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This report

Abstract

Ivacaftor for the treatment of patients with cystic fibrosis and the G551D mutation: a systematic review and cost-effectiveness analysis

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Background: Ivacaftor (Kalydeco®, Vertex Pharmaceuticals) is the first of a new class of drugs that target the underlying protein defect in cystic fibrosis (CF). It is aimed at patients with the G551D (glycine to aspartate change in nucleotide 1784 in exon 11) mutation; 5.7% of patients with CF in the UK have this mutation.

Objectives: To review the clinical effectiveness and cost-effectiveness of ivacaftor for the treatment of CF in patients aged ≥ 6 years who have the G551D mutation.

Methods: Ten databases, including MEDLINE and EMBASE, were searched from inception to July 2012. Studies that evaluated ivacaftor for the treatment of adults and children (≥ 6 years) with at least one G551D mutation were eligible. There were insufficient data to conduct a formal meta-analysis. The manufacturer of ivacaftor, Vertex Pharmaceuticals, submitted a deterministic patient-level simulation model for the assessment of the lifetime cost-effectiveness of ivacaftor. We modified the model where values were not UK-specific or not recent, or where better estimates could be found. The only change to the model structure was the addition of lung transplantations. We changed utility values, annual decline in percentage predicted forced expiratory volume in 1 second (FEV_1), and the baseline exacerbation rate, and used data from the CF Registry to estimate the relation between costs, age and percentage predicted FEV_1. Estimates of treatment effect of ivacaftor came from the clinical effectiveness review. We modelled three scenarios for the longer-term effects of ivacaftor. We also modelled an 'optimistic' scenario for patients aged < 12 years with little lung damage. We conducted a budget impact analysis to estimate the total cost to the NHS of introducing ivacaftor in England.

Results: Three studies were included: a randomised controlled trial (RCT) in adults ($n = 167$) (≥ 12 years), a RCT in children ($n = 26$) (6–11 years), and an open-label extension study of the two RCTs. Both RCTs reported significantly greater changes from baseline in all measures of lung function in patients receiving ivacaftor than in those receiving placebo. The mean difference in change in percentage predicted FEV_1 was 10.5 [95% confidence interval (CI) 8.5 to 12.5] percentage points in the adults' study and 10.0 (95% CI 4.5 to 15.5) percentage points in the children's study at 48 weeks. Improvements in lung function were seen across all subgroups investigated (age, sex, study region and lung function). There were significantly greater improvements in the ivacaftor group than in the placebo group for all outcomes assessed (exacerbations, quality of life, sweat chloride and weight) with the exception of quality of life in children.

Improvements were maintained in the open-label trial. Adverse events were mainly minor and comparable across treatment groups. Both RCTs reported more withdrawals in the placebo group than in the ivacaftor group. The incremental cost-effectiveness ratio varied between £335,000 and £1,274,000 per quality-adjusted life-year gained. The total additional lifetime costs for all eligible CF patients in England ranged from £438M to £479M; the lifetime cost for standard care only was £72M.

Conclusions: The available evidence suggests that ivacaftor is a clinically effective treatment for patients with CF and the G551D mutation; the high cost of ivacaftor may prove an obstacle in the uptake of this treatment. The main priority for further research is the long-term effectiveness of ivacaftor.

Study registration: This study is registered as PROSPERO CRD42012002516.

Source of funding: The National Institute for Health Research Health Technology Assessment programme.

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BMI	body mass index	HRQoL	health-related quality of life
CF	cystic fibrosis	HTA	Health Technology Assessment
CFQ-R	Cystic Fibrosis Questionnaire Revised	ICER	incremental cost-effectiveness ratio
CFRD	cystic fibrosis-related diabetes	IRT	immunoreactive trypsinogen
CFTR	cystic fibrosis transmembrane conductance regulator	i.v.	intravenous
		MD	mean difference
CI	confidence interval	NHS EED	NHS Economic Evaluation Database
CRD	Centre for Reviews and Dissemination	NICE	National Institute for Health and Care Excellence
DARE	Database of Abstracts of Reviews of Effects	PSA	probabilistic sensitivity analysis
		QALY	quality-adjusted life-year
DNA	deoxyribonucleic acid	QoL	quality of life
DNase	dornase alfa	RCT	randomised controlled trial
EQ-5D	European Quality of Life-5 Dimensions	RR	relative risk
		SF-36	Short Form questionnaire-36 items
FDA	US Food and Drug Administration	TIVAD	totally implantable venous access device
FEV_1	forced expiratory volume in 1 second		
		TOBI	tobramycin inhaled solution
G551D	glycine to aspartate change in nucleotide 1784 in exon 11	WHO	World Health Organization

Note

This monograph is based on the Technology Assessment Report produced for the North of England Specialised Commissioning Group: Yorkshire and the Humber Office. The full report contained a number of data that were deemed commercial-in-confidence. The present monograph presents as full a version of the report as possible while retaining readability, but some sections, sentences, tables and figures have been removed.

Scientific summary

Background

Cystic fibrosis (CF) is one of the most common genetic diseases, with over 9000 cases in the UK. It is caused by a single faulty gene which controls movement of salt and water across cells. Most of the illness caused by CF is from diseases of the lungs and repeated infections. The treatment burden associated with this condition is significant, with patients undertaking a minimum of twice-daily chest physiotherapy augmented by nebulised therapies, prophylactic antibiotics, fat-soluble vitamins and pancreatic enzyme supplements. These therapies are time-consuming but non-curative, targeting the symptoms rather than the cause of disease. Median survival of the current UK cohort with CF is estimated as 41 years.

A large number of different mutations have been identified in the gene that causes CF. New treatments are being developed that target specific mutations. Ivacaftor (Kalydeco®, Vertex Pharmaceuticals) is the first of these drugs and targets patients with the G551D (glycine to aspartate change in nucleotide 1784 in exon 11) mutation. Around 5.7% of patients with CF in the UK have this mutation. Ivacaftor has been approved by the US Food and Drug Administration and the European Commission for the treatment of patients with CF (aged ≥ 6 years) who have the G551D mutation. There are currently no similar drugs that target the underlying protein defect in CF on the market.

Objectives

This review aims to appraise the clinical effectiveness and cost-effectiveness of ivacaftor for the treatment of CF in patients aged ≥ 6 years who have at least one G551D mutation in the cystic fibrosis transmembrane conductance regulator (*CFTR*) gene. We will aim to determine the category of patients most likely to benefit from ivacaftor by assessing whether or not the effects vary according to disease severity and age.

Methods

Methods for assessing clinical effectiveness

Ten databases, including MEDLINE and EMBASE, were searched without language, date or publication status restrictions from inception to July 2012. Supplementary searches were undertaken to identify unpublished and ongoing studies and relevant conference proceedings were searched. Studies that evaluated ivacaftor for the treatment of adults and children (≥ 6 years) with at least one G551D mutation were eligible. The primary outcome was lung function. For the review of clinical effectiveness, only randomised controlled trials (RCTs) with at least 3 months' follow-up were included. Criteria were relaxed for consideration of adverse events and longer-term outcomes (> 12 months), for which open-label studies were also eligible.

The results of the searches were screened for relevance independently by two reviewers. Full-text inclusion assessment, data extraction and quality assessment were conducted by one reviewer and checked by a second. RCTs were assessed for methodological quality using the Cochrane risk of bias tool. There were insufficient data to conduct a formal meta-analysis. Data were tabulated and discussed in a narrative review. Dichotomous data were summarised as relative risks and continuous outcomes were summarised as mean differences between treatment groups together with 95% confidence intervals (CIs). Publication bias was not formally assessed owing to the very small number of trials included.

Methods for reviewing cost-effectiveness

A comprehensive search of multiple databases was undertaken to identify literature that might inform the cost-effectiveness study of ivacaftor. We identified cost studies, utility studies and full economic evaluations, that is to say those that explicitly compared different decision options. Studies were included if they contained information that had the potential to inform parameters within the de novo analysis of cost-effectiveness (information on care processes in UK setting, focus on CF population, reported longer-term effect, recent data and relevant outcomes).

Results

Results of clinical effectiveness review

Three studies fulfilled the inclusion criteria: a RCT conducted in adults ($n = 167$) (≥ 12 years) ('adults' study'), a RCT in children ($n = 26$) (6–11 years) ('children's study'), and an open-label extension study of the two included RCTs. All studies were funded by Vertex Pharmaceuticals and were conducted in centres across the USA, Australia and Europe. Ivacaftor tablets were administered at a dose of 150 mg every 12 hours. Both RCTs were 48 weeks in duration. The open-label study is ongoing and is intended to run for 96 weeks. The adults' study was rated as low risk of bias for all criteria. Fewer details were available for the study in children as this has not yet been published in full.

Both RCTs reported significantly greater changes from baseline in all measures of lung function in patients receiving ivacaftor compared with those receiving placebo at all time points assessed. The mean difference in change in percentage predicted forced expiratory volume in 1 second (FEV_1) was 10.5 (95% CI 8.5 to 12.5) percentage points in the adults' study and 10.0 (95% CI 4.5 to 15.5) percentage points in the children's study at 48 weeks. Improvements were maintained in the open-label trial. Subgroup analysis based on age, sex, study region and lung function suggested that improvements in lung function were seen across all subgroups investigated and that there were no significant differences in treatment effect between subgroups. For the children's study, the small number of participants in each subgroup meant that the study may have lacked power to detect significant differences.

The number and severity of pulmonary exacerbations were significantly reduced in the adults' study. The RR of an exacerbation in the ivacaftor group compared with the placebo group was 0.60 (95% CI 0.41 to 0.85) at 48 weeks. The study in children reported that exacerbations were uncommon in both groups. Other outcomes reported in the studies included quality of life (measured using the respiratory domain of the Cystic Fibrosis Questionnaire Revised), sweat chloride and weight. There were significantly greater improvements in the ivacaftor group compared with the placebo group for all outcomes at all time points (24 and 48 weeks) with the exception of quality of life in children, which failed to reach statistical significance.

Adverse events were mainly minor and comparable across treatment groups and studies. The most commonly reported adverse events were pulmonary exacerbation, cough, headache, upper respiratory tract infection and oropharyngeal pain. Both RCTs reported more overall withdrawals and withdrawals due to adverse events in the placebo group than in the ivacaftor group.

Results of cost-effectiveness review

Twenty-three studies were included; these assessed health-care costs, cost-effectiveness and utility to inform the economic model. None of the included studies contained information that would inform social care costs. Included studies were used to validate and contextualise assumptions in the model. Three of the 23 included studies contributed to the model.

Methods for assessing cost-effectiveness

The manufacturer of ivacaftor, Vertex Pharmaceuticals, submitted a deterministic patient-level simulation model for the assessment of the lifetime cost-effectiveness of ivacaftor for the treatment of CF in patients aged ≥ 6 years who have at least one G551D mutation in the *CFTR* gene. We used the manufacturer's model as the basis for our model, making modifications where values used by the manufacturer were not UK-specific or not recent, or where better estimates could be found. The only change made to the structure of the model was the addition of lung transplantations, which were included as ivacaftor has the potential to improve lung function which could lead to fewer lung transplantations. We changed utility values, annual decline in percentage predicted FEV_1, and the baseline exacerbation rate. Additionally, we used data from the CF Registry to estimate the relation between costs, age and percentage predicted FEV_1.

We took estimates of the treatment effect of ivacaftor from the results of the clinical effectiveness review. We modelled three possible scenarios for the longer-term effects of ivacaftor. In all scenarios the percentage predicted FEV_1 of ivacaftor-treated patients stayed stable for 96 weeks and then three alternatives were modelled for ivacaftor-treated patients:

1. Conservative scenario: percentage predicted FEV_1 declined by the same rate as in the standard-care population.
2. Intermediate scenario: percentage predicted FEV_1 declined at 66% of that of standard-care patients.
3. Optimistic scenario: percentage predicted FEV_1 stayed stable over lifetime.

In addition, we modelled a further 'optimistic' scenario for a subgroup of patients aged < 12 years with little lung damage in whom treatment with ivacaftor was assumed to result in no disease progression, resulting in quality of life and mortality rates comparable with the general population and no or limited costs for treatment of CF.

The cost of ivacaftor given by the manufacturer and used in our model was £182,000. All costs and effects were discounted by 3.5% according to the National Institute for Health and Care Excellence methods guide. The model incorporated a lifetime time horizon to estimate outcomes in terms of quality-adjusted life-years (QALYs) and costs from the perspective of the NHS. The impact of uncertainties in the model was explored through probabilistic sensitivity analysis (PSA). We conducted a budget impact analysis to estimate the total cost to the NHS of introducing ivacaftor in England.

Results of cost-effectiveness analyses

The economic evaluation of ivacaftor showed that the incremental cost-effectiveness ratio (ICER) varied between £335,000 (optimistic scenario) and £1,274,000 (conservative scenario) per QALY gained. The variation in ICERs was mostly due to large differences in QALY gains (range 1.27–5.26, discounted) between the scenarios. The additional scenarios for the subgroup of patients aged < 12 years with little lung damage resulted in an ICER of between £154,000 and £201,000 per QALY gained. The results of the PSA suggested that the impact of the remaining parameter uncertainty was small compared with the uncertainty caused by the long-term extrapolation.

We explored the budget impact for England of introducing ivacaftor to all eligible CF patients. We found that the total additional lifetime costs (discounted) for this cohort would amount to £438M to £479M, whereas the lifetime costs for standard care only would amount to £72M.

When the population treated with ivacaftor was limited to patients < 12 years with no or little lung damage, we found that the total additional lifetime costs (discounted) amounted to £51M to £113M, whereas the lifetime costs for standard care would amount to £9M to £17M.

Discussion

Clinical effectiveness

Ivacaftor is an effective treatment for adults and children with the G551D mutation, based on the results of two good-quality RCTs and an open-label follow-up study of participants from both trials. Patients treated with ivacaftor showed improvements in lung function and other outcomes, compared with placebo, at 24 and 48 weeks. Improvements were maintained after 48 weeks' open-label treatment.

The main area of uncertainty relates to the long-term clinical effectiveness of ivacaftor. The longest follow-up data currently available are for (commercial-in-confidence information has been removed) weeks' treatment with ivacaftor in adults and (commercial-in-confidence information has been removed) weeks' treatment in children. The open-label trial is intended to run for 96 weeks. When full data are available from this study, information will be available on the effectiveness for a total of 144 weeks' (just over 2.5 years') treatment with ivacaftor in adults and children. With regard to children, ivacaftor has been evaluated only in those ≥ 6 years old; its potential effect in children younger than this is unclear. The trials evaluated in this review were restricted to patients with the G551D mutation. An ongoing study, not included in this review, is investigating ivacaftor in combination with VX-809, an investigational CFTR corrector, in patients with CF and homozygous for the ΔF508 mutation. If this combination is proved to be clinically effective it would considerably expand the potential usage of ivacaftor as ΔF508 is the most common CF-causing mutation in the UK population.

Cost-effectiveness analysis

Three out of four dimensions on which ivacaftor showed an effect (percentage predicted FEV_1, weight and exacerbations) were taken into account in the model. However, the decrease in the number of exacerbations due to ivacaftor was included in the model only in so far as it affected the survival of the patients. It is reasonable to assume that a reduction in exacerbations also has a direct effect on quality of life and costs. A reduction in exacerbations would therefore lead to an increase in quality of life and a reduction in health-care costs. Owing to a lack of data we were not able to include these effects in the model. In the data source used as input for the cost of CF care by severity no distinction was made between costs for maintenance treatment and costs for exacerbations. If these effects on exacerbations had been taken into account, the gain in QALYs in the ivacaftor group might have been higher and the savings in CF-related health-care costs might have been higher, resulting in a lower ICER.

In the model, quality-of-life values and costs were assumed to be dependent on disease severity defined in terms of percentage predicted FEV_1. However, this clinical measure explains only part of the variation in quality of life and costs. Further refinements of the health states considered would provide a better reflection of the heterogeneity among patients, but as a result it would likely become more difficult to find the data required to inform transitions between health states.

From a cost-effectiveness perspective the long-term effectiveness is an important uncertainty. The various scenarios explored for this long-term effectiveness show a wide range of ICERs. Only when longer-term data on ivacaftor become available will it be clear which of these ICERs is most relevant.

Conclusions

Implications for service provision

The available evidence suggests that ivacaftor is an effective treatment for patients with CF and the G551D mutation. The high cost of ivacaftor may prove an obstacle in the uptake of this treatment; however, given that ivacaftor is an orphan drug, there is no clear benchmark to indicate whether or not ivacaftor should be considered cost-effective. On 19 December 2012 the four Specialised Commissioning Groups in England (North of England, South of England, Midlands and East, and London) announced that

ivacaftor will be funded by the NHS in England for all patients aged ≥ 6 years with CF and the G551D mutation.

Suggested research priorities

The main priority for further research is the long-term effectiveness of ivacaftor. The main uncertainty in the economic model was how the long-term effects of ivacaftor were included in the model. The ongoing open-label trial will go some way to addressing this question but will provide data only on effects up to around 2.5 years of treatment. The effectiveness of ivacaftor in children aged < 6 years is another important question although this may be difficult to address through clinical trials due to the difficulties in conducting trials in young children. The current evidence supports the use of ivacaftor only in patients with at least one G551D mutation. Such patients represent only around 5% of patients with CF. The potential benefit of ivacaftor in patients with other mutations is therefore also an important area for further research. Clinical trials in patients with other mutations are ongoing.

Study registration

This study is registered as PROSPERO CRD42012002516.

Funding

Chapter 1 Background

Description of the health problem

Cystic fibrosis (CF) is the most common, life-threatening, autosomal recessive disorder in Caucasian populations; it has an estimated carrier rate of 1 in 25 and incidence of 1 in 2500 live births.[1] It affects around 9000 people in the UK with a prevalence of 1.37 in 10,000.[2] CF was first recognised as a distinct disease in 1938.[3] It is characterised by abnormal transport of chloride and sodium, leading to thick viscous secretions in the lungs, pancreas, liver, intestine and reproductive tract, and to an increased salt content in sweat gland secretions.[4] Most of the morbidity and mortality is from pulmonary disease, which is characterised by bronchial and bronchiolar obstruction with thick tenacious secretions that are difficult to clear, colonisation by pathogenic bacteria and repeated infections.[1] There is chronic inflammation and progressive lung destruction can lead to bronchiectasis, altered pulmonary function and respiratory failure. CF can also lead to CF-related diabetes (CFRD), male infertility and liver involvement. In addition to repeated chest infections, symptoms of CF can include a troublesome cough, prolonged diarrhoea and poor weight gain.[1] The treatment burden associated with this condition is significant. Patients undertake a minimum of twice-daily chest physiotherapy frequently augmented by nebulised therapies to aid sputum clearance, take prophylactic antibiotics both orally and nebulised twice daily, take fat-soluble vitamins, take pancreatic enzyme supplements owing to pancreatic insufficiency with every fat-containing meal, and live as normal a life as possible. All of these therapies are time-consuming and are non-curative. The recurrent chest infections from which this group suffer are severe and prolonged, resulting in long courses of antibiotics, often intravenous (i.v.), and ultimately irreversible lung damage. The benefits of this regime are seen only if the treatments are adhered to which, given their burden, is not always the case. Most patients with CF eventually succumb to lung disease; however, the life expectancy of patients with CF is currently around 30 years, a considerable increase from around 6 months when the disease was first identified,[4] and is expected to increase to at least 50 years for children born in 2000.[2]

Cystic fibrosis is caused by mutations in the CF transmembrane conductance regulator (*CFTR*) gene, which was discovered in 1989.[5] It sits on chromosome 7, is some 250 kb in length, and encodes a protein of 1480 amino acids. This protein is a chloride channel present at the surface of epithelial cells in multiple organs and is responsible for aiding in the regulation of salt and water absorption and secretion. Over 1000 disease-causing alleles within this gene have been identified, although only 23 have been demonstrated to cause sufficient loss of CFTR function to confer CF disease.[6] The most common mutation is the ΔF508 mutation which is present on around 67% of CF chromosomes worldwide.[7] The G551D (glycine to aspartate change in nucleotide 1784 in exon 11) mutation, which affects approximately 5.7% of patients with CF in the UK,[8] is of interest as a new treatment has been developed targeted specifically at patients with this mutation. CFTR protein channels with the G551D mutation have a greatly reduced fraction of time that the channel spends in the open state, or 'open probability', and, therefore, have limited chloride transport ability.

Diagnosis of cystic fibrosis and genetic testing

Cystic fibrosis can be diagnosed through the sweat test, newborn screening or genetic testing.[6] The sweat test tests for elevated levels of chloride in sweat with a diagnosis of CF being made at levels above 60 mmol/l, and a possible diagnosis of CF at levels above 30 mmol/l. Newborn-screening tests have been introduced in many countries, and have been routine throughout the UK since October 2007.[9] These involve a small sample of blood being taken ('heel prick test') which is tested for high levels of immunoreactive trypsinogen (IRT). If an abnormal IRT value is identified, most newborn-screening programmes perform a combination of deoxyribonucleic acid (DNA) testing to identify known CFTR

mutations and repeat IRT testing.[10] IRT testing alone has a sensitivity of 82–100%, double IRT testing increases sensitivity to 89–100%, and IRT and DNA testing has a sensitivity of 94–100%; specificity is > 99% for all testing strategies.[11] In the UK screening programme, the initial DNA test involves testing for four mutations (ΔF508, G551D, G542X and 621+1G>T); if only one CF mutation is detected, then further DNA analysis based on 29 or 31 mutations is recommended. A range of commercial kits are available for diagnostic testing. The diagnosis is then confirmed using the sweat test.[10]

Treatment of cystic fibrosis

There is no cure for CF and current treatments generally target the complications rather than the cause of the disease.[4] Treatments can be broadly classified as nutritional repletion (e.g. pancreatic enzyme supplementation and nutritional supplementation), relief of airway obstruction (e.g. physiotherapy, drugs to improve sputum clearance, bronchodilators), treatment of airway infection (e.g. antibiotics), suppression of inflammation (e.g. steroids, high-dose ibuprofen) and lung transplantation.[4]

Ivacaftor

Ivacaftor (Kalydeco®, Vertex Pharmaceuticals) is the first in a new class of drugs known as CFTR potentiators that represent a new therapeutic approach to the treatment of patients with CF by targeting the underlying protein defect of CF. The drug facilitates increased chloride transport by potentiating the channel-open probability (or gating) of the G551D-CFTR protein.[12]

Ivacaftor is a designated orphan medicinal product.[13] It has been approved by the US Food and Drug Administration (FDA)[14] and European Commission[15] for the treatment of CF in patients aged ≥ 6 years who have the G551D mutation in the *CFTR* gene. No active comparator agents that target the underlying CFTR protein defect in CF disease exist.[16]

Chapter 2 Objective

This review aims to appraise the clinical effectiveness and cost-effectiveness of ivacaftor (150 mg twice-daily tablet for oral administration) for the treatment of CF in patients aged ≥ 6 years who have at least one G551D mutation in the *CFTR* gene. We will aim to determine the category of patients most likely to benefit from ivacaftor by assessing whether or not the effects vary according to disease severity and age.

Chapter 3 Systematic review methods

Methods for assessing clinical effectiveness

We conducted a systematic review of the evidence on the clinical effectiveness of ivacaftor (150-mg tablet for oral administration twice daily) for the treatment of CF in patients aged ≥ 6 years who have at least one G551D mutation in the *CFTR* gene. The review followed the general principles recommended in the PRISMA statement and Centre for Reviews and Dissemination (CRD) report 4.[17,18]

Identification of studies

Systematic searches were undertaken to locate randomised controlled trials (RCTs) assessing ivacaftor. Searches were not limited by date, language or publication status (unpublished or published). The following databases were searched from inception in May 2012 with searches updated in July 2012:

- MEDLINE (OvidSP) 1946–April 2012 week 4
- MEDLINE In-Process & Other Non-Indexed Citations (OvidSP) up to 2 May 2012
- MEDLINE Daily Update (OvidSP) up to 2 May 2012
- EMBASE (OvidSP) 1974–2012 week 17
- Latin American and Caribbean Health Sciences Literature (LILACS) (Biblioteca Regional de Medicina) up to 4 May 2012
- Cochrane Database of Systematic Reviews (CDSR) (Wiley Online Library) up to Issue 4:2012
- Cochrane Central Register of Controlled Trials (CENTRAL) (Wiley Online Library) up to Issue 4:2012
- *Database of Abstracts of Reviews of Effects (DARE) (Wiley Online Library) up to Issue 2:2012 (CRD) up to 3 May 2012
- *NHS Economic Evaluation Database (NHS EED) (Wiley Online Library) up to Issue 2:2012 (CRD) up to 3 May 2012
- *Health Technology Assessment (HTA) Database (Wiley Online Library) up to Issue 2:2012 (CRD) up to 3 May 2012.

*For completeness DARE, NHS EED and HTA databases were searched through both the Wiley Online Library and the CRD host sites.

The EMBASE strategies were independently peer reviewed by a second information specialist, using the Peer Review of Electronic Search Strategies Evidence-Based Checklist (PRESS-EBC).[19] Supplementary searches were undertaken to identify unpublished and ongoing studies on the following resources:

- *meta*Register of Controlled Trials (internet): www.controlled-trials.com
- National Institutes of Health Clinicaltrials.gov (internet): www.clinicaltrials.gov
- World Health Organization (WHO) International Clinical Trials Registry Platform (ICTRP) (internet): www.who.int/ictrp/en/.

The following conference proceedings were searched, where possible, from 2007 until the most recent conference (up to July 2012):

- European Cystic Fibrosis Society (ECFS) conference: www.ecfs.eu/conferences/main
- North American Cystic Fibrosis Conference (NACFC): www.nacfconference.org/
- International Congress on Pediatric Pulmonology (CIPP): www.cipp-meeting.org/index.htm.

The bibliographies of retrieved articles and relevant systematic reviews were screened for additional studies. Identified references were downloaded into EndNote bibliographic management software

(Thomson Reuters, CA, USA) for de-duplication and then into Microsoft Access (Microsoft Corporation, Redmond, WA, USA) for further assessment and handling. Details of the search strategies can be found in *Appendix 1*.

Inclusion and exclusion criteria
Studies that fulfilled the following criteria were eligible for inclusion.

Population
Children ($\geq$ 6 years) and adults with CF who had the G551D mutation on at least one *CFTR* allele. Patients with all severities of disease were eligible.

Intervention
Ivacaftor tablets.

Comparator
Any reported comparator.

Outcomes
The primary outcome was lung function [e.g. forced expiratory volume in 1 second (FEV_1)]. Other eligible outcomes included mortality, weight, body mass index (BMI), sweat chloride, respiratory symptoms, reduction in pulmonary exacerbations, exercise tolerance, adverse effects of treatment, health-related quality of life (HRQoL) and utilisation of hospital resources.

