:

- People with CF who are homozygous for the *F508del* mutation;
    - This population is relevant for all three combination therapies and established clinical management.
- People with CF who are heterozygous for the *F508del* mutation and a residual function mutation or a gating mutation in the *CFTR* gene.
    - The subgroup of people with CF who are heterozygous for the *F508del* mutation and a residual function mutation is relevant for TEZ/IVA, ELX/TEZ/IVA and established clinical management, only.
    - The subgroup of people with CF who are heterozygous for the *F508del* mutation and a gating mutation is relevant for ELX/TEZ/IVA and established clinical management, only.

4.6 Outcomes to be addressed

The outcomes to be addressed in this MTA based on the NICE scope are:

- Mortality
- Lung function, including ppFEV$_1$, forced vital capacity, lung clearance index 2.5 respiratory symptoms and transplantation
- Body mass index (BMI)
- Pulmonary exacerbations, including the frequency and severity of acute infections leading to exacerbations
- Pulmonary bacterial colonisation
- Need for hospitalisation and other treatments including use of antibiotics
- Sweat chloride
- Adverse effects of treatment
- Health-related quality of life
- If evidence allows, the relationship between baseline lung function and clinical effectiveness

5 Report methods for synthesis of evidence of clinical effectiveness

A systematic literature review (SLR) of the evidence on the clinical effectiveness of LUM/IVA, TEZ/IVA and ELX/TEZ/IVA for treating cystic fibrosis (CF) will be performed following the PRISMA statement.[24] A flow diagram illustrating the number of records identified, included and excluded at each stage of the systematic literature review will be presented according to the PRISMA reporting guidelines.[24]

5.1 Search strategy

The EAG will perform systematic searches of MEDLINE, Embase and CENTRAL, and a variety of grey literature sources, to identify all randomised controlled trials (RCTs, excluding Phase I RCTs), and all non-randomised Phase III or Phase IV clinical trials, that report on the clinical effectiveness or safety of LUM/IVA, TEZ/IVA and ELX/TEZ/IVA in people with cystic fibrosis (pwCF) with at least one *F508del* mutation.

De novo searches of MEDLINE and Embase will be conducted using search terms cystic fibrosis and LUM/IVA, TEZ/IVA and ELX/TEZ/IVA. The EAG's proposed search strategy for MEDLINE is presented in Table 9 of Appendix 9.1,[25] and the EAG's proposed search strategy for Embase is presented in Table 10 of Appendix 9.1.[26]For CENTRAL, the EAG identified the Cystic Fibrosis Trials Register as an up-to-date systematic search repository for CF RCTs that are indexed on CENTRAL.[27] The Cystic Fibrosis Trials Register is a continually-updated register of RCTs relating to CF, compiled from database searches of MEDLINE (weekly searches from 1966 to present), Embase (searched 1974 to August 1995) and CENTRAL (searched on each new issue of the Cochrane library), and also includes records hand-searched from the Journal of Cystic Fibrosis, Pediatric Pulmonology and conference abstracts. As such, the EAG's search strategy for CENTRAL will use the Cystic Fibrosis Trial Register filter and use search terms for LUM/IVA, TEZ/IVA and ELX/TEZ/IVA within this. The EAG's search strategy for CENTRAL is presented in Table 13 of Appendix 9.1, and further details of the Cystic Fibrosis Trials Register are presented in Appendix 9.1 (including Table 11 and Table 12). The Cystic Fibrosis Trials Register was the primary search of a large-scale Cochrane review relevant to the MTA, "*Corrector therapies (with or without potentiators) for people with cystic fibrosis with class II CFTR gene variants (most commonly F508del)*" (Southern *et al.* 2020).[27]

The EAG's database searches of MEDLINE and Embase will be performed separately via Ovid, and then deduplicated against each other. The remaining records will be deduplicated against the trials indexed on the Cystic Fibrosis Trial Register. The resulting records will enter screening for inclusion in the SLR.

The EAG will conduct supplementary searches to identify any records not indexed in MEDLINE, Embase or the Cystic Fibrosis Trials Register via CENTRAL, and any ongoing studies. The following grey literature searches will be performed by a single reviewer and are indexed on the Cystic Fibrosis Trials Register in CENTRAL:

Conference proceedings

- European Cystic Fibrosis Conference abstracts 2020, 2021 and 2022
- Annual North American Cystic Fibrosis Conference abstracts 2020, 2021 and 2022

Trial Registries and Registers

- US National Institutes of Health Database (ClinicalTrials.gov)
- World Health Organization International Clinical Trials Registry Platform (WHO ICTRP)
- European Medicines Agency (EMA) (www.clinicaltrialsregister.eu/ctrsearch/search)

The EAG's search strategy for WHO ICTRP and EMA will match that used by the Southern *et al.*:[27] "Cystic fibrosis AND (VX OR corrector)". For the US National Institutes of Health database search, the EAG's search strategy will be as follows: Condition or disease: cystic fibrosis AND Other terms: VX OR corrector OR "Vertex Pharmaceuticals" OR CFTR AND Study type: Interventional Studies (Clinical Trials).

CDSR/DARE/HTA database

- The Database of Abstracts of Reviews of Effects (DARE) and Health Technology Assessment (HTA) database will be searched via the Centre for Reviews and Dissemination (CRD) database, using the key word "cystic fibrosis".
- The Cochrane Database of Systematic Reviews will be searched using the key words "cystic fibrosis" and the intervention terms from Table 13 of Appendix 9.1 to identify any Cochrane Reviews relevant to the current appraisal. During scoping, the EAG identified Southern *et al.* as a Cochrane review highly relevant to the MTA. Following discussion with the Cochrane

Cystic Fibrosis and Genetic Disorders Group, the EAG was notified that the Southern *et al.* review is currently undergoing a large update, and that the review authors will be able to provide materials from the updated Cochrane review to facilitate the conduct of the EAG's systematic review, including but not limited to:

- A full list of included and excluded trials in the Cochrane review update, including reasons for exclusion
- A confidential copy of the updated Cochrane review, once available
- Details on how the Cystic Fibrosis Trials Register is compiled, and details of the latest search dates
- Discussion and clarification as required throughout the projection

HTA bodies

As the CRD Databases were last updated in March 2018, the following English-language HTA body websites will be searched to identify HTA appraisals relevant to the current MTA, with references of any eligible studies contained within the HTA documents extracted:

- NICE;
- Pharmaceutical Benefits Advisory Committee (PBAC);
- Scottish Medicines Consortium (SMC);
- Canadian Agency for Drugs and Technologies in Health (CADTH).

Each HTA body will be searched on its website of records for "cystic fibrosis".

Company submissions

- Any company submission will be searched for relevant unpublished data.

No language restrictions will be applied in any search strategy, but only records with a full-text published in English will be included in the SLR. Abstracts published in English will be included if they contain relevant data.

