Health economic modelling in Cystic Fibrosis: A systematic review

Abstract

Introduction: Cystic Fibrosis (CF) is a heritable chronic condition. Due to the genetic and progressive nature of CF, a number of interventions are available for the condition. In the United Kingdom (U.K.) average cost of CF treatment is between €49,000 to €76,000[1] per patient (1). A review of health economic modelling studies is warranted to provide decision makers and researchers with an in depth understanding of modelling practices in CF and guidance for future research.

Methods: Online searches were performed in the 5 databases, studies were included if they were: 1) Model based economic evaluation for management of Cystic Fibrosis. Articles were restricted to English language only, but no restriction was applied on publication year.

Results: Nine studies were reviewed, most were Markov cohort models. Models evaluated pharmaceutical interventions and drug adherence. Modelling structure was consistent across most articles and a range of sources were used to populate the models. Cost and utility data were based on different sources and elicitation methods respectively. The majority of models failed to incorporate significant health events which impact both cost and disease progression.

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[1] 2012

Conclusion: In our review we observed a lack of, application of European Medicines Agency (EMA) guidelines for clinical trial endpoints, model structure justifications and lastly, health-related quality of life derived utility information around important clinical events. Future work around conceptual modelling of CF progression, utility valuation of significant health events and meeting EMA guidelines for trial reporting is encouraged.

Background

Health economic modelling is a practice which allows decision makers to determine what treatments, policies or programmes to adopt and fund from constrained healthcare budgets (2). Health economic modelling can be used to synthesise the best available evidence in order to compare treatments not already addressed through clinical trials, link intermediate outcomes to final endpoints, compare interventions broadly across disease areas and evaluate decision uncertainty through sensitivity analyses (3). Models allow representation of complex real-world scenarios in a comprehensible form (4). As such, these methods are pertinent to healthcare decision making globally. In the U.K. the use of modelling is recommended by the National Institute for Health and Care Excellence (NICE) (5). In this review we focus on the health economic modelling of interventions to manage Cystic Fibrosis (CF).

Cystic Fibrosis (CF) is a genetic heritable chronic condition with no cure and varying disease severity (6). The disease follows a pattern of repetitive bacterial infections resulting in reduce respiratory capacity and eventually leads to respiratory failure and death (7). Over the last 50 years, the outcomes of individuals with CF have changed. European Union (EU) member countries have demonstrated an increase in the prevalence of CF, in the younger and older age groups, due to reduced mortality (8).

With the increasing prevalence there is an emergence of comorbidities such as CF related diabetes (CFRD) and liver disease (CFLD). A study by Lewis et al (9) on the long-term impact of CFRD on mortality demonstrated that those with CFRD from 2008 - 2012 had a 10% higher risk of mortality per person compared to those who did not have CFRD.

Individuals with CFRD over the age of 30 had significantly higher age-adjusted mortality than those without CFRD (9). The prevalence of CFLD is around 2-37% in children and young adults and considering that it is the third cause of death, which follows lung disease and complications from transplantation, it accounts for 2-4% of CF mortality (10, 11).

Breakthroughs in CF treatment over the last decade have led to improvements in health outcomes demonstrated in a range of randomised clinical trials (12-16). However, the economic impact of CF has also increased over the past three decades. Many costs of illness studies have been conducted in Europe and the United States (U.S) (17-26). Cost estimates for treatment based on data collected through regional CF centres, medical records, patient questionnaires, clinical trial and insurance claims or CF specific databases over the last three decades have demonstrated variable results. A wide range in costs, evaluated populations and different methodological approaches to calculate costs were also evident (17-26). Where stated, medical drug treatment costs have contributed to anywhere between 12 to 85% of total costs. Regression analyses demonstrates an increasing cost of care with disease severity (23). Which, over time, has been managed through an increasing range of drugs.

Per patient treatment costs in the United Kingdom (U.K.) in 1989-1990 were £8,241 (17) and in 1990 were £10,908 (18). In 2012, the per patient cost of CF treatment in the U.K. was estimated to be between €49,000 to €76,000 (1). Within Europe, the cost of CF treatment per patient was, in 1996, €23,989 (20). In 2004, this increased to €41,468 per patient per year (23). However, considerable difference in per patient treatment costs

have been demonstrated through estimates generated in other European countries. In France, the per patient treatment costs in 2001 were €16,189 (24). A wide range in cost estimates are evident from studies conducted in Germany in 2004 and 2018, € 854 - €72,291 vs. €69 - €104,477, respectively. A number of limitations in previous costing studies have been identified (27). A more recent study by Orenstein and Abood (28) in the U.S. showed that average cost of care was approximately US$131,000 in 2016.

