Health state utility data in Cystic Fibrosis: A systematic review

Introduction: Cystic Fibrosis (CF) is life-limiting, hereditable condition, with the highest prevalence in Europe. CF treatments have led to improvements in clinical symptoms, disease management and slowing disease progression. However, little is known about the health state utility (HSU) benefits through interventions, reduction in adverse events or disease status. Although HSU data has contributed to existing health economic modelling studies, a lack of such data has been highlighted. This review aims to provide a summary of all HSU data and to highlight related research gaps. Methods: Online searches were performed in 5 databases. Studies were included if they met any of the following criteria: 1) Measured utility in CF individuals, 2) Mapped between patient reported outcomes (PROMS) and preference-based instruments (e.g. CFQ-R and SF-6D), 3) Economic evaluations on the management of CF which use utility data and 4) Any CF clinical trial that reported health utility as an outcome. Results: A total of 15 studies were reviewed. Of the 15 studies, 10 provided mean health utility for specific CF populations. The remaining 5 articles provided health state utility data which was broken down in some form by CF condition relevant interventions or health states and included lung transplantation, Pulmonary exacerbation (PEx) events and Forced expiratory volume in 1 second (FEV_1). Conclusion: Current health state utility data in CF is limited. There is considerable scope for research into preference-based elicitation studies and mapping algorithms.

Correspondence to: Bishal Mohindru, Norwich Medical School, Norwich Research Park, University of East Anglia, Norwich Norfolk NR4 7TJ. UK.

E-mail: b.mohindru@uea.ac.uk

Keywords:

Health Economics, Cystic Fibrosis, Utility, Health-related quality of life, HRQOL

Introduction

Cystic Fibrosis (CF) is a life-limiting condition in the United Kingdom (U.K.), with projected prevalence in 2025 of 14,400 individuals (1). A growth rate of more than 50% compared to 2010 (1). The average annual cost per CF individual for treatment is €49,000, doubling to €76,000[1] for those with CF receiving additional caregiver support (2). As a result, even though CF has a low incidence it results in substantial economic burden (2).

Treatments received by CF individuals are leading to improvements in clinical outcomes (3-6). However, the decision for treatment provision by governing bodies like the National Institute for Health and Care Excellence (NICE) in the U.K. is based on the cost-effectiveness of the treatment (7). Health state utility (HSU) values play a central role in valuing health-related quality of life (HRQOL) to support economic evaluations and can be elicited through direct or indirect methods (8). Indirect methods utilise questionnaires, such as the EQ-5D, to determine perceived health states of those filling in the questionnaire (also known as instruments). Completion of the instrument across many domains such as mobility, pain and mental health etc. results in a score which is then matched up to a utility value. On the other hand, direct

[1] cost year 2012

methods such as time-trade off (TTO) and standard gamble (SG) present hypothetical scenarios which ultimately allows for health utility evaluation. Both these techniques generate utilities anchored at 0 (death) and 1 (full health) (8). Indirect measures are required or suggested for inclusion in economic evaluations in countries which include England, Wales, Spain, France, Finland, Poland, New Zealand and the Netherlands (9). Measures, particularly those generated through generic questionnaires, such as the EQ-5D (7) are required by regulatory bodies like NICE.

In an ideal world, for a health economist all clinical trials conducted on healthcare interventions would include some form of preference-based measure (PBM) which can provide a health utility value. This does not happen often where generic PBMs such as the EQ-5D, are included for completion by participants. One way to obtain health utility values is through mapping (8). 'Mapping' allows conversion of outcomes from one incomplete PBM, such as a patient report outcome measure (PROM), to a generic PBM which allow calculation of utility values (9), which can in turn be used for health economic modelling.

We undertake a systematic review which aims to identify all studies that determine the health state utility in CF as well as studies that provide utility data for defined populations of CF individuals. The main goal is to inform future health economic models by clarifying what data is available. Additionally, we look to inform future work by highlighting gaps in the research related to health state utility values of CF individuals.

Methodology

This study follows the Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) guidelines (10) for reporting systematic reviews.

Inclusion criteria

Although it is not entirely possible to apply the PRISMA guidelines to a HSU systematic review (11), we have attempted to do so in order to define the boundaries of this review. We have selected a Population, Intervention, Comparator, Outcome and Study Design (PICOS) framework (12), this is presented in Table 1. Although we are aware that the HSU may not be attached to a particular intervention. When we describe the intervention, we aim to describe the method of determining the HSU values.

The utility values we seek pertain to individuals of any age with CF and health states associated with these individuals. Studies that reported utility weights gained through proxy are also included. Studies utilising rating scales such as the visual analogue score (VAS) were excluded as they are not considered utility values anchored by full health and death and also risk scaling biases such as the end of scale bias (13).

Studies included in the review were assigned to 1 of 4 categories during the title and abstract screening process which included: 1) Measuring utility in CF individuals, 2) Mapped between patient reported outcomes (PROMS) and preference-based instruments (e.g. CFQ-R and SF-6D), 3) Economic evaluations on the management of CF which use utility data and 4) Any CF clinical trial that reported health utility as an outcome. Studies excluded from this review were placed in the following categories: 5) Study describing psychometric properties of CF-related instruments, 6) a CF individual's perception of treatment/disease, 7) Articles about CF but not relevant, 8) Non-CF study and lastly, 9) Book or Thesis.