Study design
For the review of clinical effectiveness, only RCTs were included. Criteria were relaxed for consideration of adverse events and longer-term outcomes (> 12 months), for which open-label studies were eligible. Studies that reported only short-term outcomes (< 3 months) were excluded.

The results of the searches were screened for relevance independently by two reviewers. The full text of studies identified as potentially relevant was obtained and assessed for inclusion by one reviewer and checked by a second. Disagreements were resolved through discussion or referral to a third reviewer where necessary.

Data extraction strategy
Data were extracted using a standardised data extraction form by one reviewer and checked by another. Disagreements were resolved through discussion or referral to a third reviewer where necessary. Data were extracted on the primary outcome, lung function, and the following additional outcomes, where reported: mortality, weight, BMI, sweat chloride, respiratory symptoms, reduction in pulmonary exacerbations, exercise tolerance, adverse effects of treatment, HRQoL and utilisation of hospital resources. Data were extracted for 24-week follow-up (intermediate) and after the longest duration of follow-up reported. If data were available for different patient subgroups (e.g. age, disease severity, region) then data were extracted separately for each subgroup. If composite end points were reported, data were extracted on the definition of the end point, results, and, if sufficient data were available, the events that contributed to the end point. There were some discrepancies in data reported in different sources. In such situations data were extracted from a single source based on the following hierarchy: supplementary results report > journal article > conference abstract > manufacturer's dossier > press release. Details on discrepancies in figures reported in the different reports are summarised in *Appendix 5*.

Critical appraisal strategy
Trials were assessed for methodological quality using the Cochrane risk of bias tool.[20] This includes items covering selection bias (random sequence generation and allocation concealment), performance bias (participant blinding), detection bias (blinding of outcome assessors), attrition bias (incomplete outcome data) and reporting bias (selective reporting of results). Each domain was assigned a rating of high, low, or

unclear. Each trial was assigned an overall rating of the risk of bias. If at least one of the domains was rated as 'high' the trial was considered at high risk of bias and if all domains were judged as 'low' the trial was considered at low risk of bias; otherwise, the trial was considered at 'unclear' risk of bias. The risk of bias assessment was incorporated into the data extraction form and was conducted as part of the data extraction process.

Methods of data synthesis

We did not have sufficient data to conduct a formal meta-analysis. Data were tabulated and discussed in a narrative review. Where possible, results were grouped by age, lung function, disease severity and prior treatment (including consideration of intolerance to treatments). Dichotomous data were summarised as relative risks (RRs) or hazard ratios together with 95% confidence intervals (CIs). If continuous data were normally distributed then mean differences (MDs) and 95% CIs were calculated; otherwise, we reported the results of non-parametric statistical analyses conducted by the study authors. Where sufficient data were available, results were displayed graphically using forest plots. Publication bias was not formally assessed because of the very small number of trials included.

Methods for reviewing cost-effectiveness evidence

A comprehensive search was undertaken to identify literature that might inform a cost-effectiveness study of ivacaftor. The search focused on original papers that reported on cost, cost-effectiveness or cost–utility analyses, studying either the diagnostic phase (genetic testing for CF mutations), the therapeutic phase (management of patients with confirmed CF), or a combination. The search was not restricted to studies on ivacaftor; evaluations of any treatment for CF were eligible. We identified cost studies, utility studies and full economic evaluations, that is to say those that explicitly compared different decision options. The intention was not to perform a systematic review, but to use the studies identified to support the critical review of the economic model provided by the manufacturer and where necessary the estimation of modified model input parameters that would address the objectives of this project.

Cost-effectiveness

Focused searches were undertaken to identify literature on cost-effectiveness and CF. Searches were limited to the last 10 years. The following resources were searched:

- MEDLINE (OvidSP)
- MEDLINE In-Process & Other Non-Indexed Citations (OvidSP)
- EMBASE (OvidSP)
- NHS EED (CRD).

Health-related quality of life

Focused searches were undertaken to identify literature on HRQoL and CF. Searches were not limited by date and the following resources were searched:

- MEDLINE (OvidSP)
- MEDLINE In-Process Citations & Other Non-Indexed Citations (OvidSP)
- EMBASE (OvidSP)
- Cost-effectiveness analysis (CEA) Registry (internet).

Guidelines and guidance

The following resources were searched for guidelines and guidance related to CF:

- National Institute for Health and Care Excellence (NICE) Guidance (internet): http://guidance.nice.org.uk
- TRIP database (limited to guidelines) (internet): www.tripdatabase.com

- Guidelines International Network (GIN) (internet)
- National Guidelines Clearinghouse (internet): www.guidelines.gov
- Cystic Fibrosis Trust: www.cftrust.org.uk.

The results of the searches were independently screened by two reviewers; disagreements were resolved through consensus. Studies were rated as include, background or exclude based on the following criteria:

Include: Studies that had potential to inform parameters within the de novo analysis of cost-effectiveness.

Background: Studies that had the potential to inform methodological issues associated with parameters within the model, albeit that parameter estimates may be absent.

Exclude: All other studies.

Full-text copies of studies rated as 'include' or 'background' based on the above criteria were obtained. Two reviewers independently assessed each full-text study for inclusion according to the following criteria:

- Likely to inform care processes in a UK setting. In some instances, a non-UK study could be included if it provided unique information (not available in UK studies) that was nonetheless informative for UK care profiling/outcome measurement.
- Focused on CF population. For reviews that focused on screening programmes for CF, these were included only if they contained useable information on the lifetime costs and/or effects of having CF.
- Reported long-term effects (> 6 months).
- Reported data that were < 10 years old (i.e. 2002 or later). Studies that included data from 2002 or earlier were included only if they provided unique information that was nonetheless informative for current UK care profiling/outcome measurement.
- Reported on at least one of the following: FEV_1, percentage predicted FEV_1, exacerbations, European Quality of Life-5 Dimensions (EQ-5D), Short Form questionnaire-36 items (SF-36), mortality, quality-adjusted life-years (QALYs).

Studies that fulfilled these criteria were further classified based on the following:

- cost-effectiveness study (Y/N)
- health-care costs reported (Y/N)
- social care costs reported (Y/N)
- disease-specific utility (FEV_1, percentage predicted FEV_1 and exacerbations) reported (Y/N)
- generic utility (e.g. EQ-5D, SF-36, QALY) reported (Y/N)
- incidence/prevalence reported (Y/N)
- mortality or similar reported (Y/N)
- model and/or probabilities reported (Y/N).

In addition the following elements were recorded within the resulting database:

- year of study data (text)
- setting (text)
- follow-up period (text)
- relevant CF study population (text).

This report contains references to confidential information. This information has been removed from the report and the results, discussions and conclusions of the report do not include the confidential information. These sections are clearly marked in the report.

Chapter 4 Systematic review results

Results of clinical effectiveness review

Quantity and quality of research available

The searches identified 256 references, of which 29 reports were considered potentially relevant and full-text copies were obtained. Three studies (16 reports) fulfilled the inclusion criteria: two Phase III RCTs and one open-label study (*Figure 1*). Three Phase II RCTs were excluded; all reported short-term outcomes only and one trial did not report any of the outcomes specified in the inclusion criteria. Details of these studies are summarised in *Appendix 4*.
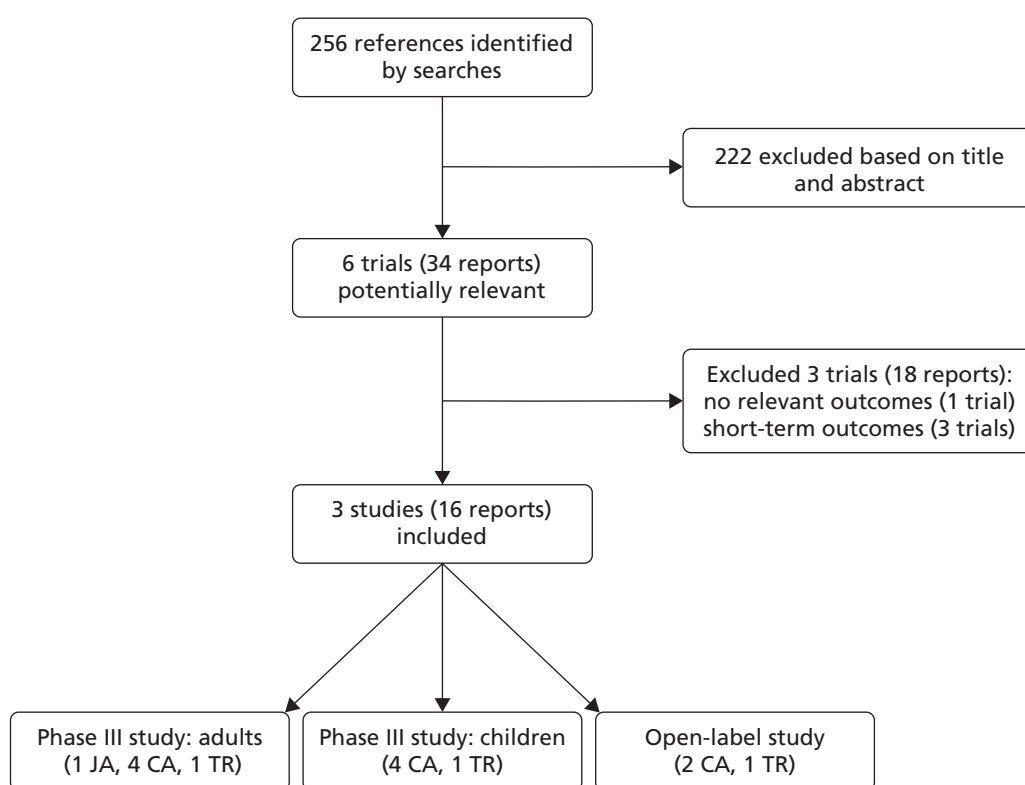
FIGURE 1 Flow of studies through the review. CA, conference abstract; JA, journal article; TR, trial registry entry.

Summary of included studies

The first RCT was conducted in adults ('adults' study') and was published as a full-text report,[21] with the study protocol and further results available as supplementary information from the journal website. Details were also reported in four conference proceedings[22–25] and one trial registry entry.[26] The second RCT was conducted in children ('children's study') and full results have not yet been reported. Details were available only from four conference abstracts,[23,24,27,28] a press release[29] and a trial registry entry.[30] An open-label extension study of the two included RCTs was also included. Details were available only from two conference abstracts,[31,32] a press release[29] and a trial registry entry.[33] Additional details on all three studies were submitted by Vertex Pharmaceuticals, the manufacturer of ivacaftor,[16] and from FDA reports prepared to support the licensing recommendation.[34–36] Confidential information provided by the manufacturer has been removed throughout this report.

Baseline details of the two included RCTs are summarised in *Table 1*. The flow of patients through each study is summarised in *Figure 2*. Both studies were funded by Vertex Pharmaceuticals and were conducted in centres across the USA, Australia and Europe. Inclusion and exclusion criteria were similar with the exception of age: the study in adults enrolled adults and children aged ≥ 12 years; the study in children was restricted to children aged 6–11 years. All patients enrolled in the adults' and children's studies were

TABLE 1 Summary of included RCTs

Features	Adults' study	Children's study
Country	North America, Europe, Australia	North America, Europe, Australia
Funding source	Vertex Pharmaceuticals (VX08-770-102)	Vertex Pharmaceuticals
Inclusion criteria	Aged ≥ 12 years; diagnosis of CF with at least one G551D mutation; FEV_1 40–90% predicted	Children aged 6–11 years; G551D mutation; FEV_1 40–105% predicted
Exclusion criteria	Ongoing illness; pulmonary exacerbation, changes in therapy for pulmonary disease, use of inhaled hypertonic saline treatment within 4 weeks of treatment, abnormal liver function, abnormal renal function, low haemoglobin; history of prolonged QT/QTc interval; history of solid organ or haematological transplantation; colonisation with organisms associated with more rapid decline in pulmonary status; concomitant use of inhibitors or inducers of CYP3A4	Acute respiratory tract infection, pulmonary exacerbation, changes in therapy for pulmonary disease, use of inhaled hypertonic saline treatment within 4 weeks of treatment, abnormal liver function, abnormal renal function, low haemoglobin
Age (years), mean (SD)	26 (9.5)	9 (1.9)
Proportion male, %	48	48
Proportion white, %	98	87
Weight (kg), mean (SD)	61 (14.1)	31 (8.6)
Height (cm), mean (SD)	167 (10.2)	134 (13.3)
Percentage predicted FEV_1, mean (SD)	64 (16.4)	84 (18.1)
Sweat chloride (mmol/l), mean (SD)	100 (10.3)	105 (11.9)
Positive for *Pseudomonas aeruginosa*, %	76	NR
Comorbidities	NR	NR
Co-interventions	Pre-study medication except hypertonic saline	NR

NR, not reported; SD, standard deviation.

	Adults' study		Children's study	
Number screened for eligibility	217		NR	
Number enrolled	167		52	
	Oral ivacaftor 150 mg/12 hours	Placebo	Oral ivacaftor 150 mg/12 hours	Placebo
Number randomised	84	83	26	26
Number treated	83	78	26	26
Completed 48 weeks	77	68	26	22
Rolled over to PERSIST study (open label)	77	67	26	22
Completed 24 weeks of open-label trial	Commercial-in-confidence information has been removed	Commercial-in-confidence information has been removed	Commercial-in-confidence information has been removed	Commercial-in-confidence information has been removed
Completed 48 weeks of open-label trial	Commercial-in-confidence information has been removed	Commercial-in-confidence information has been removed	Ongoing	Ongoing
Completed 96 weeks of open-label trial	Ongoing	Ongoing	Ongoing	Ongoing

FIGURE 2 Flow of patients through the RCTs.

eligible for inclusion in the open-label study. One patient who was in the placebo arm of the adults' study did not enter the open-label study. Oral ivacaftor tablets were administered at a dose of 150 mg every 12 hours; the two RCTs also included an arm in which patients received matching placebo. The two RCTs were 48 weeks in duration. The open-label study was a further 96 weeks in duration with results currently available for 48 weeks' follow-up (96 weeks' ivacaftor treatment) in adults and 24 weeks' follow-up (72 weeks' ivacaftor treatment) in children.

Risk of bias

The full results of the risk of bias assessment, including the support for judgement, are reported in *Appendix 3*. The rating of each bias criterion for each of the two RCTs is summarised in *Table 2*. The open-label study was not assessed for risk of bias, as this was a continuum of the two RCTs with all patients receiving ivacaftor and so issues relating to randomisation and blinding no longer applied. The study in adults was clearly reported and the availability of the study protocol meant that each of the risk of bias criteria could be assessed in detail. This study was rated as low risk of bias for all criteria. Fewer details were available for the study in children, as this has not yet been published in full. Randomisation, allocation concealment and incomplete outcome data were rated as unclear as there was insufficient information to make a judgement on these. The study was reported to have been

TABLE 2 Risk of bias in the RCTs

Criteria	Adults' study	Children's study
Randomisation	Low	Unclear
Allocation concealment	Low	Unclear
Blinding: participant	Low	Low
Blinding: outcome assessor	Low	Low
Incomplete outcome data	Low	Unclear
Selective reporting	Low	Low

double-blinded and so both blinding criteria were judged as low risk of bias. The study was also judged to be at low risk of bias for selective outcome reporting, as it appears that results for all relevant outcomes were reported.

Lung function

Both RCTs reported significantly greater changes from baseline in all measures of lung function in patients receiving ivacaftor compared with those receiving placebo at 24 and 48 weeks (*Table 3* and *Figure 3*). The primary outcome was the absolute change from baseline in the percentage predicted FEV_1, expressed as a percentage of the predicted values for patients with similar height, age and sex. The MD between ivacaftor and placebo in 'relative change from baseline in percentage predicted FEV_1' and the MD in 'actual FEV_1' at 24 and 48 weeks were also assessed. The study in adults indicated that differences in lung function between the ivacaftor and placebo groups were due to improvements in lung function in the ivacaftor group while lung function in those in the placebo group stayed approximately the same or showed very slight decreases (*Figure 4*). (Commercial-in-confidence information has been removed.) The mean change from baseline in the adults' and children's trials and in the open-label extension at the various measurement points for each treatment group are shown in *Figures 4* and *5*.

TABLE 3 Changes in lung function outcomes from baseline

Outcomes	Studies	Mean change ivacaftor (SD)	Mean change placebo (SD)	MD in change (95% CI)	*p*-value[a]
24 weeks' follow-up					
Percentage predicted FEV_1: absolute change, percentage points	Adults	10.4	–0.2	10.6 (8.6 to 12.6)	< 0.0001
	Children	12.6	0.0	12.5 (6.6 to 18.3)	< 0.0001
Percentage predicted FEV_1: relative change, %	Adults	17.6	0.7	16.9 (13.6 to 20.2)	< 0.0001
	Children	21.7	4.3	17.4 (NR)	< 0.0001
FEV_1, litres	Adults	0.4	0.0	0.4 (0.3 to 0.4)	< 0.0001
48 weeks' follow-up					
Percentage predicted FEV_1: absolute change, percentage points	Adults	10.1	–0.4	10.5 (8.5 to 12.5)	< 0.0001
	Children	NR	NR	10.0 (4.5 to 15.5)	0.0006
Percentage predicted FEV_1: relative change, %	Adults	17.5	0.8	16.8 (13.5 to 20.1)	< 0.0001
	Children	NR	NR	15.1 (NR)	NR
FEV_1, litres	Adults	0.4	0.0	0.4 (0.3 to 0.4)	< 0.0001

NR, not reported; SD, standard deviation.
a *p*-values based on mixed-effects model for repeated measures; analysis in children unclear.

Absolute change (24 weeks)	10.60 (95% CI 8.60 to 12.60)
Absolute change (48 weeks)	10.50 (95% CI 8.50 to 12.50)
Relative change (24 weeks)	16.90 (95% CI 13.60 to 20.20)
Relative change (48 weeks)	16.80 (95% CI 13.50 to 20.10)
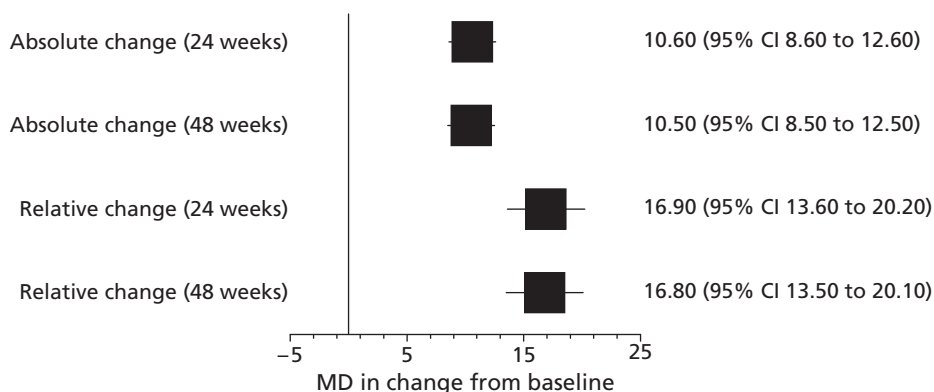
FIGURE 3 Mean difference in change from baseline in percentage predicted FEV_1 (95% CI) in patients receiving ivacaftor compared with placebo in the adults' study.
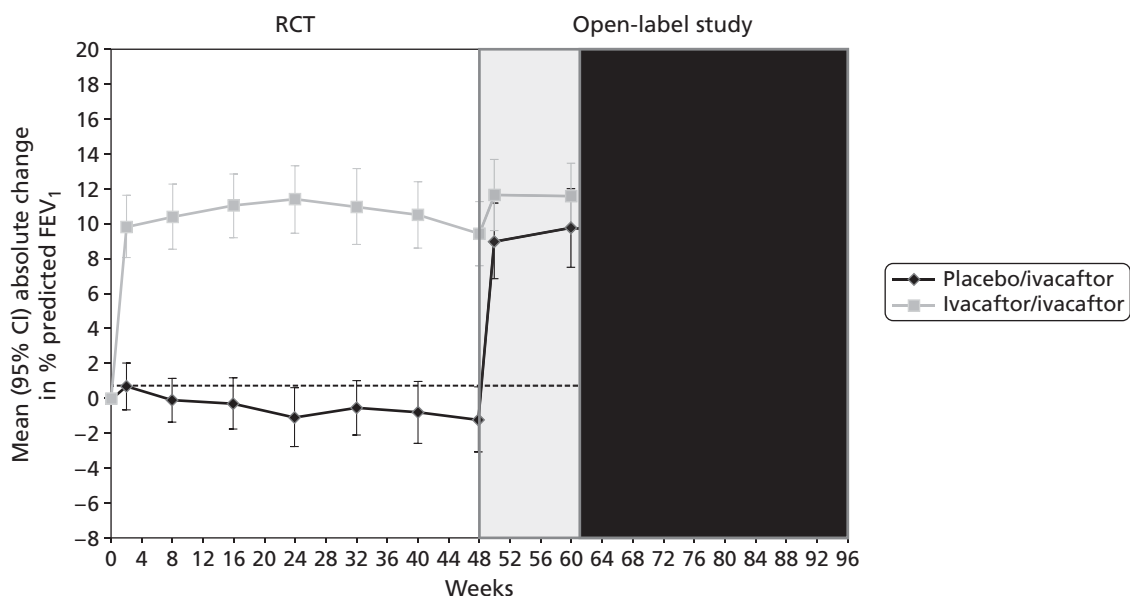
FIGURE 4 Mean absolute change from baseline in percentage predicted FEV_1 in adults in the RCT and open-label study. (Commercial-in-confidence information has been removed.)

FIGURE 5 Mean (95% CI) absolute change from baseline in percentage predicted FEV_1 in children in the RCT and open-label study. (Commercial-in-confidence information has been removed.)

The improvement in lung function occurred very soon after treatment initiation with a MD between ivacaftor and placebo in change from baseline in percentage predicted FEV_1 of 9.17% after 2 weeks of treatment in the adults' study. Results from the children's study supported this initial improvement with a MD of 12.85% after 2 weeks of treatment (commercial-in-confidence information has been removed).

The adults' study also reported results stratified according to age, sex, study region and baseline lung function. Ivacaftor treatment resulted in significant improvements in absolute change in FEV_1 for all subgroups investigated (*Table 4*). CIs around estimates stratified according to subgroup were not reported and so it was not possible to formally investigate differences between subgroups. (Commercial-in-confidence information has been removed.) The children's study did not report numerical results separately according to subgroups but results were presented graphically. This suggested that ivacaftor was associated with significantly greater improvements in absolute change in FEV_1 compared with placebo for the following subgroups: Europe, $\leq 90\%$ predicted FEV_1 and girls. No significant differences were found for Australia, North America, $> 90\%$ predicted FEV_1 or for boys, although all point estimates favoured ivacaftor. The small number of children in each subgroup means that the study may have lacked power to detect significant differences in these subgroups.

Pulmonary exacerbations

Pulmonary exacerbations were defined in the adults' study using modified Fuchs criteria[38] of new or a change in antibiotic therapy [intravenous (i.v.), inhaled or oral] for any four or more of the following symptoms: new or increased haemoptysis; increased cough; increased dyspnoea; malaise, fatigue or lethargy; temperature above 38 °C; anorexia or weight loss; sinus pain or tenderness; change in sinus discharge; change in physical examination of the chest; decrease in pulmonary function by 10%; radiographic change indicative of pulmonary infection. The number and severity of pulmonary exacerbations (patients with pulmonary exacerbation and total exacerbations) at both 24 and 48 weeks were significantly reduced in the ivacaftor group compared with placebo group in the adults' study

TABLE 4 Subgroup analysis for MD in absolute change from baseline in percentage predicted FEV_1 in adults' study at 48 weeks

Subgroups	Categories	MD in change from baseline (95% CI)	p-value
Age	< 18 years	11.4	0.005
	≥ 18 years	9.9	< 0.001
Sex	Male	11	< 0.001
	Female	11.6	< 0.001
Region	Australia	11.9	0.008
	Europe	9.9	< 0.001
	North America	9	< 0.001
Lung function	Percentage predicted FEV (≥ 70%)	10.3	< 0.001
	Percentage predicted FEV (< 70%)	10.6	< 0.001
Genotype[a]	G551D/ΔF508	10.3 (7.2 to 13.3)[b]	NR
	G551D/other	12.1 (6.8 to 17.4)	NR

NR, not reported.
a Data from analysis by FDA statistician.[37]
b *p*-value for difference between groups = 0.51.

(*Table 5* and *Figure 6*). The mean number of days with pulmonary exacerbations, mean number of days with exacerbations requiring i.v. antibiotics and number of days hospitalised with exacerbations were also significantly lower among the ivacaftor treatment group (*Table 6*). (Commercial-in-confidence information has been removed.) The authors of the study in children reported that exacerbations were uncommon in both groups.

TABLE 5 Incidence of exacerbations

Outcomes	Adults				Children			
	Ivacaftor		Placebo		Ivacaftor		Placebo	
	Events	*n*	Events	*n*	Events	*n*	Events	*n*
24 weeks' follow-up								
Number of patients with exacerbations	18	83	35	78	NR	NR	NR	NR
48 weeks' follow-up								
Number of patients with exacerbations	28	83	44	78	CiC information has been removed	CiC information has been removed	CiC information has been removed	CiC information has been removed
Number of exacerbations	47	83	99	78	CiC information has been removed	CiC information has been removed	CiC information has been removed	CiC information has been removed
Number of exacerbations requiring i.v. antibiotics	28	83	47	78	CiC information has been removed	CiC information has been removed	CiC information has been removed	CiC information has been removed
Number of exacerbations requiring hospitalisation	21	83	31	78	CiC information has been removed	CiC information has been removed	CiC information has been removed	CiC information has been removed
CiC information has been removed								
CiC information has been removed	CiC information has been removed	CiC information has been removed	CiC information has been removed	CiC information has been removed	CiC information has been removed	CiC information has been removed	CiC information has been removed	CiC information has been removed
CiC information has been removed	CiC information has been removed	CiC information has been removed	CiC information has been removed	CiC information has been removed	CiC information has been removed	CiC information has been removed	CiC information has been removed	CiC information has been removed

CiC, commercial-in-confidence; NR, not reported.

	RR
Number of patients with exacerbations (24 weeks)	0.48 (95% CI 0.30 to 0.77)
Number of patients with exacerbations	0.60 (95% CI 0.41 to 0.85)
Number of exacerbations	0.45 (95% CI 0.38 to 0.52)
Number of exacerbations requiring i.v. antibiotics	0.56 (95% CI 0.39 to 0.79)
Number of exacerbations requiring hospitalisation	0.64 (95% CI 0.40 to 1.00)

FIGURE 6 Relative risk (95% CI) of exacerbations in adults receiving ivacaftor compared with placebo (data are at 48 weeks' follow-up unless otherwise stated).