5.2 Types of studies included

RCTs (excluding Phase I RCTs), and non-randomised Phase III or Phase IV clinical trials, will be included in the SLR, and the evidence base for each intervention, age range and genotype of relevance to the NICE final scope will be reported. Following scoping searches, the EAG anticipates

the evidence base will be of different sizes between age ranges and genotypes, with some interventions having multiple Phase III or Phase IV RCTs available within a certain genotype and age range, and others with no Phase III or Phase IV RCT data. Hence, the EAG will prioritise studies for extraction based on the study designs available for each intervention, specifically:

- Data will be extracted for all included Phase III or Phase IV RCTs;
- Should no Phase III or Phase IV RCT data be available for an intervention within a group of interest, any relevant Phase II RCT data will be extracted;
- Should no Phase II, Phase III or Phase IV RCT data be available for an intervention within a group of interest, then data from all non-randomised Phase III or Phase IV clinical trials will be extracted for this group.

5.3 Inclusion and exclusion criteria

Table 4 details the inclusion and exclusion criteria of the SLR. Based on these criteria, two reviewers will independently screen all titles and abstracts according to the inclusion criteria. Full texts of any titles/abstracts that may be relevant will be obtained where possible and the full text of each study will be assessed by two independent reviewers for inclusion in the SLR. Discrepancies will be resolved by discussion, with a third reviewer resolving any outstanding conflicts.

Table 4. Inclusion and exclusion criteria of the SLR

Factor	Inclusion criteria	Exclusion criteria
Design	RCTs (excluding Phase I RCTs), and non-randomised Phase III or Phase IV trials	• Phase I RCTs • Non-randomised studies, except for Phase III or Phase IV clinical trials • Observational studies • Case reports • *In vitro* studies • SLRs/MAs[a]
Population	People with CF with at least one copy of the *F508del* mutation. Studies will be included if they contain an arm of patients of the following ages for the following interventions: • LUM/IVA, ≥1 year • TEZ/IVA, ≥6 years • ELX/TEZ/IVA, ≥2 years	• People with CF who do not have at least one copy of the *F508del* mutation • People with CF where CF genotype is not reported • The study does not report an arm of patients of the following ages for one of: LUM/IVA, ≥1 year;

	• Ivacaftor monotherapy, ≥2 years Ivacaftor monotherapy is included as comparative data forming a connected evidence network between ivacaftor monotherapy, established clinical management and ELX/TEZ/IVA may exist for the population of patients heterozygous for F508del and a gating mutation.	TEZ/IVA, ≥6 years; ELX/TEZ/IVA, ≥2 years; ivacaftor monotherapy, ≥2 years. • People without CF • Animal studies
Interventions	• LUM/IVA • TEZ/IVA • ELX/TEZ/IVA • Ivacaftor monotherapy	Any other intervention
Comparators	The interventions will be compared to each other or established clinical management	Any other comparator
Outcomes	Outcomes listed in Section 5.5	No outcomes listed in Section 5.5

[a]SLRs and MAs will be included past the abstract screening stage to enable bibliography searching, but will be excluded at full-text stage.

Abbreviations: CF: cystic fibrosis; CFTR: cystic fibrosis transmembrane regulator; MA: meta-analysis; RCT: randomised controlled trial; SLR: systematic literature review

5.4 Subgroups to be examined

The relevant subgroups for this appraisal are:

- People with CF who are homozygous for the *F508del* mutation;
    - This population is relevant for all three combination therapies and established clinical management.
- People with CF who are heterozygous for the *F508del* mutation and a residual function mutation or a gating mutation in the *CFTR* gene.
    - The subgroup of people with CF who are heterozygous for the *F508del* mutation and a residual function mutation is relevant for TEZ/IVA, ELX/TEZ/IVA and established clinical management, only.
    - The subgroup of people with CF who are heterozygous for the *F508del* mutation and a gating mutation is relevant for ELX/TEZ/IVA and established clinical management, only.

The results of the clinical effectiveness analyses may be presented for age subgroups (1–2 years, 2–5 years, 6–11 years and ≥12 years), in addition to the overall population, for outcomes that may be affected by ceiling effects in one of the subgroups, and to assess whether there might be clinically meaningful heterogeneity between the subgroups. In addition, the EAG will document whether clinical effectiveness outcome data are available by baseline lung function subgroups, or are predicted in regression analyses using baseline lung function as a predictor. The EAG will then assess whether sufficient data are reported to assess the relationship between baseline lung function and clinical effectiveness further.

5.5 Outcomes to be examined

Table 5 lists the outcomes included in the NICE final scope and the variables to be extracted for these outcomes as part of the SLR.[13] The EAG has prioritised variables likely to be included in the economic model for extraction. Table 16 of the appendix contains a wider list of variables relevant to the NICE final scope that may be extracted as part of the SLR, should they be required for economic modelling.

Table 5. Outcomes and corresponding data to be extracted as part of the SLR.

Outcomes included in NICE final scope[13]	Data to be extracted
Mortality	• All-cause mortality
Lung function	Absolute and change from baseline: • ppFEV1 • Lung clearance index 2.5 Number of people with, or time until: • Lung transplant • Need for lung transplant
Respiratory symptoms	Absolute and change from baseline: • CFQ-R respiratory domain score (*outcome only to be extracted if deemed necessary for the economic model*)

Body mass index	Absolute and change from baseline: • Weight • Weight for age z-score • BMI
Pulmonary exacerbations	• Study reported definition of pulmonary exacerbation • Any measure of absolute or relative frequency or time until: Pulmonary exacerbations • Pulmonary exacerbations requiring IV antibiotics or hospitalisation
Pulmonary bacterial colonisation	Trial defined frequency or relative frequency of: • *Pseudomonas* colonisation

Need for hospitalisation and other treatments	Trial reported:
	• Hospitalisation
	  ○ Number of days
	  ○ Number of episodes
	  ○ Planned hospitalisation vs unplanned hospitalisation
	  ○ Intensive care unit use
	• Other CF treatment use
	• Other non-CF treatment use

Adverse effects of treatment	Number of people with: • Any serious adverse event (Grade 3 and above) • Any serious treatment-emergent adverse event (Grade 3 and above) • Any trial-defined adverse event of special interest • Adverse events of particular importance as identified by the EAG's clinical experts, including: • Adverse events relating to the liver • Cataracts or lens opacities • Hypertension
Health-related quality of life	Absolute and change from baseline: • EQ-5D-5L and EQ-5D-3L • Cystic Fibrosis Questionnaire-Revised (CFQ-R), total score or respiratory domain • CFQ Child, total score or respiratory domain

	• CFQ-Parent (for child) , total score or respiratory domain If no EQ-5D measure is reported, the EAG will extract SF-36 data if available.
Sweat chloride	Absolute and change from baseline: • Sweat chloride
Not included in NICE scope	• Development of CF-related diabetes

Abbreviations: BMI: body mass index; CF: cystic fibrosis; CFQ-R: Cystic Fibrosis Questionnaire-Revised; CFTR: cystic fibrosis transmembrane regulator; EAG: external assessment group; EQ-5D: EuroQol five-dimensions: HR: hazard ratio; IV: intravenous; MA: meta-analysis; ppFEV$_1$: percent predicted forced expiratory volume in one second; RCT: randomised controlled trial; SLR: systematic literature review.