Criteria	Notes
Population	Health states of Individuals with or Valuations pertaining to CF
Intervention (Method)	Any preference elicitation technique in order to determine health utility (Excluding VAS if scales not anchored to full health and death)
Comparator	Any similar elicitation technique or nothing at all
Outcome	Utility-based weighting of different severities of CF such as forced expiratory volume in 1 second (FEV1) (mild, moderate and severe), Lung transplantation, PEx events, hospitalisation
Study types	Health related quality of life derived utility studies, clinical trials, and mapping studies
Language	English only
Time Frame	Any
Exclusion	Books, Editorials or Conference Abstracts

Table 1: Inclusion criteria

Search strategies

Search strategies were designed in order to identify the appropriate original published studies for this review. Text words, phrases, synonyms and indexing terms were selected through the Medical subject heading (MeSH) thesaurus. Preselected search strategies were also utilised from a previous study (14). Appropriate changes were made to the designed search strategies in order to tailor them to different subject heading terms in alternative databases.

Databases included for this review were: MEDLINE Ovid PubMed (PubMed + PubMed Central), PsycINFO, Web of Science, Cochrane Library (NHS EED only), Cumulative Index to Nursing and Allied Healthcare Literature (CINAHL). Google was also searched using key search terms, as the search algorithm for this database changes frequently, with the first 50 results reviewed for inclusion. No date restrictions were applied, although we restricted the language to English only.

Forward citation searching was undertaken using the Web of Science (ISI) to find further evidence which could be incorporated. Additionally, the bibliography of articles (backward citation searching) selected for full text review were hand-searched for relevant literature. The last date for conducting searches in the databases was 16th

June 2017. Conference abstracts were excluded. Search strategies are available in the supplementary material.

Study selection

Two rounds of selection were carried out by two authors (B.M and A.B.) based on the inclusion criteria. Any disagreements were adjudicated by a third author (J.W.).

Quality assessment of studies

Qualities assessment of the health utility studies was not conducted as there is no agreed reporting standard for these types of studies.

Results

Search results and study selection

A total of 2,474 articles were found through our electronic searches. This number was reduced to 1,664 after removing 810 duplicates. A further 1,433 were excluded at the title and abstract screening stage, leaving 231 articles. Of these, 201 were removed after full text review. Finally, a further 15 articles were excluded because they were conference abstracts, not written in English or presented visual analogue scores (VAS) only. A total of 15 articles were included in this review and were processed for data extraction in Microsoft® Excel by B.M and A.B. A PRISMA diagram is presented in Figure 1, to demonstrate the process of study selection.

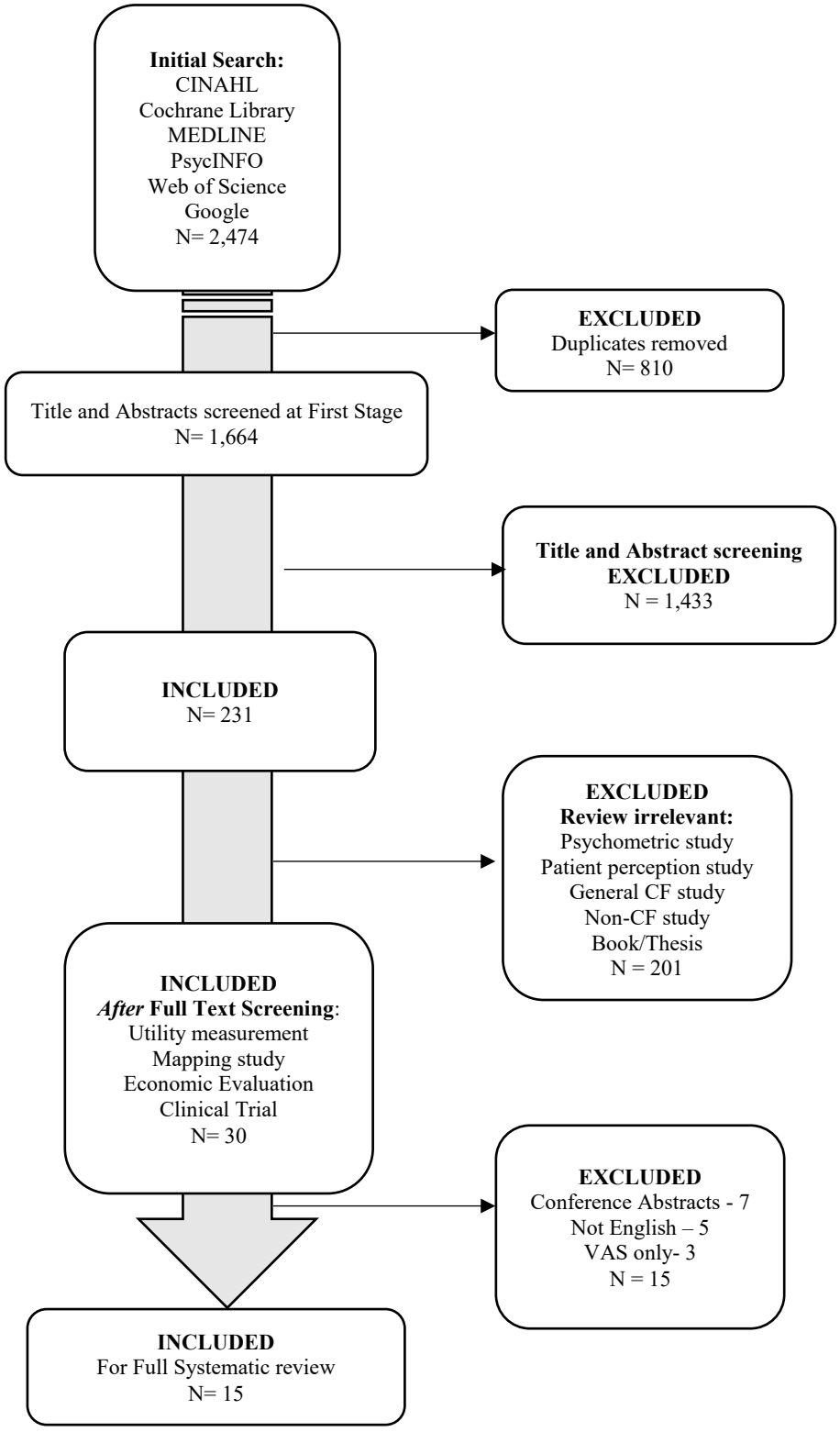

Figure 1: PRISMA diagram: Adapted from Moher et al (10), showing the process of study selection.

