Advancing the Health Economic evidence available to inform economic models and decisions about appropriate Cystic Fibrosis care

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Abstract

Cystic Fibrosis (CF) is a genetic disease which impacts multiple organs in the body. As a result, CF individuals require lifelong care. Over the years, there has been an increase in the availability of treatments for CF leading to improvements in health. However, these improvements can place significant burden on the NHS. Economic evaluations capture both the costs and the benefits of treatment, which can be further extended through health economic modelling. This framework allows decision makers to make recommendations on the use of such treatments in the NHS. This thesis focuses on improving evidence availability for the health economic modelling of CF treatments and decision about appropriate care.

A review of health economic modelling studies was carried out. Studies were evaluated for model structure, data inputs and modelling methods for areas requiring improvement. The evidence from the review and discussion with clinical experts was used to develop a De Novo health economic model. Regression modelling was used to generate novel health state transition and cost data from the U.K. CF Data Registry (2005-2016). An exemplar cost-utility analysis on Orkambi® was conducted to validate the De Novo model and input data. Statistical tests, between model consistency, clinical expert opinion and the observed data was used for validation.

The results of the study show that the input data were comparable to data found in the literature and used in existing health economic models. The De Novo model produced comparable ICER and cost estimates to those found in the literature. The methods of the work conducted in this thesis can be applied to other Data Registries. They prove to be a

strong supportive tool with great potential to improve the cost effectiveness evaluation of existing and novel treatments in the future.

Table of Contents

List of Tables

List of Figures

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List of abbreviations

Abbreviation	Definition
Abx	Antibiotics
AHRQ	Agency for Healthcare Research and Quality
BMI	Body mass index
CADTH	Canadian Agency for Drugs and Technologies in Health
CBA	Cost-benefit analysis
CCFR	Canadian Cystic Fibrosis Registry
CDF	Cumulative density function
CEA	Cost effectiveness analysis
CF	Cystic fibrosis
CF-Epi-Net	Cystic Fibrosis Epidemiological Network
CFLD	Cystic fibrosis liver disease
CFQoL	Cystic Fibrosis Quality of Life
CFQ-R	Cystic Fibrosis Questionnaire-Revised
CFRD	Cystic fibrosis related diabetes
CFTR	Cystic Fibrosis Transmembrane Regulators
CHEERS	Consolidates Health Economics Evaluation Reporting Standards
CI	Confidence interval
CINAHL	Cumulative Index to Nursing and Allied Healthcare Literature
CLM	Cumulative linked models
C-loglog	Complementary loglog

CM	Conceptual model
CMA	Cost-minimisation analysis
CPDR	Canadian Patient Registry
CRD	Centre of Reviews and Dissemination
CUA	Cost-utility analysis
DES	Discrete event simulation
DOB	Date of birth
DPI	Dry powder inhaled
DSU	Decision support unit
ECFS	European Cystic Fibrosis Society
EE	Economic evaluation
EMA	European Medicines Agency
EQ-5D	EuroQol 5-Dimension
EQ-5D— 3L	EuroQol 5-Dimension – 3-Level
EQ-5D— 5L	EuroQol 5-Dimension – 5-Level
ERG	Evidence Review Group
EU	European Union
EuroCareCF	European Coordination Action for Research in Cystic Fibrosis
FEV_1	Forced expiratory volume in 1 second
FDA	Food and Drug Administration
GEE	Generalised Estimating Equations
GEE	Generalized Estimating Equations
GLM	Generalised linear regression model

GOF	Goodness of fit
GRIM	General Record of Incidence of Mortality
HES	Hospital Episode Statistics
HRQOL	Health-related quality of life
HSU	Health state utility
HTA	Health technology assessment
HUI	Health utility index
ICER	Cost-effectiveness ratio
IP	Inpatient stay
IPD	Individual patient data
IQR	Interquartile range
IQR	Interquartile range
ISI	Institute for Scientific Information
ISPOR	International Society of Pharmaeconomics and Outcomes Research
IV	Intravenous
IV-Abx	Intravenous treatment with abtibiotics
MeSH	Medical Subject Heading
MI	Meconium ileus
NHS	National Health Service
NHS EED	National Health Service Economic Evaluation Database
NICE	National Institute for Health and Care Excellence
O-Abx	Oral antibiotic

PBM	Preference-based measure
PbR	Payment by Restults
PE_x	Pulmonary exacerbation
PI	Probability interval
PMB	Palivizumab
PR	Pulkstenis and Robinson
PRISMA	Preferred Reporting Items for Systematic Reviews
PROMS	Patient-reported outcome measures
QALY	Quality-adjusted life years
QHES	Quality of Health Economic Studies
QHES	Quality of Health Economics Studies
QOL	Quality of life
QWB	Quality of Well-Being
RBH	Royal Brunton Hospital
RCTs	Randomised controlled trials
rhDNase	Recombinant human DNase
ROI	Return on investment
SAIL	Secure Anonymised Informatic Linkage
ScHARRHUD	School of Health and Related Research Utilities Database
SD	Standard deviation
SF-6D	Short-Form 6-Dimension
SG	Standard gamble
TIP	Tobramycin inhalation powder

TIS	Tobramycin inhalation nebuliser
TPI	Tobramycin DPI
TTO	Time trade-off
U.K.	United Kingdom
U.S.	United States
UAE	United Arab Emirates
VAS	Visual analogue scale
VAT	Value added tax
VIF	Variance inflation factor
VOI	Value of information
WTP	Willingness-to-pay

1 Chapter 1: Introduction

1.1 Overview of Thesis

Cystic Fibrosis (CF) is an incurable genetic condition. Those with CF require constant care throughout their lives and over more than a decade there has been an ever-increasing availability of novel treatments which looked to improve the survival and symptoms of people with CF [3]. As a result, over the last decade there has been considerable improvement in the survival of people with CF [3]. A number of clinical trials exist which evaluate CF treatments, up to 1,200 according to a search conducted on the United States (U.S.) National Library of Medicine website [4]. However due to the comparatively short duration of such trials for a condition which is lifelong, it is unlikely that all factors considered important in deciding whether to provide such medicines are taken into account. As a result, there is a need for the long-term evaluation of such treatment, one avenue of which is the use of health economic modelling [5]. In summary, with health economic modelling improvements made possible through novel treatments is evaluated against the cost of such medicines over a longer time horizon [5]. Recent evaluation of CF treatments using such methods, particularly modulator treatments, was considered too costly according to medicines reimbursement agencies globally [6-10].

The aim of this thesis is to extend what is known about the health economic modelling of CF interventions, advance the health economic evidence available to inform such economic models and discuss their usefulness in informing decisions about the optimum provision of CF care.

The thesis was completed under a larger network of research conducted by a strategic research centre called the Cystic Fibrosis Epidemiological Network (CF-Epi-Net). The

network was funded by the Cystic Fibrosis Trust. The aim of this was to harness observational registry data to improve the lives of those with CF. The CF Data Registry from the United Kingdom (U.K.) was utilised with this aim in mind. This chapter ends with a detailed statement of the aims and objective and with an brief description of what each chapter covers.

1.2 Overview of Chapter

The sections that follow give a summary of CF as a progressive and chronic disease which is terminal in nature. They also describe the epidemiology of CF in and outside of Europe, factors associated with disease progression, resultant co-morbidities and lastly the treatment of CF. The economic burden of CF is also described in the sections that follow alongside principles of priority setting of healthcare and the tools used to support decision making in the context of healthcare provision.

1.3 Background to CF

Cystic Fibrosis (CF) is a hereditable disease and individuals with the disease inherit a faulty gene from each of their parents, which depending on the type of mutation can vary the resulting severity of the condition [11]. The mutation itself occurs on the long arm of chromosome 7 [12]. The underlying mechanisms in the body that maintains the composition of appropriate salt and water content of mucus, the Cystic Fibrosis Transmembrane Regulators (CFTR), are compromised in this condition [13]. The cells that line the lungs and other organs in the body; the epithelial cells, such as those in the digestive, pancreatic and reproductive tract, as a result are unable to transport Chloride ions across them. Downstream ion transport across the cell linings not taking place via these CFTR's later results in water not being able to travel through a mechanism called osmosis across these linings. Ultimately, the viscosity of mucus increases. Ciliary, which

are hair like linings on the surface of epithelial cells, can no longer transport mucus back up the respiratory tract. This mucus clogs and collects particularly in the lungs, leading to bacterial infection, reduction in respiratory capacity and eventually death [13].