TABLE 6 Mean number of days with exacerbations in the adults' study

Outcomes	Ivacaftor, mean (SD)	Control, mean (SD)	*p*-value[a]
Days with exacerbations	13.5 (27.3)	36.7 (49.5)	0.0007
Days with i.v. antibiotics for exacerbations	6.68 (19.43)	11.03 (20.36)	0.0183
Days hospitalised for exacerbations	3.92 (13.62)	4.15 (8.71)	0.0275

SD, standard deviation.
a *p*-values are based on stratified (by baseline percentage predicted FEV_1 severity and age group) Wilcoxon's rank-sum test.

Other outcomes

Other outcomes reported in the studies included change from baseline in ivacaftor and placebo groups for quality of life (QoL) [measured using the respiratory domain of the Cystic Fibrosis Questionnaire Revised (CFQ-R)], sweat chloride, weight, BMI and BMI-for-age *z*-score. Each of these outcomes was reported in both the adults' and children's studies at 24 and 48 weeks' follow-up and quality of life and weight were also reported in the open-label study. There were significantly greater improvements in the ivacaftor group than in the placebo group for all outcomes at all time points with the exception of quality of life in children, which failed to reach statistical significance at either 24 or 48 weeks' follow-up (*Table 7*, *Figure 7*). Patients who had received ivacaftor in the RCT continued to gain weight in the open-label study. (Commercial-in-confidence information has been removed.) The mean absolute change from baseline in CFQ-R respiratory domain scores in adults and children are summarised in *Figures 8* and *9* respectively.

TABLE 7 Mean difference in change from baseline for quality of life, sweat chloride and weight

Outcomes	Studies	Change from baseline		MD (95% CI)	*p*-value
		Ivacaftor	Placebo		
24 weeks' follow-up					
Quality of life: CFQ-R respiratory domain[a]	Adults	NR	NR	8.1 (4.7 to 11.4)	< 0.001
	Children	6.31	0.25	6.1 (–1.4 to 13.5)	0.1092
Sweat chloride, mmol/l[b]	Adults	–48.7	–0.8	–47.9 (–51.3 to –44.5)	< 0.001
	Children	–55.53	–1.21	–54.3 (–61.8 to –46.8)	< 0.0001
Weight, kg[c]	Adults	3.0	0.2	2.8 (1.8 to 3.7)	< 0.0001
	Children	3.7	1.8	1.9 (0.9 to 2.9)	0.0004
48 weeks' follow-up					
Quality of life: CFQ-R respiratory domain[a]	Adults	5.9	–2.7	8.6 (5.3 to 11.9)	< 0.001
	Children	6.1	1	5.1 (–1.6 to 11.8)	0.1354
Physical functioning domain	Adults	NR	NR	4.4	0.005
Social functioning domain	Adults	NR	NR	4.3	0.0026
Eating disturbances domain	Adults	NR	NR	3.3	0.0021
Treatment burden domain	Adults	NR	NR	3.3	0.0419
Sweat chloride, mmol/l[b]	Adults	–48.7	–0.6	–48.1 (–51.5 to –44.7)	< 0.0001
	Children	56	3	–53.5 (–60.9 to –46.0)	< 0.0001
Weight, kg[c]	Adults	3.1	0.4	2.7 (1.3 to 4.1)	< 0.0001
	Children	5.9	3.1	2.8 (1.3 to 4.2)	0.0002
BMI, kg/m^2	Adults	NR	NR	0.9	< 0.0001
	Children	NR	NR	1.1	0.0003
BMI-for-age z-score	Adults	NR	NR	0.33	0.0490
	Children	NR	NR	0.45	< 0.0001

NR, not reported.
a Mean clinically important difference = 4.
b Analysis based on mixed-effects model for repeated measures.
c Analysis based on linear mixed effect model.

(a)

Adults (24 weeks)	−47.90 (95% CI −51.30 to −44.50)
Adults (48 weeks)	−48.10 (95% CI −51.50 to −44.70)
Children (24 weeks)	−54.30 (95% CI −61.80 to −46.80)
Children (48 weeks)	−53.50 (95% CI −60.90 to −46.00)

MD in change from baseline in
sweat chloride (mmol/l)

(b)

Adults (24 weeks)	2.80 (95% CI 1.80 to 3.70)
Adults (48 weeks)	2.70 (95% CI 1.30 to 4.10)
Children (24 weeks)	1.90 (95% CI 0.90 to 2.90)
Children (48 weeks)	2.80 (95% CI 1.30 to 4.20)

MD in change from baseline in
weight (kg)

(c)

Adults (24 weeks)	8.10 (95% CI 4.70 to 11.40)
Adults (48 weeks)	8.60 (95% CI 5.30 to 11.90)
Children (24 weeks)	6.10 (95% CI −1.40 to 13.50)
Children (48 weeks)	5.10 (95% CI −1.60 to 11.80)

MD in change from baseline in
CFQ-R score

FIGURE 7 Mean difference (95% CI) in change from baseline in (a) sweat chloride, (b) weight and (c) quality of life (measured using the CFQ-R) in patients receiving ivacaftor compared with placebo.
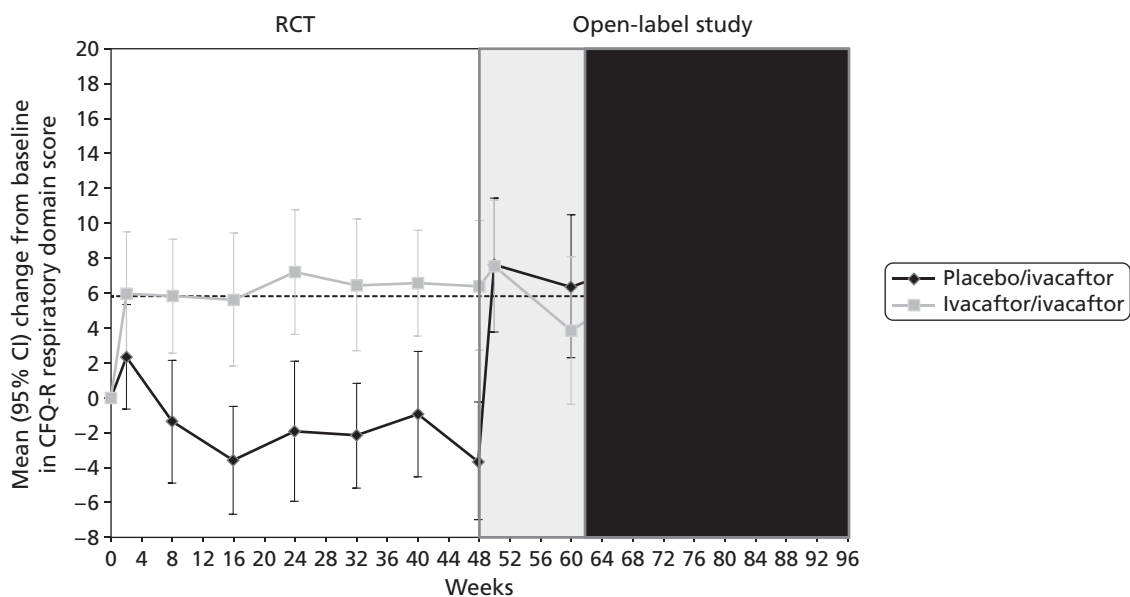
FIGURE 8 Mean (95% CI) absolute change from baseline in CFQ-R respiratory domain score in adults in the RCT and open-label study. (Commercial-in-confidence information has been removed.)
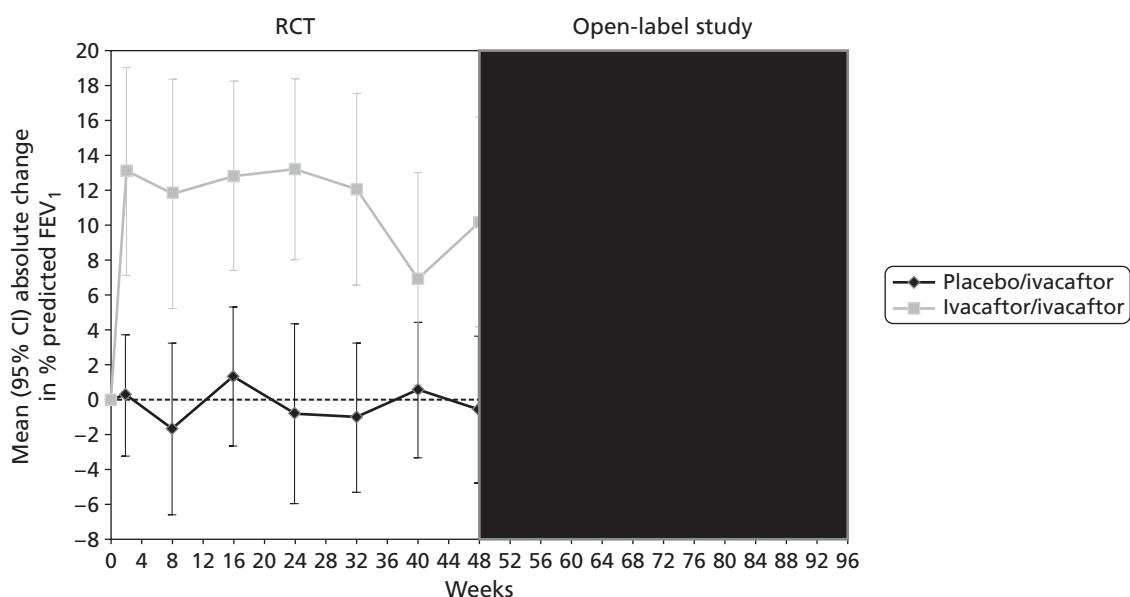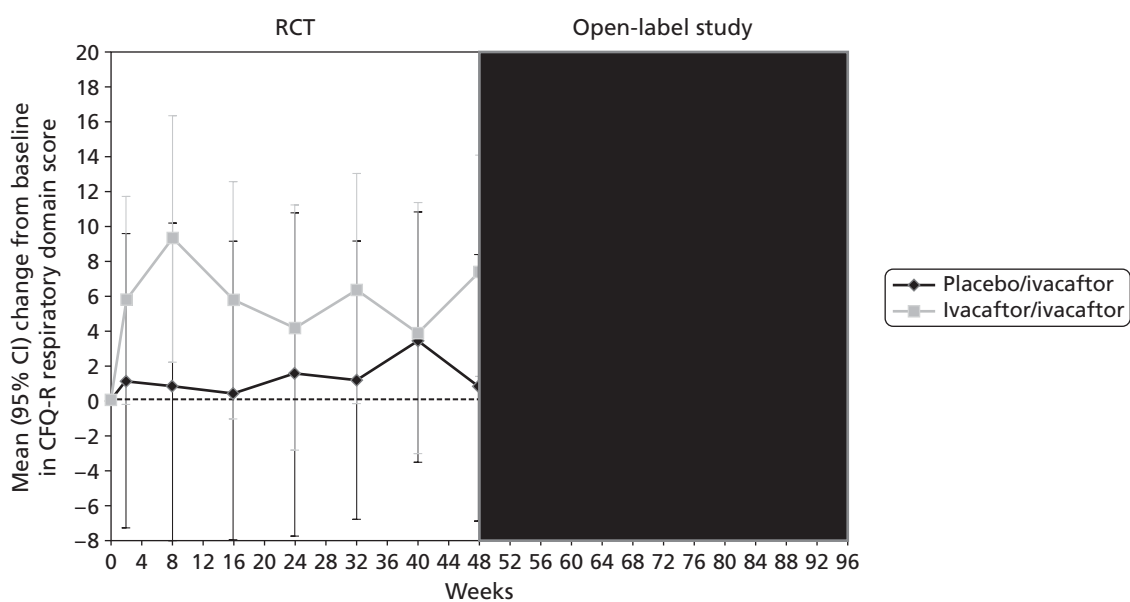

FIGURE 9 Mean (95% CI) absolute change from baseline in CFQ-R respiratory domain score in children in the RCT and open-label study. (Commercial-in-confidence information has been removed.)

Adverse events and withdrawals

Adverse events were mainly minor and comparable across treatment groups and studies (*Table 8*).
The most commonly reported adverse events were pulmonary exacerbation, cough, headache, upper
respiratory tract infection and oropharyngeal pain. *Figure 10* shows the RR for each adverse event in
intervention compared with control arms for the adults' and children's studies. In the adults' study,
there was a greater risk of a serious adverse event (RR 0.67, 95% CI 0.36 to 0.89), pulmonary
exacerbation (RR 0.64, 95% CI 0.47 to 0.85), and decreased lung function test (RR 0.25, 95% CI 0.05 to
0.82) in the placebo group and a small increased risk of rash (RR 2.52, 95% CI 1.01 to 8.05) and dizziness
(RR 9.40, 95% CI 1.51 to 56.39) associated with ivacaftor. However, these differences were not found in
the children's study, which reported RRs very close to 1 for each of these events. The children's study did
not find any significant differences between treatment groups.

TABLE 8 Number of adverse events in ivacaftor and placebo groups in each of the three included studies

Adverse events	Adults		Children		Open label	
	Ivacaftor events (*n* = 83)	Control events (*n* = 78)	Ivacaftor events (*n* = 26)	Control events (*n* = 26)	Placebo/ivacaftor (*n* = 67)	Ivacaftor/ivacaftor (*n* = 77)
Any adverse event	82	78	NR	NR	47	63
Serious adverse event	20	33	CiC information has been removed	CiC information has been removed	CiC information has been removed	CiC information has been removed
Adverse event leading to study-drug discontinuation	1	4	0	0	NR	NR
Pulmonary exacerbation	34	50	CiC information has been removed	CiC information has been removed	CiC information has been removed	CiC information has been removed
Cough	27	33	CiC information has been removed	CiC information has been removed	CiC information has been removed	CiC information has been removed
Headache	19	13	CiC information has been removed	CiC information has been removed	CiC information has been removed	CiC information has been removed
Upper respiratory tract infection	19	12	CiC information has been removed	CiC information has been removed	CiC information has been removed	CiC information has been removed
Oropharyngeal pain	17	15	CiC information has been removed	CiC information has been removed	CiC information has been removed	CiC information has been removed
Nasal congestion	17	12	CiC information has been removed	CiC information has been removed	CiC information has been removed	CiC information has been removed

TABLE 8 Number of adverse events in ivacaftor and placebo groups in each of the three included studies (*continued*)

Adverse events	Adults		Children		Open label	
	Ivacaftor events (*n* = 83)	Control events (*n* = 78)	Ivacaftor events (*n* = 26)	Control events (*n* = 26)	Placebo/ ivacaftor (*n* = 67)	Ivacaftor/ ivacaftor (*n* = 77)
Nausea	13	9	CiC information has been removed	CiC information has been removed	CiC information has been removed	CiC information has been removed
Abdominal pain	13	10	CiC information has been removed	CiC information has been removed	CiC information has been removed	CiC information has been removed
Rash	12	4	CiC information has been removed	CiC information has been removed	CiC information has been removed	CiC information has been removed
Productive cough	12	11	CiC information has been removed	CiC information has been removed	CiC information has been removed	CiC information has been removed
Diarrhoea	11	10	CiC information has been removed	CiC information has been removed	CiC information has been removed	CiC information has been removed
Nasopharyngitis	10	10	CiC information has been removed	CiC information has been removed	CiC information has been removed	CiC information has been removed
Pyrexia	10	9	CiC information has been removed	CiC information has been removed	CiC information has been removed	CiC information has been removed
Dizziness	10	1	NR	NR	NR	NR
Haemoptysis	9	17	NR	NR	NR	NR
Rales	9	8	CiC information has been removed	CiC information has been removed	CiC information has been removed	CiC information has been removed
Vomiting	9	10	CiC information has been removed	CiC information has been removed	CiC information has been removed	CiC information has been removed
Pulmonary function decreased	3	11	NR	NR	0	1
CiC information has been removed	CiC information has been removed	CiC information has been removed	CiC information has been removed	CiC information has been removed	NR	NR

TABLE 8 Number of adverse events in ivacaftor and placebo groups in each of the three included studies (*continued*)

Adverse events	Adults		Children		Open label	
	Ivacaftor events (*n* = 83)	Control events (*n* = 78)	Ivacaftor events (*n* = 26)	Control events (*n* = 26)	Placebo/ ivacaftor (*n* = 67)	Ivacaftor/ ivacaftor (*n* = 77)
CiC information has been removed	CiC information has been removed	CiC information has been removed	CiC information has been removed	CiC information has been removed	NR	NR
CiC information has been removed	CiC information has been removed	CiC information has been removed	CiC information has been removed	CiC information has been removed	CiC information has been removed	CiC information has been removed
CiC information has been removed	CiC information has been removed	CiC information has been removed	CiC information has been removed	CiC information has been removed	NR	NR
CiC information has been removed	CiC information has been removed	CiC information has been removed	CiC information has been removed	CiC information has been removed	CiC information has been removed	CiC information has been removed
CiC information has been removed	NR	NR	NR	NR	CiC information has been removed	CiC information has been removed
CiC information has been removed	NR	NR	NR	NR	CiC information has been removed	CiC information has been removed
CiC information has been removed	NR	NR	NR	NR	CiC information has been removed	CiC information has been removed

CiC, commercial-in-confidence; NR, not reported.

FIGURE 10 Relative risk (95% CI) of adverse events in ivacaftor compared with placebo for the (a) adults' and (b) children's studies. NR, not reported.

Both RCTs reported more overall withdrawals and withdrawals due to adverse events in the placebo group than in the ivacaftor group (*Table 9*). Two patients in the open-label trial discontinued treatment before the 12-week visit, one due to pregnancy and one due to the adverse event of suicidal depression.

TABLE 9 Number of withdrawals in ivacaftor and placebo groups in the adults', children's and open-label studies

	Adults		Children	
Reasons for withdrawal	**Ivacaftor**	**Placebo**	**Ivacaftor**	**Placebo**
Withdrawals on or before day 1				
Illness	0	3	0	0
Daily panic attacks	0	1	0	0
FEV$_1$ too low	0	1	0	0
Wrong genotype	0	1	0	0
Randomised by error	0	1	0	0
Required prohibited medication	1	0	0	0
Withdrawals after day 1				
Non-compliance	2	0	0	0
Required prohibited medication	1	2	0	0
Pregnancy	1	0	0	0
Withdrawal of consent	1	1	0	0
Physician decision	0	1	0	0
Unclear	0	1	0	3
Adverse event	1	3	0	1
Withdrawals during open-label study				
Adverse event	0	1	0	1
Pregnancy	0	1	0	0
Withdrew consent	2	1	0	0
Non-compliance	1	0	0	0
Total	10	18	0	5

Results of cost-effectiveness review

The health economics searches identified 1158 titles and abstracts. Of these, 66 were rated as include based on initial screening criteria and 62 were rated as background. After full-text review, 23 studies were rated as include, 17 as background and the remaining 88 were excluded (*Figure 11*). Details of the studies rated as include and background are summarised in *Appendix 6*.

Included studies focused on health-care costs, cost-effectiveness and utility to inform the economic model. None of the included studies contained information that would inform social care costs. Included studies were used to validate and contextualise assumptions in the model.

Eighteen 'included' studies that focused on cost elements contained information on health-care costs (*Figure 12*). Six studies provided data on cost-effectiveness, five of which included data based on economic models.[38–42] These studies provided useful methodological information as well as data that were used to validate the manufacturer's cost-effectiveness model. However, these studies did not model the cost-effectiveness of ivacaftor. Background studies did not contribute directly to the economic model; they were used only to inform methodological issues.

Fourteen studies provided data on utility, mortality or prevalence. Eleven studies focused on disease-specific utility measures, and six studies included valid generic tools (*Figure 13*). Three studies provided mortality data; two of these used a generic utility measure and the other used a disease-specific utility measure. Three examined incidence and prevalence; two of these also used a generic utility measure and the other used a disease-specific utility measure.
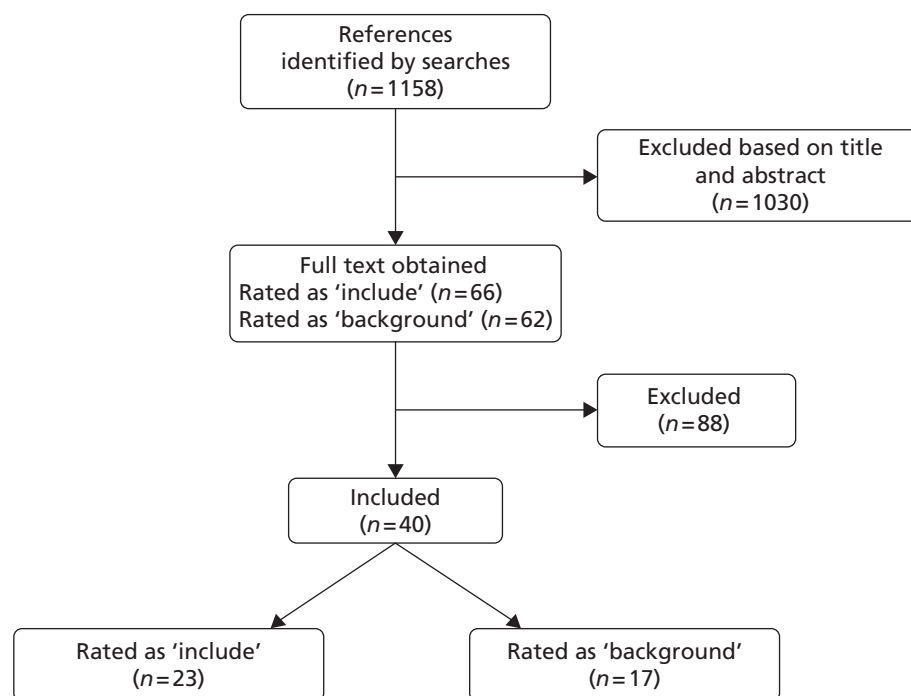
FIGURE 11 Flow of studies through the health economic review.
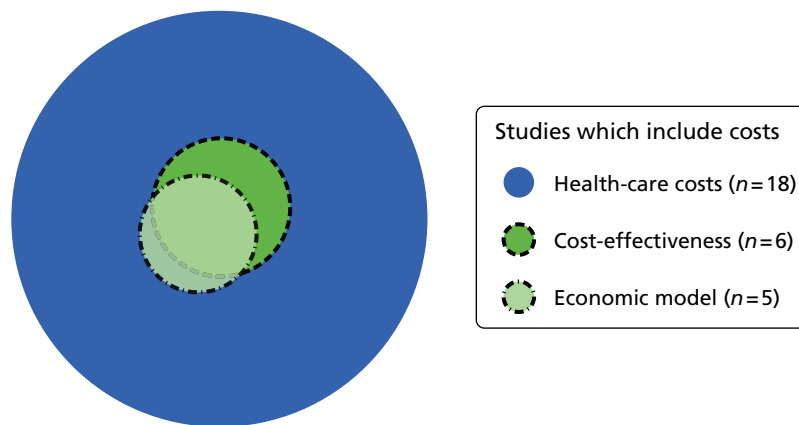
FIGURE 12 Venn diagram of included studies that included costs.
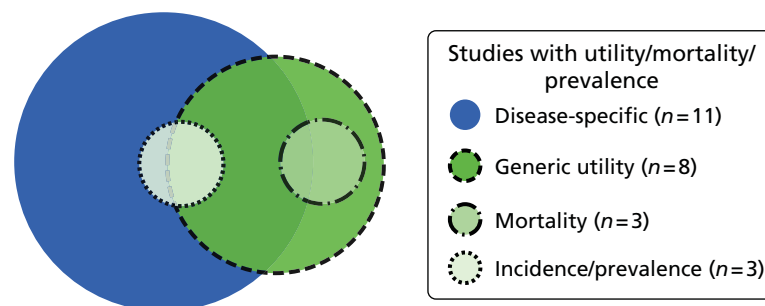
FIGURE 13 Venn diagram of included studies that included mortality/utility.

Parameter estimates

Three of the 23 included studies contributed to the model.[8,21,43] Additionally, a more contemporary, as yet unpublished, version of the UK CF Registry database (2011) was used to inform cost parameters.[44] The adults' study included in the review of clinical effectiveness was also included in the economic review.[21] UK-based generic utility values of CF patients by percentage predicted FEV_1 category were obtained from Gee *et al.*[45] and expressed in terms of SF-36. The prevalence rates of diabetes mellitus, *Staphylococcus aureus* infection and *Burkholderia cepacia* infection were derived from the UK CF Registry,[8] which was also a data source for the proportion of genotyped patients and the proportion who were eligible for, and in receipt of, a lung transplant. Following correspondence with the Cystic Fibrosis Trust, audit data from the 2011 registry were obtained. These were analysed to provide information on costing, particularly in relation to tariff bands, expensive drugs and implantation of venous access devices.

No evidence was derived from the other included studies and the studies included as background. These studies were not useful for the model as, on detailed review, they did not:

1. provide useful evidence for use in a UK setting
2. transparently report costs or effects; or
3. provide utility values that were linked to percentage predicted FEV_1 bands.

Chapter 5 Methods for assessing cost-effectiveness

Methodology and structure

The manufacturer of ivacaftor, Vertex Pharmaceuticals, submitted a health economic model for the assessment of the lifetime cost-effectiveness of ivacaftor for the treatment of CF in patients aged ≥ 6 years who have at least one G551D mutation in the *CFTR* gene.[16] This model was a deterministic patient-level simulation model. We used the manufacturer's model as the basis for our model, making modifications where necessary. Input values into the model were modified if values used by the manufacturer were not UK-specific or not recent, or better estimates could be found. We took estimates of the treatment effect of ivacaftor from the results of the clinical effectiveness review. All costs and effects were discounted by 3.5% according to the NICE methods guide.[46] The model incorporated a lifetime time horizon to estimate outcomes in terms of QALYs and costs from the perspective of the NHS. There were various uncertainties in the model regarding the input data. The impact of these uncertainties was explored through probabilistic sensitivity analysis (PSA). Below we describe the content and structure of the manufacturer's model (*Figure 14*). We then present a summary of the model inputs and any modifications that we made to these for our model.