Author	Year	Country	Subjects	Type of study	Sample size total
Solem et al	2016	USA	Patients (Adults) 12 +/> (Ivacaftor therapy in CF ptx with G551D mutation)	HRQOL study	161
Chevreul et al	2016	Multiple	Patients (Adults and Children) (or Proxy/carer) and carers	HRQOL study	920
Iskrov et al	2015	Bulgaria	Patients (Adults and Children) and carers	HRQOL study	40
Chevreul et al	2015	France	Patients (Adults and Children) (or Proxy/carer) and carers	HRQOL study	166
Angelis et al	2015	UK	Adults, Children and Caregiver (Adults, Children and Caregiver)	HRQOL study	74
Acaster et al	2015	USA	Patients. (Adults) 18 + >	Mapping study	401
Bradley et al	2013	UK	Patients (Adults) >16 years, +bacterial infection, + antibiotics medication	HRQOL study	94
Dewitt et al	2012	USA	Patients with mild lung impairment (FEV1:75 or more) and carers	Clinical trial	328
Fitzgerald et al	2005	Australia	Children, Adolescents and Adults (5-18 years)	Clinical trial	50
Yi et al	2003	USA	Patients (8-12 years) (No patients who have had lung transplant) (no further mention of actual population group)	HRQOL study	65
Suri et al	2001	UK	Children only	Clinical trial	40
Selvadurai et al	2001	Australia	Patients (8-16 years), admitted to hospital for infective PEx	HRQOL study	66
Czyzewski et al	1994	USA	Patients and carers (Children and Adolescents and Caregiver)	HRQOL study	254
Busschbach et al	1994	Netherlands	Patients (Adults)waiting for and having received and lung transplant	HRQOL study	6
Oreinstein et al	1990	USA	CF individuals older than 10 years, positive for bacterial infection and treated with a new antibiotic (proxy: examiner)	HRQOL study	28

Table 2: Summary characteristics of included studies (by descending publication date)

Study Characteristics

Table 2 summarises key study characteristics. Included studies were published from 1990 onwards. The most recent publication was 2016, with more than 20% being conducted in 2015. The duration of the studies varied, with most studies undertaking only a cross-sectional measurement, some included longitudinal follow up, up to 5 years. Studies were undertaken in many different countries in and outside of Europe, with one study (15) covering multiple countries which were part of the same BURQOL-RD research network study. The most common countries were United States of America (USA) (6) and United Kingdom (U.K.) (3). Two were from Australia (16, 17).

In Table 2, we have identified the type of study being undertaken and have categorised them. Studies focusing on determining HRQOL were categorised as HRQOL studies. Studies focusing on evaluating HRQOL in conjunction to an intervention were categorised as clinical trials. Finally, studies focusing on deriving utility values from one instrument based on outcomes from another were labelled as mapping studies.

The patients in the studies included children, adolescents and adults in different combinations such as adults and children, children only or adults only. In some cases, studies included caregivers (2, 15, 18-20), some of whom were also assessed for their health utility (2, 15, 18, 19).

The total number of individuals covered in the studies in this review equated to 2,693 CF individuals, with sample sizes ranging from 6 to 920 people. The largest sample came from a study looking at the HRQOL across multiple European countries, conducted as part of the BURQOL-RD research network study (18). The population age varied across studies, with the youngest mean age of the participant being approximately 9 years (20) and the oldest mean age being 30 years (21).

Completion of the questionnaires was undertaken with no proxy on 6 occasions (19, 21-25). The remaining studies utilised proxies in some patient groups to complete the instruments (2, 15, 18, 26, 27). Dewitt et al (26) only utilised a proxy when people with CF were under a particular age, <14 years old. Two studies were ambiguous about how the questionnaires were completed (16, 17) and one study interviewed the participants and subsequently allowed them to complete the questionnaire at home (20). Lastly, one study collected information through face -to- face interviews (28).

Author	Date	Method of obtaining utilities				Utility for health states	Value set utilised	Intervention
		Direct Utility	Multi-attribute	Mapping study	Instrument/Technique			
Solem et al	2016		✓		EQ-5D-3L	✓	Dolan et al (29)	Ivacaftor
Chevreul et al	2016		✓		EQ-5D-5L (mapping to 3L value set)	x	Multiple countries	-
Iskrov et al	2015		✓		EQ-5D-3L	x	Dolan et al (29)	-
Chevreul et al	2015		✓		EQ-5D-5L (mapping to 3L value set)	x	Perneger et al (30)	-
Angelis et al	2015		✓		EQ-5D-5L> EQ-5D-3L [2]+ VAS	x	Kind et al (31) & Dolan et al (29)	-
Acaster et al	2015		✓	✓	CFQ-R to EQ-5D-3L	✓	Dolan et al (29)	-
Bradley et al	2013		✓		EQ-5D -3L	✓	MVP Group (32)	Pulmonary Exacerbations (PEx)
Dewitt et al	2012		✓		Health Utilities index 2/3	x	Unknown	Chloride Channel Activator
Fitzgerald et al	2005		✓		Quality of Wellbeing	x	Unknown	rhDNase
Yi et al	2004	✓	✓		Time trade off, Standard gamble & Health Utilities Index 2	✓	Unknown & Direct valuation	-
Suri et al	2001		✓		Quality of Wellbeing	x	Unknown	rhDNase
Selvadurai et al	2001		✓		Quality of Wellbeing	x	Unknown	Aerobic vs Resistance training
Busschbach et al	1994	✓			Time trade off & Standard gamble	✓	Unknown & Direct valuation	Lung Transplantation
Czyzewski et al	1994		✓		Quality of Wellbeing	x	Unknown	-
Oreinstein et al	1990		✓		Quality of Wellbeing	x	Unknown	Antibiotic (Abx)