5.6 Data extraction strategy

Data will be extracted by a single reviewer using a standardised data extraction form. Study design, clinical effectiveness data will be extracted into Microsoft Excel®, and dose and adverse event data will be extracted directly into Microsoft Word®. Draft data extraction forms are provided in Table 17 to Table 25 of Appendix 9.3. Extracted data will be validated by a second reviewer and discrepancies will be resolved by discussion, with involvement of a third reviewer when necessary. Outcome data will be prioritised for extraction at the following timepoints: Week 4; Week 24; Week 48 and the timepoint of the primary outcome or end of study, if these differ from those listed. Where key relevant data for the economic model are not reported, the study authors will be contacted to gain further details. Authors will be asked to respond within two weeks of initial contact, after which time, unless the author has confirmed that they can supply the requested data, it will be assumed the data are not available. Should the study with key missing data have been sponsored by the Company, the Company, rather than the study authors, will be contacted to gain further details in the first instance.

For clinical efficacy outcomes, data will be preferentially extracted for the intention-to-treat (ITT) population, where available. For safety outcomes, data will be preferentially extracted from the safety analysis set. For missing data, estimates obtained using imputation methods will be preferentially extracted, and if multiple methods of imputation are reported, estimates based on multiple imputation or mixed-effects models will be preferred over last observation carried forward, or variants of this method.

5.7 Quality assessment strategy

The quality of the individual studies will be assessed by one reviewer, and independently checked for agreement by a second reviewer. Any disagreements will be resolved by consensus and, if necessary, a third reviewer will be consulted. Risk of bias will be assessed at both the study and key outcome level. At the study level, risk of bias will be assessed using the risk of bias table presented in Appendix 9.2. At the outcome level, risk of bias will be assessed using Version 2 of the Cochrane risk-of-bias tool for randomised trials (RoB 2).[28] The RoB 2 template will be completed for the outcomes included in Table 5 that will be included in the economic model, should any relevant data be reported. A quality assessment will not be performed for single-arm non-randomised studies, which will be assumed to be at high risk-of-bias if they are used to inform relative treatment effects.

5.8 Methods of analysis/synthesis

Extracted data and a quality assessment for each study of clinical effectiveness will be presented in tables and described as a narrative summary. The possible effects of study quality on the effectiveness data and review findings will be discussed. A feasibility assessment for network meta-analyses (NMA) of all key outcomes will be performed, by assessing of the quantity and quality of data available for each outcome at different timepoints, the similarity of study designs and assessing the transitivity assumption through comparing the distribution of potential treatment effect modifiers between studies. The EAG's clinical experts outlined that ceiling effects for some outcome measures in some individuals, e.g., ppFEV$_1$ and lung clearance index in younger children may limit the sensitivity of such measures in these groups, and also noted the difficulty in obtaining reliable measurements of ppFEV$_1$ in younger children. In addition to age-related ceiling effects, disease severity and prior treatment history may modify the magnitude of the treatment effect a patient could gain from CFTR modulator therapy. Hence, following discussion with its clinical experts and following a previous appraisal of ELX/TEZ/IVA by CADTH,[29] the EAG will assess the similarity of studies to be included in any indirect treatment comparison based upon the following study and sample characteristics: disease severity; treatment history; eligibility criteria; comparator dosing; placebo response; end-point definition and timing; definition of pulmonary exacerbation; withdrawal frequency; clinical trial setting and study design.[29]Should they be deemed feasible, NMAs will be performed to evaluate the comparative clinical effectiveness and safety for each outcome. NMAs will be performed using a Bayesian Markov Chain Monte Carlo (MCMC) simulation. Analyses will follow the techniques outlined in the NICE Decision Support Unit (DSU) Technical Support Document (TSD) 2.[30] Treatment effects will be presented as odds ratios for dichotomous data,

weighted mean differences for continuous data or as hazard ratios, where appropriate. Should both direct and indirect evidence be available for some contrasts, consistency will be assessed following the guidance outlined in NICE DSU TSD 4.[31]

Heterogeneity will be explored via subgroup analysis, although it is not expected that sufficient data for meaningful subgroup analyses will be available for subgroups other than *F508del* mutation status and age group. The Confidence in Network Meta-Analysis (CINeMA) framework will be followed to assess the confidence in the NMA results.[32]

5.9 Methods for estimating qualify of life

The EAG will preferentially extract EQ-5D-3L data to estimate patient quality of life in the RCTs included from the SLR. If no EQ-5D-3L data are reported, then EQ-5D-5L data will be extracted, if available. Similarly, if EQ-5D-5L data are not available, SF-36 data will be extracted. The EAG will also extract baseline and outcome data from the disease specific Cystic Fibrosis Questionnaire-Revised (CFQ-R) adult, child or parent scales, where available, for the overall score and respiratory domains, only.

6 Report methods for synthesising evidence of cost-effectiveness

The purpose of this MTA will be to assess the cost-effectiveness of elexacaftor/tezacaftor/ivacaftor (ELX/TEZ/IVA), lumacaftor/ivacaftor (LUM/IVA) and tezacaftor/ivacaftor (TEZ/IVA) within their marketing authorisations for treating cystic fibrosis. These interventions will be compared with each other and with established clinical management currently used in the NHS. This overarching objective will be met through identification and appraisal of:

- published economic evaluations from the literature or submitted economic evaluations from company submissions.
- HRQoL studies of people with cystic fibrosis including safety data.
- UK specific resource use data, non-UK sources will be considered if there is insufficient UK specific information.

Should the published or submitted economic evaluations prove insufficient to answer the review question; an independent *de novo* economic model will be developed.

6.1 Search strategy

The cost effectiveness search will aim to identify full economic evaluations and HRQoL studies through searches of multiple electronic databases. These databases will include MEDLINE, EMBASE, the International Network of Agencies for Health Technology Assessment (INAHTA) and the CEA Registry. In addition, experts in the field will be contacted with a request for details of published and unpublished studies of which they may have knowledge. Furthermore, identified systematic reviews and the company submission (if supplied) will be searched for additional references.

The Centre for Reviews and Dissemination (CRD) databases will not be searched as the CRD stopped adding records to the Health Technology Assessment (HTA) database in March of 2018 and the Database of Abstracts of Reviews of Effects (DARE) and NHS Economic Evaluations Database (NHS EED) in March of 2015. The EAG considers it unlikely that relevant studies will be missed from the CRD databases as the INAHTA has taken on the responsibility for the production of the HTA database.

To identify cost and resource use evidence, the EAG will search the same sources identified for the economic evidence and treatment of cystic fibrosis, together with NHS reference costs,[33] the Unit Costs of Health and Social Care (Personal Social Services Research Unit [PSSRU]),[34] the Electronic Marketing Information Tool (eMIT)[35] and the British National Formulary (BNF).[36] If the latter do not provide sufficient data to populate the economic model, a separate targeted search on costs and resource use will be conducted.

As an example, the details of the MEDLINE search strategy are presented in full in Appendix 9.1.3. The search strategy for economic evaluations will combine terms capturing the interventions or comparators of interest, the target condition (cystic fibrosis) and the validated CADTH economic evaluations search filter.[26] The search strategy for HRQoL studies will not be restricted by treatment, and will combine terms capturing the target population with HRQoL terms (adapted from Arber *et al.* 2017).[37] No language (to assess volume of foreign language studies available), setting or country restrictions will be applied to the search strategy.