Population

The starting patient population for this individual patient simulation is the population in the two RCTs included in the clinical effectiveness review (adults' and children's studies).[21,27] The analysis is therefore based on adults and children aged ≥ 6 years at the time of the start of the clinical trials in 2010. The cost-effectiveness study is conducted from a NHS perspective and so the reference population is the total CF population in England. There is therefore a potential concern regarding the generalisability of the model. To assess this, we compared baseline characteristics of patients included in the RCTs with details of patients included in the UK CF Registry, an anonymised database of all those with CF in the UK, maintained by the Cystic Fibrosis Trust (*Table 10*).[8] The median age of patients included in the UK CF Registry was lower than that of patients included in the trials, which is explained by the fact that patients aged < 6 years were excluded from the trials. The proportion male to female and median percentage predicted FEV_1 were comparable. *Table 10* provides a summary of key characteristics of patients in the ivacaftor trials compared with UK CF Registry data. We did not make any modifications to the population in the model.

Strategies

To estimate the lifetime impact of ivacaftor in terms of costs and effects (QALYs) on CF patients, standard care (standard care strategy) was compared with ivacaftor plus standard care (ivacaftor + standard care strategy). Standard care consisted of CF-related medication [pancreatic enzymes, dornase alfa (DNase) (Pulmozyme®, Roche), inhaled corticosteroids, bronchodilators, prednisone and antibiotics], devices (oxygen vests, nebulizers and other airway clearance and respiratory devices) and respiratory therapy.[16] We did not make any modifications to the strategies in the model.

Disease progression model

The model simulates the disease progression of CF patients included in the trials beyond the trial duration as an independent decline in percentage predicted FEV_1 (no change in any other characteristics, e.g. exacerbation rate). The probability of death is a function of the percentage predicted FEV_1, number of pulmonary exacerbations per year, infections with *S. aureus* (yes or no), infection with *B. cepacia* (yes or no), diabetes (yes or no), weight-for-age *z*-score and pancreatic sufficiency status (yes or no) (*Table 11*).
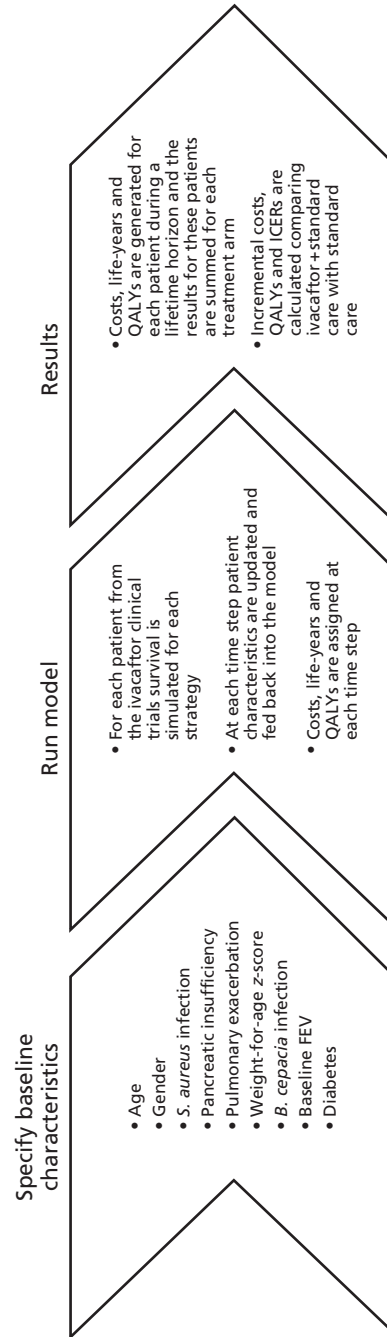
FIGURE 14 Overview of model. ICERs, incremental cost-effectiveness ratios.

Specify baseline characteristics

- Age
- Gender
- *S. aureus* infection
- Pancreatic insufficiency
- Pulmonary exacerbation
- Weight-for-age z-score
- *B. cepacia* infection
- Baseline FEV
- Diabetes

Run model

- For each patient from the ivacaftor clinical trials survival is simulated for each strategy
- At each time step patient characteristics are updated and fed back into the model
- Costs, life-years and QALYs are assigned at each time step

Results

- Costs, life-years and QALYs are generated for each patient during a lifetime horizon and the results for these patients are summed for each treatment arm
- Incremental costs, QALYs and ICERs are calculated comparing ivacaftor+standard care with standard care

TABLE 10 Baseline patient-level characteristics for trial participants compared with UK CF Registry

Characteristic	Ivacaftor Phase III trials	UK CF Registry
Median age (years)	20	17
Sex (% female)	52%	47%
Median baseline percentage predicted FEV_1	71%	74%
Mean weight-for-age z-score	−0.41	NA
Pancreatic insufficiency	93%	NA
P. aeruginosa infection (age > 12 years)	76%	50.4%

NA, not applicable.

TABLE 11 Patient-level hazard equation for mortality[47]

Covariates	Liou *et al.*[47] β-coefficient (SE)	Reference values	Manufacturer input values 6–11 years	12+ years	Sources	(Modified) input values 6–11 years	12+ years	Sources
Sex (female = 1, male = 0)	0.15 (0.074)	47.0%	Patient dependent		Trial data (Vertex 2012)	Patient dependent		Trial data (Vertex 2012)
Percentage predicted FEV_1	−0.042 (0.0025)	67.7%	Patient dependent		Trial data (Vertex 2012)	Patient dependent		Trial data (Vertex 2012)
Weight-for-age z-scores	−0.28 (0.041)	−0.85	Patient dependent		Trial data (Vertex 2012)	Patient dependent		Trial data (Vertex 2012)
Pancreatic sufficiency	−0.14 (0.23)	5.3%	Patient dependent		Trial data (Vertex 2012)	Patient dependent		Trial data (Vertex 2012)
Diabetes mellitus	0.44 (0.098)	6.1%	28%	28%	UK CF Registry 2010	28%	28%	UK CF Registry 2010
S. aureus infection	−0.25 (0.09)	30.6%	30%	30%	UK CF Registry 2010	30%	30%	UK CF Registry 2010
B. cepacia infection	1.41 (0.19)	3.2%	2%	2%	UK CF Registry 2010	2%	2%	UK CF Registry 2010
Number of acute exacerbations (0–5)	0.35 (0.024)	1.10	0.00	1.40	Trial data (Vertex 2012)	0.51	0.83	Goss *et al.*[48]
Number of acute exacerbations (0–5) × *B. cepacia* infection	−0.28 (0.06)							

SE, standard error.

Improvement in the percentage predicted FEV_1, exacerbations and weight-for-age *z*-score associated with ivacaftor[21] is translated into better survival of the patients. Each individual from the two RCTs with certain baseline characteristics runs through each treatment arm of the model. Every 3 months, patients' characteristics are updated, based on efficacy outcomes and natural disease progression, and fed back into the model to estimate the survival of the patient. The estimated 3-monthly survival probability is then multiplied by the survival probability at the beginning of the 3-month period leading to cumulative survival probabilities. In addition, the HRQoL and health-care costs for the patients during the 3-month period are calculated. HRQoL values defined in terms of utility values were assumed to be dependent on the level of percentage predicted FEV_1 with a decrease in percentage predicted FEV_1 resulting in a decrease in utility. Costs were assumed to be dependent on percentage predicted FEV_1 and on age with a decrease in percentage predicted FEV_1 age resulting in an increase in costs. Adding up all the costs and effects generated in each time step leads to total costs and effects for each individual for both strategies. Average costs and QALYs per strategy are then used to estimate the incremental cost-effectiveness ratio (ICER).

Modified disease progression

The only change made to the structure of the model was the addition of lung transplantations. Lung transplantations were added to the model as ivacaftor has the potential to improve the percentage predicted FEV_1, which could lead to fewer lung transplantations and therefore savings in CF-related health-care costs. We have assumed that individuals with a percentage predicted $FEV_1 \leq 30\%$ are eligible for lung transplantation, although only 17% of them receive a transplantation.[8,37] Reasons for this include not meeting the requirements for the waiting list and the unavailability of matching donors once on the waiting list. After transplantation patients were assumed to have lower mortality rates and improved QoL. In transplanted patients costs for ivacaftor and CF-related health-care use were assumed to be zero and all inclusive follow-up costs after transplantation were applied. The inclusion of lung transplantations is important because preventing the need for lung transplantation could increase the incremental effectiveness and reduce costs of the ivacaftor + standard care strategy compared with the standard care strategy.

Model parameters

The inputs into the model are summarised below together with changes that we made to improve the model and make it more applicable to the UK setting.

Survival function

The probability of dying was estimated by means of a hazard function adapted from Liou *et al.*[47] depending on age, sex, percentage predicted FEV_1, number of pulmonary exacerbations, infections with *S. aureus*, infection with *B.cepacia*, diabetes, weight-for-age *z*-score and pancreatic sufficiency status (see *Table 11*). This study found no evidence of an association between other clinical parameters (e.g. height and infection with *P. aeruginosa*) and survival; these parameters were therefore not included in the survival function. *Table 11* presents the original survival function based on Liou *et al.*,[47] the input estimates used by the manufacturer and our updated input estimates. The hazard function was estimated by subtracting the value of each individual patient characteristic from the reference values listed in *Table 11*.

The *proportion female* in the Liou *et al.*[47] study was 47% and was used as a reference value for the survival function. This reference value is compared with the sex status of patients included in the ivacaftor trials. *Baseline values of percentage predicted FEV$_1$* are based on individual baseline estimates of the patients and compared with a reference baseline percentage predicted FEV_1 value of 67.7%.[47] The *weight-for-age z-score* was assumed to be constant over a lifetime period from the baseline score. Individual weight-for-age *z*-score estimates were used for the simulation of the disease progression and compared with a reference value of –0.85 based on Liou *et al.*[47] The number of *exacerbations*, based on trial data,[1] was age dependent; patients aged ≥ 12 years treated with standard care were assumed to experience 1.4 exacerbations annually, while patients between 6 and 11 years were assumed to

experience zero events annually. These estimations of the exacerbations are kept constant during the entire model duration and were compared with a reference value of 1.1 exacerbations per year.[47] The prevalence of *diabetes mellitus*, *S. aureus* infection and *B. cepacia* infection were not available from the trial data, and therefore age-specific percentages of patients with these conditions were derived from the UK CF Registry Annual Data Report[8] and compared with the presented reference values.[47] *Pancreatic insufficiency* has a negative impact on the survival of patients and was therefore included in the survival function. Individual pancreatic insufficiency status is compared with the reference value.[47]

Modified survival function

Generally, we used the same input values as the manufacturer. However, we adjusted the annual exacerbation rates as the manufacturer included an annual exacerbation rate of 1.4 for patients aged ≥ 12 years based on 78 patients receiving standard care during the 48 weeks of the adults' trial. Patients aged < 12 years of age were assumed to experience no exacerbations in the original model. In our modified model the annual exacerbation rate was assumed to be dependent on percentage predicted FEV_1 and age. Based on two figures presented in a paper by Goss *et al.*[48] we estimated the association between the mean annual pulmonary exacerbation rate and the mean percentage predicted FEV_1 separately for patients with CF < and ≥ 18 years of age. The final estimated equations were:

1. mean annual exacerbation rate in patients < 18 years of age = $8.5938 \times \exp[-0.035 \times$ percentage predicted $FEV_1]$
2. mean annual exacerbation rate in patients ≥ 18 years of age = $3.7885 \times \exp[-0.026 \times$ percentage predicted $FEV_1]$.

The patient-level data on baseline percentage predicted FEV_1 from the trials were incorporated into the estimated equations to calculate the exacerbation rate for each patient. Based on these estimates the mean annual baseline exacerbation rate was estimated to be 0.51 for patients < 12 years of age and 0.83 for patients ≥ 12 years of age. These rates were applied in the model for the standard care group.

Survival after transplantation

A major modification to the model was the inclusion of lung transplantation. Patients undergoing lung transplantation have a different mortality rate from other CF patients. We derived the probability of dying after a lung transplantation from 2009–10 UK data (*Table 12*).[49] Note that we always used the most recent estimate of survival probability available. From this, we derived a probability per cycle of dying in the first year after transplantation of 0.057. For all following years (2–10), we derived one probability of death between years 2 and 10. This probability of 0.57 ($1 - 0.895 \times 0.824 \times 0.585$) translates into a probability per cycle of 0.023.

Survival general population

In *Treatment effect* we will introduce four scenarios in which the use of ivacaftor in a subgroup of patients (children < 12 years with good lung function) leads to survival as in the general UK population. We used age- and sex-specific life tables for these survival probabilities.[50]

TABLE 12 Survival probability after lung transplantation

Years of transplant	Periods	Survival probabilities
2005–8	1-year survival	0.790
2002–4	Survival second year given survival first year	0.895
2002–4	Survival fifth year given survival second year	0.824
1996–8	Survival tenth year given survival fifth year	0.585

Annual decline in percentage predicted forced expiratory volume in 1 second

The age-dependent annual decline in percentage predicted FEV_1 in the standard care arm was based on expert consultation. An annual decline in percentage predicted FEV_1 of 2% was used for patients aged between 10 and 20 years. For patients < 10 years or > 20 years the manufacturer assumed an annual decline of 1%.

Modified annual decline in percentage predicted forced expiratory volume in 1 second

In our modified model the annual decline in percentage predicted FEV_1 in the standard care group was based on the Epidemiologic Study of Cystic Fibrosis, a large prospective, multicentre, observational study designed to characterise the natural history of pulmonary disease and growth in a large population of patients with CF in the USA and Canada with predicted FEV_1 (*Table 13*).[51,52]

Treatment effect

Based on the results of the clinical trials, treatment with ivacaftor was assumed to lead to an (almost) immediate improvement in the percentage predicted FEV_1, the decline in percentage predicted FEV_1 and the weight-for-age *z*-score, and a reduction in the annual number of exacerbations.

An initial age-dependent absolute improvement from baseline percentage predicted FEV_1 was applied to model the impact of ivacaftor on percentage predicted FEV_1 and possible reductions in the number of lung transplantations. This improvement (difference between ivacaftor group and placebo), based on the Phase III RCTs, was 10.5% in patients ≥ 12 years at treatment initiation[21] and 10% for patients between 6 and 11 years.[27]

For the long-term assessment of clinical effectiveness, extrapolation beyond observed data was required. The manufacturer assumed as base-case scenario that owing to the treatment no decline in percentage predicted FEV_1 would occur thereafter. Alternative efficacy scenarios for the rate of FEV_1 decline in the ivacaftor–standard care treatment arm were also investigated by the manufacturer (*Table 14*).

The trials[21,27] showed an improvement in weight-for-age *z*-score. This improvement was age dependent and was estimated to be 0.33 for patients aged ≥ 12 years at treatment initiation. Children aged between 6 and 11 years at treatment initiation have an initial increase of 0.39. The initial increase remains over a lifetime period.

The annual reduction in the total number of exacerbations due to ivacaftor was estimated in the clinical trials to be 0.8 (RR 0.45).[21] This absolute reduction is used only for patients ≥ 12 years since the model assumed that patients younger than 12 do not experience exacerbations. The absolute decline of 0.8 exacerbations was kept constant over the whole model duration. In the manufacturer's submission, ivacaftor was assumed not to influence the prevalence of diabetes or infections and therefore the same prevalence was used for the ivacaftor–standard care strategy.

TABLE 13 Annual decline in percentage predicted FEV_1 by age class (standard care)[51]

Age groups (years)	Numbers of patients	Decline in percentage predicted FEV_1
6–8	1811	1.12%
9–12	1696	2.39%
13–17	1359	2.34%
18–24	2793	1.92%
25+	1368	1.45%

TABLE 14 Long-term efficacy assumptions

Manufacturer		Current model	
Scenarios	Descriptions	Scenarios	Descriptions
Base-case manufacturer	Patients treated with ivacaftor experience no annual decline in percentage predicted FEV_1 over a lifetime horizon	'Optimistic' scenario	Same
Scenario 1	Ivacaftor patients experience an annual decline in percentage predicted FEV_1 of 50% the standard care rate, beginning instantly on treatment initiation and continuing over a lifetime time horizon	Not modelled	
Scenario 2	Ivacaftor patients experience no decline in FEV_1 for 90 weeks following treatment initiation. After 90 weeks, ivacaftor patients decline at 66% of the annual standard care rate (based on findings from an evaluation of DNase)[53]	'Intermediate' scenario	Same but decline starts after 96 weeks
Scenario 3	Ivacaftor patients experience no decline in FEV_1 for 90 weeks following treatment initiation. After 90 weeks, ivacaftor patients decline at the same annual rate as standard care patients	'Conservative' scenario	Same but decline starts after 96 weeks
Subgroup analysis	Not conducted	Additional 'optimistic' scenario: < 12 years, FEV_1 > 70% or 90%	No decline in ivacaftor-treated patients, survival and utility as general population

Modified treatment effects

We made a number of changes regarding treatment effects. Instead of assuming a steady decline in percentage predicted FEV_1 in the standard care group, we assumed a decline of 0.4% in the first 48 weeks for patients ≥ 12 years, based on the RCT data.[21] After this period, the earlier reported annual decline in percentage predicted FEV_1 becomes relevant. For the ivacaftor group, we modelled an immediate increase in percentage predicted FEV_1 of 10.1%, which resulted in a difference between the two groups of 10.5%, as observed in the RCT. For patients aged < 12 years, we assumed no decline in the first 48 weeks for the standard care group and an immediate 10% increase for the ivacaftor group.

Additionally, instead of deriving an absolute reduction in exacerbations, we used the rate ratio of 0.45 to estimate the total number of exacerbations in the ivacaftor treatment group using the updated exacerbation rates described in *Survival function*. For patients aged < 12 years, no reduction in exacerbations was assumed, as exacerbations were rare in both treatment groups.

Finally, in the scenarios investigated, the duration of no decline in percentage predicted FEV_1 in the ivacaftor group was changed from 90 weeks to 96 weeks, as the results of the open-label study provided evidence for treatment effects up to this time point.

For our analyses, we have opted to consider the manufacturer base case, scenario 2 and scenario 3 as relevant and thus we present all results for these three scenarios (see *Table 14*). We considered scenario 1 less relevant, as it does not reflect results found in the clinical studies, and so this scenario was not modelled.

As ivacaftor corrects the underlying protein defect of CF, the assumption could be made that treatment with ivacaftor prevents any further deterioration in individuals who begin taking ivacaftor before any permanent impairment occurs, although evidence for this assumption (as with all assumptions on long-term effectiveness) is lacking. This would imply that ivacaftor might be effective in young children

(e.g. < 12 years) who have little or no lung damage at the start of treatment and that no further progression would occur while these patients remain on ivacaftor treatment. This means that the percentage predicted FEV_1 would be close to normal ($\geq 90\%$) for the remaining lifetime, which would be equivalent to the life expectancy in the general population. Furthermore, no or very little standard care for CF treatment would be required.

Based on this assumption, we calculated the cost-effectiveness and budget impact for an additional 'optimistic scenario' in a subgroup of patients. In this scenario, the individual patient simulation was programmed to select only patients from the total 206 patients included in the manufacturer's model who were < 12 years and had little or no lung damage. Because the latter criterion is rather arbitrary, two different cut-off values were used to define normal lung function: a percentage predicted $FEV_1 > 70\%$ or $> 90\%$. Applying the limit of 70% resulted in the inclusion of 36 patients (17.5%) and applying the limit of 90% resulted in only 20 (9.7%) patients. Treatment with ivacaftor in these patient groups was assumed to result in no progression of the disease, which was modelled in three ways: (1) mortality was set to that of the general population, (2) utilities were set to those of the general population and (3) no lung transplant was required. Furthermore, two different assumptions were made for costs of standard care, which were assumed to be either zero or equal to the Band 1 tariff (see *Costs of standard care*) plus the costs of DNase.

This resulted in four separate analyses:

- analysis 1: baseline percentage predicted FEV1 > 70%, standard care costs zero
- analysis 2: baseline percentage predicted FEV1 > 70%, standard care costs Band 1 tariff plus DNase costs
- analysis 3: baseline percentage predicted FEV1 > 90%, standard care costs zero
- analysis 4: baseline percentage predicted FEV1 > 90%, standard care costs Band 1 tariff plus DNase costs.

Utilities
The manufacturer used utility values that were measured during the clinical trials. These utility values were obtained using baseline and end-of-trial (i.e. 48-week) EQ-5D scores obtained from patients in the trials. This generic measure of HRQoL was then adjusted by North American/European normative values to determine the utility scores. These utilities were linked to disease severity expressed in percentage predicted FEV_1. *Table 15* presents the utility values by percentage predicted FEV_1 category used in the manufacturer's model.

Modified utilities
The utilities presented by the manufacturer appear unrealistically high as utilities for the general population are reported to range from 0.94 for people aged < 25 years of age to 0.91 for people aged 35–44 years.[54] In addition, utilities in chronic obstructive pulmonary disease are in the range of 0.79 (percentage predicted FEV_1 50–80%) to 0.65 (percentage predicted $FEV_1 < 30\%$).[55] For our modified model we based the utility estimates on SF-36 health-related utilities derived from Gee *et al.*[43] (*Table 16*). These UK estimates of the utility specified by three severity groups seemed to have more face validity.

TABLE 15 Utility values by percentage predicted FEV_1 category from ivacaftor clinical trials

Percentage predicted FEV_1 categories	Quality-of-life values
Normal (percentage predicted $FEV_1 \geq 90\%$)	0.97
Mild (percentage predicted FEV_1 70–89%)	0.95
Moderate (percentage predicted FEV_1 40–69%)	0.93
Severe (percentage predicted $FEV_1 < 40\%$)	0.91

TABLE 16 Utility values (SF-36) by percentage predicted FEV_1 category[43]

Percentage predicted FEV_1 categories	Number of patients	Utility (SD)
Mild (percentage predicted $FEV_1 > 70\%$)	60	0.803 (20.1)
Moderate (percentage predicted FEV_1 40–69%)	97	0.749 (20.5)
Severe (percentage predicted $FEV_1 < 40\%$)	66	0.688 (20.2)

SD, standard deviation.

We took the utility post transplantation from a study by Anyanwu *et al.*[56] This study reported quality-of-life data from a cross-sectional study of 255 patients who had had single or bilateral lung or heart–lung transplants. QoL was measured using the EQ-5D. As most CF patients undergo a bilateral transplantation, we used utilities for these types of transplant. In the first 6 months post-transplant QoL is slightly lower than in the following months. We used the weighted average (weighted by months, the group > 36 months was assumed to contribute 24 months) of these utilities (*Table 17*) as input for the model.

Utilities for the general population used in the additional scenario for the subgroup of patients aged < 12 years with good lung function were obtained from Sullivan *et al.* (*Table 18*).[57]

Costs of standard care
The annual costs of CF patients in the manufacturer's model consist of two components: drug costs of standard care and the cost of CF care. The age-specific annual drug costs of standard care treatment were

TABLE 17 Utility values post transplantation

Times post transplant, months	Utility	SD	*n*	SE
0–6	0.75	0.17	14	0.045
7–18	0.83	0.17	16	0.043
19–36	0.81	0.19	21	0.041
> 36	0.82	0.19	28	0.036
Weighted average	0.81			0.040

SD, standard deviation; SE, standard error.

TABLE 18 Utility values in the general population

Age groups (years)	EQ-5D
0–9	1.00
10–19	0.91
20–29	0.91
30–39	0.88
40–49	0.84
50–59	0.80
60–69	0.77
70–79	0.72
≥ 80	0.66

calculated based on a retrospective claims study of US health-care costs and utilisation among patients with CF.[58] Three sources[59–61] were used to obtain relationships between costs, age and disease severity category. Three disease severity categories were defined: mild (percentage predicted $FEV_1 \geq 70\%$), moderate (percentage predicted FEV_1 of 40–69%) and severe (percentage predicted $FEV_1 < 40\%$). The relative proportions in each age group are multiplied by the costs per disease severity category. US dollars were converted to UK pounds.

Modified costs of standard care

The original cost data used in the model were not UK specific and were therefore updated for the current analyses. The UK uses a yearly banding system. For the period 2012–13 there are seven bands of increasing complexity in treatment used to assign costs to patients with CF (*Table 19*). The bandings cover most treatment costs directly related to CF for a patient during a financial year.[62] Patient care, outpatient attendances, home care support, home visits by the multidisciplinary team, general support for patients and carers, i.v. antibiotics (delivered in secondary care) and annual review investigations are included in the bandings. Usage of 'high cost' inhaled/nebulised drugs [colistimethate sodium, tobramycin, DNase and aztreonam lysine (Cayston®, Gilead)], surgeries, insertion of gastrostomy devices (percutaneous endoscopic gastrostomy) and totally implantable venous access devices (TIVADs) and primary care-prescribed medication are not included in the tariff bands. The tariffs are defined by complications, therapies, hospitalisation and supplemental feeding. Annual costs per patient in a tariff band are provided in *Table 19*.

The CF Registry assigns patients to bands according to the matrix in *Table 19* and the accompanying instructions[62] using data from the UK Cystic Fibrosis Registry.[63] We contacted the CF Registry and obtained the following individual-level data for 2011: date of birth, percentage predicted FEV_1, nebulised tobramycin inhaled solution (TOBI) solution (y/n), colistimethate sodium (y/n), DNase (y/n), gastric feeding tube (y/n), and the payment by results tariff band.[63] Data were available on 7329 patients, of whom 6209 were aged ≥ 6 years. Of these patients, 5786 had a percentage predicted FEV_1 recorded; missing values were mostly in the younger patients. In order to examine overall spend, we assigned cost estimates to each patient in the registry. We attached annual costs per patient according to each band (see *Table 19*). Drug usage dosage and pricing assumptions were derived from *British National Formulary*,[64] and then cross-checked with dosage recommendations provided by the CF Trust Antibiotic Working Group.[59] The variable of gastric feeding tube included all prevalent patients rather than incident cases. Thus, we did not attach costs to these. However, as only 7% of the patients aged ≥ 6 years have a gastric feeding tube, the number of incident cases per year may be assumed to be limited. Note that no data were available on implantation of TIVAD or use of aztreonam lysine. The costs that we attached to each occurrence in the database are listed in *Table 20*. We then added all costs per patient and performed a regression analysis to explore the relationship between costs, percentage predicted FEV_1 and age. We considered two models, one with and one without an interaction between age and percentage predicted FEV_1. The adjusted R^2 of both models were approximately equal (27%), while the tolerance in the model with interaction suggested that there might be a collinearity issue. We have therefore opted to use the model without interaction. The parameter estimates are found in *Table 21*.

In the additional scenario for the subgroup of patients < 12 years of age with no or little lung damage, costs for standard care were assumed to be either zero or as high as the Band 1 tariff (£5210 per annum) (Department of Health, 2012) plus the costs for DNase (£6041), that is to say £11,251 per annum for their remaining lifetime.[62] Costs of DNase are added to those of Band 1 because this drug is not covered by the bands but we believe that it is likely that these patients would also receive this drug.