It is evident that cost of CF care is changing. In light of changing costs of CF care and increasing long term survival many interventions related to the management of CF have been evaluated for their cost-effectiveness to determine their future benefit and burden.

Based on resource scarcity, that limited resources meet unlimited need, the healthcare sector utilises economic evaluation to determine what new technologies, policies or healthcare models to implement. Facilitating comparison of healthcare programmes on the ground of costs and effectiveness or benefit, economic evaluations come in many forms. They allow decision makers to determine what to invest in at the opportunity cost of not investing in other programmes (2).

Although in all economic evaluations costs and benefits are considered, the defining factor of the type is based on how the unit of effect or benefit is measured. Cost effectiveness analysis (CEA) is the evaluation of benefit in natural units (e.g. life years gained, breast cancers detected, reduction in blood pressure, emergency admissions avoided). Cost utility analysis (CUA) form of economic evaluation involves the use of quality adjusted life years (QALYs) as the measure of effectiveness or benefit. Accepted as a reference standard by NICE (5), the utility aspect of CUA is a composite of QALYs,

which combines life years gained with a measure of preference or value for a particular health state. These measure of preference, also named utilities, can take a value between 0 (dead) – 1 (full health) (2). Cost effectiveness analyses outcomes are presented as an incremental cost-effectiveness ratio (ICER), which is a measure of incremental cost and benefit of new treatment against the incremental cost and benefit of the next best available treatment. The ICER supports decision makers in determining whether the new intervention is cost effective. In cases where the new treatment is both more effective but also costlier, the price per additional value of unit effect such as £20,000 to £30,000 per QALY is utilised by NICE to help establish whether investing in the intervention is an efficient use of healthcare resources (29).

A recent evidence report by the Institute for Clinical and Economic Review in the U.S. reviewed the effectiveness and value of modulator treatments in CF. The report highlighted that two regulatory bodies, the Canadian Agency for Drugs and Technologies in Health (CADTH) and NICE, decided not to provide Orkambi® (Vertex Pharmaceuticals) (30, 31) and Ivacaftor (Kalydeco®) on the basis of the cost of treatment being too high (32). Subsequently the institute developed a cost effectiveness model for a range of modulating treatments and found them all not cost effective. Despite some modulator treatments being designated as orphan drugs (33, 34) and being approved for use in Europe (35), they have not been provided for patients in the U.K. The high price of drugs associated with rare diseases like CF have resulted in unfavorable ICERs despite being efficacious treatments. The issue of high ICERs being associated with the use of

conventional cost effectiveness analysis on orphan drugs has been discussed in the past (36, 37) and is highlighted in the economic evaluation of CF interventions.

In light of recent appraisals of CF treatments, it is important to understand how the effects of different CF treatments are evaluated in health economic models as many treatments simultaneously change a range of outcome measures including lung function, exacerbation rate and intravenous antibiotic treatment. It is also important to determine the quality of reporting utilised in evaluations using checklists for model reporting which include Consolidated Health Economic Evaluation Reporting Standards (CHEERS) checklist (38), Quality of Health Economic Studies (QHES) instrument (39) and the recently published recommendations by the Panel on Cost-effectiveness in Health and Medicine in the U.S (40) for studies conducted in the U.S.

Through this review we aim to develop a better understanding of the health economic evidence presented in model based economic evaluations around the management of CF and of health economic modelling practices in CF. We pay particular attention to model design and appropriate use of input parameters. Equipped with a holistic overview of the practices used in modelling CF interventions, future health economic modelling studies could employ novel model structures and carry out value of information analysis in order to determine the direction of future research in CF.

Methodology

This systematic review follows guidance provided both by the PRISMA group (41) and the Centre of Reviews and Dissemination (CRD) (42).

Inclusion Criteria

The inclusion criteria are specified in Table 1. Economic evaluations not based on the management of Cystic Fibrosis, Cystic Fibrosis clinical trials and studies not relevant to Cystic Fibrosis were excluded.