1.3.1 Mutation classification

In total there are currently 2,092 mutation classes in CF according to the CFTR1 mutations database [14], in the CFTR gene. These CFTR mutations in CF can be placed into 6 classes [15-17]. Table 1 below demonstrates the 6 classes of mutation described by Quon et al [17]. This mutation classification links to the severity of CF disease in each individual patient to their phenotype, the physical manifestation of their mutation. Classes I-III are mutations that occur in both copies of the CFTR gene on the pair of chromosomes, classes IV-VI are mutations that occur on the single allele from the pair of chromosomes [17].

Table 1: Mutation classification [17]

MUTATION CLASS	DESCRIPTION
I	leads to no synthesis of CFTR protein
II	leads to CFTR protein processing defects
III	lead to decrease in the opening of the CFTR channel
IV	leads to reduced Chloride ion conductance
V	leads to reduced synthesis of the CFTR protein
VI	leads to reduced stability of the CFTR protein at the surface of the biological cell

Studies have shown that mutation class I-III have been linked to worse lung deterioration, pancreatic insufficiency and are deemed ‘high risk’ [18], whereas for those with class IV-

VI mutations, there is milder lung deterioration and pancreatic insufficiency and are deemed ‘low-risk’ [18].

Of those who are deemed high-risk, the most common single mutation is F508Del with more than 80% of those in Europe having at least one single allele with this mutation [19]. As a result, a lot of focus has been directed in the treatment of this mutation class which comes under class II using the conventional classification system [17].

1.3.2 Epidemiology

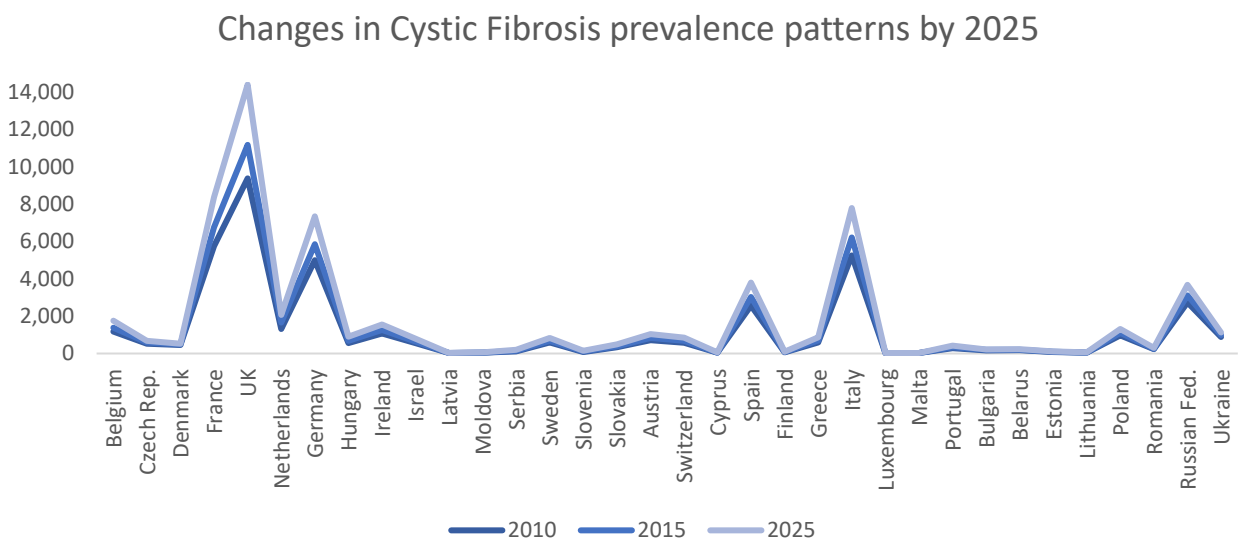
Epidemiological investigation demonstrates how often and in which different types of people CF occurs. The populations at risk of CF varies greatly dependent on which continent is discussed. A number of studies have investigated the epidemiology of CF in European (EU) and Non-European (Non-EU) countries [20-23]. However, prevalence and incidence data is more complete and representative in more developed EU and Non-EU countries.

1.3.2.1 Europe

Data on individuals who have Cystic Fibrosis in Europe is available from the European Cystic Fibrosis Society [24] and is well documented. This society provides information through a patient registry designed to allow users to measure, survey and compare aspects of CF and its care in countries across Europe [24]. Figure 1 presents the prevalence data for a range of European countries which were taken from Burgel et al [25]. Burgel et al [25] further go on to forecast future prevalence of CF in European countries through use of longitudinal data/assumptions and modelling. Figure 2 shows the changes that are forecasted to take place within 34 European countries by the year 2025. It is evident through the literature that the number of individuals with CF are on the

rise. By 2025, a 50% increase in overall, 75% increase in adult and 20% increase in child CF is forecasted [25].

Figure 1: Patterns of Cystic Fibrosis prevalence by 2025



Recent investigation on the incidence of CF in Europe conducted by Farrell et al [21] shows the incidence for a range of European countries, drawn out from the literature (Table 2). It can be seen from Table 2 that Ireland has the highest incidence followed by Slovakia. Future trends in the increasing number of CF individuals, Figure 2, also follows the pattern in Table 2.

Table 2: CF incidence by country [21]

COUNTRY	CF INCIDENCE PER LIVEBIRTH (1 IN EVERY:)
Austria	3500
Belgium	2850
Bulgaria	2500
Cyprus	7914
Czech Rep.	2833
Denmark	4700
Estonia	4500
Finland	25000
France	4700
Germany	3300
Greece	3500
Ireland	1353
Italy	4238
Netherlands	4750
Poland	5000
Portugal	6000
Romania	2056
Slovakia	1800
Slovenia	3000
Spain	3750
Sweden	5600
UK	2381

1.3.2.2 Non-European

Prevalence information on CF is not so readily available in countries outside of Europe. However, studies do exist that look at the prevalence of CF. Other countries outside Europe however also include the United States (U.S.). The U.S. has the most complete and up to date CF Data Registry globally [26]. The prevalence of CF in the U.S. is similar to that of the whole of Europe, with only a small marginal difference [23].

In Asia, studies based mainly on retrospective analysis and case studies span over two decades [27]. Studies investigating prevalence in Asia are on poorly collected patient information and diagnosis and is under representative. Furthermore, evidence presented from countries such as Jordan, Bahrain, Japan, United Arab Emirates (UAE) and India demonstrates that, data collection methods vary, duration of data collection does not go beyond after the year 2000 and the diagnostic standards for detecting the presence of CF differ [27].

Incidence data is overlooked in developing non-European countries due to high mortality rates, malnutrition, tuberculosis and diarrhoeal diseases. Lack of CF Registries, under-diagnosis and under-reporting of CF only add to this current problem [27]. As a result, information on prevalence and incidence of CF outside the EU (not including the U.S.) may not be representative.

1.3.3 Survival and Mortality in Cystic Fibrosis

Over the last half a century the resultant outcomes of individuals with CF has changed considerably. Around 60 years ago, children born with CF would not live past 5 years of age [12]. The first step of mortality prevention was the treatment of malnutrition with pancreatic enzymes to counteract the pancreatic insufficiency. Treatment of lung infections, a predominant catalyst of lung function decline in CF individuals followed [12].

Investigation of survival in CF patients both in and outside of the EU over the last two decades has been undertaken [22, 26, 28-32]. European mortality data evaluated through CF patient registries compared to use of data from the Statistical Office of the European Union (EuroStat) has demonstrated small differences in overall mortality trends [22, 30]. However, the underlying improvement demonstrated in the survival of individuals with CF is in the same direction.

European CF registries contain data of more than 29,000 individuals from 35 European Union (EU) and Non-EU countries[22]. Although mean age of individuals within Europe was 17.9 years, differences between EU and Non-EU countries do exist. European Union members demonstrated an increase in the number of CF individuals, particularly in the younger and older age groups when compared to Non-EU countries (due to reduction in mortality). One in every 21 CF individuals in the EU were aged over 40, whereas only 1 in every 50 individuals were aged over 40 in Non-EU countries [22]. Such difference in overall survival shows that where CF individuals reside can have an impact on their long-term survival. Although these differences come to light within Europe, it is important to understand that a majority of registry data comes from 4 well established country specific registries, one of which is the U.K CF Registry. These datasets contribute up to 75 % of the data collated in European registries. This means that people from Non-EU countries are under-represented and further work in developing similar standards of data collection is required in these countries [22].

Other mechanisms of measuring mortality within CF individuals across Europe have also been investigated [30, 31, 33, 34]. Data from the EuroStat (1994 – 2010) demonstrated 5,130 deaths from CF across Europe over this particular time period [30]. Compared to

the McCormick et al [22] paper, clear differences in mortality over short periods in earlier life years of CF individuals is evident.