6.2 Inclusion and exclusion criteria

The titles and abstracts of papers identified through the searches outlined above will be independently assessed for inclusion by two reviewers using the following criteria:

Inclusion criteria:

- All economic evaluations (cost-effectiveness, cost-utility, cost-benefit, cost-consequence or cost minimisation);
- Any setting (to be as inclusive as possible);
- Intervention or comparators as defined at the beginning of Section 6 (as well as in Section 4.2 and Section 4.4);
- Study outcomes reported in terms of life-years gained (LYG) or quality adjusted life years (QALYs);
- Full publications in English (numbers of relevant non-English studies will be reported);
- Quality of life studies in cystic fibrosis.

Exclusion criteria:

- Abstracts with insufficient methodological details;
- Systematic reviews.

6.3 Data extraction strategy

Data will be extracted by one reviewer using a standardised data extraction table and checked by a second reviewer for accuracy. Disagreement will be resolved by discussion; however, if no consensus is reached, a third reviewer will be consulted. In cases where there are missing data or unclear reporting in the published or submitted economic evidence or quality of life studies, attempts will be made to contact authors. Authors will be asked to respond within two weeks of initial contact, after which time, unless the author has confirmed that they can supply the requested data, it will be assumed the data are not available. Should the study with key missing data have been sponsored by the Company, the Company, rather than the study authors, will be contacted to gain further details in the first instance.

Studies published in the UK will be reported in greater detail than non-UK studies as they are more likely to be relevant to the NHS. If sufficient EQ-5D data are found during the searches for utility data, the EAG will restrict the data extraction to EQ-5D data. Table 6 and Table 7 show the health economic evaluation and quality of life data that will be sought from each study. In addition, the reason for exclusion of each excluded study will be documented (Table 8).

Table 6. Health economic evaluation data extraction table

Author, year, country	Perspective, discounting & cost year	Model type	Patient population	Intervention/ comparator	Outcomes	Cost-effectiveness results incl. uncertainty
Reviewer's comments:						
Abbreviations: QALY, quality adjusted life year.						

Table 7. Quality of life data extraction table

Author, year, country	Sample size	Patient population	Instrument (Valuation)	Utility results
Reviewer's comments:				
Abbreviations:				

Table 8. Data exclusion table

Bibliographic reference	Reasons for exclusion
Abbreviations:	

6.4 Quality assessment strategy

All published economic evaluations in English identified within the review and any economic evaluations submitted by companies to NICE will be subject to critical appraisal. The methodological quality of each economic evaluation will be assessed against the Drummond checklist for economic evaluations[38] (see Table 26 Appendix **Error! Reference source not found.**). Each economic evaluation will be assessed by one health economist and the details of the assessment checked by a second health economist. Disagreement will be resolved by discussion; however, if no consensus is reached, a third health economist will be consulted.

6.5 Methods of analysis

6.5.1 Published and submitted economic evaluations

A narrative summary and accompanying data extraction tables will be presented to summarise evidence from published or submitted economic evaluations.

6.5.2 Economic modelling

Should the economic evidence identified prove insufficient to answer the review question; a *de novo* economic model will be developed using an appropriate software package. The structure of the *de novo* model will be informed by economic evaluations identified in the published literature and company submissions; all structural assumptions will be documented and accompanying rationales provided. It is anticipated that the models developed for TA398[17] and TA266[15] will help inform the *de novo* modelling approach.

The clinical effectiveness parameters required for the economic model will be informed by the review of clinical effectiveness discussed in Section 5. In addition, parameters such as estimates of health-related quality of life (HRQoL) (utility data) will be informed by the published literature, identified in the systematic review. If the EAG is provided with relevant unpublished HRQoL data from the company, these will be assessed for inclusion in the economic model. In cases where parameters required to populate the model are not available from published studies or company submissions, expert clinical opinion will be considered.

As per the NICE methods guide,[39] the cost effectiveness of the interventions will be estimated in terms of an incremental cost per QALY, as well as the net health benefit (NHB). As there are several technologies under assessment for this MTA, NHB may be informative when applying decision-making modifiers. Net health benefits will be presented using values placed on a QALY gain of £20,000 and £30,000. Full incremental analysis will be presented when there are multiple potential interventions that can be used in the same patient population (e.g., based on genotype group).

As appropriate, cost data will be obtained from NHS reference costs[33], Unit Costs of Health and Social Care,[34] eMit[35], BNF,[36] and published sources or company submissions. Costs will consist of direct medical costs (e.g. drug costs and cost of adverse events, monitoring and administering treatment) and direct non-medical costs (e.g. healthcare professional's costs). Resource use and costs will be valued from the NHS and Personal Social Services perspective. Both costs and outcomes will be discounted at 3.5% per annum after the first year in accordance with NICE methods guide.[39] The time horizon for the economic analysis will be lifetime to reflect any differences in costs or outcomes between the technologies under comparison.

6.6 Methods for estimating quality of life

As discussed in Section 4, prior to the introduction of CFTR modulators, the goal of CF treatment was to manage symptoms, in particular to improve lung function, and prevent and/or reduce complications associated with the disease. In contrast, CFTR modulators, such as the interventions under consideration for this MTA, aim to address the underlying cause of cystic fibrosis.[40] Ideally, evidence of the impact of treatments included in this review on HRQoL will be available directly from identified trials. In the absence of such evidence, any *de novo* economic model may use indirect evidence on quality of life from alternative literature sources, such as related technology appraisals or clinical guidelines. In accordance with NICE methods guide,[39] utility values will be taken from studies that have been based on the general population preferences elicited using a choice-based method. Preference will be given to EQ-5D values for measuring HRQoL in adults. Utility data will also be adjusted for age using data from the Health Survey of England.[41]

6.7 Analysis of uncertainty

As a standard, the model will be probabilistic; that is, all appropriate input parameters will be entered as probability distributions to reflect their imprecision and Monte Carlo simulation will be used to reflect this uncertainty in the model's results. In addition, uncertainty will also be explored through one-way sensitivity analysis. The outputs of probabilistic sensitivity analysis (PSA) will be presented in the cost-effectiveness plane and through the use of cost-effectiveness acceptability curves. One-way sensitivity analysis outputs will be presented in tables and tornado diagrams. Where possible, uncertainty pertaining to the structural assumptions used will be assessed in scenario analyses using alternative structural assumptions.

7 Handling the company submission(s)

All data submitted by the company will be considered if received by the EAG by the end of February 2023. Data arriving after this date will not be considered. If the data meet the inclusion criteria for the review they will be extracted and quality assessed in accordance with the procedures outlined in this protocol. Any economic evaluations included in the company submission, provided it complies with NICE's advice on presentation, will be assessed for clinical validity, reasonableness of assumptions and appropriateness of the data used in the economic model. If the EAG judge that the existing economic evidence is not robust, then further work will be undertaken, either by adapting what already exists or developing a *de-novo* model. The EAG is aware of additional data from the CF Registry becoming available in June 2023. The released data will be reviewed by the EAG and, if

appropriate, incorporated into the economic model. Data arriving from the CF Registry past the end of June may not be considered.