Criteria	Notes
Population	Individuals with Cystic Fibrosis, no age restriction
Intervention	The management of Cystic Fibrosis, not including any form of screening pre or post birth
Comparator	Any (including usual care)
Outcome	Incremental Cost Effectiveness Ratios (ICER), Net Benefit and/or Cost per unit of Effect.
Study types	Cost-effectiveness (CEA), cost-utility (CUA), cost-benefit (CBA), which include Health Economic Models
Language	English only
Time Frame	Any
Exclusion	• Screening programmes looking at terminating CF related pregnancies or diagnosing newborns with CF (antenatal or post-natal screening) • Studies that DO NOT utilise health modelling techniques: e.g. Markov model, decision trees, patient-level simulations • Books/Thesis

Table 1: Review inclusion criteria, following PICOS framework

Study selection

Study selection was carried out by two authors (B.M and A.B.). Any disagreements were adjudicated by a third author (J.W.).

Search Strategies

Databases included in the review were: MEDLINE (Ovid), American Economic Association (EconLit), Health Management Information Consortium (HMIC), National Healthcare Service (NHS) Economic Evaluation Database (EED) (NHS EED), Cochrane

Library, PubMed (PubMed + PubMed Central) and Cumulative Index to Nursing and Allied Healthcare Literature (CINAHL). Google was searched using key terms, only selecting the first 50 links.

Medical subject heading (MeSH), truncation (*) and Boolean operators (AND/OR) were used to select and combine important text words, phrases, synonyms and indexing terms. Modifications were made to some search strategies to match appropriate mapping terms in each database.

Forward citation searching undertaken using the Web of Science (ISI) and hand-searching the bibliography of selected articles were undertaken to find further evidence which could be incorporated. Finally, no date, but only English language restrictions were applied. The last date for conducting searches in the databases was November 17th, 2017. The search strategies used are available in the supplementary material.

Quality assessment of studies

Articles included in this review underwent quality of reporting assessment through use of Consolidated Health Economic Evaluation Reporting Standards (CHEERS) checklist (38) Quality of Health Economic Studies (QHES) instrument (39) and the Panel on Cost-effectiveness in Health and Medicine in the U.S (40).

Results

Search results and study selection

A total of 896 articles were found through the electronic searches, which reduced to 813 after the removal of 83 duplicates (Figure 1). Thirty-seven articles were retrieved for full text screening and evaluated against the inclusion criteria.

Of the 37 articles, 23 were excluded as they did not contain health economic modelling. A further 4 were conference abstracts with no full text available, and one was not published in English (43). Nine articles were included for data extraction.
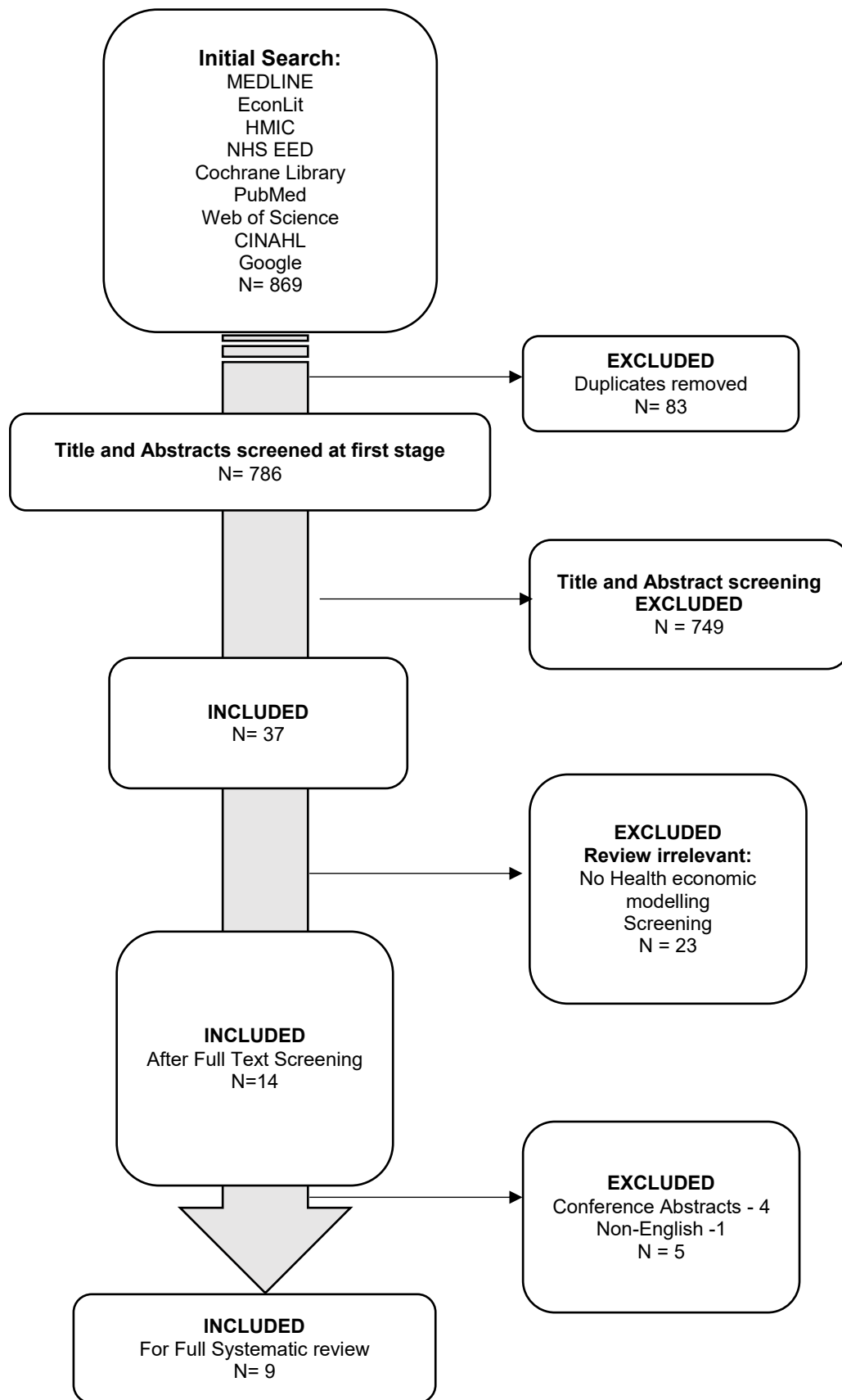
Figure 1: PRISMA diagram: process of study identification (41).