A number of studies have evaluated the rate of mortality across Europe for individuals with CF [26, 29-31]. Similarly, studies have been conducted outside of Europe [28, 32]. Corey and Farewell [28] conducted an analysis of the Canadian Patient Data Registry (CPDR) over a period of two decades. The analysis showed, compared to 1970-1974, the risk of death significantly decreased by 45% during 1985-1989. However, no further research on the changing trends of mortality in Canada has been undertaken. The Canadian Cystic Fibrosis Registry annual reported improvements in survival in their most recent report [35]. The mean age of survival in Canada is around 51 years [35]. Similar to Canadian mortality data, Australian state and territories General Record of Incidence of Mortality (GRIM) data covering a period of 26 years (1979-2005) was evaluated. The data showed that overall mean age of survival was 27 years by 2005, moving up significantly from 13 years in 1979 [32].

1.3.4 Diagnosis of Cystic Fibrosis

Data from 35 Europe countries show that 17% of CF diagnoses are made at birth (0 months), with overall 59% of them occurring before the age of 12 months [22]. Diagnoses of CF also occurs up until the age of 40 and differences do exist between diagnosis dependent on whether it is an EU or non-EU country. European countries have higher proportions diagnosed at an early age compared to Non-EU countries, which have higher proportions diagnosed later.

According to the National Institute for Health and Care Excellence (NICE) guideline document, CF is most often detected through newborn screening in the U.K. [36], at a median age of 3 months. Clinical and expert opinion also states that most often diagnosis

is made through this route (Siobhan Carr, 13th July 2017). Similarly, NHS choices [37] states that CF is diagnosed through sweat and genetic testing which are tests conducted during newborn screening.

Diagnosis of CF however has always been challenging due to cases that bring about uncertainty and challenging diagnostic dilemmas [38]. Nevertheless, sweat chloride testing has been the gold standard for CF diagnosis [38].

1.3.5 Impact of CF on FEV_1

As mentioned in section 1.2 reduction in respiratory capacity leads to disease progression in CF. Cystic Fibrosis, a multi organ disease, is assessed for progressive disease through the use of the lungs, although there are a number of other avenues for measuring progression [39]. Lung function in general can be measured in a number of ways. However, the primary technique used in CF, is spirometry. This is a test which assesses how much and how quickly an individual can move air in and out of the lungs. Forced expiratory volume in 1 second (FEV_1) is measured by asking an individual to forcefully exhale air in 1 second. This is the most common measurement used in diagnosing disease progression in CF. Although there is literature that discusses the importance of such a measure and the current potential challenges with measuring and using FEV_1 in CF in more recent years [40]. Additional factors which have been associated with effecting FEV_1 in those with respiratory diseases include body mass index (BMI), age, bacterial infection status, pancreatic insufficiency and CF related diabetes (CFRD) [41]. To assess the prognosis of a CF individual, the FEV_1 measurement obtained from spirometry is compared to a reference population (FEV_1 percent predicted, referred to as $ppFEV_1$) which is the FEV_1 of the average population of similar age, sex, BMI [41]. This measure of $ppFEV_1$ is considered the best general measure of lung disease [41]. Furthermore,

FEV_1 has been linked to mortality [41, 42], health related quality of life (HRQOL) [43] and is a the primary outcome measure in a number of clinical trials [44-46] and as a result this bolsters its use.

1.3.6 Impact of CF on HRQOL

There are a number of studies which have evaluated the impact of CF on HRQOL [43, 47, 48] and shown that CF affects HRQOL. Studies not only exist on the cross-sectional impact but also on the longitudinal impact of CF on HRQOL [49]. As such including evaluation of HRQOL in CF is important. This is further discussed in Chapter 3.

1.3.7 Treatment of Cystic Fibrosis

Cystic fibrosis is a long-term chronic condition, which has no cure [37] and a wide range of treatments are available [37]. Medications for pulmonary problems exist in the form of antibiotics for chest infections, medicines to break down thick sticky mucus for removal from the lungs, bronchodilators to widen airways for ease of breathing and steroid medications to treat nasal polyps [37].

Rapid investigation of the literature showed no signs of clinical care pathways that exist providing an overview of the patient journey from diagnosis to long-term treatment throughout their life course. However, guidelines are provided around treatments and therapies to improve long-term outcomes for patients with CF. NICE guidelines on the diagnosis and management of CF exist and highlight key aspects of CF that have the biggest impact on long-term mortality and progression of respiratory aspects of CF [36].

1.3.8 Prognostic Indicators

Many studies on the long-term survival of CF individuals mention a comprehensive list of factors that affect disease progression. These include but are not limited to sex [50, 51], mutation class/status [50], age [50, 51], FEV_1 [42, 51, 52], Cystic Fibrosis related Diabetes

(CFRD) [42], weight [42, 51], pancreatic insufficiency [42], bacterial infections [42], pulmonary exacerbation events (PEx) [42], psychosocial status [51] and treatment regimens [51].

Discussion with experts and examples of evidence from the above literature show that a wide range of variables have an impact on the long-term outcome of individuals with CF and include CFRD, PEx and CRLD.

1.3.9 Pulmonary Exacerbation

Pulmonary changes within individuals who have CF is a cause for the majority of morbidity and mortality. Clinically, worsening of CF is correlated with worsening of respiratory symptoms and range from cough, sputum production, weight loss, anorexia and fatigue [53] [54]. This sudden decrease in pulmonary function due to restriction or obstruction of the airways in the lungs lead to pulmonary exacerbations (PEx) [53]. Pulmonary exacerbation is a common clinical trial outcome measure in CF [55] and has been linked to a reduction in quality of life (QOL), higher costs, increased mortality, lower baseline FEV_1, faster decline in FEV_1, greater risk of lung transplant and increased clinical burden among patients [54, 56, 57]. As a result PEx's are key events that clinicians aim to impact with preventative and therapeutic protocols [58]. However, in the past there have been issues highlighted around what defines an PEx event and what criteria should be considered [59].

Correlated to mortality in CF individuals, the worse the FEV_1 values the higher the risk of lung transplantation or death. An outcome of interest directly correlated with a reduction in FEV_1 is the number PEx's [60]. The number of PEx's experienced over time increases with age in CF patients [61].

A study conducted over approximately 7 years attributed lung function, FEV_1 decline to PEx events, which require antibiotic treatment [60]. Furthermore, the number of exacerbations a CF patient experiences can make patients 7.9% worse off than those who experience no such events [60]. In a 5-year survival model, PEx events had a significantly large impact on survival, resulting in a 12% decrease in the overall FEV_1 value [42]. Similar studies show PEx events link to decreases in FEV_1 and an increase risk of lung transplantation and mortality [56]. Further associating PEx with FEV_1, studies have shown that proportions of PEx events are linked to inability to recover to baseline FEV_1 values [54]. A large proportion of costs related to hospitalisation of individuals with CF are attributed to PEx events [58]. Pulmonary exacerbation events are also associated with a reduction in HRQOL [62]. Given the relationship between PEx and mortality and PEx and reduction in HRQOL, there is considerable treatment burden from such events [53]. Evidence presented in studies for use of rhDNase therapy show that such therapy resulted in a reduction in risk of exacerbation events which ultimately translated into improvements in HRQOL, FEV_1 and reduction in hospitalisation costs [63].

It can be understood that PEx events are a central feature in CF disease progression. PEx management within CF is an important outcome for clinicians. Exacerbation events have been described as equally important in reducing disease progression and maintaining long-term health [40].

1.3.10 Cystic Fibrosis related Diabetes

Cystic Fibrosis related Diabetes (CFRD) often found within individuals with CF is associated with higher rates of mortality, especially women who as a result are at high risk of early death [64]. Even in the presence of CFRD the eventual reason for death is respiratory failure as CRFD is directly linked to lung function decline [64]. A longitudinal

study evaluated the impact of CFRD on long-term mortality as well as the impact of CFTR genotype, age and sex [64]. The results showed 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 [64].

1.3.11 Cystic Fibrosis related Liver disease

Due to the changing nature of CF survival in recent years, pathologies in different organs systems have become more common. Due to improvement in long-term survival, cystic fibrosis related Liver disease (CFLD) is becoming more common within the CF population [65]. 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 [65, 66]. Independent risk factors associated with CFLD and severe CFLD include sex (male), F508Del Homozygous status and history of meconium ileus (MI) [67]. Additional retrospective studies on an Australian cohort of CF individuals showed that those with CFLD had a higher risk of CFRD, hospitalisation and bone disease [68].