Table 3: Summary of utility data collection (by descending publication date)

[2] EQ-5D 5L used but value set for conversion is for EQ-5D 3L

Utility elicitation

Table 3 provides a summary of utility collection procedures, value sets used and interventions considered.

From the 15 studies evaluated in this review, 13 studies reported utility scores described by multi-attribute utility instruments (MAUI). A combination of direct and indirect utility elicitation methods were used to derive utilities. The most common multi-attribute instrument used to derive utility was the EQ-5D (2, 15, 18, 19, 22, 23). This included different version of the EQ-5D, the 3L and 5L. Studies that utilised the EQ-5D-5L version of the instrument (2, 15, 18) mapped their results to the 3L instrument due to the lack of a value set at the time, which is what NICE recommends (7). This method of deriving utilities was followed by utility elicitation through the Quality of Well-being instrument (QWB) (16, 17, 20, 24, 27). Lastly, the Health Utilities Index (HUI), version 2 and 3 were used in two studies (26, 28). Direct elicitation via TTO and SG was used by two studies (25, 28).

Converting HRQOL scores into utilities

We aimed to identify the value sets that were used to convert the multi-attribute scores into utility values. The U.K. value set was based on a study the by Dolan et al (29) was commonly used to calculate utility values for studies using the EQ-5D-3L instrument, although it was not used exclusively for U.K. studies. Only on two other occasions were different value set utilised for the EQ-5D-3L, by Chevreul et al (15) who used a French value set (30) for a French study and by Chevreul et al (18) who utilised multiple value sets for different European countries. Chevreul et al (18) also applied value sets from

different countries to the multi-attribute instrument scores in cases where value sets were not available for that particular country.

Five studies were investigated to understand which value sets they had utilised to convert Quality of Wellbeing scores into utilities (16, 17, 20, 24, 27). There was no clear information about the value set in any study. However, we are aware that the utility scoring algorithm is available from the developers of the instrument (8).

Finally, two studies utilised the HUI, versions 2 and 3 (26, 28). Neither study provided information around the value sets that were used to calculate their respective utilities.

Mapping between instruments

A single study was found in this review that undertook mapping from the Cystic Fibrosis Questionnaire- Revised (CFQ-R) disease specific multi-attribute instrument to the EQ-5D-3L (21).

Health State-derived utility

Of the 15 studies included in this review, only 5 provided data which were broken down in some form by CF disease relevant interventions or health states. These included health states related to the following: lung transplantation (25), PEx events (22, 23) and FEV_1 (21, 28).

Lung Transplantation

Lung transplantation utility data were separated by type of transplantation, bilateral and also by the time-points prior to and after the transplant (25).

This study measured utility at three-time points for individuals with bilateral transplant. This included before, during and after the lung transplant where the utilities were 0.8, 0.4 and 0.9, respectively (25).

Pulmonary exacerbations

PEx utility was separated by the following health states, PEx requiring/ not requiring hospitalisation and the time periods prior to and after the events (22) and mild/ moderate/ severe PEx (23). It is evident from the data that increasing severity of PE events decreases the EQ-5D utility index. Utility values were 0.85, 0.79 and 0.60 for No, mild and severe PEx events respectively (23).

Utility derived by the time since PEx event start and finish was investigated by Solem et al (22) and was based on whether the individual required hospitalisation or not. For PEx events that required hospital admission, utility was the worst during the period during the build-up to a PEx event (0.76). Utility up to 8 weeks prior to PEx was much better (0.9) compared to time periods up to 8 weeks after the event (0.85). This relationship is not evident in the non-hospitalised PEx events group, for the EQ-5D utility index score, with the utility score being highest 1-4 weeks after the PEx.

FEV_1

FEV_1 utility data were separated either by three (21) or four categories (28) of severity. This included the conventional mild, moderate and severe categorisation. Yi et al (28) further separate them into the following, <40% predicted, 40%-59% predicted, 60%-79% predicted and >79% predicted FEV_1. The studies undertook FEV_1 evaluation using different approaches. Acaster et al (21) mapped the CFQ-R instrument to the EQ-5D 3L by 3 FEV_1 severity levels. Yi et al (28) used combination of a direct utility approach of

TTO and SG in addition to HUI2 instrument to determine utility and categorise FEV_1 by 4 severity levels.

The calculated utility data in the Acaster et al (21) study shows a decrease in utility score with increasing severity according to the EQ-5D-3L (data not shown). This relationship is not so evident in some cases for Yi et al (28). For instance, the HUI2 utility index scores do not decrease with increasing severity. This is also evident in the SG utility data across the varying FEV_1 severity, with utility for 40-59% FEV_1 (0.96) being better than that of >79% FEV_1 (0.92). A similar pattern is evident in the TTO utility data.