Summary of included

Author	Type of Model			Intervention	
	Cohort Model	Decision tree	Individual patient simulation model	Pharmaceutical	Adherence
Panguluri et al *(44)*			✓	✓	✓
Tappenden et al *(45)*	✓				✓
McGirr et al (*(46)*	✓			✓	
Dilokthornsakul et al *(47)*	✓			✓	
Schechter et al *(48)*	✓			✓	
Tappenden et al *(49)*	✓			✓	
Whiting et al *(50)*			✓	✓	
Christopher et al *(51)*		*2		✓	
McIntyre et al *(52)*	✓			✓	

Table 2: Summary of included studies

Table 2 provides an overview of the included studies. Of the 9 articles, 6 were Markov models, addressed as cohort models and 2 individual patient simulation models, addressed as individual patient simulation models. One was ambiguous in terms of the type of modelling it undertook and we were unable to speak to the author to clarify this (51).

The cohort model splits health and costs into distinct mutually exclusive categories called health states, which cohorts can travel between. Over a period of time, called a cycle, a cohort of individuals within the model accrue cost and benefits which ultimately

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2 Unknown if decision tree

summaries the average patient experience (3). In individual patient simulation models patients move through the model one at a time, rather than as a cohort. The advantage of such models over cohort model is their memory feature, will allows accumulation of patient history (such as previous health event) which can be utilised to determine, future movement in the model, costs and effects (3).

Five studies evaluated the impact of a range of pharmaceutical interventions (46-49, 52), of which one was a Health Technology Assessment (HTA) report (49). Two studies evaluated the impact of better drug adherence (44) or an adherence intervention (45) on reducing pulmonary exacerbations (PEx), nebuliser device costs, days receiving antibiotics, and/or the impact of reduced PEx events on FEV_1. One study evaluated the impact of pharmaceutical interventions through use of a patient level simulation model (50), which again was a HTA report. Lastly, one study evaluated the impact of rhDNase (51) on CF disease progression and the other Dornase Alpha on long-term patient survival (52).

Pharmaceutical interventions

Interventions and populations considered

Within the 5 cohort models, very few interventions were evaluated. The types of treatments covered include antibiotics (Tobramycin, Aztreonam Lysine, Colistimethate Sodium), monoclonal antibodies (Palivizumab (PMB)), CFTR modulators (Ivacaftor) and an inhalation device with adherence measurement compared to current CF care (45). Two studies compared treatment to no treatment, rhDNase vs. no treatment and PMB vs. no treatment (46, 51). Two studies utilised individual patient simulation models (44, 50) to evaluate the impact of Tobramycin inhalation nebuliser (TIS) vs. Tobramycin inhalation