TABLE 19 Cystic fibrosis bands[62]

Banding definitions		Bands						
		1	1A	2	2A	3	4	5
Therapies	Maximum number of total days of i.v. antibiotics	0	14	28	56	84	112	≥113
	Nebulised antibiotics (*P. aeruginosa* infection)		Yes					
	Long-term (> 3 months) nebulised antibiotics or DNase			Yes				
	Long-term (> 3 months) nebulised antibiotics and DNase				Yes			
Hospitalisations	Maximum number of total days in hospital		0	7	14	57	112	≥113
Supplemental feeding	Nasogastric feeds				Yes			
	Gastrostomy					Yes		
Complications	CF-related diabetes or ABPA without other complications				Yes			
	CF-related diabetes and ABPA					Yes and (FEV1 ≥ 60%)	Yes and (FEV1 < 60%)	
	Massive haemoptysis or pneumothorax					Yes and (FEV1 ≥ 60%)	Yes and (FEV1 < 60%)	
	CF related Diabetes and Gastrostomy					Yes and (FEV1 ≥ 60%)	Yes and (FEV1 < 60%)	
	Non-tuberculous mycobacterium treated or difficult-to-treat infections (e.g. MRSA or *B. cepacia*) requiring other nebulised antibiotics, e.g. meropenem, Cayston®, vancomycin					Yes		
Annual costs per patient		£5210	£7707	£7707	£12,457	£19,067	£34,388	£41,458
Per cent of patients (≥6 years, England)		15%	1%	18%	32%	24%	8%	3%

ABPA, allergic bronchopulmonary aspergillosis; i.v., intravenous; MRSA, methicillin-resistant *Staphylococcus aureus*.

TABLE 20 Annual costs of expensive medication outside bands

Drugs	Annual costs[64]
Nebulised TOBI solution	£7123
Colistin	£3358
DNase	£6041

TABLE 21 Regression coefficients annual costs, standard care

Variables	β	SE
Constant	41083.87	588
Age	−100.78	12
Percentage predicted FEV_1	−254.34[a]	6

SE, standard error.

a Note that this coefficient is based on a notation of percentage predicted FEV_1 as for example 80 in case it is 80%, whereas the health economic model uses a value of 0.80. Thus, in the HE model the percentage predicted FEV_1 value is multiplied by 100 when using the regression equation.

Cost of ivacaftor

The drug costs of standard care and the CF costs are the same in the ivacaftor–standard care strategy as in the standard care strategy. The annual cost of ivacaftor was set at £182,000 (Vertex 2012) (*Table 22*). The number of years until the patent of ivacaftor expires was assumed to be 14 years; the manufacturer assumed that after this a generic drug would be launched at a lower price of £20,000 (Vertex 2012).[16] The manufacturer used an adherence rate for ivacaftor of 91% based on the Phase III trials,[21,27] but they indicated that real-world adherence rates are typically lower than those observed in clinical studies. The observed efficacy of ivacaftor is based on the observed adherence rate of 91%; a reduction of adherence would be likely to impact on efficacy.

Costs of lung transplantation

For the lung transplantation part of the model, two cost estimates are relevant: the cost of the transplantation itself and the costs of follow-up (*Table 23*). For the cost of the transplantation we used the 2010 reference costs.[65] We combined the costs for elective in-hospital stay with the costs of excess elective hospital days, which resulted in an estimate of £42,018 per transplantation.

The costs of follow-up were based on a study by Anyanwu *et al.*[66] In this study, costs are reported for up to 15 years after transplantation (between years 10 and 15 based on extrapolation). We used the costs as reported for bilateral transplantation as these are most common (in 2010, 26 out of 29 transplants) in CF patients. As these costs were reported in 1999 UK pounds and were discounted at 6%, we first reversed

TABLE 22 Parameters relating to ivacaftor treatment costs

Parameter	Value	Source
Annual drug costs, brand	£182,000	Vertex 2012
Annual drug costs, generic	£20,000	Vertex 2012
Adherence rate	91%	Vertex 2012

TABLE 23 Cost procedure and follow-up for bilateral lung transplantation

Parameter	Costs per year
Procedure	£42,018
Follow-up year 1	£21,634
Follow-up year 2	£13,063
Follow-up year 3	£13,733
Follow-up year 4–10	£8249
Follow-up subsequent years	£4590

the discounting and then adjusted the 1999 UK pounds to 2011 UK pounds using a price index of 1.48.[67,68] It is important to realise that the costs per year reported by Anyanwu *et al.*[66] are per transplanted patient, whereas our model required input per patient still alive. Thus, the costs reported by Anyanwu *et al.*[66] were adjusted according to the survival rates in the same study. Note that once patients have had a lung transplant, only the above-described follow-up costs apply and thus costs for treatment of CF were assumed to be zero.

Model assumptions

The main model assumptions made in the cost-effectiveness analysis are summarised below:

- The starting patient population for the individual patient simulation is the population included in the two RCTs included in the clinical effectiveness review. We assumed that this population is representative of the total CF population in England.
- The efficacy of ivacaftor will translate into better survival based on a survival function presented by Liou *et al.*[37]
- We assumed that the population under investigation was comparable with the population from Liou *et al.*[37]
- The age-specific annual decline in percentage predicted FEV_1 was based on the epidemiologic study of CF in a large population of patients with CF in the USA and Canada. We assumed that these declines were also appropriate for the UK population.
- Patients treated with standard care experience a decline in FEV_1 as reported in the RCTs for the first 96 weeks; thereafter an age-dependent annual decline based on a large epidemiologic study was used.
- The weight-for-age *z*-score was assumed to be constant over a lifetime period from the baseline score.
- The annual exacerbation rate was assumed to be dependent on percentage predicted FEV_1 and age.
- For patients < 12 years old, no reduction in exacerbations was assumed, as exacerbations were rare in both treatment groups.
- The QoL of patients after a lung transplant was based on the patients who have undergone a bilateral transplant as the majority of transplants are bilateral.
- Average dosages are used to estimate the costs of the high-cost drugs.
- The annual cost of ivacaftor was assumed to be £182,000.
- The number of years until the ivacaftor patent expires was assumed to be 14 years.
- The annual cost of a generic drug was assumed to be £20,000.
- The adherence rate to ivacaftor was assumed to be 91% based on the Phase III trials.

Probabilistic sensitivity analyses

There are various uncertainties in the model with regards to the input data. The impact of these uncertainties was explored through PSA. Values used are summarised in *Table 24*.

Budget impact

When deciding whether or not to fund drugs in England, those which go through the NICE appraisal process are usually compared with an ICER threshold (NICE guidance). However, different decision rules might apply to orphan drugs (for diseases with a prevalence lower than 5 in 10,000)[69] and the macro (total population) impact of introducing a new expensive treatment might be an important consideration. The manufacturers included a budget impact analysis but we could not use this as it was based on non-UK values and assumptions. We therefore conducted our own budget impact analysis for England to estimate the budget impact of total lifetime costs and first-year costs. Budget impact is equal to the mean cost per individual × population size. Total lifetime costs per individual were derived from the results of the main cost-effectiveness analysis and first-year costs per individual were estimated by running the cost-effectiveness model for the first year. Different values were obtained for the three different scenarios (conservative, optimistic, intermediate) for lifetime costs. For first-year costs a single value was obtained as the three scenarios were identical for the first year. Discounted costs were used for all analyses.

The population size (number of patients eligible for treatment with ivacaftor) in England was estimated based on the data in *Table 25*. These show that the total number of people in England eligible for treatment with ivacaftor is 271.

Results from CF Registry data suggested that 4.7% of patients had unknown gene mutation. With the introduction of ivacaftor, these patients would need to be tested in order to determine if they were eligible for this treatment. We therefore incorporated the costs required to screen the 289 patients (aged ≥ 6) for whom the gene mutation is unknown, which was not considered in the cost-effectiveness analysis. The additional costs of a CF mutation test in these patients were added to the ivacaftor + standard care treatment arm. The cost of the CF mutation test was estimated to be £160.[70]

We also conducted a sensitivity analysis for the additional optimistic subgroup analysis. We estimated the number of patients aged 6 to 11 years with $FEV_1 > 70\%$ and $> 90\%$ who would be eligible for ivacaftor treatment based on the data in *Table 26*. This suggested that 48 children with a $FEV_1 > 70\%$ and 25 children with a $FEV_1 > 90\%$ would be eligible for treatment. A further 52 children with a $FEV_1 > 70\%$ and 27 with a $FEV_1 > 90\%$ would not have been genotyped.

TABLE 24 Model parameters included in PSAs

PSA input parameters	Parameters	Mean	SE	Distribution
Coefficients survival curve	b_gender	0.150	0.0740	Normal
	b_fev1%	−0.042	0.0025	Normal
	b_ # exacerbations	0.350	0.0240	Normal
	b_diabetes	0.440	0.0980	Normal
	b_Sa Infection	−0.250	0.0900	Normal
	b_Bc Infection	1.410	0.1900	Normal
	b_panc sufficiency	−0.140	0.2300	Normal
	b_wt	−0.280	0.0410	Normal
	b_Bc inf * exacer	−0.280	0.0600	Normal
Utility (FEV$_1$ ≥ 70%)		0.80	0.0259	Beta
Utility (40% ≤ FEV$_1$ < 70%)		0.75	0.0208	Beta
Utility (< 40%)		0.69	0.0249	Beta
Utility (post Tx)		0.81	0.0400	Beta
Absolute number of exacerbations per year standard care ≥ 12 years		0.83	0.0308	Normal
Absolute number of exacerbations per year standard care < 12 years		0.51	0.0500	Normal
Reduction (RR) in exacerbations for ivacaftor patients		0.45	0.0357	Normal
Initial increase in FEV$_1$ percentage predicted for ivacaftor patients, ≥ 12 years		0.10	0.0121	Normal
Initial increase in FEV$_1$ percentage predicted for ivacaftor patients, < 12 years		0.10	0.0630	Normal
Initial increase in weight-for-age *z*-score for ivacaftor patients ≥ 12 years		0.33	0.0200	Normal
Initial increase in weight-for-age *z*-score for ivacaftor patients, < 12 years		0.39	0.0800	Normal
Coefficients standard care cost equation	const	£41,084	£588	Normal
	b_age	−£100	£12	Normal
	b_FEV1	−£254	£6	Normal
Probability lung Tx per cycle		0.046	0.0084	Beta
Probability of death per cycle after Tx first year		0.057	0.0057	Beta
Probability of death per cycle after Tx subsequent years		0.023	0.0023	Beta
Cost Tx		£42,018	£4202	Normal
Cost FU Tx first year		£21,634	£2163	Normal
Cost FU Tx second year		£13,063	£1306	Normal
Cost FU Tx third year		£13,733	£1373	Normal
Cost FU Tx years 4–10		£8249	£825	Normal
Cost FU Tx subsequent years		£4590	£459	Normal

FU, follow-up; SE, standard error; Tx, transplantation.

TABLE 25 Estimate of number of patients eligible for ivacaftor treatment

Patient groups	Prevalence, %	Number of people	Denominator	Source
Number of patients with CF in England	NA	7329	NA	CF Trust
Number of CF patients ($\geq$ 6)	NA	6209	NA	CF Trust
Number of CF patients ($\geq$ 6) with the G551D mutation	4.4%[a]	271	6209	Estimate
Percentage not genotyped	4.7[a]	289	6209	Estimate

NA, not applicable.
a   Provided by CF Registry from 2010 data.

TABLE 26 Estimate of number of children aged 6 to 12 years with little or no lung damage eligible for ivacaftor treatment

Patient groups	Prevalence (%)	Number of people	Denominator	Source
Number of CF patients aged 6–12 years	NA	1283	NA	CF Trust
Number of CF patients aged 6–12 years with percentage predicted $FEV_1 > 70\%$	NA	1096	NA	CF Trust
Number of CF patients aged 6–12 years with percentage predicted $FEV_1 > 90\%$	NA	581	NA	CF Trust
Number of CF patients aged 6–12 years with percentage predicted $FEV_1 > 70\%$ and G551D mutation	4.4%[a]	48	1096	Estimate
Number of CF patients aged 6–12 years with percentage predicted $FEV_1 > 90\%$ and G551D mutation	4.4%[a]	25	581	Estimate
Percentage with $FEV_1 > 70\%$ not genotyped	4.7[a]	52	1096	Estimate
Percentage with $FEV_1 > 90\%$ not genotyped	4.7[a]	27	581	Estimate

NA, not applicable.
a   Provided by CF Registry from 2010 data.

Chapter 6 Results of cost-effectiveness analyses

Costs, effects and cost-effectiveness

Conservative scenario

In the conservative scenario, the percentage predicted FEV_1 of ivacaftor-treated patients stays stable for 96 weeks, after which it declines by the same rate as in the standard care population. Without discounting, treatment with ivacaftor leads to a lifetime additional cost of £2.1M (standard care £0.4M, ivacaftor + standard care £2.5M) while gaining 2.7 life-years (standard care 16.25, ivacaftor + standard care 18.94) or 2.18 QALYs (standard care 12.29, ivacaftor + standard care 14.47). After discounting costs and effects, the additional costs of ivacaftor amount to £1.6M, with a gain in life-years of 1.52 and a gain in QALYs of 1.27, leading to an ICER of £1.27M. The ratio of costs to effects is least favourable for the younger age groups, becoming more favourable as the age at start of treatment increases (*Table 27*). The PSA suggests that the ICER is likely to be between £980,000 and £1.85M per QALY gained (see *Table 30*).

Optimistic scenario

In the optimistic scenario, the percentage predicted FEV_1 of ivacaftor-treated patients stays stable over lifetime, while in standard care patients the percentage predicted FEV_1 declines over time. Without discounting, treatment with ivacaftor leads to a lifetime additional cost of £2.5M (standard care £0.4M, ivacaftor + standard care £2.9M) while gaining 19.8 life-years (standard care 16.25, ivacaftor + standard care 36.00) or 16.3 QALYs (standard care 12.29, ivacaftor + standard care 28.66). After discounting costs and effects, the additional costs of ivacaftor amount to £1.8M, with a gain in life-years of 6.20 and a gain in QALYs of 5.26, leading to an ICER of £334,775. The ratio of costs to effects is most favourable for the younger age groups and increases slightly as the age at the start of treatment increases (*Table 28*). The PSA suggests that, given the parameter uncertainty, the ICER is likely to be between £284,000 and £401,000 per QALY gained (see *Table 30*).

Intermediate scenario

The intermediate scenario lies between the conservative and optimistic scenarios, with the percentage predicted FEV_1 of ivacaftor-treated patients declining after 96 weeks at a rate of 66% of that of standard care patients. Without discounting, treatment with ivacaftor leads to a lifetime additional cost of £2.2M (standard care £0.4M, ivacaftor + standard care £2.6M) while gaining 5.29 life-years (standard care 16.25, ivacaftor + standard care 21.54) or 4.27 QALYs (standard care 12.29, ivacaftor + standard care 16.56). After discounting costs and effects, the additional costs of ivacaftor amount to £1.7M, with a gain in life-years of 2.58 and a gain in QALYs of 2.16, leading to an ICER of £771,297. As in the conservative scenario, the ratio of costs to effects is least favourable for the younger age groups and becoming more favourable as the age at the start of treatment increases (*Table 29*). The PSA suggests that the ICER is likely to be between £607,699 and £1.05M per QALY gained (*Table 30*).

Subgroup analysis: 'optimistic scenario' in young children with good lung function

Tables 31 to *34* show that assuming no further disease progression for the proportion of the trial population who were aged < 12 years and had specified baseline lung function would reduce the ICER substantially (range £154,257 to £200,268) in comparison with the optimistic scenario for the whole population, which had an ICER of £334,775 (see *Optimistic scenario*). This is for three main reasons: reduced mortality (and thus increased life expectancy), increased utility (and thus increased QALYs) and reduced cost of standard care (to zero in scenarios 1 and 3).

TABLE 27 Results for the conservative scenario per patient, discounted

Age groups (years)	Total costs, £		Total LYs		Total QALYs		Incrementals			ICER	
	Standard care	Standard care + ivacaftor	Standard care	Standard care + ivacaftor	Standard care	Standard care + ivacaftor	Cost, £	LYs	QALYs	Cost/ LY, £	Cost/ QALY, £
6–9	377,369	2,254,478	16.64	17.90	12.78	13.91	1,877,109	1.25	1.13	1,497,903	1,659,110
10–14	336,038	2,135,961	13.90	15.34	10.56	11.80	1,799,924	1.44	1.25	1,249,949	1,444,225
15–19	301,868	2,031,015	12.68	14.09	9.62	10.83	1,729,147	1.41	1.21	1,230,573	1,433,410
20–24	261,493	1,902,274	11.33	12.74	8.64	9.77	1,640,781	1.40	1.14	1,168,744	1,441,148
25–29	214,716	1,711,345	8.76	10.45	6.55	7.92	1,496,630	1.69	1.37	886,942	1,090,397
30–34	184,657	1,599,947	7.84	9.62	5.87	7.31	1,415,291	1.78	1.44	795,865	983,073
35–39	148,188	1,411,962	6.30	8.16	4.70	6.17	1,263,774	1.85	1.48	681,394	854,858
40–44	130,071	1,316,147	5.63	7.51	4.18	5.68	1,186,075	1.88	1.50	630,479	789,149
45+	96,733	1,071,256	3.98	5.83	2.93	4.35	974,519	1.85	1.41	526,010	689,186
Overall	267,393	1,882,254	11.34	12.86	8.60	9.87	1,614,861	1.52	1.27	1,062,219	1,273,805

LY, life-year.

TABLE 28 Results for the optimistic scenario per patient, discounted

Age groups (years)	Total costs, £		Total LYs		Total QALYs		Incrementals			ICER	
	Standard care	Standard care + ivacaftor	Standard care	Standard care + ivacaftor	Standard care	Standard care + ivacaftor	Cost, £	LYs	QALYs	Cost/ LY, £	Cost/ QALY, £
6–9	377,369	2,330,496	16.64	23.92	12.78	19.18	1,953,127	7.28	6.40	268,296	305,181
10–14	336,038	2,260,721	13.90	21.01	10.56	16.71	1,924,684	7.10	6.15	271,041	312,824
15–19	301,868	2,178,788	12.68	19.45	9.62	15.45	1,876,920	6.77	5.83	277,442	321,971
20–24	261,493	2,064,591	11.33	17.61	8.64	13.89	1,803,099	6.28	5.25	287,253	343,167
25–29	214,716	1,895,717	8.76	14.31	6.55	11.17	1,681,002	5.55	4.62	302,847	364,130
30–34	184,657	1,784,942	7.84	13.20	5.87	10.32	1,600,285	5.36	4.45	298,361	360,008
35–39	148,188	1,593,925	6.30	10.98	4.70	8.49	1,445,737	4.68	3.79	308,897	381,088
40–44	130,071	1,492,938	5.63	10.04	4.18	7.76	1,362,867	4.41	3.59	308,889	380,158
45+	96,733	1,236,253	3.98	7.39	2.93	5.59	1,139,521	3.41	2.66	333,780	429,077
Overall	267,393	2,029,969	11.34	17.53	8.60	13.86	1,762,567	6.20	5.26	284,501	334,775

LY, life-year.

TABLE 29 Results for the intermediate scenario per patient, discounted

Age groups (years)	Total costs, £		Total LYs		Total QALYs		Incrementals			ICER	
	Standard care	Standard care + ivacaftor	Standard care	Standard care + ivacaftor	Standard care	Standard care + ivacaftor	Cost, £	LYs	QALYs	Cost/ LY, £	Cost/ QALY, £
6–9	377,369	2,283,223	16.64	19.33	12.78	15.15	1,905,854	2.69	2.37	708,537	803,059
10–14	336,038	2,176,018	13.90	16.62	10.56	12.89	1,839,980	2.72	2.33	677,537	788,304
15–19	301,868	2,080,394	12.68	15.29	9.62	11.85	1,778,526	2.61	2.22	682,368	799,394
20–24	261,493	1,956,552	11.33	13.83	8.64	10.69	1,695,059	2.50	2.05	677,498	825,322
25–29	214,716	1,769,591	8.76	11.28	6.55	8.60	1,554,875	2.52	2.05	617,920	758,240
30–34	184,657	1,659,432	7.84	10.41	5.87	7.96	1,474,776	2.57	2.09	574,244	705,951
35–39	148,188	1,469,508	6.30	8.78	4.70	6.69	1,321,320	2.48	1.99	532,964	663,811
40–44	130,071	1,372,635	5.63	8.07	4.18	6.14	1,242,564	2.45	1.97	507,393	631,814
45+	96,733	1,123,009	3.98	6.18	2.93	4.63	1,026,276	2.21	1.69	464,920	606,125
Overall	267,393	1,930,690	11.34	13.91	8.60	10.76	1,663,297	2.58	2.16	645,780	771,297

LY, life-year.

TABLE 30 Results for the PSA

Measures	Conservative scenario			Optimistic scenario			Intermediate scenario		
	Incremental cost, £	Incremental QALY	ICER, £	Incremental cost, £	Incremental QALY	ICER, £	Incremental cost, £	Incremental QALY	ICER, £
Mean	1,613,491	1.25	1,313,333	1,762,287	5.24	338,293	1,655,640	2.05	814,401
SD	12,800	0.17	178,467	15,517	0.39	24,349	15,324	0.20	73,733
Min.	1,590,459	0.87	980,700	1,708,888	4.36	284,473	1,614,532	1.55	607,699
Median	1,613,534	1.27	1,278,072	1,763,910	5.21	338,723	1,654,904	2.05	811,036
Max.	1,643,041	1.68	1,845,752	1,802,561	6.171	400,559	1,693,060	2.76	1,047,179

max., maximum; min., minimum; SD, standard deviation.

TABLE 31 Scenario 1: baseline FEV$_1$ >70%, standard care cost Band 1

Strategies	Total costs, £ (disc.)	Total costs, £ (undisc.)	Total LYs (disc.)	Total LYs (undisc.)	Total QALYs (disc.)	Total QALYs (undisc.)	Incremental costs, £ (disc.)	Incremental QALYs (disc.)	Cost per QALY, £ (disc.)
Standard care	360,185	606,412	16.89	27.06	13.06	20.73	NA	NA	Reference
Ivacaftor + standard care	2,354,701	4,113,770	26.18	72.18	24.08	72.87	1,994,516	11.02	180,987

Disc., discounted; LY, life-year; NA, not applicable; undisc., undiscounted.

TABLE 32 Scenario 2: baseline FEV$_1$ >70%, standard care cost zero

Strategies	Total costs, £ (disc.)	Total costs, £ (undisc.)	Total LYs (disc.)	Total LYs (undisc.)	Total QALYs (disc.)	Total QALYs (undisc.)	Incremental costs, £ (disc.)	Incremental QALYs (disc.)	Cost per QALY, £ (disc.)
Standard care	360,185	606,412	16.89	27.06	13.06	20.73	NA	NA	Reference
Ivacaftor	2,060,130	3,301,687	26.18	72.18	24.08	72.87	1,699,945	11.02	154,257

Disc., discounted; LY, life-year; NA, not applicable; undisc., undiscounted.

TABLE 33 Scenario 3: baseline FEV_1 >90%, standard care cost Band 1

Strategies	Total costs (disc.), £	Total costs (undisc.), £	Total LYs (disc.)	Total LYs (undisc.)	Total QALYs (disc.)	Total QALYs (undisc.)	Incremental costs (disc.), £	Incremental QALYs (disc.)	Cost per QALY (disc.), £
Standard care	352,444	621,317	18.01	29.86	14.07	23.07	NA	NA	Reference
Ivacaftor + standard care	2,351,687	4,088,066	26.09	71.31	24.05	72.20	1,999,243	9.98	200,268

Disc., discounted; LY, life-year; NA, not applicable; undisc., undiscounted.

TABLE 34 Scenario 4: baseline FEV_1 >90%, standard care cost zero

Strategies	Total costs (disc.), £	Total costs (undisc.), £	Total LYs (disc.)	Total LYs (undisc.)	Total QALYs (disc.)	Total QALYs (undisc.)	Incremental costs (disc.), £	Incremental QALYs (disc.)	Cost per QALY (disc.), £
Standard care	352,444	621,317	18.01	29.86	14.07	23.07	NA	NA	Reference
Ivacaftor	2,058,197	3,285,701	26.09	71.31	24.05	72.20	1,705,752	9.98	170,869

Disc., discounted; LY, life-year; NA, not applicable; undisc., undiscounted.

Budget impact

When we translate the per-patient results from the previous section to population costs, we find that the total lifetime cost of treating all ivacaftor-eligible patients in England ($n = 271$; see *Chapter 5*, *Budget impact*) is £510M for the conservative scenario, £550M for the optimistic scenario and £523M for the intermediate scenario, plus one-time genetic testing costs of 289 × £160 = £46,240. The total lifetime costs of treating patients with standard care would amount to £72M. The incremental costs (additional cost of ivacaftor compared with standard care alone) are £438M for the conservative scenario, £479M for the optimistic scenario and £451M for the intermediate scenario. The total additional costs in the first year (assuming all eligible patients receive ivacaftor) would amount to £43M, while the first-year costs for standard care are £5.6M. Note that in the first year, all scenarios produce the same result.

The estimate for the total lifetime cost of treating all patients aged 6–12 years who have baseline percentage predicted $FEV_1 > 70\%$ in England ($n = 48$; see *Chapter 5*, *Budget impact*) with ivacaftor is £99M for the scenario with no standard care cost (scenario 2) and £113M for the scenario with Band 1 and DNase costs for standard care (scenario 1). One-time genetic testing costs of £8320 (52 × £160) should be added to each scenario. The incremental costs (additional cost of ivacaftor compared with standard care alone) is £81M for the zero-cost standard care scenario and £96M for the scenario with Band 1 and DNase costs for standard care. In the scenario where standard care is zero for ivacaftor patients, the total additional costs in the first year would amount to £7M whereas assuming that the standard care for ivacaftor patients includes Band 1 and DNase leads to total additional costs in the first year of £7.5M. The first-year costs for standard care patients (i.e. without ivacaftor) are £0.8M.

The estimate for the total lifetime cost of treating all patients aged 6–12 years who have baseline percentage predicted $FEV_1 > 90\%$ in England ($n = 25$; see *Chapter 5*, *Budget impact*) with ivacaftor is £51.5M for the scenario with no standard care cost and £58.8M for the scenario with Band 1 and DNase costs for standard care. One-time genetic testing costs of £4320 (27 × £160) should be added to each scenario. The incremental costs (additional cost of ivacaftor compared with standard care alone) is £42.6M for the zero-cost standard care scenario and £50.0M for the scenario with Band 1 and DNase costs for standard care. In the scenario where standard care is zero for ivacaftor patients, the total additional costs in the first year would amount to £3.7M, whereas assuming that the standard care for ivacaftor patients includes Band 1 and DNase leads to total additional costs in the first year of £4M. The first-year costs for standard care patients (i.e. without ivacaftor) are £0.4M.