Any 'commercial in confidence' data taken from a company's submission, and specified as confidential in the supplied check list, will be highlighted in blue and underlined in the assessment report (followed by an indication of the relevant company name, for example, in brackets). Any 'academic in confidence' data taken from a company's submission, and specified as confidential in the supplied check list, will be highlighted in yellow and underlined in the assessment report. Any 'depersonalised' data taken from a company submission, and specified as confidential in the check list, will be highlighted in pink and underlined in the assessment report (followed by an indication of the relevant company name, for example, in brackets).

8 Competing interests of authors

None.

9 Appendices

9.1 Search strategies

9.1.1 EAG database searches

Table 9. EAG search strategy for MEDLINE via Ovid.

#	Searches	Results 09/02/2023
1	exp Cystic Fibrosis/	39398
2	cystic fibrosis.tw.	49115
3	(fibrocystic adj10 disease adj10 pancreas).tw.	215
4	mucoviscidos$.tw.	1471
5	(cystic$ adj10 fibros$).tw.	49960
6	exp Cystic Fibrosis Transmembrane Conductance Regulator/	10551
7	(f508del or deltaF508 or CFTR).mp.	13052
8	or/1-7	58100
9	(ivacaftor or Kalydeco or VX*770 or "VX 770" or "873054 44 5" or IVA).ti,ab.	13212
10	(lumacaftor or VX*809 or "VX 809" or VRT826809 or "VRT 826809" or "936727 05 8" or "EGP8L81APK" or LUM).ti,ab.	5229

11	(elexacaftor or VX*445 or "VX 445" or "2216712 66 0" or RRN67GMB0V or "WHO 11180" or WHO11180 or ELX).ti,ab.	4592
12	(tezacaftor or VX*661 or "VX 661" or "1152311 62 0" or 8RW88Y506K or TEZ).ti,ab.	4743
13	(Orkambi or "1815566 23 4" or S900006790 or SCHEMBL19410545).ti,ab.	57
14	(Symkevi or Symdeko or "1969264 35 4" or "D11042").ti,ab.	5
15	(Trikafta or Kaftrio or "2398469 65 1").ti,ab.	54
16	or/9-15	14048
17	8 and 16	1182
18	exp animals/ not humans.sh.	5091444
19	17 not 18	1153
Database(s): Ovid MEDLINE(R) and Epub Ahead of Print, In-Process, In-Data-Review & Other Non-Indexed Citations, Daily and Versions 1946 to February 08, 2023 The number of hits are reported from a search during the protocol development stage for illustration only. The search will be re-performed once the project commences.		

Table 10. EAG search strategy for Embase via Ovid.

#	Searches	Results 09/02/2023
1	exp Cystic Fibrosis/	80856
2	cystic fibrosis.tw.	75473
3	(fibrocystic adj10 disease adj10 pancreas).tw.	17
4	mucoviscidos$.tw.	1029
5	(cystic$ adj10 fibros$).tw.	76616
6	exp Cystic Fibrosis Transmembrane Conductance Regulator/	9573
7	(f508del or deltaF508 or CFTR).mp.	22091
8	or/1-7	99131
9	exp ivacaftor/	2996
10	(ivacaftor or Kalydeco or VX*770 or "VX 770" or "873054 44 5" or IVA).ti,ab.	22365
11	exp lumacaftor/	1272
12	(lumacaftor or VX*809 or "VX 809" or VRT826809 or "VRT 826809" or "936727 05 8" or "EGP8L81APK" or LUM).ti,ab.	8602
13	exp elexacaftor/	260

14	(elexacaftor or VX*445 or "VX 445" or "2216712 66 0" or RRN67GMB0V or "WHO 11180" or WHO11180 or ELX).ti,ab.	7381
15	exp tezacaftor/	492
16	(tezacaftor or VX*661 or "VX 661" or "1152311 62 0" or 8RW88Y506K or TEZ).ti,ab.	7531
17	(Orkambi or "1815566 23 4" or S900006790 or SCHEMBL19410545).ti,ab.	231
18	(Symkevi or Symdeko or "1969264 35 4" or "D11042").ti,ab.	65
19	(Trikafta or Kaftrio or "2398469 65 1").ti,ab.	163
20	or/9-19	24852
21	8 and 20	4275
22	21 not ((exp animal/ or nonhuman/) not exp human/)	4073
Database(s): Embase 1974 to February 08, 2023 The number of hits are reported from a search during the protocol development stage for illustration only. The search will be re-performed once the project commences.		

9.1.2 Cystic Fibrosis Trials Register

The register is maintained by the Cochrane Cystic Fibrosis and Genetic Disorders Group, and is compiled from database searches of MEDLINE (weekly searches from 1966 to present), Embase (searched 1974 to August 1995) and CENTRAL (searched on each new issue of the Cochrane library), and also includes records hand-searched from the Journal of Cystic Fibrosis, Pediatric Pulmonology and conference abstracts. Full details of the current search strategies used to compile the Cystic Fibrosis Trials Register are given in Table 11 and Table 12. Records identified from the searches used to generate the Cystic Fibrosis Trials Register are manually screened by an information specialist, and only references that are RCTs or possible RCTs are included in the register. The EAG considers the Cystic Fibrosis Trials Register to provide an up-to-date, comprehensive and systematic search of randomised control trials relating to cystic fibrosis, which includes all interventions and comparators relevant to the current MTA.

Table 11. Cochrane Cystic Fibrosis and Genetic Disorders Group CENTRAL search strategy used to compile the Cystic Fibrosis Trial Register

ID	Search Term
1	(cystic next fibros*)
2	CYSTIC FIBROSIS

3	CYSTIC FIBROSIS TRANSMEMBRANE CONDUCTANCE REGULATOR
4	Cftr
5	(fibrocystic and pancrea*)
6	mucoviscido*
7	(#1 or #2 or #3 or #4 or #5 or #6)
8	(#7 and (not sr-cf))

Searches are performed on each new issue of the Cochrane Library, which is published monthly. Search terms shown in capitals are MeSH terms.

Table 12. Cochrane Cystic Fibrosis and Genetic Disorders Group MEDLINE search strategy used to compile the Cystic Fibrosis Trial Register

ID	Search Term
1	randomized controlled trial.pt.
2	controlled clinical trial.pt.
3	randomized.ab.
4	placebo.ab.
5	drug therapy.fs.
6	randomly.ab.
7	trial.ab.
8	groups.ab.
9	1 or 2 or 3 or 4 or 5 or 6 or 7 or 8
10	exp animals/ not humans.sh
11	9 not 10
12	exp Cystic Fibrosis/
13	cystic fibrosis.tw.
14	fibrocystic adj10 disease adj10 pancreas.tw.
15	mucoviscidos$.tw.
16	(cystic$ adj10 fibros$).tw.
17	or/12-16

18	11 and 17

The current search strategy for Ovid MEDLINE is provided. Other strategies have been used previously and searched on SilverPlatter CD-Rom, from 1966 to 2002 and monthly on Ovid from 2003 to the present.