powder (TIP) and Ivacaftor in CF individuals, respectively. Two studies evaluated the impact of Ivacaftor and usual care alone to only usual care (47, 50), which consisted of CF-related medication, devices and respiratory therapy (50). Two articles evaluated the impact of dry inhalation to nebulisation for antibiotics (44, 49), although one looked at the impact of adherence (44) and the other at different antibiotic treatments (49). One additional study evaluated the impact of inhalation of two different types of antibiotics (48). All studies that evaluated pharmaceutical interventions provided information about their baseline populations. Studies selected for review utilised patient data from randomised controlled trials (RCTs). One study utilised the U.K. CF Trust registry for their patient data (45). In one study, the effectiveness data utilised to populate the model was based on premature infants with chronic lung disease being treated with Palivizumab (PMB) (46). The populations included in the models include both adults and children (44, 45, 48, 50, 51), children (46) and adults (49) alone.

Evaluation type, time horizon and discounting

Cost-utility analysis (CUA) in which the quality-adjusted life year (QALY) is the measure of outcome was the most common type of economic evaluation undertaken. Cost-effectiveness analysis (CEA) was the second most common evaluation method utilised but was conducted in conjunction to cost-utility analysis in three studies (44, 46, 47). Models estimated costs and outcomes over a lifetime horizon except for two studies (44, 48) which utilised a 10 and 3-year time horizon respectively. Discounting was applied to both cost and outcomes for all but three studies (47, 51, 52). In the case of Dilokthornsakul et al (47) discounting was only applied to the costs and not the the clinical outcomes in hopes to forecast the clinical impact of Ivacaftor over a lifetime. On the other hand

Christopher et al (51) or McIntyre et al (52) did not provide justification for not discounting their outcomes. For all other studies base case discounting varied from 3% (44, 47, 48), 3.5% (45, 49, 50) to 5% (46). Further scenarios evaluating the impact of varying the discounting rates through sensitivity analysis was undertaken for all pharmaceutical interventions except one (52).

Model health states

Cohort models assume patients transition between different health states. The five cohort models evaluated in this review had a different number of health states into which the patients could enter. The most common structure was one which contained 5 health states (45-47, 49), 1) mild, 2) moderate, 3) severe forced expiratory volume in one second (FEV_1), 4) transplant and 5) death. Schechter et al (48) utilitsed a 14-health state structure, breaking the common 5-health state model FEV_1 categories into 9 categories based on FEV_1, with additional health states after lung transplantation.

For the remaining four models, the Panguruli et al (44) individual level simulation model contained three states into which patient parameters were entered. These included FEV_1, PEx events and overall survival, with no health state for lung transplantation.

The model in the Whiting et al (50) HTA report simulates the probability of death through a function of key variables such as gender, FEV_1, pancreatic insufficiency, diabetes mellitus, bacterial infection and number of PEx events. Christopher et al (51) and McIntyre et al (52) did not adequately describe their model structures or present diagrams in their publications.

Country and perspective

The health economic models were based within three countries, Canada (46), UK (45, 49-52) and United States (U.S.) (44, 47, 48). The modelling adopted an NHS (45, 49, 50, 52), US payer (44, 47), Canadian Healthcare (46), third party payer (48) and regional health authority (U.K.) perspective (51).

Data sources and Outcome measures

Data for all models focusing on pharmaceuticals were gathered from sources including clinical trials, CF registries, country specific life-tables, drug registries, pharmaceutical companies, personal communication and journal articles.

Although a majority of the studies were cost-utility analyses, all but two articles (45, 49) provide outcomes beyond the QALYs and ICERs. Additional outcome measures provided include survival (44), different aspects of costs (44), life years gained (46-48, 51, 52) reduction in hospitalisation (48), lifetime cost (47), probability of lung transplantation (47) and budget impact analyses (46, 47).

Table 3 shows all other outcomes that were also considered as part of the modelling analyses. We can see that five studies provide additional cost effectiveness outcomes as part of their analyses.

Outcome	Author				
	McGirr et al (46)	Dilokthornsakul et al (47)	Schechter et al (48)	Christopher et al (51)	McIntyre et al (52)
Life years gained	0.03/0.13 (All CF vs High risk only)	18.25 +	0.0162	2-7 +	3-7
Reduction in hospitalisation	-	-	-0.8377	-1.3 days	- 65 days
Lifetime costs	$294,702/$296,539 (All CF vs High risk only)	$3,374,584	-	-	£233,070
Probability of lung transplant	-	-18.27% (absolute)	-	-	-
Budget impact analysis	$1,420,072/$284,014 (All CF vs High risk only)	$0.087/$0.083/$0.074 (3/5/10 year time horizon, respectively)	-	-	-