Chapter 7 Discussion

Statement of principal findings

Clinical effectiveness

The clinical effectiveness review found that ivacaftor is an effective treatment for adults and children with the G551D mutation based on two RCTs, one in adults and one in children, and an open-label extension trial of the two included RCTs. The studies were generally well conducted and were rated as low or unclear on all risk of bias domains; limited details available on the study in children resulted in some domains being rated as unclear. All outcomes assessed in the review showed greater improvements in the ivacaftor group than in the placebo group. All differences were statistically significant ($p < 0.02$) with the exception of QoL in children where differences between ivacaftor and placebo favoured ivacaftor but failed to reach statistical significance at either 24- or 48-week follow-up. Ivacaftor was associated with an absolute increase of around 10% in the percentage predicted FEV_1 compared with baseline values while levels in patients treated with placebo stayed around the same. Results from the open-label study showed that improvements in lung function, quality of life and weight were maintained after a further 48 weeks of treatment with ivacaftor (96 weeks' total treatment). Subgroup analysis showed similar improvements in lung function for all subgroups investigated. This suggests that the effects of ivacaftor do not differ significantly according to age, sex, geographical region or baseline lung function. Ivacaftor does not appear to be associated with an increased risk of adverse events or withdrawals.

Cost-effectiveness

The economic evaluation of ivacaftor showed that the ICER varies between £334,000 and £1.27M per QALY gained, depending on the assumptions made for the long-term effectiveness of ivacaftor. We explored three scenarios: conservative, optimistic and an intermediate scenario. The variation between ICERs was mostly due to large differences in QALYs gained between the scenarios, which varied between 1.27 and 5.26. We found that the impact of the remaining parameter uncertainty is small compared with the uncertainty caused by the long-term extrapolation. An additional optimistic scenario for the subgroup of patients < 12 years of age with no or little lung damage resulted in an ICER of between £154,000 and £200,000 per QALY gained.

We also explored the budget impact for England of introducing ivacaftor to all eligible CF patients. We found that the total additional lifetime costs (discounted) for this cohort would amount to £438M to £479M, whereas the lifetime costs for standard care only would amount to £72M. The total additional costs in the first year would amount to £43M (including the costs for genetic testing) while the costs for standard care would amount to only £5.6M.

When the population treated with ivacaftor is limited to patients < 12 years of age with no or little lung damage, we found that the total additional lifetime costs (discounted) amount to £51M to £113M, whereas the lifetime costs for standard care only would be between £9M and £17M. The total additional costs in the first year would amount to £3.7M to £7.5M (including the costs for genetic testing) while the costs for standard care only would amount to £0.4M to £0.8M.

Strengths and limitations

Clinical effectiveness

Extensive literature searches were conducted in an attempt to maximise retrieval of relevant studies. These included electronic searches of a variety of bibliographic databases, screening references of included publications, as well as screening of clinical trials registers and conference abstracts to identify unpublished

studies. Despite this, we were able to identify only two RCTs and one open-label study which met the inclusion criteria for our review. This finding is to be expected because ivacaftor is a very new drug and so has currently been evaluated only by the manufacturer.

Clear inclusion criteria were specified in the protocol for this review. The eligibility of studies for inclusion is therefore transparent. In addition, we have provided specific reasons for excluding all of the studies which were assessed as full-text papers. We restricted inclusion into the review to studies that reported a minimum of 3 months' follow-up. We felt that follow-up shorter than this was insufficient to establish a sustained treatment effect. This resulted in the exclusion of three small Phase II trials, all of which reported positive effects of ivacaftor. The review process followed recommended methods to minimise the potential for error and/or bias.[18] Search results were independently screened for relevance by two reviewers, and full-text inclusion assessment, data extraction and quality assessment were done by one reviewer and checked by a second. Any disagreements were resolved by consensus. We conducted a formal quality assessment to evaluate the risk of bias in the included studies. This was limited by the lack of published details on the children's trial, which resulted in this trial being rated as unclear on some domains.

The small number of studies conducted in different patient groups (adults and children) meant that it was not possible to conduct a formal meta-analysis. Instead results were presented grouped on outcome to provide an overview of the evidence available for each outcome. The small number of included studies also meant that it was not possible to formally investigate the potential for publication bias. However, the risk of publication bias is likely to be very low. All trials of ivacaftor identified by the searches (both included and excluded) were conducted by the manufacturers and were registered on trial registries, which were searched as part of our systematic searches. It would not have been possible for anyone other than the manufacturer to conduct a trial of ivacaftor prior to it being licensed. Licensing was only granted in the USA on 31 January 2012,[14] and so there would not have been time for new studies to be conducted since these data and for results to have been published that would have fulfilled our inclusion criteria. Details were available from multiple sources for the two included RCTs. The primary report of the adults' study included a supplementary file containing detailed results information. However, some information was lacking from this report, in particular information on the variability of effect estimates (CIs and standard deviations). Other sources were therefore used to locate this information, in particular documents available via the FDA website[34–36] and supplementary data provided by Vertex. The children's study and the open-label study have not yet been reported as full-text journal articles. Information relating to these studies was therefore obtained from conference abstracts,[27] the FDA website,[34–36] a Vertex press release,[29] and the confidential dossier supplied by the manufacturer.[16] A problem with obtaining results from multiple sources was that there were slight discrepancies in figures reported in different reports. We therefore developed a hierarchy to select a single estimate to contribute to the results of the review. We also included details of differences in results in *Appendix 5*. These differences were all small and unlikely to have impacted on the conclusions of the review.

The methods of analysis in the included RCTs appeared statistically robust. This was supported by the FDA analysis of these studies, which included various sensitivity analyses using different statistical methods. These analyses all showed similar results for the primary outcome of percentage predicted FEV_1 through to week 24.[36]

Cost-effectiveness

We performed a critical appraisal of the model submitted by the manufacturer, and were able to improve many model inputs, such as the quality-of-life estimates, the costs of standard care and the natural decline in percentage predicted FEV_1. We were also able to include lung transplantation (with its associated survival, quality-of-life and follow-up costs) to the model.

The patient population in the model was based on the patients included in the two RCTs. Comparison of baseline characteristics of these patients with characteristics of all CF patients in the UK obtained from the UK CF registry showed that the patient populations were comparable with respect to the proportion of

male to female and the median FEV_1. However, the percentage of patients with a chronic *P. aeruginosa* infection was higher in our patient population (76% in the adult population) compared with 51% in the total UK CF population aged > 12 years. This could indicate that despite the comparable FEV_1 the patient population in the model included more patients whose lungs were already severely and irreversibly damaged by CF, which may have an influence on the generalisability of the results.

The survival function used in the model requires an estimate of the annual number of exacerbations per patient. The annual exacerbation rates for the standard care group used in the manufacturer model, 1.4 for patients ≥ 12 years and 0 for patients < 12 years, were based on the small numbers of patients in the two trials ($n = 78$ and $n = 28$, respectively) and an observation period of 48 weeks. We adapted these rates because they were based on small sample sizes and obtained from a trial population, which is generally a selective population due to the inclusion and exclusion criteria used. The current clinical trials, for example, included only patients with clinically stable CF without any respiratory infection or exacerbation in the 4 weeks before the start of the study. Furthermore, studies reporting on exacerbation frequencies should at least have a follow-up of 1 year to account for seasonal variation. Therefore, the annual exacerbation rates in the adapted model were based on a large, continuous, observational registry, the US CF Patient Registry, which most likely resulted in exacerbation rates that were more representative for the total CF population than the trial estimates.

In the model, we have included lung transplantation, assuming that patients with a percentage predicted $FEV_1 < 30\%$ are eligible for a lung transplant. However, in reality, eligibility is increasingly based on additional factors as, in the past years, the survival of patients with a percentage predicted $FEV_1 < 30\%$ has markedly increased.[71] Additionally, the costs of follow-up of transplanted patients were based on a study by Anyanwu *et al.*[66] However, it is unclear if these costs also include the potential CF-related costs that will still occur for CF complications in other organs. Thus, it is possible that the post-transplantation costs should be higher. However, both the percentage of patients eligible for lung transplant and the post-transplantation costs have a very minimal impact on the ICER.

Three out of four dimensions on which ivacaftor showed an effect (percentage predicted FEV_1, weight and exacerbations) were taken into account in the model. However, the decrease in the number of exacerbations due to ivacaftor was included in the model only in so far as it affected the survival of the patients. A reduction in exacerbations results in decreased mortality and so reduced exacerbations contributes to life-year gains. It is reasonable to assume that a reduction in exacerbations also has a direct effect on lung function, QoL and costs. Studies by Saunders *et al.*[72,73] show that there is a strong association between frequency of exacerbations and a decline in lung function. In addition, a study by Britto *et al.*[74] found that pulmonary exacerbations in the past 6 months were negatively associated with both physical and psychosocial measures of quality of life. Furthermore, treatment of pulmonary exacerbations is associated with high health-care costs, especially for inpatient hospital care and medication.[75] A reduction in exacerbations would therefore lead to an increase in quality of life and a reduction of health-care costs. However, due to a lack of valid data on the association between CF exacerbations and QoL (in terms of utility values) and the costs of a CF exacerbation, the independent impact of exacerbations on QoL and costs could not be included in the model. The CF bandings cover most costs for patients with CF but it was not possible to disentangle maintenance costs from treatment costs for exacerbations. Ideally, we would have added an event probability to the model, indicating per cycle what the probability of an exacerbation is, possibly dependent on age and percentage predicted FEV_1. However, such data were neither found in the literature nor available in the clinical study reports of ivacaftor. One of the challenges in modelling exacerbations explicitly is that a treatment-related reduction in exacerbations is often a result of both an indirect impact through lung function and a direct impact. In order to avoid double counting, we would have needed patient-level data on all lung function measurements and all dates when exacerbations occurred. Also, information about the severity of the exacerbation would be required. Additionally, valid data would need to be found on the costs of a CF exacerbation. In the data source used as input for the cost of CF care by severity no distinction was made between costs for maintenance treatment and costs for exacerbations. If the treatment effects on

exacerbations could have been taken into account then the gain in QALYs in the ivacaftor group might have been higher and the savings in CF-related health-care costs might have been higher, resulting in a lower ICER.

In the model, quality-of-life values and costs were assumed to be dependent on disease severity defined in terms of percentage predicted FEV_1. However, a study by Gee *et al.*[76] showed that this clinical measure explains only part of the variation in QoL and they suggested that other clinical and social factors might also be important, such as social support and coping strategies. Our analysis of the cost data from the CF registry showed the same, that only 26% of variance was explained by age and percentage predicted FEV_1. As always in modelling diseases, further refinements of the health states considered would provide a better reflection of the heterogeneity among patients, but as a result it would likely become more difficult to find the data required to inform transitions between health states.

The costs of standard care included in the model are not complete. The CF tariff bands do not include surgery for certain device implantations nor do they include costs of medications prescribed by the general practitioner. Thus, the true costs of standard care in CF will be higher than the costs used in the model, which would decrease the ICER. However, the impact of these additional costs for standard care would probably have a minimal impact on the ICER given that the annual cost of standard care was only a very small fraction of total annual cost given the price of ivacaftor of £182,000.

One of the main challenges in estimating lifetime cost and QALYs is extrapolating from short-term trial data, in this case the time horizon for the randomised component being only 48 weeks, although up to 96 weeks with some open-label data. On this basis we constructed a set of scenarios based on various assumptions regarding the degree of maintenance of the treatment effect. We make no claim as to which scenario is more likely. However, given expert opinion that ivacaftor might permanently correct the underling biochemical disorder, it does seem likely that young children with little or no lung damage will do much better. Therefore, we conducted a subgroup analysis on children up to age 12 with little or no permanent lung damage, which assumed they would have length and quality of life as if they had been cured of the CF.

The budget impact analysis was performed only for the cohort of CF patients as observed in the year 2011. The impact of new patients becoming eligible for the treatment with ivacaftor after that year was not taken into account. Lifetime costs for ivacaftor for this group of patients would have been lower, because these patients will be treated for fewer years before the drug comes off patent.

Uncertainties

Clinical effectiveness

The main uncertainty relates to the long-term clinical effectiveness of ivacaftor. The available RCTs were only 48 weeks in duration. The open-label trial provided information on an additional 48 weeks of ivacaftor treatment in adults and 24 weeks in children, meaning that data are currently available for 96 weeks of treatment with ivacaftor in adults and 72 weeks of treatment in children. The open-label trial is intended to run for 96 weeks; when full data are available from this study, information will be available on the effectiveness of a total of 144 weeks' (just over 2.5 years') treatment with ivacaftor in adults and children.

Ivacaftor has been evaluated only in adults and children ≥ 6 years. Its potential effect in children younger than this is unclear. It may be that treating patients at a very young age with ivacaftor is more effective as it may prevent some of the complications of CF from developing. Ivacaftor works by correcting the underlying deficit in chloride ion transport. This is supported by the results of the systematic review which show improvements in sweat chloride levels, with levels in ivacaftor-treated patients returning to within normal ranges (i.e. below the threshold required for a diagnosis of CF) within 2 weeks of treatment with

ivacaftor. It would therefore appear reasonable to hypothesise that treating very young patients in whom no lung damage or infection has yet developed may prevent symptoms of CF from ever developing. However, until trials with long-term follow-up are done in this age group of children the potential harms and benefits remain uncertain. The trials to date focus on the impact of ivacaftor on lung function. If ivacaftor works by correcting the *CFTR* defect and is given before damage has occurred to other organs such as the pancreas, then it may also prevent damage to these organs, thereby preventing the occurrence of complications associated with CF, such as diabetes. Further evidence on the effects of ivacaftor on other organs is required to address this issue.

The trials evaluated in this review were restricted to patients with the G551D mutation. These represent only around 5.7% of the UK population with CF. A study of 140 patients homozygous for the ΔF508 mutation did not find a significant difference in percentage predicted FEV_1 between patients treated with ivacaftor and those receiving placebo after 16 weeks of treatment. Adverse events were similar between the groups and there were some small benefits of ivacaftor on other outcomes.[77,78] A further study is ongoing which is investigating ivacaftor in combination with VX-809, an investigational CFTR corrector, in patients with CF and homozygous for the ΔF508 mutation.[79] This trial is still ongoing but early results suggest potentially beneficial effect of the drug combination. If this combination is proved to be effective it would considerably expand the potential usage of ivacaftor as the ΔF508 is the most common CF-causing mutation in the UK population.[7]

Cost-effectiveness

From a cost-effectiveness perspective the long-term effectiveness is also the main uncertainty. The various scenarios explored for this long-term effectiveness show a wide range of ICERs. Only when longer-term data on ivacaftor become available will it be clear which of these ICERs is most relevant.

Additional uncertainty is caused by the long-term costs of ivacaftor. In the model, it is assumed that, after 14 years, a generic version of ivacaftor will be available at £20,000 (as opposed to £182,000 for the branded version). This information was obtained from the manufacturer and therefore assumed to be best possible estimates. It is clear that the costs of ivacaftor are the main driver of the results, and thus the lifelong cost estimates should be interpreted with care. If the patent expiry for ivacaftor were to occur sooner or if the generic costs are lower, the lifetime costs for treatment with ivacaftor would be lower, resulting in a lower cost-effectiveness ratio compared with standard care.

Adoption of a societal perspective might have been interesting; however, this was beyond the scope of the review, which was to estimate the cost-effectiveness of ivacaftor from the perspective of the NHS. However, had such an analysis been undertaken it is likely that savings in costs for informal care and productivity loss in those treated with ivacaftor would have reduced the ICER.

Also, given that ivacaftor is an orphan drug, there is no clear benchmark to indicate whether or not ivacaftor should be considered cost-effective. Several other orphan drugs are in current use despite ICERs being considerably higher than the threshold of £20,000 to £30,000 applied in most NICE appraisals;[69] some examples of these are shown in *Table 35*.

TABLE 35 Orphan drugs: prevalence of condition and ICER[69]

Products	Conditions	Number of people with condition in UK	Preliminary estimated ICER (£ per QALY)
Agalsidase beta (Fabrazyme®, Genzyme)	Fabry's disease	200	203,009
Imiglucerase (Cerezyme®, Genzyme)	Gaucher's disease (types I and III)	270	391,244
Laronidase (Aldurazyme®, Genzyme)	Mucopolysaccharidosis (type I)	130	334,880
Miglustat (Zavesca®, Actelion)	Gaucher's disease (type I)	270	116,800
Nonacog alfa (BeneFIX®, Wyeth)	Haemophilia B	350	172,500
Iloprost (Ventavis®, Bayer Schering)	Primary pulmonary hypertension	100	23,324

Chapter 8 Conclusions

Implications for service provision

The available evidence suggests that ivacaftor is a clinically effective treatment for patients with CF and the G551D mutation. The high cost of ivacaftor may prove an obstacle in the uptake of this treatment; the economic evaluation showed that the ICER for ivacaftor + standard care compared with standard care only varies between £334,000 and £1.27M per QALY gained.

The estimate of the increased cost in the first year of prescribing ivacaftor to about 271 eligible individuals was found to be approximately £43M compared with the total annual cost of caring for all 7329 individuals with CF in England of approximately £150.2M.

On 19 December 2012, the four Specialised Commissioning Groups in England (North of England, South of England, Midlands and East, and London) announced that ivacaftor will be funded by the NHS in England for all patients aged ≥ 6 years with CF and the G551D gene mutation.[80]

Suggested research priorities

The main area where further research is required, to inform both clinical effectiveness and cost-effectiveness questions, is the long-term effectiveness of ivacaftor. The main area of uncertainty in the economic model related to how the long-term effects (beyond 96 weeks) of ivacaftor were included in the model. The ongoing open-label trial will go some way to addressing this question but will provide data only on effects up to around 2.5 years of treatment. The effectiveness of ivacaftor in children aged < 6 years is another potentially important question although this may be difficult to address through clinical trials due to the difficulties in conducting such trials in young children. The current evidence only supports the use of ivacaftor in patients with at least one G551D mutation. Such patients represent only around 5% of patients with CF. The potential benefit of ivacaftor in patients with other mutations is therefore also an important area for further research. Clinical trials in patients with certain mutations are ongoing.

From an economic perspective further research to inform how exacerbations can be fully accounted for in an economic model would improve the economic model. Although we have attempted to include these in our model a more sophisticated method of analysis is required which could appropriately model the additional benefits that ivacaftor may have on exacerbations above the effects which it has on percentage predicted FEV_1. Further information on the costs of standard care and primary care costs of cystic fibrosis would also be helpful for the model. Although such data would be likely to be dominated by the costs of ivacaftor, they would help to increase the validity of the model.

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Contributions of authors

Penny Whiting and **Marie Westwood** planned and performed the systematic review and interpretation of evidence.

Maiwenn Al, **Laura Burgers** and **Martine Hoogendoorn** planned and performed the cost-effectiveness analyses and interpreted results.

Nigel Armstrong and **Steve Ryder** contributed to planning and interpretation of cost-effectiveness analysis and acquisition of cost data for modelling. Laura Burgers and Steve Ryder planned and performed the systematic review and interpretation of health economic evidence.

Alex Allen devised and performed the literature searches and provided information support to the project.

Jos Kleijnen and **Hans Severens** provided senior advice and support to the systematic review and cost-effectiveness analyses, respectively.

All parties were involved in drafting and/or commenting on the report.

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Appendix 1 Literature search strategies

Clinical effectiveness

EMBASE (OvidSP) 1974–2012 week 17
Searched 3 May 2012.

1. Ivacaftor/ (72)
2. (Ivacaftor or Kalydeco or VX-770 or VX770 or 873054-44-5 or ivacaftorum).af. (138)
3. or/1-2 (138)

MEDLINE (OvidSP) 1946–April 2012 week 4
Searched 3 May 2012.

1. (Ivacaftor or Kalydeco or VX-770 or VX770 or 873054-44-5 or ivacaftorum).af. (10)

MEDLINE In-Process & Other Non-Indexed Citations (OvidSP) up to 2 May 2012

MEDLINE Daily Update (OvidSP) up to 2 May 2012
Searched 3 May 2012.

1. (Ivacaftor or Kalydeco or VX-770 or VX770 or 873054-44-5 or ivacaftorum).af. (3)

Cochrane Database of Systematic Reviews (CDSR) (Wiley Online Library) up to 2012 issue 4

Cochrane Central Register of Controlled Trials (CENTRAL) (Wiley Online Library) up to 2012 issue 4

Database of Abstracts of Reviews of Effects (DARE) (Wiley Online Library) up to 2012 issue 2

Health Technology Assessment (HTA) Database (Wiley Online Library) up to 2012 issue 2

NHS Economic Evaluation Database (NHS EED) (Wiley Online Library) up to 2012 issue 2
Searched 3 May 2012.

#1 (Ivacaftor OR Kalydeco OR VX-770 OR VX770 OR VX 770 OR 873054-44-5 OR ivacaftorum)

CDSR retrieved no records.

CENTRAL retrieved five records.

DARE retrieved no records.

HTA retrieved no records.

NHS EED retrieved 0 records.

Database of Abstracts of Reviews of Effects (DARE) (CRD) up to 3 May 2012

Health Technology Assessment (HTA) Database (CRD) up to 3 May 2012

NHS Economic Evaluation Database (NHS EED) (CRD) up to 3 May 2012
Searched 3 May 2012.

#1 (Ivacaftor OR Kalydeco OR VX-770 OR VX770 OR VX 770 OR 873054-44-5 OR ivacaftorum)

DARE retrieved no records.

HTA retrieved no records.

NHS EED retrieved no records.

Latin American and Caribbean Health Sciences Literature (LILACS) (VHL)
URL: http://lilacs.bvsalud.org/en

Searched 4 May 2012.

Ivacaftor OR Kalydeco OR VX-770 OR VX770 OR 873054-44-5 OR ivacaftorum (0)

ClinicalTrials.gov
URL: http://clinicaltrials.gov/ct2/search/advanced

Searched 4 May 2012.

Ivacaftor OR Kalydeco OR VX-770 OR VX770 OR VX 770 OR 873054-44-5 OR ivacaftorum (18)

mRCT – metaRegister of Controlled Trials (internet)
URL: www.controlled-trials.com/mrct/search.html

Searched 4 May 2012.

Ivacaftor OR Kalydeco OR VX-770 OR VX770 OR VX 770 OR 873054-44-5 OR ivacaftorum (12)

World Health Organization International Clinical Trials Registry Platform (ICTRP) (internet)
URL: www.who.int/ictrp/en

Searched 4 May 2012.

Ivacaftor OR Kalydeco OR VX-770 OR VX770 OR VX 770 OR 873054-44-5 OR ivacaftorum (18)

European Cystic Fibrosis Society (ECFS) Conferences – searched titles (no abstracts available)

URL: www.ecfs.eu/meetings/ecfs

Year	Ivacaftor	Kalydeco	VX-770	G551D	Total abstracts found after deduplication
2011	0	0	2	1	**3**
2010	0	0	2	1	**3**
2009	0	0	2	2	**4**
2008	0	0	0	1	**1**
2007	0	0	0	0	**0**
Total					**11**

Eleven references retrieved.

NACFC: The Annual North American Cystic Fibrosis Conferences

URL: www.nacfconference.org

Year	Ivacaftor	Kalydeco	VX-770	G551D	Total abstracts found after deduplication
2011[a]	1	0	14	12	**17**
2010[b]	0	0	8	8	**10**
2009[b]	0	0	7	8	**13**
2008[b]	0	0	3	1	**3**
2007[b]	0	0	1	10	**10**
Total					**53**

Fifty-three references retrieved.
a Searched titles and abstracts.
b Searched titles for papers, searched titles and abstracts for posters.

CIPP: International Congress on Pediatric Pulmonology

URL: www.cipp-meeting.org/index.htm

Searched titles (no abstracts available).

Year	Ivacaftor	Kalydeco	VX-770	G551D	Total abstracts found after deduplication
2011	0	0	0	0	**0**
2010	0	0	1	1	**1**
2009	**No conference**				
2008	**Unable to search so browsed abstracts**				**0**
2007	**Abstracts unavailable through website**				
Total					**1**

One reference retrieved.

Update searches

EMBASE (OvidSP) 2012 week 10–2012 week 26

Searched 6 July 2012.

1. Ivacaftor/ (89)
2. (Ivacaftor or Kalydeco or VX-770 or VX770 or 873054-44-5 or ivacaftorum).af. (156)
3. or/1-2 (156)
4. (20121$ or 20122$).em. (43,3317)
5. 3 and 4 (29)

MEDLINE (OvidSP) 2012–June 2012 week 4

Searched 6 July 2012.

1. (Ivacaftor or Kalydeco or VX-770 or VX770 or 873054-44-5 or ivacaftorum).af. (12)
2. 2012$.ed. (414,936)
3. 1 and 2 (4)

MEDLINE In-Process & Other Non-Indexed Citations (OvidSP) 2012–5 June 2012

MEDLINE Daily Update (OvidSP) 2012–5 June 2012

Searched 6 July 2012.

1. (Ivacaftor or Kalydeco or VX-770 or VX770 or 873054-44-5 or ivacaftorum).af. (3)
2. 2012$.ed. (29,802)
3. 1 and 2 (1)

Cochrane Database of Systematic Reviews (CDSR) (Wiley Online Library) 2012–Issue 6:2012

Cochrane Central Register of Controlled Trials (CENTRAL) (Wiley Online Library) 2012–Issue 6:2012

Database of Abstracts of Reviews of Effects (DARE) (Wiley Online Library) 2012–Issue 2:2012

Health Technology Assessment (HTA) Database (Wiley Online Library) 2012–Issue 2:2012

NHS Economic Evaluation Database (NHS EED) (Wiley Online Library) 2012–Issue 2:2012

Searched 6 July 2012.

#1 (Ivacaftor OR Kalydeco OR VX-770 OR VX770 OR VX 770 OR 873054-44-5 OR ivacaftorum), in 2012 **0**

CDSR retrieved no records.

CENTRAL retrieved no records.

DARE retrieved no records.

HTA retrieved no records.

NHS EED retrieved no records.

Database of Abstracts of Reviews of Effects (DARE) (CRD) up to 7 June 2012

Health Technology Assessment (HTA) Database (CRD) up to 7 June 2012

NHS Economic Evaluation Database (NHS EED) (CRD) up to 7 June 2012
Searched 6 July 2012.