Population based-utility

Of the 15 studies included in this review, 10 provide mean utility for specific CF populations. The studies cover populations on the following treatment/intervention: rhDNase (16, 24), antibiotics (27), aerobic vs resistance training (17), education (20) and chloride channel activator (26). Four additional articles simply observed the mean utility of CF individuals across Europe (2, 15, 18, 19). These studies particularly focus on characterising change in utility pre and post intervention over time.

Recombinant Human DNase (rhDNase)

Recombinant Human DNase (rhDNase) was evaluated in two clinical trials (16, 24). Each study targeted different population groups, children only (24) or children and adults (16). Both studies utilised a multi-attribute instrument to obtain utility data, the Quality of Wellbeing instrument (QWB) Although, Suri et al (24) study did not provide utility data post treatment with rhDNase, only including a baseline QWB score of 0.61 for their CF study population.

Suri et al (24) evaluated two different rhDNase treatment regimens, once daily or alternative days of rhDNase against twice daily hypertonic saline. The QWB scores following the 12-week trial showed no significant difference between the treatment options.

Fitzgerald et al (16) evaluated the impact of administering rhDNase before or after physiotherapy treatment as part of a clinical trial. The results showed significant difference in QWB between the two treatment periods, 0.778 vs 0.752 ($p<0.05$). But it is not clear in the article what period represents which treatment option.

Chloride Channel Activator

The impact of Denufosol, a chloride channel activator, on CF individuals with mild impairment in lung function was evaluated over 48-weeks in a clinical trial (26). The study utilised the HUI2/3 to evaluate the utility of treatment, but there were no significant changes in utility of the treatment period in either instrument.

Aerobic vs Resistance training

Selvadurai et al (17) looked to determine the impact of aerobic vs resistance training on QWB subsequent to a pulmonary infection. Significant changes ($p<0.05$) in quality of life were only seen in the aerobic training group. However, this is poorly presented and difficult to quantify.

Education intervention

A clinical education intervention was provided to children and adolescents in order to determine QWB derived utility (20). The interdependent respondent agreement between parent/caregiver and adolescent CF individual in terms of utility was evaluated. Utility scores were 0.79 and 0.76 for caregivers and adolescents respectively.

Antibiotics

Quality of wellbeing was applied to CF individuals being treated for PEx with oral Ciprofloxacin (27). Change in QWB was scored in the patient sample subsequent to treatment and showed a mean change of 0.104 but the worse and best change in QWB were -0.201 and 0.209, respectively.

Cohort studies

Finally, four studies (2, 15, 18, 19) evaluate the health derived utility in a range of European countries as part of the BURQOL-RD Research Network. The overall population covered within the individual countries were based on the same criteria, CF patient centre or its equivalent in different countries and CF Trust registries. Three studies were in depth publications (2, 15, 19), whilst the remaining article was a summary of the before mentioned articles with many additional countries which were evaluated as part of the project (18). The countries included Germany, Hungary, Italy, Spain and Sweden.

Evaluation of the individual published studies showed discrepancies in the data. Not all the data in Chevreul et al (18) matched those figures provided within either Chevreul et al (15), Angelis et al (2) or Iskrov et al (19). Further evaluation of the number of patients utilised to reflect the EQ-5D-3L utility index data showed for example in Angelis et al (2), that different population numbers were used to calculate the utility score, 37 vs 33, respectively. A similar case is evident in the other two publications (15, 19).

Discussion

Health economic modelling has become a key component of healthcare decision making and it's use is recommended by NICE for technology appraisals (7). However, in order to

undertake health economic modelling, there needs to be sufficient data to populate the model which in turn should reflect disease progression (33). Previous models have highlighted a lack of health outcomes evidence to inform CF health economic models (14, 34), particularly around the health outcomes data.

Health state derived utility values were only available for 5 studies (21-23, 25, 28). They focused only on lung transplantation, PEx events and FEV_1. These studies have substantial limitations in their application. The lung transplantation data presented covers only bilateral lung transplantation (25). The treatment sample in Busschbach et al (25) was small. Utilisation of health utility data derived from these CF individuals for health economic modelling should be undertaken with caution. Additionally, these CF individuals were hypothetically put into different lung transplantation health states and were described as overestimating their utility (25).

PEx event data presented covered a 16 to 48-week (22, 23) and has limited application for this particular health state due to the nature of the populations and treatments being investigated. Solem et al (22) evaluated the impact of Ivacaftor on PEx events. Data from Bradley et al (23), examines health utility of those who are taking oral or inhaled antibiotics. So, utility values can only be applied in CF individuals taking those treatments.

FEV_1 derived health state utility was investigated in two articles (21, 28). Acaster et al (21) categorised FEV_1 derived utility into three states: mild, moderate and severe, which was self-reported in a cohort of self-diagnosed CF individuals. Yi et al (28) reported and categorised FEV_1 derived utility into 4 states, the data produced from this study has been utilised to model an antibiotic treatment in CF (35). Due to unconventional nature of categorising the FEV_1 severity into four categories, the model by McGirr et al (35) had to

transform these values to fit a three-health state FEV_1 severity model. Previous models in CF have generally utilised three FEV_1 health states (34, 36, 37).

A total of 10 studies evaluated health utility in a range of different CF populations. These studies provided mean values at cross sectional time points, every 12 weeks for up to a year and a half. The majority of the utility information was gathered using the EQ-5D (3L/5L). These studies are of particular interest as the EQ-5D is the reference case instrument recommended by NICE for use in all Health Technology Appraisals (HTA) (7). From the studies that evaluated health utility with the EQ-5D we can understand that the population samples in all three studies (2, 15, 19) are quite different as well as the possible application of the utility data obtained from the studies.