Table 3: Further outcomes evaluated (by author and outcome)

Costs

Cost data for the models were gathered from a variety of sources. Cost for different stages of FEV_1 severity was based on Austrialian CF registry data (46), Insurance claims data (48), Private databases (44), US Kaiser Permanente's CF centre data (47), UK CF registry data (45, 50), Department of Health tariff banding (50), NHS national tariff (45) and a study conducted by Robson et al (17) (52). Not all studies separated cost of CF by FEV_1/disease severity. In the case of Tappenden et al (49) costs for CF care were assumed to be identical between treatment arms and thus were excluded from the evaluation. Christopher et al (51) considered the cost of rhDNase derived from the British National Formulary (BNF) and savings generating through reduction in hospital stays through Extra Contractual Referrals (ECRs).

Incremental cost effectiveness ratios

Incremental cost effectiveness ratios (ICERs) were expressed in a range of ways in the models evaluating pharmaceuticals. Dilokthornskul et al (47) showed incremental improvements in life expectancy, lung transplantation reduction, increase in QALYS and incremental lifetime costs of US$3,374,584 for a hypoethetical cohort of 1,000 patients. McGirr et al (46) showed incremental improvement in QALYs at a cost of C$61,550-157,332 per QALY, dependent on the assumed discount rate. Schechter et al (2015) demonstrated that Aztreonam was dominant over Tobramycin through improvement in QALYs, life years and reduction in hospitalisation. Tappenden et al (49) provides ICER values for QALYs for two different dry inhalation antibiotic treatments compared to a nebulised form. The results of the modelling state that Tobramycin DPI (TPI) dominates all other treatments. Whiting et al (50) undertook cost effectiveness analysis in three scenarios, optimistic, intermediate and conservative. The estimated ICERs were £335,000, £771,000 and £1.2 million per QALY gained, respectively. Tappenden et al (45) demonstrate that an adherence intervention dominated current care. Panguruli et al (44) reported a base case ICER which was a cost saving, saving $133,000 per QALY gained for TIP compared to TIS. Christopher et al (51) demonstrated that use of rhDNase in CF individuals over a life time resulted in a cost per life year gained of £52,550. McIntyre et al (52) demonstrated a cost of £27,269 per life year gained for lifetime treatment with Dornase Alpha.

Utility

Evaluation of the models utilitising a cost-utility approach shows some overlap in the literature sources utilised to derive QALYs. Health related quality of life (HRQOL) was linked to FEV_1 severity, pulmonary exaccerbation and adverse events. Three different

instruments/methods were used to derive utility weights from HRQOL of adults and adolescents (caregiver perspective) which include EQ-5D (44, 45, 48, 49), SF-36 (50) and a Standard gamble approach (46).

Four studies included disutility around pulmonary exacerbation events (44-46, 49) using the same data sources (53, 54). One source included disutlity around respiratory syncytial virus infection (55). Three different studies were utilised to include utility of lung transplantation and used the EQ-5D (56) (45, 49, 50), Visual analogue scale (VAS) (48, 57) and a standard gamble approach (SG) (46, 58).

Sensitivity analysis

The robustness of the results were tested with 1 way, 2-way, probabilistic and deterministic sensitivity analyses for all the models included in this review. A range of scenario analyses were also used to determine their impact on the cost effectiveness of interventions.

Quality assessment of the studies

Quality of reporting assessment undertaken using the CHEERS checklist showed that the studies of medium quality according to the QHES checklist (46-48) failed to provide adequate reporting of information in the methods and results sections according to the CHEERS checklist. On the contrary studies of high quality according to the QHES instrument (45, 49, 50) had very good quality of reporting in their publications against the CHEERS checklist.

Studies conducted in the U.S. were also evaluted against the Panel on Cost-effectiveness in Health and Medicine criteria (40). According to the checklist the U.S based studies

were lacking in a number of reporting criteria requirements and considerable work in improving these is required for future studies who decide to undertake any health economic modelling.

Discussion

This is the first systematic review to summarise the cost effectiveness of interventions in CF as predicted through economic models and in particular the modelling practices that lead to those estimates. It is not surprising that the estimates of cost-effectiveness provided by the models vary widely given that the interventions evaluated and setting in which they are used all vary widely. However, this review aimed in particular to identify the current issues in the health economic modelling of CF. The modelling approaches utilised also vary widely despite the comparatively limited number of studies included in this review. Three different types of modelling approaches have been reported in this review and each has its own advantages and disadvantages (3).