#1 (Ivacaftor OR Kalydeco OR VX-770 OR VX770 OR VX 770 OR 873054-44-5 OR ivacaftorum) **0**

DARE retrieved no records.

HTA retrieved no records.

NHS EED retrieved no records.

Latin American and Caribbean Health Sciences Literature (LILACS) (VHL)
URL: http://lilacs.bvsalud.org/en

Searched 6 July 2012.

(Ivacaftor OR Kalydeco OR VX-770 OR VX770 OR 873054-44-5 OR ivacaftorum) (0)

ClinicalTrials.gov 1 May 2012–6 July 2012
URL: http://clinicaltrials.gov/ct2/search/advanced

Searched 6 July 2012.

Ivacaftor OR Kalydeco OR VX-770 OR VX770 OR VX 770 OR 873054-44-5 OR ivacaftorum l received from 01/05/2012 to 06/07/2012 (5)

*m*RCT – *meta*Register of Controlled Trials (internet)
URL: www.controlled-trials.com/mrct/search.html

Searched 6 July 2012.

Four out of five registers, i.e. not ClinicalTrials.gov.

Ivacaftor OR Kalydeco OR VX-770 OR VX770 OR VX 770 OR 873054-44-5 OR ivacaftorum (1)

Downloaded into Word file: Trials_Update1.

World Health Organization International Clinical Trials Registry Platform (ICTRP) (internet) 1 May 2012–6 July 2012
URL: www.who.int/ictrp/en

Searched 6 July 2012.

Intervention: Ivacaftor OR Kalydeco OR VX-770 OR VX770 OR VX 770 OR 873054-44-5 OR ivacaftorum (3)

Title: Ivacaftor OR Kalydeco OR VX-770 OR VX770 OR VX 770 OR 873054-44-5 OR ivacaftorum (two duplicates)

Downloaded into Word file: Trials_Update1.

European Cystic Fibrosis Society (ECFS) Conferences
URL: www.ecfs.eu/meetings/ecfs

Searched 19 July 2012.

Searched titles – no abstracts available.

Year	Ivacaftor	Kalydeco	VX-770	G551D	Total abstracts found after deduplication
2012	9	0	0	6	**9**
Nine references retrieved.					

Downloaded into Word file: ECFS_Update1.

NACFC: The Annual North American Cystic Fibrosis Conferences
URL: https://www.nacfconference.org

Searched 19 July 2012.

Year	Ivacaftor	Kalydeco	VX-770	G551D	Total abstracts found after deduplication
2012	Conference not occurred yet				

CIPP International Congress on Pediatric Pulmonology
URL: www.cipp-meeting.org/index.htm

Searched *Paediatric Respiratory Reviews* supplement 1 as e-mailed by CIPP.

Searched 25 July 2012.

Searched titles – no abstracts available.

Year	Ivacaftor	Kalydeco	VX-770	G551D	Total abstracts found after deduplication
2012	1	1	0	0	**1**

Cost-effectiveness

MEDLINE (OvidSP) 2002–May 2012 week 1
Searched 11 May 2012.

1. cystic fibrosis/ (26,164)
2. ((Cystic adj2 fibrosis) or mucoviscidosis).ti,ab,ot,hw. (34,176)
3. CF.ti,ot. (1276)
4. (pancreas adj3 fibrocystic adj3 disease$).ti,ab,ot,hw. (16)
5. or/1-4 (34,859)
6. economics/ (26,269)
7. exp "costs and cost analysis"/ (164,214)
8. economics, dental/ (1840)
9. exp "economics, hospital"/ (17,877)
10. economics, medical/ (8463)
11. economics, nursing/ (3861)
12. economics, pharmaceutical/ (2325)
13. (economic$ or cost or costs or costly or costing or price or prices or pricing or pharmacoeconomic$).ti, ab. (359,328)
14. (expenditure$ not energy).ti,ab. (15,019)
15. (value adj1 money).ti,ab. (18)
16. budget$.ti,ab. (15,258)
17. or/6-16 (475,664)
18. ((energy or oxygen) adj cost).ti,ab. (2417)
19. (metabolic adj cost).ti,ab. (636)
20. ((energy or oxygen) adj expenditure).ti,ab. (13,970)
21. or/18-20 (16,385)
22. 17 not 21 (471,962)
23. letter.pt. (745,733)
24. editorial.pt. (297,634)
25. historical article.pt. (282,385)
26. or/23-25 (1,312,332)
27. 22 not 26 (446,294)
28. 5 and 27 (667)
29. animals/ not (animals/ and humans/) (3,620,832)
30. 28 not 29 (657)
31. remove duplicates from 30 (639)
32. limit 31 to yr="2002 -Current" (307)

Economics filter
Centre for Reviews and Dissemination. NHS EED Economics Filter: Medline (Ovid) monthly search [internet].

York: Centre for Reviews and Dissemination; 2010 (cited 28 September 2010).

URL: www.york.ac.uk/inst/crd/intertasc/nhs_eed_strategies.html

MEDLINE In-Process & Other Non-Indexed Citations (OvidSP) 2002–10 May 2012

MEDLINE Daily Update (OvidSP) 2002–10 May 2012
Searched 11 May 2012.

1. cystic fibrosis/ (13)
2. ((Cystic adj2 fibrosis) or mucoviscidosis).ti,ab,ot,hw. (860)
3. CF.ti,ot. (153)
4. (pancreas adj3 fibrocystic adj3 disease$).ti,ab,ot,hw. (2)
5. or/1-4 (999)
6. economics/ (3)
7. exp "costs and cost analysis"/ (127)
8. economics, dental/ (0)
9. exp "economics, hospital"/ (16)
10. economics, medical/ (0)
11. economics, nursing/ (0)
12. economics, pharmaceutical/ (2)
13. (economic$ or cost or costs or costly or costing or price or prices or pricing or pharmacoeconomic$).ti, ab. (28,438)
14. (expenditure$ not energy).ti,ab. (752)
15. (value adj1 money).ti,ab. (2)
16. budget$.ti,ab. (1477)
17. or/6-16 (29,977)
18. ((energy or oxygen) adj cost).ti,ab. (158)
19. (metabolic adj cost).ti,ab. (44)
20. ((energy or oxygen) adj expenditure).ti,ab. (649)
21. or/18-20 (833)
22. 17 not 21 (29,739)
23. letter.pt. (18,035)
24. editorial.pt. (11,136)
25. historical article.pt. (158)
26. or/23-25 (29,322)
27. 22 not 26 (29,403)
28. 5 and 27 (27)
29. animals/ not (animals/ and humans/) (2139)
30. 28 not 29 (27)
31. remove duplicates from 30 (27)
32. limit 31 to yr="2002 -Current" (22)

Economics filter
Centre for Reviews and Dissemination. NHS EED Economics Filter: Medline (Ovid) monthly search [internet].

York: Centre for Reviews and Dissemination; 2010 [cited 28 September 2010].

URL: www.york.ac.uk/inst/crd/intertasc/nhs_eed_strategies.html

EMBASE (OvidSP) 2002–2012 week 18
Searched 11 May 2012.

1. cystic fibrosis/ (41,722)
2. ((Cystic adj2 fibrosis) or mucoviscidosis).mp. (48,828)
3. CF.ti,ot. (2503)

4. (pancreas adj3 fibrocystic adj3 disease$).mp. (16)
5. or/1-4 (49,844)
6. health-economics/ (31,568)
7. exp economic-evaluation/ (183,852)
8. exp health-care-cost/ (176,126)
9. exp pharmacoeconomics/ (152,648)
10. or/6-9 (423,153)
11. (econom$ or cost or costs or costly or costing or price or prices or pricing or pharmacoeconomic$).ti, ab. (504,978)
12. (expenditure$ not energy).ti,ab. (20,285)
13. (value adj2 money).ti,ab. (1089)
14. budget$.ti,ab. (20,942)
15. or/11-14 (526,198)
16. 10 or 15 (774,146)
17. letter.pt. (784,623)
18. editorial.pt. (406,289)
19. note.pt. (515,518)
20. or/17-19 (1,706,430)
21. 16 not 20 (696,305)
22. (metabolic adj cost).ti,ab. (744)
23. ((energy or oxygen) adj cost).ti,ab. (2877)
24. ((energy or oxygen) adj expenditure).ti,ab. (17,302)
25. or/22-24 (20,179)
26. 21 not 25 (691,788)
27. exp animal/ (1,778,262)
28. exp animal-experiment/ (1,613,173)
29. nonhuman/ (3,832,807)
30. (rat or rats or mouse or mice or hamster or hamsters or animal or animals or dog or dogs or cat or cats or bovine or sheep).ti,ab,sh. (4,657,237)
31. or/27-30 (6,588,417)
32. exp human/ (13,530,525)
33. exp human-experiment/ (300,208)
34. 32 or 33 (13,531,960)
35. 31 not (31 and 34) (52,04,957)
36. 26 not 35 (643,011)
37. 5 and 36 (1330)
38. limit 37 to embase (1088)
39. remove duplicates from 38 (1086)
40. limit 39 to yr="2002 -Current" (745)

Economics filter

Centre for Reviews and Dissemination. NHS EED Economics Filter: EMBASE (Ovid) (weekly search) [internet].

York: Centre for Reviews and Dissemination; 2010 [cited 28 September 2010].

URL: www.crd.york.ac.uk/crdweb/html/helpdoc.htm#embase

NHS Economic Evaluation Database Centre for Reviews and Dissemination 2002–3 May 2012

Searched 3 May 2012.

1. MeSH DESCRIPTOR Cystic Fibrosis (86)
2. (Cystic near2 fibrosis) (271)
3. (mucoviscidosis) (0)
4. (pancreas near3 fibrocystic near3 disease*) (0)
5. #1 OR #2 OR #3 OR #4 (271)
6. (#5) IN NHSEED (52)
7. (#6) FROM 2002 TO 2012 (22)

Health Economic Evaluations Database (HEED) (Wiley Online Library) 2002–21 May 2012

Searched 21 May 2012.

Using compound search.

1. All Data: 'CYSTIC FIBROSIS' OR 'mucoviscidosis' OR 'CF' AND
2. Journal Date: >= 2002

Sixty-five references were retrieved.

Health-related quality of life

MEDLINE (OvidSP) 1946–May 2012 week 1

Searched 11 May 2012.

1. cystic fibrosis/ (26,164)
2. ((Cystic adj2 fibrosis) or mucoviscidosis).ti,ab,ot,hw. (34,176)
3. CF.ti,ot. (1276)
4. (pancreas adj3 fibrocystic adj3 disease$).ti,ab,ot,hw. (16)
5. or/1-4 (34,859)
6. (sf36 or sf 36 or short form 36 or shortform 36).ti,ab. (12,308)
7. (sf thirtysix or sf thirty six or shortform thirtysix or shortform thirty six or short form thirty six or short form thirtysix or short form thirty six).ti,ab. (1)
8. (sf6 or sf 6 or short form 6 or shortform 6 or sf six or sfsix or shortform six or short form six).ti,ab. (890)
9. (euroqol or euro qol or eq5d or eq 5d).ti,ab. (2653)
10. (hql or hrql or hqol or h qol or hrqol or hr qol).ti,ab. (7311)
11. (hye or hyes).ti,ab. (52)
12. health$ year$ equivalent$.ti,ab. (36)
13. (hui or hui1 or hui2 or hui3 or hui4 or hui-4 or hui-1 or hui-2 or hui-3).ti,ab. (692)
14. (quality of well being or quality of wellbeing or qwb).ti,ab. (315)
15. (Disability adjusted life year$ or Disability-adjusted life year$ or health adjusted life year$ or health-adjusted life year$ or years of healthy life or healthy years equivalent or years of potential life lost or years of health life lost or quality adjusted life year$).ti,ab. (5478)
16. (QALY$ or HRQOL or HRQL or DALY$ or HALY$ or YHL or HYES or YPLL or YHLL).ti,ab. (11,747)
17. (health$ adj3 utilit$).ti,ab. (1526)
18. (Time trade-off or time tradeoff or TTO or Standard gamble).ti,ab. (1266)
19. ((Cystic Fibrosis adj2 Questionnaire$) or CFQ).ti,ab. (146)
20. or/6-19 (28,430)

21. 5 and 20 (127)
22. animals/ not (animals/ and humans/) (3,620,832)
23. 21 not 22 (127)
24. remove duplicates from 23 (125)

MEDLINE In-Process & Other Non-Indexed Citations (OvidSP) up to 10 May 2012

MEDLINE Daily Update (OvidSP) up to 10 May 2012
Searched 11 May 2012.

1. cystic fibrosis/ (13)
2. ((Cystic adj2 fibrosis) or mucoviscidosis).ti,ab,ot,hw. (860)
3. CF.ti,ot. (153)
4. (pancreas adj3 fibrocystic adj3 disease$).ti,ab,ot,hw. (2)
5. or/1-4 (999)
6. (sf36 or sf 36 or short form 36 or shortform 36).ti,ab. (719)
7. (sf thirtysix or sf thirty six or shortform thirtysix or shortform thirty six or short form thirty six or short form thirtysix or short form thirty six).ti,ab. (0)
8. (sf6 or sf 6 or short form 6 or shortform 6 or sf six or sfsix or shortform six or short form six).ti,ab. (309)
9. (euroqol or euro qol or eq5d or eq 5d).ti,ab. (209)
10. (hql or hrql or hqol or h qol or hrqol or hr qol).ti,ab. (507)
11. (hye or hyes).ti,ab. (1)
12. health$ year$ equivalent$.ti,ab. (1)
13. (hui or hui1 or hui2 or hui3 or hui4 or hui-4 or hui-1 or hui-2 or hui-3).ti,ab. (56)
14. (quality of well being or quality of wellbeing or qwb).ti,ab. (10)
15. (Disability adjusted life year$ or Disability-adjusted life year$ or health adjusted life year$ or health-adjusted life year$ or years of healthy life or healthy years equivalent or years of potential life lost or years of health life lost or quality adjusted life year$).ti,ab. (431)
16. (QALY$ or HRQOL or HRQL or DALY$ or HALY$ or YHL or HYES or YPLL or YHLL).ti,ab. (841)
17. (health$ adj3 utilit$).ti,ab. (118)
18. (Time trade-off or time tradeoff or TTO or Standard gamble).ti,ab. (75)
19. ((Cystic Fibrosis adj2 Questionnaire$) or CFQ).ti,ab. (7)
20. or/6-19 (2158)
21. 5 and 20 (7)
22. animals/ not (animals/ and humans/) (2139)
23. 21 not 22 (7)
24. remove duplicates from 23 (7)

EMBASE (OvidSP) 1974–2012 week 18

Searched 11 May 2012.

1. cystic fibrosis/ (41,722)
2. ((Cystic adj2 fibrosis) or mucoviscidosis).mp. (48,828)
3. (pancreas adj3 fibrocystic adj3 disease$).mp. (16)
4. CF.ti,ot. (2503)
5. or/1-4 (49,846)
6. (sf36 or sf 36 or short form 36 or shortform 36).ti,ab. (17,443)
7. (sf thirtysix or sf thirty six or shortform thirtysix or shortform thirty six or short form thirty six or short form thirtysix or short form thirty six).ti,ab. (1)
8. (sf6 or sf 6 or short form 6 or shortform 6 or sf six or sfsix or shortform six or short form six).ti,ab. (1381)
9. (euroqol or euro qol or eq5d or eq 5d).ti,ab. (4305)
10. (hql or hrql or hqol or h qol or hrqol or hr qol).ti,ab. (10,640)

11. (hye or hyes).ti,ab. (62)
12. health$ year$ equivalent$.ti,ab. (41)
13. (hui or hui1 or hui2 or hui3 or hui4 or hui-4 or hui-1 or hui-2 or hui-3).ti,ab. (935)
14. (quality of well being or quality of wellbeing or qwb).ti,ab. (365)
15. (Disability adjusted life year$ or Disability-adjusted life year$ or health adjusted life year$ or health-adjusted life year$ or years of healthy life or healthy years equivalent or years of potential life lost or years of health life lost or quality adjusted life year$).ti,ab. (7550)
16. (QALY$ or HRQOL or HRQL or DALY$ or HALY$ or YHL or HYES or YPLL or YHLL).ti,ab. (17,567)
17. (health$ adj3 utilit$).ti,ab. (2194)
18. (Time trade-off or time tradeoff or TTO or Standard gamble).ti,ab. (1639)
19. ((Cystic Fibrosis adj2 Questionnaire$) or CFQ).ti,ab. (272)
20. or/6-19 (41,148)
21. 5 and 20 (251)
22. animal/ or animal experiment/ (3,374,417)
23. (rat or rats or mouse or mice or murine or rodent or rodents or hamster or hamsters or pig or pigs or porcine or rabbit or rabbits or animal or animals or dogs or dog or cats or cow or bovine or sheep or ovine or monkey or monkeys).mp. (5,438,846)
24. or/22-23 (5,438,846)
25. exp human/ or human experiment/ (13,531,960)
26. 24 not (24 and 25) (4,385,166)
27. 21 not 26 (251)
28. limit 27 to embase (235)
29. remove duplicates from 28 (235)

Cost-effectiveness Analysis Registry (internet)
URL: https://research.tufts-nemc.org/cear4

Searched 14 May 2012.

Searched for 'Articles' using the term 'cystic' (6)

Searched for 'Ratios' using the term 'cystic' (14)

Searched for 'Weights' using the term 'cystic' (23)

A total of 43 references were retrieved.

Guidance

National Institute for Health and Care Excellence Guidance (internet)
URL: http://guidance.nice.org.uk

Searched 11 May 2012.

Searched for 'cystic fibrosis'.

Limited to information type: guidance.

Six references retrieved.

TRIP database (internet)

URL: www.tripdatabase.com

Searched 11 May 2012.

Searched for 'cystic fibrosis' in title.

Limited to guidelines.

Sixteen references retrieved.

Guidelines International Network (internet)

Searched 11 May 2012

Searched for 'cystic fibrosis'.

Seven references retrieved.

National Guidelines Clearinghouse (internet)

URL: www.guidelines.gov

Searched 11 May 2012.

Searched for 'cystic fibrosis' in title.

Three references retrieved.

US Food and Drug Administration

URL: www.fda.gov

Searched 11 May 2012.

Searched for 'cystic fibrosis' in title.

Limited to guidance.

Two references retrieved.

Cystic Fibrosis Trust

URL: www.cftrust.org.uk

Searched 11 May 2012.

Browsed website publications.

Seventeen references retrieved.

Appendix 2 Risk-of-bias assessment results

Criteria	Adults		Children	
	Support for judgement	Rating	Support for judgement	Rating
Randomisation	Randomisation in 1 : 1 ratio. Randomisation stratified according to age ($\geq$ 18 years) and pulmonary function (= 70% of predicted FEV1). Randomisation code will be produced by Vertex; exact details not reported (from protocol)	Low	No details	Unclear
Allocation concealment	Final randomisation list will be provided to the Interactive Voice Response System or Interactive Web Response System. Copy of the final randomisation list will be archived at Vertex in sealed tamper evidence envelopes (protocol)	Low	No details	Unclear
Blinding: participant	Study described as 'double blind' and 'the subjects, all site personnel including the investigator, the study monitor, and the Vertex study team will be blinded', details of a number of site personnel who will not be blinded or situations in which they will be informed of treatment allocation was provided. Appears that VX-770 and placebo will look the same – 'similar in size and appearance and will be supplied as blue film-coated tablets' (protocol)	Low	Described as double blind; no further details	Low
Blinding: outcome assessor	All outcomes assessors will be blinded to treatment allocation although for some outcome they will be aware of the results for the outcome (protocol)	Low	Described as double blind; no further details	Low
Incomplete outcome data	Five withdrawals prior to treatment in placebo group and one in ivacaftor group. Ten withdrawals after treatment started in placebo group and six in ivacaftor group. Missing data were not imputed. For some outcomes last observation carried forward will be use (protocol). Denominator was total number of patients treated not just completers	Low	Four withdrawals in placebo, none in ivacaftor. No details on analysis	Unclear
Selective reporting	All primary and secondary outcomes reported; some tertiary outcomes not reported in paper but appears to be more due to space than problem of selective outcome reported	Low	Results appear to have been reported for all outcomes including the primary outcome although we did not have access to protocol	Low

Appendix 3 Data extraction tables

Randomised controlled trials

Study details	Selection criteria	Participants (mean, range/SD)	Sample size and interventions	Withdrawals
Trial registry number: NCT00909532[21,22,26] **Country:** North America, Australia, Europe **Funding:** Vertex Pharmaceuticals (VX08–770–102) **Study design:** parallel group **Study duration:** 48 weeks	**Inclusion criteria:** diagnosis of CF with at least one G551D mutation. FEV₁ predicted 40–90%. Genotype confirmed using a 32-mutation panel (Ambry Genetics) **Exclusion criteria:** other illnesses that confounded the study results; ongoing illness; pulmonary exacerbation or changes in therapy (including antibiotics) for pulmonary disease within 4 weeks before first dose of study drug; abnormal liver tests; abnormal renal function tests; history of prolonged QT/QTc interval; history of solid organ or haematological transplantation; colonisation with organisms associated with more rapid decline in pulmonary status; concomitant use of inhibitors or inducers of CYP3A4; use of inhaled hypertonic saline treatment – this was required to be stopped for at least 4 weeks prior to day 1 of treatment	**Mean age:** 26 (12–53) years **Proportion male:** 48% **Ethnicity:** proportion non-Hispanic or non-white: 2% **Weight:** 62 (30–110) kg **BMI:** 22 (15–39) kg/m² **Height:** 167 (142–190) cm **Percentage predicted FEV₁:** 64 (32–98)% **Sweat chloride:** 100 (58–128) mmol/l **Comorbidities:** not stated	**Total number eligible:** 217 **Total number randomised:** 167 **Placebo** *Number randomised:* 83 *Number treated:* 78 *Co-interventions:* pre-study medication except hypertonic saline: (commercial-in-confidence information has been removed) **Intervention: ivacaftor** *Dose:* 150 mg *Dose frequency:* every 12 hours *Number randomised:* 84 *Number treated:* 83 *Co-interventions:* pre-study medication except hypertonic saline: (commercial-in-confidence information has been removed)	**Placebo:** 10 withdrawals (four adverse events, one physician's decision, two required prohibited medication, one withdrew consent, two other); 83 assigned to placebo; 78 received placebo; 68 completed 48 weeks of treatment **Ivacaftor:** Six withdrawals in ivacaftor group (one adverse event, two non-complicans, one pregnancy, one prohibited medication, one withdrew consent); 83 received ivacaftor; 77 completed 48 weeks of treatment All but one of the patients (placebo group) entered the open-label extension study

Study details	Selection criteria	Participants (mean, range/SD)	Sample size and interventions	Withdrawals
Trial registry number: NCT00909727[29,30]	**Inclusion criteria:** children aged 6 to 11 years; G551D-*CFR* mutation; FEV₁ 40–105% predicted	**Mean age:** 9 (6–11) years	**Total number eligible**: NR	Four withdrawals in placebo group, one due to adverse event. No withdrawals in ivacaftor group
Country: North America, Australia, Europe	**Exclusion criteria:** acute respiratory tract infection, pulmonary exacerbation, changes in therapy for pulmonary disease, use of inhaled hypertonic saline treatment within 4 weeks of treatment, abnormal liver function, abnormal renal function, low haemoglobin	**Male:** 48%	**Total number randomised:** 52	
		Ethnicity: NR	**Placebo**	
Funding: Vertex Pharmaceuticals		**Weight:** 31 (9) kg	*Number randomised:* 26	
		BMI: 17 (2) kg/m²	*Number treated:* 26	
Study design: parallel group		**Height:** 134 (13) cm	*Co-interventions:* not stated	
Study duration: 48 weeks		**Percentage predicted FEV₁:** 84 (18)%	**Intervention: ivacaftor**	
		Sweat chloride: 105 (12) mmol/l	*Dose:* 150 mg	
		Comorbidities: NR	*Dose frequency:* every 12 hours	
			Number randomised: 26	
			Number treated: 26	
			Co-interventions: not stated	

NR, not reported; QT interval is a measure of the time between the start of the Q wave and the end of the T wave in the heart's electrical cycle; QTc is a corrected QT; SD, standard deviation.

Open-label trial

Study details	Selection criteria	Participants (mean, range/SD)	Sample size and interventions	Withdrawals
Trial registry number: NCT01117012[31] **Country:** North America, Australia, Europe **Funding:** Vertex Pharmaceuticals **Study design:** open label **Study duration:** 96 weeks; data available only for patients who completed 12 weeks' follow-up	**Inclusion criteria**: all patients enrolled in STRIVE (adults) and ENVISION (children) studies (Commercial-in-confidence information has been removed) (Commercial-in-confidence information has been removed)	(Commercial-in-confidence information has been removed) **Ethnicity**: NR **Weight**: (commercial-in-confidence information has been removed) **BMI**: NR **Height**: NR **Percentage predicted FEV₁**: 67.4 (29.1–110.4; SD = 19.1)% **Sweat chloride**: NR **Comorbidities**: NR	**Intervention:** Ivacaftor 150 mg, every 12 hours *Number treated*: 144	One patient who had previously received placebo discontinued ivacaftor (Commercial-in-confidence information has been removed) 67 originally in placebo arm, 77 in ivacaftor arm

NR, not reported; SD, standard deviation.

Appendix 4 Table of excluded studies

Three Phase II trials reported in 18 publications did not reach the review inclusion criteria:

Trial registry number	Phase of trial	Number of participants	Reason for exclusion
NCT00457821[1–14]	Phase II; two separate studies	Trial 1: 20; Trial 2: 19	Short-term outcomes only (2–4 weeks depending on trial)
NCT01262352[15]	Phase II; ongoing	Target 20; 10 recruited at time of conference abstract	Short-term outcomes only (4 weeks' duration)
NCT01161537[16–18]	Phase II; ongoing	Unclear; four recruited at time of conference abstract	Short-term outcomes only (8 weeks' duration followed by open-label study). No clinically relevant outcomes as specified in the review protocol

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Appendix 5 Discrepancies in reporting of results

Adults' trial

Results data which were reported differently in different reports of the same trial:

Outcomes	Measures	Time periods	Paper[21]	Supplementary data, %[21]	Dossier[16]
Percentage predicted FEV$_1$: relative change	Mean difference in change from baseline	24 weeks	17.1	16.9 (13.6, 20.2)	17.1 and 17.2
Percentage predicted FEV$_1$: relative change	Mean difference in change from baseline	48 weeks		16.8 (13.5, 20.1)	17.0

Relative risks reported in publications that were different from those that we calculated using the reported raw data:

Outcomes	Durations of follow-up	RR (95% CI) Paper[21]	Calculated from raw data
Number of patients with exacerbation	24 weeks	0.38 (0.22 to 0.64)	0.48 (0.30 to 0.77)
Number of patients with exacerbation	48 weeks	0.43 (0.27 to 0.68)	0.60 (0.41 to 0.85)

Children's trial

Results data which were reported differently in different reports of the same trial:

Outcomes	Measures	CA, %[27]	Dossier, %[16]	Press release, %[29]
Percentage predicted FEV$_1$: relative change	Mean difference in change from baseline	17.4	15.8	17.4
Percentage predicted FEV$_1$: relative change	Mean difference in change from baseline	15.1	12.8	NR

CA, conference abstract; NR, not reported.