As the first study to review the literature for information around health utility of particular health states in CF, we identified that there are few studies which focus their attention on deriving utility data for CF individuals for the health states that may be needed to model the cost-effectiveness of interventions for CF. Considering the improvements in CF mortality and morbidity over the last 50 years which are largely related to improvements in screening (38, 39) and treatment of the condition (1, 40), this finding comes as a surprise. Especially since health economic models currently exist which look at the cost-effectiveness of a range of interventions available to CF individuals (14, 34-37, 41, 42) . For this dearth of evidence to come to light at this time suggests that CF research around health utilities has been slow.

Health state derived utility values found in this review have limited application due to the treatments being considered. Such studies do not allow for the generalisability of the

health utility data to CF patients as the studies have selectively picked certain CF individuals for inclusion into their clinical trials.

Future work should look at health state utility elicitation, longitudinal health utility measurement and mapping studies. Health state preference elicitation could focus on significant adverse events such as PEx, CF related diabetes (CFRD), CF related Liver disease (CFLD) and other life-long complications such as Distal Intestinal Obstruction Syndrome. Attempts should be made to measure utility as close to the event as possible. Similarly, health utility of adults with differing FEV_1 could be assessed multiple times annually or collected on encounter of complications or adverse events. Such longitudinal measurement will allow for more reflective health economic evaluation of interventions. Such studies of health utility using the EQ-5D would also allow research to address problems around ceiling effects of the instrument which have been mentioned in NICE appraisals of Orkambi® (43) and the published literature (22). This in turn would provide evidence of the appropriateness of the EQ-5D as a health utility measure in CF.

Research into health utility derived from the EQ-5D is appropriate as the first measure in the U.K. as it is considered the most appropriate measure by NICE (7). When studies use different measures, other than the EQ-5D, to determine health utility this inherently prevents cross comparison against other instruments used in different studies. As we know from this study a number of different methods have been used to determine health utility, but what decides which measure is the best or most appropriate? Using a single instrument to measure health utility would prevent this problem from arising. Studies conducted in the past around the comparison of utility data obtained from different instruments showed that there was poor to moderate agreement between instruments.

These differences can subsequently impact the cost per quality-adjusted life year (QALY) ratio (8).

Another avenue for health state preference elicitation data could be the CF Trust registry, who recently launched a study looking at quality of life (QOL) in CF adults (44, 45). Although further information on the instruments used needs to be ascertained.

Evident from the review, there is only one study looking at mapping one PBM instrument to the generic EQ-5D (21). Currently many instruments exist which measure patient-reported outcome measures (PROMs) which do not have an associated preference-based scoring system, so do not allow for utility and subsequent (QALYs) measurement. Future mapping studies between PROMs and PBM could allow for better availability of utility and QALY data, which would prove useful for health economic modelling in CF. An added incentive to undertake such studies, especially in the U.K. could be the fact that NICE recommend undertaking mapping in the absence of EQ-5D data in clinical trials (7). Evaluation of the James Lind Alliance (JLA) for the top research priorities identified for CF showed QOL evaluation, particularly for the long term effects of Cystic Fibrosis transmembrane receptors (CFTR) modulators, was suggested (46). This further emphasises what patients, clinicians, nurses and other healthcare staff consider to be priorities of research in CF.

Limitation of this review

This review only considered full text articles, abstracts identified in this review would have been useful additions as full text articles. A study by Giron et al (47) evaluated EQ-5D-3L derived utility in Spanish patients who had mild or moderate PEx events, L'abbe et al (48) evaluated HRQOL in CF lung transplantation patients and Yarlas et al (49) evaluated CF

HRQOL in CF individuals in Europe and United States (U.S.). These articles would prove useful additions to this review if/when a future update if available. A total of 5 studies were excluded from this review as they were in language other than English. Incorporation of these articles could have contributed towards to better understanding of general country and population specific utility.

Conclusion

This review aimed to determine the level of available utility information around CF, particularly related to various health states. The studies identified were cross-sectional with little application for longitudinal evaluations without the use of assumptions. Work on eliciting health state preferences particularly for FEV_1, PEx events (by severity) and lung transplantation require further work, some areas more than others. However, new studies on health state utility data is warranted for CFRD, Liver disease (CFLD) and intestinal obstructive syndrome. Further research on identifying health state utility value data needs for decision modelling for CF treatment would also prove beneficial for the health economic modelling of CF related treatments in order to aid future decision making in CF.

Conflict of interest

None

Acknowledgements

This review was undertaken as part of a PhD funded by the Cystic Fibrosis Trust in Collaboration with the Epi-Net group.