1.3.12 New Modulator treatments

As stated earlier, CF is genetic disease which manifests in different organs in the body due to the CFTR receptor being present throughout the body. A number of existing treatments have already been mentioned in section 1.2.7. However, novel treatments which are becoming more available which target the underlying CFTR defect have not been discussed and these also include treatments that support the expression of the CFTR receptor at the cell membrane surface. Such treatments are called correctors [69, 70] or potentiators [69, 71]. Correctors, such as Orkambi®, support the correct folding of

the CFTR protein to enable it to function and is more prevalent in those with at least one copy of the F508Del mutation which is a large population of CF individuals globally. Potentiators, such as Ivacaftor® activate the CFTR protein at the cell surface which allow high channel activation for transport of ions across the cell membrane [69] and is used in the G551D mutation class but its use has been expanded to other mutation classes [69]. The use of such therapies have been identified as a clear objective and are considered to have great promise to substantially impact disease progression if began close to diagnosis as possible such as subsequent to newborn screening [72].

A number of clinical trials exist which have evaluated the effectiveness of such treatments [73, 74]. The treatments have a variable effect on FEV_1, improvement in HRQOL and PEx [72, 73] and have a very high cost per person [75].

1.3.12.1 Orkambi®

Orkambi® (Vertex Pharmaceuticals) is a combination treatment of Ivacaftor/Lumacaftor [76]. It was first approved for use by the U.S. Food and Drug Administration (FDA) and the EMA in 2015 for those who were F508Del Homozygous and >12 years old. However, recently the treatment was opened up to those who are above the age of 2 [76]. Lumacaftor is a corrector while Ivacaftor is a potentiator of the CFTR. This mean that the corrector results in more receptors being made, inside the cell, and thus transported to the cell surface. The potentiator increases the opening of the receptor on the cell surface. This combination results in better transport of ions across the cell membrane [77]. Orkambi has been linked to a number of improvement in patient outcomes [76] but at a considerable cost [75].

1.4 Economic burden of Cystic Fibrosis

Respiratory conditions, in which CF fits due to its impact on the lungs, have a considerable economic burden. This translates into an annual cost in excess of €380 billion spread over 28 European countries, formed of direct primary care, hospital care, productivity loss and life years lost [78].

The U.K. along with many other developed countries are contributing increasing amount of economic activity to the healthcare sector [79]. Over the last decade, the long-term survival in individuals with CF has changed. Children are now able to live longer into adulthood [80]. Due to this change in the nature of disease progression and mortality, economic impact of CF has increased both direct (medical and non-medical) and indirect costs [80].

A U.K. adult and non-adult population with an average age of 18 years, whose caregivers were on average 37 years old, had an average annual cost of €48,603 per CF patient [80]. Direct non-healthcare, direct healthcare and loss of productivity were the largest to smallest proportion of costs for CF care. Of the direct healthcare costs, medication, hospitalisation and primary care visits were the three largest areas of costs. Informal care costs on average were €21,447 per person. Loss of productivity was composed of sick leave (29%) and early retirement (71%) due to CF. The presence of a caregiver was related to a severe burden of disease on the CF individual. With the presence of caregiver support, the cost of CF care approximately doubled, those requiring support with personal care cost an average of €76,271 a year [80].

An analysis conducted within the Australian CF Data Registry provided a cost breakdown by disease severity. The data showed an expected increase in cost by severity grouping, US $10,151, US $25,647, and US $33,691 respectively for mild, moderate and severe

disease (per patient, per year). Later lifetime costs of CF treatment were projected to be US $306,332 per CF patient [81].

However, the costs presented above do not account for the cost of new modulator treatments. The cost of stand-alone treatment with modulators such as Ivacaftor (also called Lumacaftor®) was £104,000 per person in the U.K. (not including value-added tax (VAT)) [10] and cost of Orkambi® was £105,000 per person [75]. This led to a deadlock between reimbursement authorities and the manufacturer (Vertex Pharmaceuticals®) in the U.K. due to the drugs not meeting the threshold of cost effectiveness [75]. More recently an agreement on the reimbursement of Orkambi® has been reached based on a number of terms [82].

1.5 Economic Evaluations

Economic evaluations (EE) support difficult and unavoidable questions in healthcare [83]. Resources are scare and we cannot produce all desired outputs or consequences from finite inputs, in this case cost. This means that decisions need to be made as to what is spent where, also known as opportunity cost. An investment of inputs in one area will mean that the opportunity of investment elsewhere is being given up [83]. Due to the nature of healthcare decision-making, the inherent link that exists between decision-making and healthcare resource use, it has subsequent effects further outside healthcare. There is a need to consider the costs and benefits of healthcare interventions. This consideration of costs and benefits, economic evaluation, are analyses and subsequent comparisons conducted on cost and effects of different healthcare interventions [83, 84]. As such, interventions can be deemed as ways in which population health can be improved which may include pharmaceutical or surgical interventions and screening or public health programmes [5]. The framework available through economic evaluations

provide valuable and organised consideration of all available effects on health and healthcare costs as well as effects outside this remit [83].

A range of methods exist which can be utilised in order to conduct an economic evaluation.

Cost effectiveness analysis (CEA) is comparative analysis of an alternative and current therapy in terms of a natural effect of unit measure. For example, a novel hypertension intervention could look to decrease blood pressure in treatment recipients. In order to conduct a CEA the resultant measure of incremental cost per unit effect would be cost per mmHg reduction, which is the unit of blood pressure, which would equate to cost per mmHg reduction. Alternative natural unit of effect could also include cost per stroke avoided [83]. Cost effectiveness studies are useful to decision makers who are interested in one particular aspect of a disease for example hypertension or stroke. However, CEA have a number of disadvantages. The measure of unit effect used in CEA are dependent on the unit of consequence used i.e. mmHg reduction or number of strokes prevented. As a result, comparing two different treatments across broad groups of healthcare is such cases is difficult. This as a result make it difficult to measure opportunity cost (i.e. benefit forgone) between areas of healthcare which may be funded from the same source e.g. National Healthcare Service (NHS) healthcare budget [83]. Decision makers often want to compare the benefits gained from a new intervention and compare it to those of other healthcare interventions that may be displaced if the new intervention were made available in the NHS [83]. As a result, use of alternative forms of EE, Cost-utility analysis (CUA), are advised by reimbursement agencies such as NICE [85].

Cost-utility analysis use generic non-disease specific health outcomes for the effect side of the EE [83]. Generic outcomes allow interventions across health disciplines to be compared as like for like. Utility is the cornerstone of such comparisons of healthcare interventions as it encompasses different aspects of health which an individual may value such as length of life as well as quality [83]. Such utility measurements help determine the effect of health interventions on the long term physiological and psychosocial aspects of an individual's health. This measurement of utility can be achieved through a preference-based healthcare instrument (questionnaire). This measurement of utility gauges an individual's preference for a particular scenario. This utility can later be translated into Health-related quality of life (HRQOL) and then converted into a generic outcome, the Quality-adjusted life year (QALY) [83].

Cost-benefit analysis (CBA) is an EE that measures the effect of an intervention in monetary terms. Cost-benefit analysis allows comparison of benefits gained from a healthcare intervention against others healthcare interventions or interventions in different sectors. Cost-benefit analysis provides a decision maker to judge the best programme in terms of return on investment (ROI) analysis. However, assigning monetary value to health care be difficult. Although a range of methods can be used to determine the monetary value of effect gained through healthcare interventions and include Willingness-to-Pay (WTP) studies [83].

Cost-minimisation analysis (CMA) is used in situations where the effect of treatment in both interventions is considered equivalent. As a result, the analysis is focused on how much cheaper one intervention is to the other. However, it has been argued that CMA is not considered a full economic evaluation [83].

In the U.K. NICE for their technology appraisals recommend the use of CUA for evaluating interventions for their cost-effectiveness. Called the reference case [86], evaluations are done using specific health utility measurements, perspectives and using a particular rate of discounting also.

Considering the already described complex nature of CF as a condition and its effect both the quality and length of life and treatments effecting both these aspects, a CUA approach is adopted in this thesis (Chapter 6).

1.5.1 Economic Evaluations in decision-making

Due to the increasing pressure on resources and the changing demographics of countries, a shift from simply looking at the clinical effectiveness of an intervention to the use of supportive methods to aid decision making and reimbursement of healthcare provision has been increasing over the past 20 years [83]. NICE who are the main health technology assessment (HTA) organisation in England and Wales and who make recommendations regarding the availability of treatments for a multitude of conditions, require the use of EE (and specially CUA [86]) as part of the evidence to support recommendations for reimbursement.