Open-label trial

Results data which were reported differently in different reports of the same trial:

Outcomes	Measures	Ivacaftor			Placebo		
		CA	Dossier	Press release	CA	Dossier	Press release
Percentage predicted FEV$_1$: absolute change, percentage points	Mean change from baseline (SD)	11.1 (9.7)	Same	11.6	10.8 (9.5)	9.7 (9.7)	10.9 (NR)
Percentage predicted FEV$_1$: relative change, %	Mean change from baseline (SD)	18.7 (17.0)	Same	19.4	19.9 (20.1)	17.0 (19.3)	19.9 (NR)

CA, conference abstract; NR, not reported; SD, standard deviation.

Appendix 6 Overview of included and background studies for health economics review

Included studies

Author	Year	Cost-effectiveness	Health-care cost	Social care cost	Disease-specific utility	Generic utility	Incidence prevalence	Mortality	Model probability	Year of data	Setting	Time horizon	n with CF
Wertz et al.[81]	2011	–	✓	–	–	–	–	–	–	2004–9	USA	2004–9	832
Briesacher et al.[82]	2011	–	✓	–	–	–	–	–	–	2001–7	USA	2001–7	3273
O'Sullivan et al.[83]	2011	–	✓	–	–	–	–	–	–	2006	USA	12 months	1064
Woodward et al.[84]	2010	–	✓	–	–	–	–	–	–	2008	USA	4 years	262
Braccini et al.[85]	2009	–	✓	–	–	–	–	–	–	2002–6	Italy	4 years	61
Schreyogg et al.[86]	2006	–	✓	–	–	–	–	–	–	2004	Germany	6 months	131
van den Akker-van Marle et al.[87]	2006	–	✓	–	–	–	–	–	–	2004	Holland	NA	NA
Thornton et al.[39]	2005	✓	✓	–	✓	–	–	–	✓	2003	UK	12 months	196
Iles et al.[88]	2003	✓	✓	–	✓	–	–	–	–	2002	UK	2 years	71
Baumann et al.[40]	2003	–	✓	–	✓	–	–	–	✓	2002	Germany	12 months	138
Sangiry et al.[89]	2012	–	✓	–	–	–	–	–	–	2005–8	USA	12 months	358
Dewitt et al.[90]	2012	–	✓	–	✓	✓	–	–	–	2008	USA	48 weeks	352
Abbott et al.[91]	2009	–	–	–	–	✓	–	✓	–	1996–2006	UK	10 years	223
Ramsey et al.[21]	2011	–	–	–	✓	✓	–	–	–	2009–11	USA	48 weeks	161
Gee et al.[43]	2002	–	–	–	✓	✓	–	–	–	2002	UK	6 months	223
Becker et al.[92]	2011	✓	✓	–	–	–	–	–	–	2004–8	US	12 months	NA
Aherns et al.[27]	2011	–	–	–	✓	–	–	–	–	2010	UK	48 weeks	52 aged 6–11 years

Author	Year	Cost-effectiveness	Health-care cost	Social care cost	Disease-specific utility	Generic utility	Incidence prevalence	Mortality	Model probability	Year of data	Setting	Time horizon	n with CF
Loadman et al.[93]	2010	–	–	–	–	✓	–	✓	–	1986–2008	Canada	1–5 years	72
Simpson et al.[38]	2005	✓	✓	–	✓	✓	–	✓	✓	1998	UK	Lifetime	NA
ScHARR[41]	2012	✓	✓	–	✓	✓	✓	–	✓	NA	UK	Lifetime	NA
UK CF Registry report 2010[8]	2011	–	✓	–	✓	–	✓	–	–	2010	UK	1 year	9385
CFT antibiotic treatment[59]	2009	–	✓	–	–	–	–	–	–	2009	UK	NA	NA
KSR[42]	2011	✓	✓	–	✓	✓	✓	–	✓	2008–9	UK	Lifetime	341

CFT, Cystic Fibrosis Trust; KSR, Kleijnen Systematic Reviews; NA, not applicable.

Background studies

Author	Year	Cost-effectiveness	Health-care cost	Social care cost	Disease-specific utility	Generic utility	Incidence prevalence	Mortality	Model probability
Eidt-Koch et al.[94]	2009	–	–	–	–	✓	–	–	–
Elphick et al.[95]	2009	–	–	–	✓	✓	–	–	–
Weiner et al.[96]	2008	–	✓	–	✓	✓	–	–	–
Guerriere et al.[97]	2008	–	–	✓	–	–	–	–	–
Radhakrishnan et al.[98]	2008	✓	✓	✓	–	–	–	–	–
Elphick et al.[99]	2005	–	–	–	✓	–	–	–	–
Yi et al.[100]	2004	–	–	–	✓	✓	–	–	–
Wark et al.[101]	2009	–	–	–	✓	–	–	–	–
Mayer-Hamblett et al.[102]	2007	–	–	–	✓	✓	–	–	–
Ashish et al.[103]	2010	–	✓	–	–	–	–	–	–
Smalarz et al.[104]	2009	–	✓	–	–	–	–	–	–
Abbott et al.[105]	2011	–	–	–	–	✓	–	–	–
Flume et al.[78]	2011	–	–	–	✓	–	–	–	–
Elborn et al.[106]	2011	–	–	–	✓	–	–	–	–
Hofer et al.[107]	2011	–	–	–	✓	✓	–	–	–
Bradley et al.[108]	2011	–	–	–	✓	✓	–	–	–
Cystic Fibrosis Trust Standards[1]	2010	–	✓	–	–	–	–	–	–

Appendix 7 Review protocol

Ivacaftor for cystic fibrosis

Protocol

Plain English Summary

Cystic Fibrosis (CF) is one of the most common, inherited diseases in white populations. Around 1 in every 2500 babies born in the UK has CF and there are over 9000 people in the UK with CF. CF is caused by a single faulty gene which controls the movement of salt and water in and out of cells. This results in thick sticky mucous clogging up the internal organs (e.g. lungs, pancreas, liver, intestine and reproductive tract) making it difficult to breathe and digest food. Other symptoms can include a troublesome cough, prolonged diarrhoea and poor weight gain. Most of the illness caused by CF is from diseases of the lungs and repeated infections. There is no cure for CF and most treatments (e.g. physiotherapy, antibiotics for infections, drugs to suppress inflammation) target the symptoms rather than the cause of disease. Median survival of the current UK cohort with CF is estimated as 41 years. Most patients die from lung disease. Life expectancy is increasing and is expected to increase to at least 50 years for children born in 2000.

A large number of different mutations have been identified in the gene that causes CF. New treatments are being developed which target specific mutations. Ivacaftor (brand name Kalydeco, Vertex Pharmaceuticals) is the first of these drugs and targets patients with the "G551D" mutation. Around 4.4% of patients with CF in the UK will have at least one G551D mutation. Ivacaftor represents a new approach to treating patients with CF as it targets the underlying cause of CF. It aims to increase salt movement through the cell by targeting a specific protein. Ivacaftor is classed as an "orphan drug" which means that has been developed specifically to treat a rare disease. It has been approved by the American Food and Drug Administration for the treatment of patients with CF who are at least 6 years old and have the G551D mutation. There are currently no similar drugs which target the underlying protein defect in CF on the market.

This review aims to evaluate the effectiveness of ivacaftor tablets for the treatment of cystic fibrosis (CF) in patients age 6 years and older who have at least one G551D mutation. The review will consider both clinical effectiveness (improvement in patients' symptoms and adverse events) and cost effectiveness (cost of treatment).

2. Decision problem

2.1 Objectives
This review aims to appraise the clinical and cost effectiveness of ivacaftor 150 mg tablet for oral administration for the treatment of cystic fibrosis (CF) in patients age 6 years and older who have at least one G551D mutation in the *CFTR* gene. We will aim to determine the category of patients most likely to benefit from Ivacaftor by assessing whether the effects vary according to disease severity and age.

2.2 Background
Cystic Fibrosis is the most common, life-threatening, autosomal recessive disorder in Caucasian populations; it has an estimated carrier rate of 1 in 25 and incidence of 1 in 2500 live births.[1] It affects around 9000 people in the UK with a prevalence of 1.37/10,000.[2] CF was first recognised as a distinct disease in 1938.[3] It is characterised by abnormal transport of chloride and sodium, leading to thick viscous secretions in the lungs, pancreas, liver, intestine, and reproductive tract and to an increased salt content in sweat gland secretions.[4] Most of the morbidity and mortality is from pulmonary disease, which is characterised by bronchial and bronchiolar obstruction with thick tenacious secretions that are difficult to

clear, colonisation by pathogenic bacteria and repeated infections.[1] There is chronic inflammation and progressive lung destruction can lead to bronchiectasis, altered pulmonary function, and respiratory failure. CF can also lead to CF related diabetes (CFRD), male infertility and liver involvement. In addition to repeated chest infections, symptoms of CF can include a troublesome cough, prolonged diarrhoea and poor weight gain.[1] Most patients with CF eventually succumb to lung disease and survival of patients with CF is currently around 41 years, a considerably increase from around 6 months when the disease was first identified,[4] and is expected to increase to at least 50 years for children born in 2000.[2]

CF is caused by mutations in the CF transmembrane conductance regulator (CFTR) gene which was discovered in 1989.[5] It sits on chromosome 7, is some 250 kB in length, and encodes a protein of 1480 amino acids. This protein is a chloride channel present at the surface of epithelial cells in multiple organs and is responsible for aiding in the regulation of salt and water absorption and secretion. Over 1000 disease-causing alleles within this gene have been identified although only 23 have been demonstrated to cause sufficient loss of CFTR function to confer CF disease.[6] The most common mutation is the F508 mutation which is present on around 67% of CF chromosomes worldwide.[7] The G551D (glycine to aspartate change in nucleotide 1784 in exon 11), which affects approximately 4.4% of patients with CF in the UK,[8] is of interest as a new treatment has been developed targeted specifically at patients with this mutation. CFTR protein channels with the G551D mutation have a greatly reduced fraction of time that the channel spends in the open state, or "open probability," and, therefore, have limited chloride transport ability.

Diagnosis of CF and genetic testing

The gold standard for the diagnosis of CF is the sweat test.[6] This tests for elevated levels of chloride in sweat with a diagnosis of CF being made at levels above 60 mmol/L, and a possible diagnosis of CF at level above 30 mmol/L. New born screening tests have been introduced in many countries, and have been routine throughout the UK since October 2007.[109] These involve a small sample of blood being taken ("heel prick test") which is tested for high levels of immunoreactive trypsinogen (IRT). If an abnormal IRT value is identified, most new born screening programmes perform a combination of DNA testing to identify known CFTR mutations and repeat IRT testing.[10] IRT testing alone has a sensitivity of 82–100%, double IRT testing increases sensitivity to 89–100% and IRT and DNA testing has a sensitivity of 94–100%; specificity is > 99% for all testing strategies.[11] In the UK screening programme, the initial DNA test involves testing for four mutations (F508, G551D, G542X and 621 + 1G > T), if only one CF mutation is detected then further DNA analysis based on 29 or 31 mutations is recommended. A range of commercial kits are available for diagnostic testing. The diagnosis is then confirmed using the sweat test.[10]

Treatment of CF

There is no cure for CF and current treatments target the complications rather than cause of the disease.[4] Treatments can be broadly classified as nutritional repletion (e.g. pancreatic enzyme supplementation and nutritional supplementation), relief of airway obstruction (e.g. physiotherapy, drugs to improve sputum clearance, bronchodilators), treatment of airway infection (e.g. antibiotics), suppression of inflammation (e.g. steroids, high-dose ibuprofen) and lung transplantation.[4]

Ivacaftor

Ivacaftor (brand name Kalydeco, Vertex Pharmaceuticals) is the first in a new class of drugs known as CFTR potentiators which represents a new therapeutic approach to the treatment of patients with CF by targeting the underlying protein defect of CF. The drug facilitates increased chloride transport by potentiating the channel-open probability (or gating) of the G551D-CFTR protein.[12]

Ivacaftor is a designated orphan medicinal product.[13] It has been approved by the FDA for the treatment of CF in patients aged 6 years or older who have a G551D mutation in the CFTR gene[14] and is the subject of a European Union marketing authorisation application. No active comparator agents that target the underlying CFTR protein defect in CF disease exist.[16]

3. Report methods for synthesis of evidence of clinical effectiveness

We will conduct a systematic review of the evidence on the clinical effectiveness of ivacaftor 150 mg tablet for oral administration for the treatment of cystic fibrosis (CF) in patients age 6 years and older who have at least one G551D mutation in the *CFTR* gene. The review will follow the general principles recommended in the PRISMA statement and CRD report 4.[17,18]

3.1 Search strategy

Literature searches will be undertaken in several stages to identify relevant information, such as eligible studies, evidence-based health technology assessments (HTAs), systematic reviews, economic evaluations, guidelines and health-related quality of life data. The EMBASE strategies will be independently peer reviewed by a second Information Specialist, using the PRESS-EBC checklist.[19]

Clinical effectiveness

Searches will be undertaken to locate randomised controlled trials using ivacaftor. They will not be limited by date, language or publication status (unpublished or published). The following databases will be searched:

- MEDLINE (OvidSP)
- MEDLINE In-Process & Other Non-Indexed Citations (OvidSP)
- EMBASE (OvidSP)
- Latin American and Caribbean Health Sciences Literature (LILACS) (VHL)
- http://lilacs.bvsalud.org/en/
- Cochrane Database of Systematic Reviews (CDSR) (Wiley Online Library)
- Cochrane Central Register of Controlled Trials (CENTRAL) (Wiley Online Library)
- Database of Abstracts of Reviews of Effects (DARE) (Wiley Online Library & CRD)
- NHS Economic Evaluation Database (NHS EED) (Wiley Online Library & CRD)
- Health Technology Assessment Database (HTA) (Wiley Online Library & CRD)

Supplementary searches will be undertaken on the following resources to identify unpublished and on-going studies:

- *meta*Register of Controlled Trials (internet) (http://www.controlled-trials.com)
- NIH Clinicaltrials.gov (internet) (http://www.clinicaltrials.gov)
- WHO International Clinical Trials Registry Platform (ICTRP) (internet) (http://www.who.int/ictrp/en/)

Scanning abstracts and programmes of relevant conferences will enable identification of relevant studies and projects. The following conference proceedings will be searched from 2007–2012:

- European Cystic Fibrosis Society (ECFS) conference (http://www.ecfs.eu/conferences/main)
- North American Cystic Fibrosis Conference (NACFC) (https://www.nacfconference.org/)
- International Congress on Pediatric Pulmonology (CIPP) (http://www.cipp-meeting.org/index.htm)

The bibliographies of retrieved articles and relevant systematic reviews will be checked for additional studies. Identified references will be downloaded into Endnote bibliographic management software for further assessment and handling.

3.2 Inclusion criteria

Studies that fulfil the following criteria will be eligible for inclusion:

Population: Children (6 years and older) and adults with cystic fibrosis who have the G551D mutation on at least one *CFTR* allele. Patients with all severities of disease will be eligible.

Intervention: Ivacaftor tablets.

Comparator: Any reported comparator.

Outcomes: The primary outcome will be lung function (e.g. per cent predicted forced expiratory volume in one second (FEV_1)). Other eligible outcomes include mortality, weight, BMI, sweat chloride, respiratory symptoms, reduction in pulmonary exacerbations, exercise tolerance, adverse effects of treatment, health-related quality of life and utilisation of hospital resources. Studies that only report short-term outcomes (< 3 months only) will be excluded.

Study design: For the review of clinical effectiveness, only RCTs will be included. Criteria will be relaxed for consideration of adverse events, for which open label studies will be eligible.

The results of the searches will be screened for relevance independently by two reviewers. Full text of studies identified as potentially relevant will be obtained and assessed for inclusion by one reviewer and checked by a second. Disagreements will be resolved through discussion or referral to a third reviewer where necessary.

3.3 Data extraction strategy
Data will be extracted by one reviewer using a standardised data extraction form and checked by another. Disagreements will be resolved through discussion or referral to a third reviewer where necessary. Data will be extracted on the primary outcome, lung function (e.g. percept predicted forced expiratory volume in one second (FEV_1)), and the following additional outcomes: mortality, weight, BMI, sweat chloride, respiratory symptoms, reduction in pulmonary exacerbations, exercise tolerance, adverse effects of treatment, health-related quality of life and utilisation of hospital resources. Data will be extracted after 24 weeks (intermediate) treatment and after the longest duration of follow-up reported. If data are available for different patient subgroups (e.g. age, disease severity, region) then data will be extracted separately for each subgroup. If composite end points are reported, data will be extracted on the definition of the end point, results, and, if sufficient data are available, the events that contributed to the end point.

3.4 Quality assessment strategy
Trials will be assessed for methodological quality using the Cochrane Risk of Bias tool.[20] This includes items covering selection bias (random sequence generation and allocation concealment), performance bias (participant blinding), detection bias (blinding of outcome assessors) attrition bias (incomplete outcome data), and reporting bias (selective reported). There is also an addition field for other sources of bias. We believe that all important concerns about bias are include in the other domains in the tool and so no further domains will be added. Each domain is assigned a rating of high, low, or unclear. Each trial will be assigned an overall rating of the risk of bias. If at least one of the domains is rated as "high" the trial will be considered at high risk of bias, if all domains are judged as "low" the trial will considered at low risk of bias, otherwise the trial will be considered at "unclear" risk of bias. The risk of bias assessment will be incorporated into the data extraction form and will be conducted as part of the data extraction.

3.5 Methods of analysis/synthesis
We do not anticipate having sufficient data to conduct a formal meta-analysis. Data will be tabulated and discussed in a narrative review. Details of the components of best supportive care, where reported in the included studies, will be clearly described. If sufficient data are available results will be grouped by age, lung function, disease severity, and prior treatment (including consideration of intolerance to treatments). Dichotomous data will be summarised as relative risks or hazard ratios together with 95% confidence intervals (CIs). Continuous outcomes will be summarised as mean differences between treatment groups together with 95% CIs; where appropriate mean differences between groups in mean change from baseline will be calculated. If sufficient data are available, results will be displayed graphically using forest plots. Publication bias will not be formally assessed as we only expect to include a very small number of trials. Standard methods to detect publication bias will therefore not be possible.

4. Report methods for synthesising evidence of cost effectiveness

4.1 Identifying and reviewing published cost-effectiveness studies

Focussed searches will be undertaken to identify literature on cost-effectiveness and cystic fibrosis. Searches will be limited to the last ten years. The following resources will be searched:

- Medline (OvidSP)
- Medline In-Process Citations (OvidSP)
- Embase (OvidSP)
- NHS Economic Evaluation Database (NHS EED) (CRD)
- Health Economic Evaluation Database (HEED)

Health-related Quality of Life

Focussed searches will be undertaken to identify literature on HRQoL and cystic fibrosis. Searches will not be limited by date and the following resources will be searched:

- Medline (OvidSP)
- Medline In-Process Citations & Other Non-Indexed Citations (OvidSP)
- Embase (OvidSP)
- CEA Registry (internet)

Guidelines and guidance

The following resources will be searched for guidelines and guidance related to cystic fibrosis:

- NICE Guidance (internet) (http://guidance.nice.org.uk/)
- TRIP database (limited to guidelines) (internet) (http://www.tripdatabase.com/)
- Guidelines International Network (GIN) (internet)
- National Guidelines Clearinghouse (internet) (http://www.guidelines.gov)
- Cystic Fibrosis Trust (http://www.cftrust.org.uk/)

Searches will focus on original papers that report on cost, cost-effectiveness or cost-utility analyses, either studying the diagnostic phase (genetic testing for CF mutations), therapeutic phase (management of patients with confirmed CF), or a combination. Note that this search does not only include studies on ivacaftor, but evaluations of any treatment for CF. For our assessment cost studies, utility studies and full economic evaluations, i.e. those that explicitly compare different decision options will be selected. Clinical trials as well as modelling studies and cohort studies will be relevant within the frame of our project. The intention is not to perform a systematic review, but to use the studies identified to support the development of an economic model and estimation of model input parameters that will aim to answer the research questions of this project.

The results and the methodological quality of the studies selected will be summarised. Data extraction will focus on interventions compared, indicated population, main results in terms of costs and consequences of the alternatives compared, and the incremental cost-effectiveness, but also on methods of modelling used (if applicable), for example relating to extrapolation of study results, analytical methods and robustness of the study findings.

4.2 Evaluation of cost-effectiveness

If an economic evaluation is provided by the manufacturer it will be assessed for clinical validity, reasonableness of assumptions and appropriateness of the data used in the economic model. If the team 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. Such de novo economic evaluation will be undertaken from a NHS and social care perspective. The model will draw together evidence from literature

and study reports concerning treatment efficacy, withdrawal, treatment related adverse events, relevant diagnostic interventions, chronic care costs, and HRQoL. The model structure will be developed such that the effects of treatment on lung function, exacerbations, quality of life and treatment costs can be incorporated. The level of detail will depend on available evidence. Specifically, the impact of treatment on resource use in pulmonary exacerbations in both the primary and secondary care settings will be taken into account if data allows. If evidence allows, subgroups by age, lung function, disease severity, and prior treatment (including consideration of intolerance to treatments) may be considered. Additionally, the impact of treatment on resource use in pulmonary exacerbations in both the primary and secondary care settings will be taken into account if data allows.

Costs will be identified through literature searches. As genetic testing is essential to the use of ivacaftor it will be part of the assessment. If possible with the data available, the assessment of ivacaftor will consider the impact of treatment on progression through treatment bands over time, and take in to account any service implications (e.g. changes in type/duration/frequency of hospital activity). In line with current recommendations, costs and health outcomes will be discounted at 3.5%. Key health economic outcomes are likely to include the cost per life year gained, and the cost per quality adjusted life year (QALY) gained. The cost-effectiveness of interventions will be compared incrementally against each other.

Sensitivity analysis will be undertaken to examine the key determinants of cost-effectiveness. Probabilistic sensitivity analysis (PSA) will be undertaken to generate information on the likelihood that each treatment produces the greatest amount of net benefit. The results of this PSA will be presented as cost-effectiveness acceptability curves (CEACs).

5. Timetable/milestones

Milestone	Deadline
Protocol Submitted	22 May
Searches	10 May
Reference Screening	10 May
Inclusion assessment	14 May
Data extraction and quality assessment	24 May
SR results section draft	24 May
Health economic results to KSR	29 June
Health economics section complete	6 July
Report to commissioner	10 July
Comments from Commissioner	31 July
Final report	17 August

6. Team members' contributions
Penny Whiting will be the main reviewer on this project and will maintain day-to-day running of the review. Marie Westwood will act as second reviewer. Both reviewers have contributed to the study protocol and will carry out the study selection, data extraction, analysis and production of the final report. Maiwenn Al will be health economic lead for this project, and thus be responsible for the cost-effectiveness study.

Appendix: Draft search strategy

EMBASE (OvidSP): 1974-2012/wk17

Searched 3.5.12

1. Ivacaftor/ (72)
2. (Ivacaftor or Kalydeco or VX-770 or VX770 or 873054-44-5 or ivacaftorum).af. (138)
3. or/1-2 (138)

Appendix 8 PRISMA checklist

Section/topic	#	Checklist item	Reported on page #
Title			
Title	1	Identify the report as a systematic review, meta-analysis, or both	Title page and p. v
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	pp. v–vi
Introduction			
Rationale	3	Describe the rationale for the review in the context of what is already known	_Chapter 1_, pp. 1–2
Objectives	4	Provide an explicit statement of questions being addressed with reference to participants, interventions, comparisons, outcomes, and study design (PICOS)	_Chapter 2_, p. 3
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	p. xix and _Appendix 7_, PROSPERO, CRD42012002516 www.crd.york.ac.uk/prospero/
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	_Chapter 3, Inclusion and exclusion criteria,_ p. 6
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	_Chapter 3, Identification of studies_, pp. 5–6
Search	8	Present full electronic search strategy for at least one database, including any limits used, such that it could be repeated	_Appendix 1_, pp. 69–81
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)	_Chapter 3, Inclusion and exclusion criteria,_ p. 6
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	_Chapter 3, Data extraction strategy_, p. 6
Data items	11	List and define all variables for which data were sought (e.g. PICOS, funding sources) and any assumptions and simplifications made	_Chapter 3, Data extraction strategy_, p. 6
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	_Chapter 3, Critical appraisal strategy_, pp. 6–7
Summary measures	13	State the principal summary measures (e.g. risk ratio, difference in means)	_Chapter 3, Methods of data synthesis_, p. 7

Section/topic	#	Checklist item	Reported on page #
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	*Chapter 3, Methods of data synthesis*, p. 7
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)	Not applicable
Additional analyses	16	Describe methods of additional analyses (e.g. sensitivity or subgroup analyses, meta-regression), if done, indicating which were pre-specified	Not applicable
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	*Chapter 4, Quantity and quality of research available* and *Figure 1*, p. 9
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	*Chapter 4, Summary of included studies*, pp. 10–11; *Table 1*, p. 10; and *Appendix 3*, pp. 85–8
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)	*Chapter 4, Risk of bias*, pp. 11–12; *Table 2*, p. 12; and *Appendix 2*, p. 83
Results of individual studies	20	For all outcomes considered (benefits or harms), present, for each study: (a) simple summary data for each intervention group, (b) effect estimates and confidence intervals, ideally with a forest plot	*Tables 3* to *9* and *Figures 3* to *10*, pp. 12–24
Synthesis of results	21	Present results of each meta-analysis done, including confidence intervals and measures of consistency	Not applicable
Risk of bias across studies	22	Present results of any assessment of risk of bias across studies (see Item 15)	Not applicable
Additional analysis	23	Give results of additional analyses, if done [e.g. sensitivity or subgroup analyses, meta-regression (see Item 16)]	Not applicable
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. healthcare providers, users, and policy makers)	*Chapter 7, Statement of principal findings*, p. 51
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)	*Chapter 7, Clinical effectiveness*, pp. 51–2
Conclusions	26	Provide a general interpretation of the results in the context of other evidence, and implications for future research	*Chapter 8*, p. 57
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	p. vi and p. xix

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