In order to appraise the models and the appropriateness of the evidence we assessed different aspects of the economic evaluations. We looked at data from the clinical trials underpinning the models, HRQOL/utility studies, costs, ICERs and lastly the model structures.

Clinical trial data

Evaluation of the European Medicines Agency (EMA) information published around CF showed a list of outcomes considered important for collection in clinical trials of CF (59). Evaluation of the clinical evidence utilised within the economic models showed that the

endpoints reported in the different trials underpinning the models varied and not all studies followed the guidance set by the EMA for CF.

All trials conducted to evaluate the clinical effectiveness of different treatment options evaluated FEV_1 as their primary outcome measure. Secondary and tertiary outcomes considered in the clinical trials included change in FEV_1 over the trial period, change in sweat chloride, change in weight, time to/number of and duration of PEx events, quality of life (QOL), number of days admitted to hospital and the need for antibiotic therapy. Collection of these outcomes have been clinically justified by the EMA (59).

It was evident after evaluation against the EMA guidelines that data were collected for PEx events in some clinical effectiveness studies of CF interventions (44, 47-50). However, not all PEx event data was utilised when undertaking health economic modelling of the intervention (44, 46, 47). A similar finding was observed for hospitalisation and antibiotic use (47, 50). Although this may seem unrelated to the modelling of CF, data sources provide vital input and future trials should aim to meet the EMA guidelines (59) which can in turn be utilised in the health economic modelling of CF interventions.

Utility/ HRQOL data

Utility data were presented for each model described by the review where the QALY was an outcome measure for different health states. These included FEV_1 based disease severity, transplantation and PEx events. The evidence presented in all the different economic evaluations around utilities for the intervention themselves were based on a range of sources, but they did use similar data in a majority of cases (44, 45, 47-49).

Only one trial collected HRQOL information, which met the requirements of the NICE reference case (50) but the utility estimates were considered inflated by NICE HTA evaluation team. As a result, utility values for the Whiting et al (50) model are based on utilities that are also used by Dilokthornsakul et al (47).

Utility values for transplantation were also included in the models. The utility of lung transplantation was measured through a range of methods across the evaluated studies. Disutility from PEx event was only included in four studies (44, 45, 48, 49) and the source of the disutility data was the same (53, 54) in three studies. Panguruli et al (44) simply stated the decrement in utility without further elaborating on the source. Dilokthornsakul et al (47) failed to incorporate disutility of PEx despite there being data on the number of PEx events and subsequent healthcare utilisation in their clinical trial studies. Similarly, although data were available from the clinical trials around PEx events and subsequent healthcare utilisation, Whiting et al (50) failed to account for disutility of such events. Their model only accounted for PEx through its impact on long-term survival. However, they do state that reduction in PEx events could also have additional impact outside survival.

Cost Data

Evaluation of the cost evidence in the models showed that a range of sources were utilised. McGirr et al (46) utilised an study based on Australian patients to calculate cost per mild, moderate or severe FEV_1 health state and lung transplantation (27) to determine the cost effectiveness of PMB. But these cost estimates are averages for patients across 0-30+ years of age. Similarly, lung transplantation costs are based on CF individuals between 11-13 years old. However, the population in the model is that of less than 2 years.

Two studies evaluated the cost effectiveness of Ivacaftor (47, 50). Dilokthornsakul et al (47) utilised 1996 cross-sectional US Kaiser Permanente's regional CF centre data to determine health state specific costs (22). Other models reviewed in this work which were also based in the US (48) used an alternative source to determine healthcare utilisation costs for US CF individuals (60). In comparison to the Kaiser Permanente's regional CF centre data, which was conducted on 136 individuals in 1 year, Briesacher et al (60) evaluated longitudinal healthcare utilisation in 3,723 CF individuals from 2001-2007 and adjusted for disease burden and time trends in medical costs.

Most importantly, the Lieu et al (22) study was conducted prior to the introduction of new maintenance therapies (60) and subsequent studies looking at the cost of CF in a similar setting (61) have shown a 140% increase (60) in costs compared to those calculated by Lieu et al (22). Lung transplantation costs inputs in Dilokthornsakul et al (47) utilise 2011 data, although more up to date costs on single and double lung transplantation data exist for 2014 (62).

Whiting et al (50) utilised a banding system to reflect disease state specific costs (63) due to increasing treatment complexity and NHS reference costs for lung transplantation.