A number of countries use EE to aid decision making, with many requiring submissions of economic data/analyses prior to an intervention receiving approval for use in the resident population. The use of EE however is more prominent in single-payer healthcare systems such as the NHS in the U.K. compared to multi-payer systems such as the U.S [83].

1.5.2 Decision analytical modelling

The definition of decision analytical modelling is …'*a systematic approach to decision making under uncertainty'…*[5]. Given the nature of economic evaluations being carried

out alongside clinical trials, such trials for healthcare interventions are often only carried out for a specified time period or until a clinically significant difference is found between the intervention and comparator [87]. Single intervention clinical trials are useful for conducting EE and vital for generating evidence on the impact of new treatments. However, there are reasons why use of decision analytical modelling may help in enhancing and supporting decision making further. Due to cost, management and ethical implications not all relevant options may be included in a clinical trial and subsequently the trial based economic evaluations [83]. Similarly, limiting economic evaluations to in clinical trial analyses have their own shortfalls [83] and subsequently requires EE of an intervention to draw from other sources for cost, utility and clinical effectiveness [83]. Such circumstances encourage the use of decision analytical modelling which can also assess an interventions cost effectiveness under conditions of uncertainty [83].

As a result, evidence has to be drawn from various sources to allow comparison of interventions through other methods. As such, decision analytical modelling enables comparison of healthcare interventions and brings together a range of datasets to target a specific decision problem [83].

With increases in the need for conducting economic evaluations to support decision making there have been subsequent increases in the need for decision modelling as a platform for undertaking such comparisons [5]. This can be demonstrated through guidelines published by NICE which require submissions of economic evaluations to include aspects of decision analytical modelling being conducted [5]. The increase in utilisation of health economic modelling can be directed to a range of reasons which are aimed to support decisions makers which include use of all relevant information or data,

consideration of all relevant competing interventions/comparators, use of an appropriate time-horizon and calculation of decision uncertainty through use of sensitivity analyses.

1.5.2.1 Principles of Good practice in Decision modelling

In accordance with the working guidelines of the International Society of Pharmaeconomics and Outcomes Research (ISPOR), decision analytical models are meant to aid decision-making [88]. Thus, the relationship between the inputs (data and assumptions) and the outcomes should be transparent. This transparency should exist in all aspects of the model and the assumptions around the structure, linkages between variables, disease incidence/prevalence, treatment efficacy/effectiveness, mortality, health-state utility, resource utilisation/costs and any added value judgements as considered by the decision makers [88].

Decision analytical models quality can be evaluated in three major areas: structure, data and validation. In accordance with structural quality, the model should include all appropriate inputs and outcomes that reflect the perspective of the evaluation i.e. if the model is to take a societal perspective then appropriate costs and consequence should be included which are applicable to that population group [88]. Similarly, the overall structure of the model and the constituent health states should reflect the theory behind the health condition, which includes reflection of linkages between direct and/or indirect variables such as body mass index (BMI) and mortality. As a result, exclusion of health states is not recommended if it is based on the lack of data [88].

Data inputs are subdivided into three categories, data identification, data modelling and data incorporation. In terms of data identification, it is recommended that all data be identified systematically. Additionally, where possible, a case to identify reasonable

attempts made to obtain additional data should be presented before modelling is conducted [88].

The data modelling refers to the mathematical steps used to convert the original empirical data into a form that is useful for decision modelling. These include incorporation of treatment effectiveness, interval probabilities of disease progression, mortality (disease specific and all-cause), health-related quality of life, costs, inflation, discounting, and data modelling relevant assumptions [88].

Lastly, data incorporation largely covers units of measurement within the model, types of modelling, the different types of sensitivity analyses that can be conducted and half-cycle correction [88].

The validation aspect of good research practice in health economic modelling covers three areas: internal, between-model and external validity. Internal validation testing of models involves debugging and ensuring that the model works accordingly to answer the research question. Between-model validation aims to understand difference between new and existing models with explanation of any difference in the outcomes given by the modeller. External validity in models is based on them representing the best available evidence [88].

1.6 NICE technology appraisal in Cystic Fibrosis

Due to the lack of NICE patient treatment pathways in CF there are no firm clinical treatment maps which can be utilised to develop appropriate health economic models in CF. Discussions with experts highlighted key aspects of CF that should be incorporated into the models themselves which are described later in Chapter 4. In order to understand the health economic modelling practices, the current data utilised within these models and overall, how well these models reflect CF disease progression based on the literature

and expert opinion, an evaluation of current NICE guidance on the treatment of CF was undertaken.

Health technology guidance review documents on the NICE website covered antibiotic treatment [89], correctors and potentiators of the CFTR protein [10] and muco-active agents [90].

Evaluation of the evidence and interpretation section within the guidance document for antibiotic treatment identified key areas of evidence that was lacking. The NICE assessment group identified that appropriate HRQOL data which reflects the NICE reference case was not collected in both the intervention and comparator groups [89]. Similarly, evidence presented from the trials around the clinical effectiveness of the interventions did not present information on PEx events in one trial. The comparator trial, although it does not provide information around PEx events, lung disorders was used as a proxy within the evaluation by the NICE assessment group. The assessment group commented that more clinically relevant outcomes should be included such as frequency of PEx events and antibiotic use alongside surrogate outcomes such as $ppFEV_1$ [89]. The NICE assessment group also identified a common shortfall that exist which included a short-term lung function improvement and no assessment of QALY gains in trials [89].

Evaluation of the evidence section within the guidance document for CFTR correctors and potentiators identified key areas of evidence that were presented in the economic model that reflect the recommendations set by the European Medicines Agency (EMA) [91]. Appropriate collection and representation of data for pulmonary exacerbation events, antibiotics use and hospital admissions was undertaken for the economic model. Other important variables that were accounted in the submitted model include CFRD status and

pancreatic insufficiency [36]. The NICE Evidence Review Group (ERG) stated that the model covered appropriate aspect of Cystic Fibrosis.

Evaluation of the evidence presented within the NICE guidance document for mucoactive agents [90] identified adequate measurement of pulmonary exacerbation events and subsequent hospital care utilisation. The trials representing the intervention however fell short of collecting appropriate HRQOL data, failing to reflect the NICE reference case requirements. The ERG further went on to comment that current measures of quality of life (QOL) may not accurately represent the consequences of having CF and the impact of any appropriate treatment for the Cystic Fibrosis [90].

After reflection on the NICE guidance document for CF diagnosis and management [36], a range of important variables were missing from the reviewed NICE appraisal documents which could have substantial impact on the long-term outcomes after inclusion into the economic model. These included frequency of PEx events, HRQOL data, identification of CFRD, Pancreatic insufficiency and Liver disease (as these both influence mortality/survival; Sections 1.2.9 and 1.2.10).

In order to fully elucidate the shortfalls in the health economic modelling of CF interventions it is important that a range of analyses are conducted which have been proposed in the thesis objectives.

1.7 Aims and objectives

The aim of this thesis is to extend what is known about the health economic modelling of CF interventions, advance the health economic evidence available to inform such economic models and decisions about appropriate CF care. As highlighted in the previous section (Section 1.5), NICE evaluated current treatments and found a number of shortfalls upon their evaluation. As a result, in an attempt to further understand shortfalls in the

cost-effectiveness analysis of CF interventions the evidence in the wider literature will be evaluated.

Areas of particular interest are:

1) Health economic modelling structure for evaluation of CF interventions

2) Application of statistical methods on the U.K. CF Data Registry to determine:

   a) health state transitions probabilities

   b) cost band transitions probabilities

   c) lung transplant probabilities.

Specifically, the aims of this thesis are to understand:

1) How are Cystic Fibrosis medications evaluated for their cost-effectiveness?

   I have answered this by:

   a. Identifying and reviewing the current state of the economic modelling literature for CF with the view to identify potential areas of importance that can be addressed within this PhD.

   b. Identifying and reviewing health utility data that exists for the health economic modelling of CF.

2) How can the Registry Data be used in the development of parameters to inform health economic modelling in the context Cystic Fibrosis treatments? With particular emphasis on:

   a. Demonstrating how existing statistical methods can be utilised to develop health state transition or other probability estimates

b. Generate new U.K. based health state transition (including mortality) probabilities for those who are F508Del Homozygous based on data from the U.K. CF Trust Data Registry.
c. Generate new U.K. based Cost band probabilities by health state from the U.K. CF Trust Data Registry to allow best possible estimates of cost
d. Generating new U.K. based Lung Transplant probabilities from U.K. CF Trust Data Registry
e. Developing a novel health economic model structure based on disease progression, data availability and clinical expert opinion in the U.K.
f. Developing a health economic model incorporating the estimates generated in objectives a) to d) into objective e) to evaluate an exemplar intervention, Orkambi®.