References

1. Burgel P-R, Bellis G, Olesen HV, Viviani L, Zolin A, Blasi F, et al. Future trends in cystic fibrosis demography in 34 European countries. European Respiratory Journal. 2015;46(1):133.
2. Angelis A, Kanavos P, López-Bastida J, Linertová R, Nicod E, Serrano-Aguilar P. Social and economic costs and health-related quality of life in non-institutionalised patients with cystic fibrosis in the United Kingdom. BMC Health Services Research. 2015;15(1):428.
3. McKone EF, Borowitz D, Drevinek P, Griese M, Konstan MW, Wainwright C, et al. Long-term safety and efficacy of ivacaftor in patients with cystic fibrosis who have the Gly551Asp-CFTR mutation: a phase 3, open-label extension study (PERSIST). The Lancet Respiratory Medicine. 2014;2(11):902-10.
4. Davies JC, Wainwright CE, Canny GJ, Chilvers MA, Howenstine MS, Munck A, et al. Efficacy and safety of ivacaftor in patients aged 6 to 11 years with cystic fibrosis with a G551D mutation. American journal of respiratory and critical care medicine. 2013;187(11):1219-25.
5. Konstan MW, Wagener JS, Pasta DJ, Millar SJ, Jacobs JR, Yegin A, et al. Clinical use of dornase alpha is associated with a slower rate of FEV1 decline in cystic fibrosis. Pediatric pulmonology. 2011;46(6):545-53.
6. Ramsey BW, Pepe MS, Quan JM, Otto KL, Montgomery AB, Williams-Warren J, et al. Intermittent Administration of Inhaled Tobramycin in Patients with Cystic Fibrosis. New England Journal of Medicine. 1999;340(1):23-30.
7. NICE. National Institute for Health and Care Excellence- Guide to the methods of technology appraisal 2013 (PMG9) 2013 [Available from: https://www.nice.org.uk/process/pmg9/resources/guide-to-the-methods-of-technology-appraisal-2013-pdf-2007975843781.
8. Brazier J, Ratcliffe J, Saloman J, Tsuchiya A. Measuring and Valuing Health Benefits for Economic Evaluation: Oxford University Press; 2017.
9. Wailoo AJ, Hernandez-Alava M, Manca A, Mejia A, Ray J, Crawford B, et al. Mapping to Estimate Health-State Utility from Non–Preference-Based Outcome Measures: An ISPOR Good Practices for Outcomes Research Task Force Report. Value in Health. 2017;20(1):18-27.
10. Moher D, Liberati A, Tetzlaff J, Altman DG. Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. PLoS medicine. 2009;6(7):e1000097.

11. Sampson CJ, Tosh JC, Cheyne CP, Broadbent D, James M. Health state utility values for diabetic retinopathy: protocol for a systematic review and meta-analysis. Systematic Reviews. 2015;4(1):15.
12. CRD. Centre for Reviews and Dissemination-guidance for undertaking reviews in health care: University of York; 2009 [
13. Whitehead SJ, Ali S. Health outcomes in economic evaluation: the QALY and utilities. British Medical Bulletin. 2010;96(1):5–21.
14. Whiting PA, Maiwenn; Burgers, Laura; Westwood, Marie; Ryder, Steve; Hoogendoorn, Martine; Armstrong, Nigel; Allen, Alex; Severens, Hans; and Kleijnen, Jos. Ivacaftor for the treatment of patients with cystic fibrosis and the G551D mutation: a systematic review and cost-effectiveness analysis. NIHR Journals Library. 2014;18(18).
15. Chevreul K, Berg Brigham K, Michel M, Rault G. Costs and health-related quality of life of patients with cystic fibrosis and their carers in France. Journal of Cystic Fibrosis. 2015;14(3):384-91.
16. Fitzgerald DA, Hilton J, Jepson B, Smith L. A crossover, randomized, controlled trial of dornase alfa before versus after physiotherapy in cystic fibrosis. Pediatrics. 2005;116(4):e549-54.
17. Selvadurai HC, Blimkie CJ, Meyers N, Mellis CM, Cooper PJ, Van Asperen PP. Randomized controlled study of in-hospital exercise training programs in children with cystic fibrosis. Pediatric pulmonology. 2002;33(3):194-200.
18. Chevreul K, Michel M, Brigham KB, Lopez-Bastida J, Linertova R, Oliva-Moreno J, et al. Social/economic costs and health-related quality of life in patients with cystic fibrosis in Europe. The European journal of health economics : HEPAC : health economics in prevention and care. 2016;17 Suppl 1:7-18.
19. Iskrov Georgi G, Stefanov Rumen S, López-Bastida J, Linertová R, Oliva-Moreno J, Serrano-Aguilar P. Economic Burden And Health-Related Quality Of Life Of Patients With Cystic Fibrosis In Bulgaria. Folia Medica2015. p. 56.
20. Czyzewski DI, Mariotto MJ, Bartholomew LK, LeCompte SH, Sockrider MM. Measurement of Quality of Well Being in a Child and Adolescent Cystic Fibrosis Population. Medical Care. 1994;32(9):965-72.
21. Acaster S, Pinder B, Mukuria C, Copans A. Mapping the EQ-5D index from the cystic fibrosis questionnaire-revised using multiple modelling approaches. Health and Quality of Life Outcomes. 2015;13(1):33.
22. Solem CT, Vera-Llonch M, Liu S, Botteman M, Castiglione B. Impact of pulmonary exacerbations and lung function on generic health-related quality of life in patients with cystic fibrosis. Health and Quality of Life Outcomes. 2016;14(1):63.
23. Bradley JM, Blume SW, Balp M-M, Honeybourne D, Elborn JS. Quality of life and healthcare utilisation in cystic fibrosis: a multicentre study. European Respiratory Journal. 2013;41(3):571.
24. Suri R, Metcalfe C, Lees B, Grieve R, Flather M, Normand C, et al. Comparison of hypertonic saline and alternate-day or daily recombinant human deoxyribonuclease in children with cystic fibrosis: a randomised trial. Lancet (London, England). 2001;358(9290):1316-21.
25. Busschbach JJ, Horikx PE, van den Bosch JM, Brutel de la Riviere A, de Charro FT. Measuring the quality of life before and after bilateral lung transplantation in patients with cystic fibrosis. Chest. 1994;105(3):911-7.
26. Dewitt EM, Grussemeyer CA, Friedman JY, Dinan MA, Lin L, Schulman KA, et al. Resource use, costs, and utility estimates for patients with cystic fibrosis with mild impairment in lung function: analysis of data collected alongside a 48-week multicenter clinical trial. Value in health : the journal of the International Society for Pharmacoeconomics and Outcomes Research. 2012;15(2):277-83.