A total of four studies evaluated the cost-effectiveness of antibiotic treatments (44, 45, 48, 49), all of which evaluated tobramycin in solution/nebuliser. Although the reference cost year for the studies ranged from 2011 to 2016, there was considerable difference in cost of antibiotic treatments. A similar scenario exists for Aztreonam where there is up to a 4-fold cost difference between studies (45, 48). The reason for such difference is unapparent.

ICERs

The ICERs for the treatments in the cost effectiveness models were evaluated. Given the difference between countries for the same drug, this demonstrated that it is difficult to generalise country specific results to others. This highlights the possible variability in CF clinical treatment patterns, difference in drug pricing across countries and in secondary or primary healthcare utilisation and ultimately the health policy agenda for particular countries.

Model structure

Just over a quarter of the models evaluated in this review did not provide a justification for using a model structure based on 5 health states (47, 48). Considering CF's multifactorial nature, disease models lack a similar approach. The structure utilised by McGirr et al (46) was based on a study conducted on an Australian CF registry dataset which separated out disease severity by lung function scores (FEV_1). Two additional health states, death and transplant, were added at this point. Prior to this the model structure itself is based on another cost analysis study conducted by Lieu et al (22) which was designed based on advice from the CF Foundation.

Evidence presented by Tappenden et al (49) defined the health states through information presented in their HTA report which detailed the conceptualisation of the decision problem (64). The probability of transitioning between the defined states were based on data from systematic reviews looking at the plausibility of relationships between intermediate and final endpoints as well as expert opinion (64). The additional Tappenden et al (45) paper simply refers back to the 2014 publication in reference to the structure of the model. Whiting et al (50) utilised a patient-level simulation model, demonstrating the probability of death as a function of age, gender, bacterial infection, pancreatic insufficiency, PEx

events, weight, baseline FEV_1 value and diabetes. A structure and a description is presented in the HTA report. Panguluri et al (44) also utilised a patient level simulation model for their adherence study. They utilised this model particularly due to the advantages of using individual patient data over cohorts of patients. The model was also appropriate for the data being utilised and the model structure was consistent against guidelines published by Brennan et al (65).

Future research direction

The evidence presented in this review suggests that health economic aspects of CF disease modelling require better access to data and more representative modelling methods. Future health economic modelling could attempt to focus on conceptualising a model that is relevant to CF, one that incorporates separate health states such as PEx or intravenous antibiotic use which are known to be important for patients (66) as they are predictive of longer term survival (67, 68) and cost considerable resources (69). Future models could also take account of co-morbidities such as Diabetes and Liver disease. Although EMA guidelines make no mention of diabetic and liver disease status for identification in CF clinical effectiveness studies, both these conditions are becoming more common in CF patients (9-11, 59). The impacts of these comorbidities on the long-term mortality becoming clearer (9-11). Given the recent workshop on clinical trial endpoints in CF (59), future trials should aim to follow or improve the availability of such data. This is not only important for the clinical effectiveness aspect of CF interventions, but also on any subsequent analyses or evaluations, which are dependent the quality of such data for their findings.

As for cost data, such information could be gathered from more robust sources such as Hospital Episode Statistics (HES), Secure Anonymised Information Linkage (SAIL) data bank or their equivalent in Europe. This would allow for more up-to-date healthcare utilisation and costing which are longitudinal and consider time trends of CF treatment.

However, to truly evaluate the long-term survival of CF individuals, it is necessary to evaluate all interventions within a single epidemiological model but also include the impact of post transplantation complications and mortality.

Moreover, given the importance of HRQOL as an outcome in CF, future research should aim at understanding the evidence base around the availability of utility-based outcome information, which is required to assess QALY's in HTA submissions to NICE.

Limitation of this review

This review only included studies written in English. However, this only resulted in the exclusion of one article, making the introduction of bias unlikely. We believe that the published literature gives a reflection of the methods that are being applied and most models used to underpin submissions to regulatory bodies are likely to be subsequently published, assuming they meet acceptable quality standards at peer review.

Conclusion

This review aimed to evaluate the modelling practices utilised in the health economic evaluation of CF. Clinical trial data underpinning the models in a majority of cases aimed to follow the guidelines set by the EMA, but not all studies demonstrated this.

It is evident through the data, particularly the two studies on adherence to antibiotics, that PEx can have considerable impact on both the costs and outcomes of CF individuals.

Therefore, further study into this highly relevant clinical endpoint should be encouraged. Health utility measurement of PEx and other relevant health states is needed for incorporation into health economic modelling. Given the different cost data sources utilised in the models, even in the same country, attempts to utilise more robust sources could help reduce methodological variability and variability in ICER estimates.

Conflict of interest

None

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