In summary this chapter has outlined CF as a disease, its economic burden and the shortfalls from a health economics perspective at the time in the evaluation of CF treatments in the U.K.

The following chapters will develop these themes and meet the aims and objectives of the thesis in the following ways. Chapter 2 reports on a systematic review to identify all relevant CF health economic modelling studies. This includes an evaluation of identified literature to look at the health economic modelling practices used in CF with particular interest on how this can be improved. Chapter 3 reports on a systematic review to identify all evidence around the health utility data which is available for utilisation in the health economic analysis of CF interventions. Chapter 4 reports on the U.K. CF Data Registry, De Novo model conceptualisation process and description of the data cleaning processes

employed to prepare the U.K. CF Registry Data for use in exemplar economic evaluation of Orkambi®. Chapter 5 focuses on the use of statistical methods on the U.K CF Data Registry to generate inputs for the exemplar health economic evaluation of Orkambi®. Chapter 6 looks at using the inputs from Chapter 5 and De Novo model from Chapter 4 to carry out an exemplar cost utility analysis of Orkambi® which was also validated using a between model consistency approach. Lastly, the thesis will be summarised and concluded upon (Chapter 7).

1.8 Work published from this thesis

1.8.1 Formatting of publications

Chapters 2 and 3 present verbatim the content of papers that have been published in academic journals during candidature. The chapters have been formatted so as to be consistent with the rest of this thesis to meet the University requirements for using work conducted as part of a thesis which has been subsequently published. This allows the incorporation of work conducted (Chapters 2 & 3) to be included. Further information about this can be found in the link provided below, in section 7 (n) of the document:

https://my.uea.ac.uk/documents/20142/274589/RDPD+3+-+Research+Degrees+Submission+Presentation+Consultation+and+Borrowing+of+Theses_M.pdf

1.8.2 Permission from the Journals

Permission was sought and received when reutilising the material published which composed both Chapter 2 and 3.

Permission was given on 27th November 2020.

The Journal of Cystic Fibrosis publication [92] state the following: as the author of this Elsevier article, you retain the right to include it in a thesis or dissertation, provided it is

not published commercially. Permission is not required, but please ensure that you reference the journal as the original source. For more information on this and on your other retained rights, please visit: https://www.elsevier.com/about/our-business/policies/copyright#Author-rights. No changes were made to the above article.

The Journal of Pharmacoeconomics Open publication [93] was made open access and as such is available under the following license:

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No changes were made to the above article.

1.8.3 Authors and Contribution

Below is a list of the publications, their citations and information of the primary author which indicates level of contribution made.

1. Bishal Mohindru, David Turner, Tracey Sach, Diana Bilton, Siobhan Carr, Olga Archangelidi, Arjun Bhadhuri, Jennifer A. Whitty. Health economic modelling in Cystic Fibrosis: A systematic review. Journal of Cystic Fibrosis. Volume 18, Issue 4. 2019. Pages 452-460. ISSN 1569-1993. https://doi.org/10.1016/j.jcf.2019.01.007

PhD candidate, Bishal Mohindru (BM) and supervisors Prof Jennifer Whitty (JW) and Mr David Turner (DT) conceived the systematic review. BM designed and undertook the searches and collated the data, with assistance from Arjun Bhadhuri (AB). BM, with assistance from JW, DT, Prof Tracey Sach, Dr Diana Bilton, Dr Siobhan Carr, Dr

Olga Archangelidi, interpreted the data. BM drafted the manuscript. All authors subsequently contributed to the review and revision of the manuscript and approved the final version.

2. Mohindru, B., Turner, D., Sach, T. et al. Health State Utility Data in Cystic Fibrosis: A Systematic Review. PharmacoEconomics Open 4, 13–25 (2020). https://doi.org/10.1007/s41669-019-0144-1

PhD candidate, Bishal Mohindru (BM) and supervisors Prof Jennifer Whitty (JW) and Mr David Turner (DT) conceived the systematic review. BM designed and undertook the searches and collated the data, with assistance from Arjun Bhadhuri (AB). BM, with assistance from JW, DT, Prof Tracey Sach, Dr Diana Bilton, Dr Siobhan Carr, Dr Olga Archangelidi, interpreted the data. BM drafted the manuscript. All authors subsequently contributed to the review and revision of the manuscript and approved the final version.

1.9 Conferences

A number of conferences were attended as part of this PhD which were funded by the EPI-NET project. Below is a list of these conferences and details of poster presentations or talks given.

- U.K. Cystic Fibrosis Conference (Birmingham) (2017) – Oral poster presentation
- Postgraduate Faculty of Medicine and Health conference (2018) (University of East Anglia) – Oral poster presentation
- U.K. Cystic Fibrosis Conference (Nottingham) (2018) – Oral poster presentation
- Postgraduate Faculty of Medicine and Health conference (2019) (University of East Anglia) – Oral poster presentation

- European Cystic Fibrosis Conference (Liverpool) (2019) – Oral presentation; Penny lane: delivering value in cystic fibrosis healthcare; Health economic analysis using UK CF Registry Data

2 Chapter 2: Health economic modelling in Cystic Fibrosis - A systematic review

2.1 Introduction

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. As CF is a rare condition with consequences over a long period of time the health economic model has been widely used to evaluate cost-effectiveness.

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 [94]. The report highlighted that two regulatory bodies, the Canadian Agency for Drugs and Technologies in Health (CADTH) and NICE, decided, at the time, not to provide Orkambi®(Vertex Pharmaceuticals) [7, 8, 10] and Ivacaftor (Kalydeco®) on the basis of the cost of treatment being too high [6]. Subsequently the institute developed a cost effectiveness model for a range of modulating treatments and found them all not cost effective. The high price of drugs associated with rare diseases like CF have resulted in unfavourable incremental cost effectiveness rations (ICERs) despite there being evidence of effectiveness. The issue of high ICERs being associated with the use of conventional cost effectiveness analysis on orphan drugs has been discussed in the past [83, 95] 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 evaluate the quality of reporting found in published CF models. A number of checklists for model reporting quality are available, including: Consolidated Health Economic Evaluation Reporting Standards (CHEERS) checklist [96], Quality of Health Economic Studies (QHES) instrument [97] and the recently published recommendations by the Second Panel on Cost-Effectiveness in Health and Medicine in the U.S [98] for studies conducted in the U.S.

2.2 Aims and Objectives

The purpose of this review is to identify studies using economic models for CF. Through this I aim to develop a better understanding of the methods used including, model structures, data inputs, modelling methods, and interventions evaluated. I consider potential limitations with current modelling methods and potential ways in which CF modelling could be developed and improved.

2.3 Methodology

This systematic review follows guidance provided both by the PRISMA group [99] and the Centre of Reviews and Dissemination (CRD) [100].

2.3.1 Inclusion Criteria

The inclusion criteria are specified in Table 3. Economic evaluations not based on the management of Cystic Fibrosis, Cystic Fibrosis clinical trials and studies not relevant to Cystic Fibrosis were excluded.

Table 3: Review inclusion criteria, following PICOS framework

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

2.3.2 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.).

2.3.3 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.

2.3.4 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 [96], Quality of Health Economic Studies (QHES) instrument [97] and the Panel on Cost-effectiveness in Health and Medicine in the U.S [98].