Table 13. EAG search strategy of CENTRAL to identify records for inclusion in the systematic literature review, using the Cystic Fibrosis Trial Register (SR-CF filter)

ID	Search	Hits (13/02/2023)
1	SR-CF	8506
2	(ivacaftor* OR Kalydeco OR VX*770 OR "VX 770" OR "873054 44 5" OR IVA)	1820
3	(lumacaftor OR VX*809 OR "VX 809" OR VRT826809 OR "VRT 826809" OR "936727 05 8" OR "EGP8L81APK" OR LUM)	604
4	(elexacaftor OR VX*445 OR "VX 445" OR "2216712 66 0" OR RRN67GMB0V OR "WHO 11180" OR WHO11180 OR ELX)	96
5	(tezacaftor OR VX*661 OR "VX 661" OR "1152311 62 0" OR 8RW88Y506K OR TEZ)	439
6	(Orkambi OR "1815566 23 4" OR S900006790 OR SCHEMBL19410545)	27
7	(Symkevi OR Symdeko OR "1969264 35 4" OR "D11042")	8
8	(Trikafta OR Kaftrio OR "2398469 65 1")	8
9	#2 OR #3 OR #4 OR #5 OR #6 OR #7 OR #8	2577
10	#1 AND #9	333

The number of hits are reported from a search during the protocol development stage for illustration only. The search will be re-performed once the project commences.

9.1.3 EAG search strategies for economic evaluations and HRQoL

Table 14. EAG economic evaluations search strategy via MEDLINE

#	Searches	Results 09/02/23
1	Economics/	27491
2	exp "Costs and Cost Analysis"/	262563
3	Economics, Nursing/	4013
4	Economics, Medical/	9239

5	Economics, Pharmaceutical/	3093
6	exp Economics, Hospital/	25676
7	Economics, Dental/	1920
8	exp "Fees and Charges"/	31303
9	exp Budgets/	14075
10	budget*.ti,ab,kf.	35101
11	(economic* or cost or costs or costly or costing or price or prices or pricing or pharmacoeconomic* or pharmaco-economic* or expenditure or expenditures or expense or expenses or financial or finance or finances or financed).ti,kf.	273884
12	(economic* or cost or costs or costly or costing or price or prices or pricing or pharmacoeconomic* or pharmaco-economic* or expenditure or expenditures or expense or expenses or financial or finance or finances or financed).ab. /freq=2	367915
13	(cost* adj2 (effective* or utilit* or benefit* or minimi* or analy* or outcome or outcomes)).ab,kf.	202532
14	(value adj2 (money or monetary)).ti,ab,kf.	2950
15	exp models, economic/	16176
16	economic model*.ab,kf.	4078
17	markov chains/	15900
18	markov.ti,ab,kf.	28160
19	monte carlo method/	31914
20	monte carlo.ti,ab,kf.	58636
21	exp Decision Theory/	12998
22	(decision* adj2 (tree* or analy* or model*)).ti,ab,kf.	35530
23	or/1-22	873651
24	exp Cystic Fibrosis/	39398
25	cystic fibrosis.tw.	49115
26	(fibrocystic adj10 disease adj10 pancreas).tw.	215
27	mucoviscidos$.tw.	1471
28	(cystic$ adj10 fibros$).tw.	49960

29	exp Cystic Fibrosis Transmembrane Conductance Regulator/	10551
30	(f508del or deltaF508 or CFTR).mp.	13052
31	or/24-30	58100
32	(ivacaftor* or Kalydeco or VX*770 or "VX 770" or "873054 44 5" or IVA).mp.	13709
33	(lumacaftor or VX*809 or "VX 809" or VRT826809 or "VRT 826809" or "936727 05 8" or "EGP8L81APK" or LUM).mp.	5742
34	(elexacaftor or VX*445 or "VX 445" or "2216712 66 0" or RRN67GMB0V or "WHO 11180" or WHO11180 or ELX).mp.	4747
35	(tezacaftor or VX*661 or "VX 661" or "1152311 62 0" or 8RW88Y506K or TEZ).mp.	4942
36	(Orkambi or "1815566 23 4" or S900006790 or SCHEMBL19410545).mp.	70
37	(Symkevi or Symdeko or "1969264 35 4" or "D11042").mp.	8
38	(Trikafta or Kaftrio or "2398469 65 1").mp.	74
39	or/32-38	14859
40	23 and 31 and 39	54

Database(s): Ovid MEDLINE(R) ALL 1946 to February 8th, 2023

The number of hits are reported from a search during the protocol development stage for illustration only. The search will be re-performed once the project commences.

Table 15. EAG HRQoL search strategy, via MEDLINE

#	Searches	Results 09/02/23
1	Quality-Adjusted Life Years/	15402
2	Value of Life/	5800
3	(qaly$ or qald$ or qale$ or qtime$).ti,ab,kf.	14064
4	(quality adjusted or adjusted life year$).ti,ab,kf.	22413
5	disability adjusted life.ti,ab,kf.	4999
6	daly$1.ti,ab,kf.	4405

7	((index adj3 wellbeing) or (quality adj3 wellbeing) or qwb).ti,ab,kf.	1130
8	(multiattribute$ or multi attribute$).ti,ab,kf.	1265
9	(utility adj3 (score$1 or scoring or valu$ or measur$ or evaluat$ or scale$1 or instrument$1 or weight or weights or weighting or information or data or unit or units or health$ or life or estimat$ or elicit$ or disease$ or mean or cost$ or expenditure$1 or gain or gains or loss or losses or lost or analysis or index$ or indices or overall or reported or calculat$ or range$ or increment$ or state or states or status)).ti,ab,kf.	42360
10	utility.ab. /freq=2	22657
11	utilities.ti,ab,kf.	9075
12	disutili$.ti,ab,kf.	601
13	(HSUV or HSUVs).ti,ab,kf.	105
14	health$1 year$1 equivalent$1.ti,ab,kf.	40
15	(hye or hyes).ti,ab,kf.	77
16	(hui or hui1 or hui2 or hui3).ti,ab,kf.	1913
17	(illness state$1 or health state$1).ti,ab,kf.	8103
18	(euro qual or euro qual5d or euro qol5d or eq-5d or eq5-d or eq5d or euroqual or euroqol or euroqual5d or euroqol5d).ti,ab,kf.	15788
19	(eq-sdq or eqsdq).ti,ab,kf.	1
20	(short form$ or shortform$).ti,ab,kf.	42627
21	(sf36$ or sf 36$ or sf thirtysix or sf thirty six).ti,ab,kf.	26008
22	(sf6 or sf 6 or sf6d or sf 6d or sf six or sfsix or sf8 or sf 8 or sf eight or sfeight).ti,ab,kf.	3893
23	(sf12 or sf 12 or sf twelve or sftwelve).ti,ab,kf.	6082
24	(sf16 or sf 16 or sf sixteen or sfsixteen).ti,ab,kf.	33

25	(sf20 or sf 20 or sf twenty or sftwenty).ti,ab,kf.	354
26	(15D or 15-D or 15 dimension).ti,ab,kf.	6011
27	(standard gamble$ or sg).ti,ab,kf.	13719
28	(time trade off$1 or time tradeoff$1 or tto or timetradeoff$1).ti,ab,kf.	2309
29	or/1-28	183358
30	exp Cystic Fibrosis/	39398
31	cystic fibrosis.tw.	49115
32	(fibrocystic adj10 disease adj10 pancreas).tw.	215
33	mucoviscidos$.tw.	1471
34	(cystic$ adj10 fibros$).tw.	49960
35	exp Cystic Fibrosis Transmembrane Conductance Regulator/	10551
36	(f508del or deltaF508 or CFTR).tw.	11374
37	or/30-36	58018
38	29 and 37	312
Database(s): Ovid MEDLINE(R) ALL 1946 to February 8th, 2023 The number of hits are reported from a search during the protocol development stage for illustration only. The search will be re-performed once the project commences.		