27. Orenstein DM, Pattishall EN, Nixon PA, Ross EA, Kaplan RM. Quality of well-being before and after antibiotic treatment of pulmonary exacerbation in patients with cystic fibrosis. Chest. 1990;98(5):1081-4.
28. Yi MS, Britto MT, Wilmott RW, Kotagal UR, Eckman MH, Nielson DW, et al. Health values of adolescents with cystic fibrosis. The Journal of Pediatrics. 2003;142(2):133-40.
29. Dolan P. Modeling valuations for EuroQol health states. Med Care. 1997;35(11):1095-108.
30. Perneger TV, Combescure C, Courvoisier DS. General Population Reference Values for the French Version of the EuroQol EQ-5D Health Utility Instrument. Value in Health. 2010;13(5):631-5.
31. Kind P, Hardman G, Macran S. UK population norms for EQ-5D. Centre for Health Economics, University of York; 1999.
32. MVP Group. The measurement and valuation of health. Final report on the modelling of valuation tariffs: Centre for Health Economics; 1995 [Available from: https://www.york.ac.uk/media/che/documents/reports/MVH%20Final%20Report.pdf.
33. Roberts M, Russell LB, Paltiel AD, Chambers M, McEwan P, Krahn M, et al. Conceptualizing a Model: A Report of the ISPOR-SMDM Modeling Good Research Practices Task Force-2. Value in health : the journal of the International Society for Pharmacoeconomics and Outcomes Research. 2012;15(6):804-11.
34. Tappenden P, Harnan S, Uttley L, Mildred M, Carroll C, Cantrell A. Colistimethate sodium powder and tobramycin powder for inhalation for the treatment of chronic Pseudomonas aeruginosa lung infection in cystic fibrosis: systematic review and economic model. Health technology assessment (Winchester, England). 2013;17(56):v-xvii, 1-181.
35. McGirr AA, Schwartz KL, Allen U, Solomon M, Sander B. The cost-effectiveness of palivizumab in infants with cystic fibrosis in the Canadian setting: A decision analysis model. Human Vaccines & Immunotherapeutics. 2017;13(3):599-606.
36. Tappenden P, Sadler S, Wildman M. An Early Health Economic Analysis of the Potential Cost Effectiveness of an Adherence Intervention to Improve Outcomes for Patients with Cystic Fibrosis. PharmacoEconomics. 2017;35(6):647-59.
37. Dilokthornsakul P, Hansen RN, Campbell JD. Forecasting US ivacaftor outcomes and cost in cystic fibrosis patients with the G551D mutation. European Respiratory Journal. 2016.
38. Heinemann Mitja L, Hentschel J, Becker S, Prenzel F, Henn C, Kiess W, et al. Einführung des deutschlandweiten Neugeborenenscreenings für Mukoviszidose. LaboratoriumsMedizin2016. p. 373.
39. Wang L, Freedman SD. Laboratory tests for the diagnosis of cystic fibrosis. American journal of clinical pathology. 2002;117 Suppl:S109-15.
40. European Respiratory Society. European Lung White Book: Chapter 14: European Respiratory Society; 2014 [Available from: https://www.erswhitebook.org/chapters/cystic-fibrosis/.
41. Schechter MS, Trueman D, Farquharson R, Higuchi K, Daines CL. Inhaled aztreonam lysine versus inhaled tobramycin in cystic fibrosis. An economic evaluation. Annals of the American Thoracic Society. 2015;12(7):1030-8.
42. Panguluri S, Gunda P, Debonnett L, Hamed K. Economic Evaluation of Tobramycin Inhalation Powder for the Treatment of Chronic Pulmonary *Pseudomonas aeruginosa* Infection in Patients with Cystic Fibrosis. Clinical Drug Investigation. 2017;37(8):795-805.
43. NICE. National Institute for Health and Care Excellence (NICE). Lumacaftor–ivacaftor for treating cystic fibrosis homozygous for the F508del mutation. Technology appraisal guidance [TA398] NICE website: NICE; 2016 [Available from: https://www.nice.org.uk/guidance/ta398/chapter/3-Evidence#cost-effectiveness.

44. Taylor-Robinson D, Archangelidi O, Carr B, Siobhán., Cosgriff R, Gunn E, Keogh RH, et al. Data Resource Profile: The UK Cystic Fibrosis Registry. International Journal of Epidemiology. 2017;47(1):9-10e.
45. Cystic Fibrosis Trust. Annual Registry Report 2016 Cystic Fibrosis Trust website 2016 [Available from: https://www.cysticfibrosis.org.uk/~/media/documents/the-work-we-do/uk-cf-registry/2016-registry-annual-data-report.ashx?la=en.
46. James Lind Alliance. Cystic Fibrosis Top 10 James Ling Alliance: James Ling Alliance; 2018 [Available from: http://www.jla.nihr.ac.uk/priority-setting-partnerships/cystic-fibrosis/top-10-priorities.htm.
47. Giron R, Reig JP, Olveira C, Pastor MD, Prados C, Quintana-Gallego E, et al. 125 Influence of pulmonary exacerbations on health status of cystic fibrosis patients. Health UTIlities and Quality of Life Study (HUTIQOL). Journal of Cystic Fibrosis.15:S82-S3.
48. L'Abbe JM, Loadman Joyce M, Bentley MJ, Lien DC. Quantifying health status and functional outcomes following lung transplant. The Journal of Heart and Lung Transplantation. 2004;23(2):S72.
49. Yarlas A, O'Callaghan L, Lopes V, Suthoff E, Wagener J. PRS55 - Measuring Generic Health-Related Quality Of Life And Impact Of Health Resource Utilization In Adults With Cystic Fibrosis. Value in Health. 2015;18(7):A503.