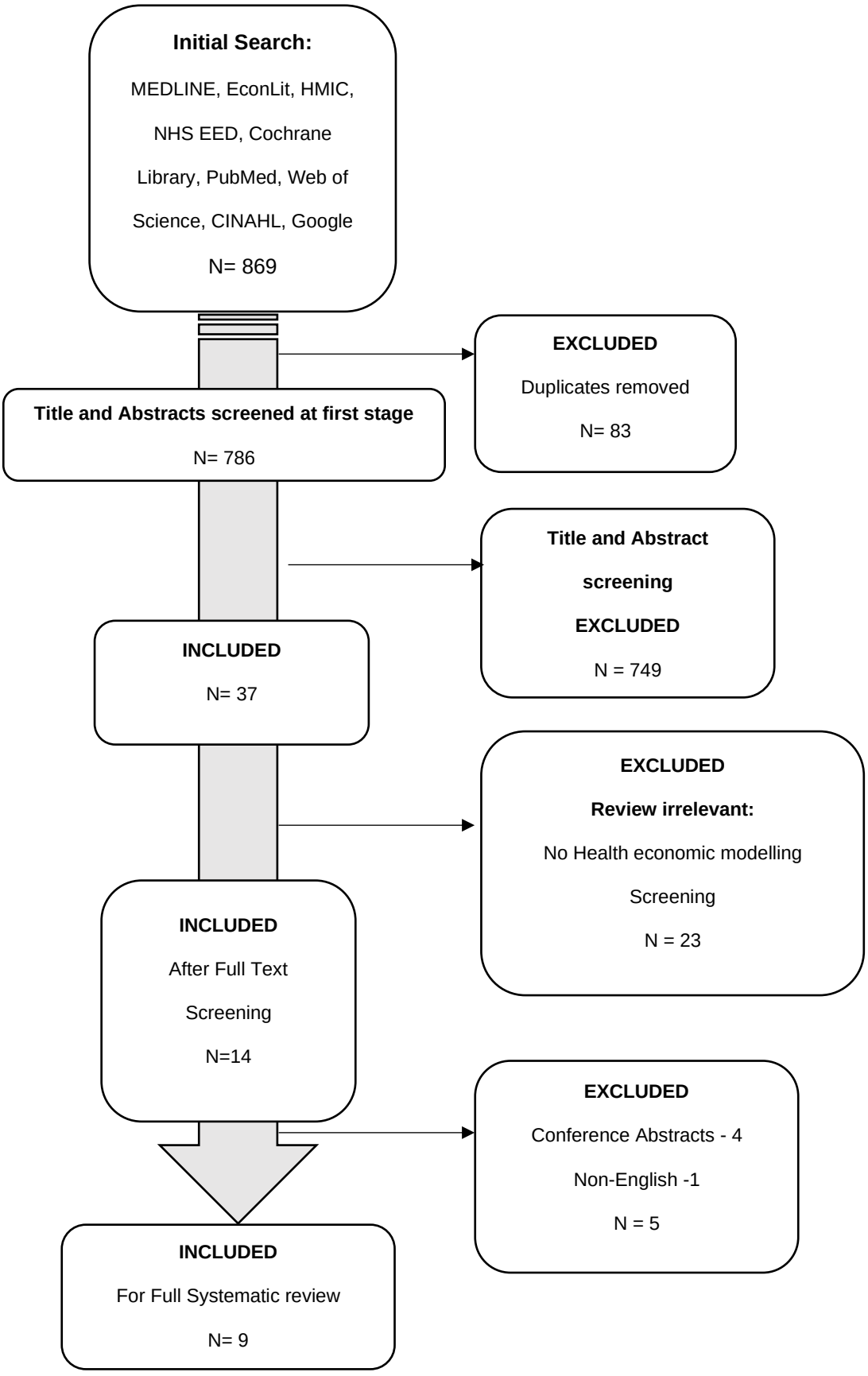
2.4 Results

2.5 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 2). 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 [4]. Nine articles were included for data extraction.

Figure 2: PRISMA diagram: process of study identification [99]



2.6 Summary of included studies

Table 4:Summary of included studies

Author	Type of Model			Intervention	
	Cohort Model	**Decision tree**	**Individual patient simulation model**	**Pharmaceutical**	**Adherence**
Panguluri et al [101]			✓	✓	✓
Tappenden et al [102]	✓				✓
McGirr et al [103]	✓			✓	
Dilokthornsakul et al [104]	✓			✓	
Schechter et al [105]	✓			✓	
Tappenden et al [106]	✓			✓	
Whiting et al [107]			✓	✓	
Christopher et al [108]		*[1]		✓	
McIntyre et al [109]	✓			✓	

[1] Unknown if decision tree

Table 4 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 I was unable to speak to the author to clarify this [108]. 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 summaries the average patient experience [5]. 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 [5].

Five studies evaluated the impact of a range of pharmaceutical interventions [103-106, 109], of which one was a Health Technology Assessment (HTA) report [106]. Two studies evaluated the impact of better drug adherence [101] or an adherence intervention [102] 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 [107], which again was a HTA report. Lastly, one study evaluated the impact of rhDNase [108] on CF disease progression and the other Dornase Alpha on long-term patient survival [109].

2.7 Pharmaceutical interventions

2.7.1 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 [102]. Two studies compared treatment to no treatment, rhDNase vs. no treatment and PMB vs. no treatment [103, 108]. Two studies utilised individual patient simulation models [101, 107] 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 [104, 107], which consisted of CF-related medication, devices and respiratory therapy [107]. Two articles evaluated the impact of dry inhalation to nebulisation for antibiotics [101, 106], although one looked at the impact of adherence [101] and the other at different antibiotic treatments [106]. One additional study evaluated the impact of inhalation of two different types of antibiotics [105].

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 [102]. 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) [103]. The populations included in the models include both adults and children [101, 102, 105, 107, 108], children [103] and adults [106] alone.

2.7.2 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 [101, 103, 104]. Models estimated costs and outcomes over a lifetime horizon except for two studies [101, 105] which utilised a 10 and 3-year time horizon respectively. Discounting was applied to both cost and outcomes for all but three studies [104, 108, 109]. In the case of Dilokthornsakul et al [104] 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 [108] or McIntyre et al [109] did not provide justification for not discounting their outcomes. For all other studies base case discounting varied from 3% [101, 104, 105], 3.5% [102, 106, 107] to 5% [103]. Further scenarios evaluating the impact of varying the discounting rates through senstitivity analysis was undertaken for all pharmaceutical interventions except one [109].

2.7.3 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 [102-104, 106], 1) mild, 2) moderate, 3) severe forced expiratory volume in one second (FEV_1), 4) transplant and 5) death. Schechter et al [105] utilised 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 [101] individual patient 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 [107] HTA report simulates the probability of death through a function of key variables such as sex, FEV_1, pancreatic insufficiency, diabetes mellitus, bacterial infection and number of PEx events. Christopher et al [108] and McIntyre et al [109] did not adequately describe their model structures or present diagrams in their publications.

2.7.4 Country and perspective

The health economic models were based within three countries, Canada [103], UK [102, 106-109] and United States (U.S.) [101, 104, 105]. The modelling adopted an NHS [102, 106, 107, 109], US payer [101, 104], Canadian Healthcare [103], third party payer [105] and regional health authority (U.K.) perspective [108].

2.7.5 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 [102, 106] provide outcomes beyond the QALYs and ICERs. Additional outcome measures provided include survival [101], different aspects of costs [101], life years gained [103-105, 108, 109] reduction in hospitalisation [105], lifetime cost [104], probability of lung transplantation [104] and budget impact analyses [103, 104].

Table 5 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.

Table 5: Further outcomes evaluated (by author and outcome)

Outcome	Author				
	McGirr et al [103]	Dilokthornsakul et al [104]	Schechter et al [105]	Christopher et al [108]	McIntyre et al [109]
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)	-	-	-

2.7.6 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 [103], Insurance claims data [105], Private databases [101], US Kaiser Permanente's CF centre data [104], UK CF registry data [102, 107], Department of Health tariff banding [107], NHS national tariff [102] and a study conducted by Robson et al [110]. Not all studies separated cost of CF by FEV_1/disease severity. In the case of Tappenden et al [106] costs for CF care were assumed to be identical between treatment arms and thus were excluded from the evaluation. Christopher et al [108] 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).

2.7.7 Incremental cost effectiveness ratios

Incremental cost effectiveness ratios (ICERs) were expressed in a range of ways in the models evaluating pharmaceuticals. Dilokthornskul et al [104] 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 [103] showed incremental improvement in QALYs at a cost of CAD$61,550-157,332 per QALY, dependent on the assumed discount rate. Schechter et al [105] demonstrated that Aztreonam was dominant over Tobramycin through improvement in QALYs, life years and reduction in hospitalisation. Tappenden et al [106] 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 [107] 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 [102] demonstrate that an adherence

intervention dominated current care. Panguruli et al [101] reported a base case ICER which was a cost saving, saving $133,000 per QALY gained for TIP compared to TIS. Christopher et al [108] 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 [109] demonstrated a cost of £27,269 per life year gained for lifetime treatment with Dornase Alpha.

2.7.8 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 [101, 102, 105, 106], SF-36 [107] and a Standard gamble approach [103].

Four studies included disutility around pulmonary exacerbation events [101-103, 106] using the same data sources [48, 111]. One source included disutlity around respiratory syncytial virus infection [112]. Three different studies were utilised to include utility of lung transplantation and used the EQ-5D [113] [102, 106, 107], Visual analogue scale (VAS) [105, 114] and a standard gamble approach (SG) [103, 115].

2.7.9 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.

2.8 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 [103-105] 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 [102, 106, 107] 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 [98]. 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.