9.2 List of outcomes identified as potentially relevant for extraction

Table 16. Expanded list of outcomes and corresponding data that will be extracted as part of the SLR, should the outcome be required for economic modelling.

Outcomes included in NICE final scope[13]	Data to be extracted
Mortality	• All-cause mortality
Lung function	Absolute and change from baseline: • ppFEV1 • Forced vital capacity (FVC) • Forced expiratory flow (FEF) at 25–75% of FVC • Any other spirometry measure • Lung clearance index 2.5

	• Radiological measures of lung disease • Any other measure of lung function • Lung transplant • Need for lung transplant • Time until lung transplant
Respiratory symptoms	Absolute and change from baseline: • CFQ-R respiratory domain
Body mass index	Absolute and change from baseline: • Weight • Height • Weight for age z-score • BMI • BMI for age z-score
Pulmonary exacerbations	• Study reported definition of pulmonary exacerbation • Any measure of absolute or relative frequency or time until:Pulmonary exacerbations • Pulmonary exacerbations requiring IV antibiotics or hospitalisation • Any other measure of severity of exacerbation
Pulmonary bacterial colonisation	Trial defined frequency or relative frequency of: • *Pseudomonas* colonisation • Other pulmonary bacterial colonisation, by pathogen, including *S. aureus and B. cepacia*
Frequency and severity of acute infections	Trial defined frequency or relative frequency of: • Pulmonary exacerbations

	• Pulmonary exacerbations requiring IV antibiotics or hospitalisation • Acute infections • Acute infections by severity

Need for hospitalisation and other treatments	Trial reported:
	• Hospitalisation
	  ○ Number of days
	  ○ Number of episodes
	  ○ Time until next hospitalisation
	  ○ Planned hospitalisation vs unplanned hospitalisation
	  ○ Intensive care unit use
	• Other CF treatment use
	• Other non-CF treatment use

Adverse effects of treatment	Number of people with • Any serious adverse event (Grade 3 and above) • Any serious treatment-emergent adverse event (Grade 3 and above) • Any trial-defined adverse event of special interest • Adverse events of particular importance as identified by the EAG's clinical experts, including: • Adverse events relating to the liver • Cataracts or lens opacities • Hypertension • Any other adverse event
Health-related quality of life	Absolute and change from baseline: • EQ-5D-5L and EQ-5D-3L, including sub-scores where reported • Cystic Fibrosis Questionnaire-Revised (CFQ-R), including sub-domains • CFQ Child • CFQ-Parent If no EQ-5D measure is reported, the EAG will extract SF-36 data if available.

Sweat chloride	Absolute and change from baseline: • Sweat chloride
Not included in NICE scope	• Any reported pancreatic outcomes • Development of CF-diabetes •

Abbreviations: BMI: body mass index; CF: cystic fibrosis; CFQ-R: Cystic Fibrosis Questionnaire-Revised; CFTR: cystic fibrosis transmembrane regulator; EAG: external assessment group; EQ-5D: EuroQol five-dimensions: HR: hazard ratio; IV: intravenous; MA: meta-analysis; $ppFEV_1$: percent predicted forced expiratory volume in one second; RCT: randomised controlled trial; SLR: systematic literature review.

9.3 Draft data extraction forms

Table 17. EAG draft table for data extraction of study characteristics.

Characteristic	Description
Study name	
Study references (insert citations from reference manager)	
Country(ies) where the clinical trial was conducted	
Multicentre trial (number, location)	
Trial sponsor(s)	
Clinical trial start date	
Clinical trial end date	
Trial design (e.g. parallel, crossover, or cluster trial)	
Trial duration (treatment duration and follow-up)	
Trial intervention 1 (dose and frequency)	
Trial intervention 2 (dose and frequency)	
…	
Trial intervention n (dose and frequency)	
Inclusion criteria	
Exclusion criteria	
Concomitant medications permitted	
Concomitant medications not permitted	
Outcomes reported	
Subgroups reported	
Are data presented concerning relationship between baseline lung function and clinical effectiveness	

(provide details and location in the sources where these data are reported)	

Note: Data extraction to be performed in Microsoft Excel. The Word tables are used to illustrate the data that will be extracted. Additional categories may be added during the review if deemed necessary for the economic model.

Table 18. EAG draft table for data extraction of patient baseline characteristics.

Characteristic	Intervention (N=)	Comparator (N=)
Mean or median age at baseline, years		
Gender, n (%)		
• *Male, n (%)*		
• *Female, n (%)*		
• *Other, n (%)*		
• *Not reported, n (%)*		
Geographic region		
• *North America, n (%)*		
• *Europe, n (%)*		
• *Asia, n (%)*		
• *Australia, n (%)*		
• *Other, n (%)*		
Race, n (%)		
• *White, n (%)*		
• *Black or African American, n (%)*		
• *Asian, n (%)*		
• *Other, n (%)*		
• *Not reported, n (%)*		
F508del homozygous, n (%)		
F508del heterozygous, n (%)		
• Non *F508del* mutation 1 (class)		
• Non *F508del* mutation 2		
• …		
• Non *F508del* mutation n		
Weight, kg		
BMI		
Weight-for-age z score		
$ppFEV_1$		
Lung clearance index 2.5		

Sweat chloride, mmol/L		
Pancreatic insufficient		
CF-Diabetes		
Infection at baseline (by pathogen type)		
CFTR-modulator use at baseline		
Socioeconomic status (any measure)		
HRQoL		
EQ-5D-5L total score (EQ-5D-3L if reported instead)		
CFQ-R/ CFQ Child/ CFQ-Parent		
• Respiratory		
Prior treatment		
Dornase alfa		
Azithromycin		
Inhaled antibiotic		
Brocnchodilator		
Inhaled corticosteroids		
Inhaled hypertonic saline		
CFTR-modulator (by type, if available)		
Other treatment 1		
Other treatment 2		
…		
Other treatment n		

Note: Data extraction to be performed in Microsoft Excel. The Word tables are used to illustrate the data that will be extracted. Additional categories may be added during the review if deemed necessary for the economic model.

Abbreviations: BMI: body mass index; CF: cystic fibrosis; CFQ-R: Cystic Fibrosis Questionnaire-Revised; CFTR: cystic fibrosis transmembrane regulator; cm: centimetres; EQ-5D: EuroQol five-dimensions: kg: kilograms; ppFEV$_1$: percent predicted forced expiratory volume in one second.

Table 19. EAG draft table for data extraction of information on interventions administered in clinical effectiveness studies

Characteristic	Intervention (N=)	Comparator (N=)
Study name		
Drug name		
Dose		
Frequency		
Relative dose intensity		
Missed doses		
Mean dose received		

Wastage		
Dose interruptions		
Note: Data extraction to be performed in Microsoft Excel. The Word tables are used to illustrate the data that will be extracted. Additional categories may be added during the review if deemed necessary for the economic model.		

Table 20. EAG draft table for data extraction of patient disposition.

Characteristic	Intervention (N=)	Comparator (N=)
Study name		
All subjects		
Randomised		
Safety set		
Full analysis set/ITT population		
m-ITT population		
Completed treatment		
Discontinued treatment		
• *Reason*		
• *Reason*		
• *Reason*		
• *Reason*		
Completed study		
Discontinued study		
• *Reason*		
• *Reason*		
• *Reason*		
• *Reason*		
Note: Data extraction to be performed in Microsoft Excel. The Word tables are used to illustrate the data that will be extracted. Additional categories may be added during the review if deemed necessary for the economic model. Abbreviations: ITT: intent-to-treat.		

Table 21. EAG draft table for data extraction of concomitant medication use.

Medication	Intervention (N=)	Comparator (N=)
Study name		
Medication 1		
Medication 2		
Medication 3		
…		
Medication n		

Note: Data extraction to be performed in Microsoft Excel. The Word tables are used to illustrate the data that will be extracted. Additional categories may be added during the review if deemed necessary for the economic model.

Table 22. EAG draft table for data extraction of continuous outcomes of interest.

Outcome XX, Week XX	Intervention (N=)	Comparator (N=)
Study name		
Baseline mean (SD), 95% CI		
N in analysis		
Mean change from baseline		
p-value within treatment		
Mean difference from reference		
p-value vs reference		

Note: Data extraction to be performed in Microsoft Excel. The Word tables are used to illustrate the data that will be extracted. Additional categories may be added during the review if deemed necessary for the economic model.

Abbreviations: CI: confidence interval; SD: standard deviation

Table 23. EAG draft table for data extraction of dichotomous outcomes of interest

Outcome XX, Week XX	Intervention (N=)	Comparator (N=)
Study name		
Participants with events		
N events		
Event rate per year		
Rate ratio / Hazard ratio / Odds ratio, 95% CI		
p-value vs reference		

Note: Data extraction to be performed in Microsoft Excel. The Word tables are used to illustrate the data that will be extracted. Additional categories may be added during the review if deemed necessary for the economic model.

Table 24. EAG draft table for data extraction of adverse events

Week XX	Intervention (N=)	Comparator (N=)
Study name		
SEAs (Grade 3 or above)		
Any		
SAE 1		
SAE 2		
…		

SAE n		
Serious TEAEs (Grade 3 or above)		
Any		
Serious TEAE 1		
Serious TEAE 2		
…		
Serious TEAE n		
AE of special interest (trial defined)		
Any		
AE of special interest 1		
AE of special interest 2		
…		
AE of special interest n		
Liver AEs		
Any		
Liver AE 1		
Liver AE 2		
…		
Liver AE n		
Cataracts (lens opacities)		
Hypertension		

Note: Data extraction to be performed in Microsoft Excel. The Word tables are used to illustrate the data that will be extracted. Additional categories may be added during the review if deemed necessary for the economic model.

Abbreviations: SAE: serious adverse event; TEAE: treatment-emergent adverse event.

Table 25. EAG draft table for the quality assessment of clinical effectiveness studies

Component	Rating for risk of bias			Comments
	Low	Unclear	High	
Study name				
Random sequence generation				
Allocation concealment				
Blinding (who [participants, personnel], and method)				
Blinding of outcome assessment				
Incomplete outcome data (people who discontinued/ changed treatment, people lost to follow-up)				
Selective reporting				

Note: Data extraction to be performed in Microsoft Excel. The Word tables are used to illustrate the data that will be extracted.

Table 26. Drummond checklist

Item	Yes	No	Not clear	Not appropriate
Study design				
1. The research question is stated.	☐	☐	☐	☐
2. The economic importance of the research question is stated.	☐	☐	☐	☐
3. The viewpoint(s) of the analysis are clearly stated and justified.	☐	☐	☐	☐
4. The rationale for choosing alternative programmes or interventions compared is stated.	☐	☐	☐	☐
5. The alternatives being compared are clearly described.	☐	☐	☐	☐
6. The form of economic evaluation used is stated.	☐	☐	☐	☐
7. The choice of form of economic evaluation is justified in relation to the questions addressed.	☐	☐	☐	☐
Data collection				
8. The source(s) of effectiveness estimates used are stated.	☐	☐	☐	☐
9. Details of the design and results of effectiveness study are given (if based on a single study).	☐	☐	☐	☐
10. Details of the methods of synthesis or meta-analysis of estimates are given (if based on a synthesis of a number of effectiveness studies).	☐	☐	☐	☐
11. The primary outcome measure(s) for the economic evaluation are clearly stated.	☐	☐	☐	☐
12. Methods to value benefits are stated.	☐	☐	☐	☐
13. Details of the subjects from whom valuations were obtained were given.	☐	☐	☐	☐
14. Productivity changes (if included) are reported separately.	☐	☐	☐	☐
15. The relevance of productivity changes to the study question is discussed.	☐	☐	☐	☐
16. Quantities of resource use are reported separately from their unit costs.	☐	☐	☐	☐

17. Methods for the estimation of quantities and unit costs are described.	☐	☐	☐	☐
18. Currency and price data are recorded.	☐	☐	☐	☐
19. Details of currency of price adjustments for inflation or currency conversion are given.	☐	☐	☐	☐
20. Details of any model used are given.	☐	☐	☐	☐
21. The choice of model used and the key parameters on which it is based are justified.	☐	☐	☐	☐
Analysis and interpretation of results				
22. Time horizon of costs and benefits is stated.	☐	☐	☐	☐
23. The discount rate(s) is stated.	☐	☐	☐	☐
24. The choice of discount rate(s) is justified.	☐	☐	☐	☐
25. An explanation is given if costs and benefits are not discounted.	☐	☐	☐	☐
26. Details of statistical tests and confidence intervals are given for stochastic data.	☐	☐	☐	☐
27. The approach to sensitivity analysis is given.	☐	☐	☐	☐
28. The choice of variables for sensitivity analysis is justified.	☐	☐	☐	☐
29. The ranges over which the variables are varied are justified.	☐	☐	☐	☐
30. Relevant alternatives are compared.	☐	☐	☐	☐
31. Incremental analysis is reported.	☐	☐	☐	☐
32. Major outcomes are presented in a disaggregated as well as aggregated form.	☐	☐	☐	☐
33. The answer to the study question is given.	☐	☐	☐	☐
34. Conclusions follow from the data reported.	☐	☐	☐	☐
35. Conclusions are accompanied by the appropriate caveats.	☐	☐	☐	☐

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