2.9 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 [5]. In order to appraise the models and the appropriateness of the evidence I assessed different aspects of the economic evaluations. I looked at data from the clinical trials underpinning the models, HRQOL/utility studies, costs, ICERs and lastly the model structures.

2.9.1 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

[91]. 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 [91].

It was evident after evaluation against the EMA guidelines that data were collected for PEx events in some clinical effectiveness studies of CF interventions [101, 104-107]. However, not all PEx event data were utilised when undertaking health economic modelling of the intervention [101, 103, 104]. A similar finding was observed for hospitalisation and antibiotic use [104, 107]. 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 [91] which can in turn be utilised in the health economic modelling of CF interventions.

2.9.2 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 [101, 102, 104-106].

Only one trial collected HRQOL information, which met the requirements of the NICE reference case [107] but the utility estimates were considered inflated by NICE HTA evaluation team. As a result, utility values for the Whiting et al [107] model are based on utilities that are also used by Dilokthornsakul et al [104].

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 [101, 102, 105, 106] and the source of the disutility data were the same [48, 111] in three studies. Panguruli et al [101] simply stated the decrement in utility without further elaborating on the source. Dilokthornsakul et al [104] 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 [107] 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.

2.9.3 Cost Data

Evaluation of the cost evidence in the models showed that a range of sources were utilised. McGirr et al [103] utilised an study based on Australian patients to calculate cost per mild, moderate or severe FEV_1 health state and lung transplantation [81] 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 [104, 107]. Dilokthornsakul et al [104] utilised 1996 cross-sectional US Kaiser Permanente's regional CF centre data to determine health state specific costs [116]. Other models reviewed in this work which were also based in the US [105] used an alternative source to determine healthcare utilisation costs for US CF individuals [117]. In comparison to the Kaiser Permanente's regional CF centre data, which was conducted on 136 individuals in 1 year, Briesacher et al [117] 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 [116] study was conducted prior to the introduction of new maintenance therapies [117] and subsequent studies looking at the cost of CF in a similar setting [118] have shown a 140% increase [117] in costs compared to those calculated by Lieu et al [116]. Lung transplantation costs inputs in Dilokthornsakul et al [104] utilise 2011 data, although more up to date costs on single and double lung transplantation data exist for 2014 [119].

Whiting et al [107] utilised a banding system to reflect disease state specific costs [60] due to increasing treatment complexity and NHS reference costs for lung transplantation.

A total of four studies evaluated the cost-effectiveness of antibiotic treatments [101, 102, 105, 106], 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 [102, 105]. The reason for such difference is unapparent.

2.9.4 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.

2.9.5 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 [104, 105]. Considering CF's multifactorial nature, disease models lack a similar approach. The structure utilised by McGirr et al [103] 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 [116] which was designed based on advice from the CF Foundation.

Evidence presented by Tappenden et al [106] defined the health states through information presented in their HTA report which detailed the conceptualisation of the decision problem [120]. 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 [120]. The additional Tappenden et al [102] paper simply refers back to the 2014 publication in reference to the structure of the model. Whiting et al [107] utilised a patient-level simulation model, demonstrating the probability of death as a function of age, sex, 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 [101] 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 [121].

2.10 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 [62] as they are predictive of longer term survival [42, 60] and cost considerable resources [122]. 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 [64-66, 91]. The impacts of these comorbidities on the long-term mortality becoming clearer [64-66]. Given the recent workshop on clinical trial endpoints in CF [91], 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.

2.11 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. I 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.

2.12 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.

2.12.1 Update of review

The initial search conducted in this chapter was until 17th November 2017. Searches were updated to 31st October 2020. A total of 7 additional studies were found. Of these 4 did not satisfy the inclusion/exclusion criteria: 1 was a systematic review of CF modelling studies (this chapter) [92]; 3 were CF screening studies [123-125]. Two studies were cost effectiveness of Orkambi® [126, 127] and the last study was a cost-effectiveness study on Mannitol [128]. As a result, only the three studies were evaluated further. Particularly the two cost effectiveness studies on Orkambi® will be covered in more detail in section 6.5 of Chapter 6. A brief description of the cost-effectiveness study of Mannitol® [128] is given below.

2.12.2 Summary of study(s)

In summary, the cost effectiveness study on Mannitol® [128] utilised an individual patient simulation model to evaluate a pharmaceutical intervention. The patient population considered were those with CF in Australia. The evaluation was a cost utility analysis over a lifetime horizon and both cost and outcomes were discounted at 5%. The perspective taken for the analysis was an Australian national healthcare system perspective.

The model itself was based on 4 primary health states, No event, PEx, lung transplant and death within two FEV_1 categories considered, <30 or equal to or more than 30. The author [128] states that the model structure was reviewed by both Australian and U.K. HTA authorities. Additional between model comparisons for validity were made against a single more recent cost effectiveness study in CF, which was not included in this review as it was not a cost-effectiveness study [129].

Disease progression in the model is based on an Australian dataset of 855 patients with CF. A linear regression model was developed to generate annual rate of decline in FEV_1. Rate of decline in FEV_1 was based on age, sex, BMI and number of inpatient days in hospital days per quarter (as a proxy for severe PEx events) [128]. Those who were hospitalised compared to those who were not, had a 1.44% higher chance of annual decline in FEV_1. Based on age, the annual decline was 1.5% FEV_1 per year until the age of 30, after which the FEV_1 increases per year. This clinically does not make sense, and the author [128] said this is most likely due to survival bias in the dataset as healthier patients out-survive the unhealthier patients. As a result, it was assumed in the dataset that FEV_1 decline post 30 years would remain unchanged [128]. Mortality was also based on the same dataset.

Health utility was taken from a clinical trial conducted on the use of Mannitol [130]. However, further evaluation of the published article did not show data collected in relation to health utility.

Costs were based on a paper published in 2011 [81] which reflected an Australian cross section cohort from the Australian CF Data Registry.

2.13 Chapter summary

In this Chapter, the different cost effectiveness models for management interventions in CF for their were evaluated. They were assessed under a number of areas (section 2.7). Overall, in terms of quality, majority of studies were of medium or low quality and did not meet the respective quality assessment guidelines. Only a handful did and were of high quality. Improvements were also suggested for the future model structures utilised to evaluation CF management interventions.

One important future direction was the evaluation of the level of evidence available in the literature around health utility, as this was described as lacking in the chapter and

most often utilised the same source of information which in itself was based on a small sample size. Furthermore, disutility of treatment with antibiotics was not accounted for in most models. Chapter 3 reviews the existing evidence around the health utility data available in CF for use in future cost effectiveness evaluations.

3 Chapter 3: Health state utility data in Cystic Fibrosis: A systematic review

3.1 Introduction

In the previous Chapter, a review of the health economic modelling studies was undertaken to shed light on existing modelling practices as well as the sources of data used for such evaluations. A shortfall in evidence around health utility data were highlighted. To shed light on the availability of health utility data for the health economic modelling of CF interventions. I conducted a systematic review on health state utility data in CF.

Treatments received by CF individuals are leading to improvements in clinical outcomes [131-134]. However, the decision for treatment provision by governing bodies like the NICE in the U.K. is based on the cost-effectiveness of the treatment [86]. 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 [135]. 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 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) [135]. 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 [136]. Measures, particularly those

generated through generic questionnaires, such as the EQ-5D [86] 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 [135]. '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 [136], which can in turn be used for health economic modelling.

3.2 Aims and Objectives

I conducted 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, I look to inform future work by highlighting gaps in the research related to health state utility values of CF individuals.

3.3 Methodology

This study follows the Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) guidelines [99] for reporting systematic reviews.

3.3.1 Inclusion criteria

Although it is not entirely possible to apply the PRISMA guidelines to a HSU systematic review [137], I have attempted to do so in order to define the boundaries of this review. I have selected a Population, Intervention, Comparator, Outcome and Study Design (PICOS) framework [100], this is presented in Table 6. Although I am aware that the HSU may not be attached to a particular intervention. When I describe the intervention, I aim to describe the method of determining the HSU values.

The utility values I 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 [138].

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.

Table 6: Inclusion criteria

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

3.3.2 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 [107]. 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 I 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 15th March 2019. Conference abstracts were excluded. Search strategies are available in the supplementary material.

3.3.3 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.).

3.3.4 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.

3.4 Results

3.5 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 Bishal Mohindru and Arjun Bhadhuri. A PRISMA diagram is presented in Figure 3, to demonstrate the process of study selection.

Figure 3: PRISMA diagram: Adapted from Moher et al [99], showing the process of study selection.

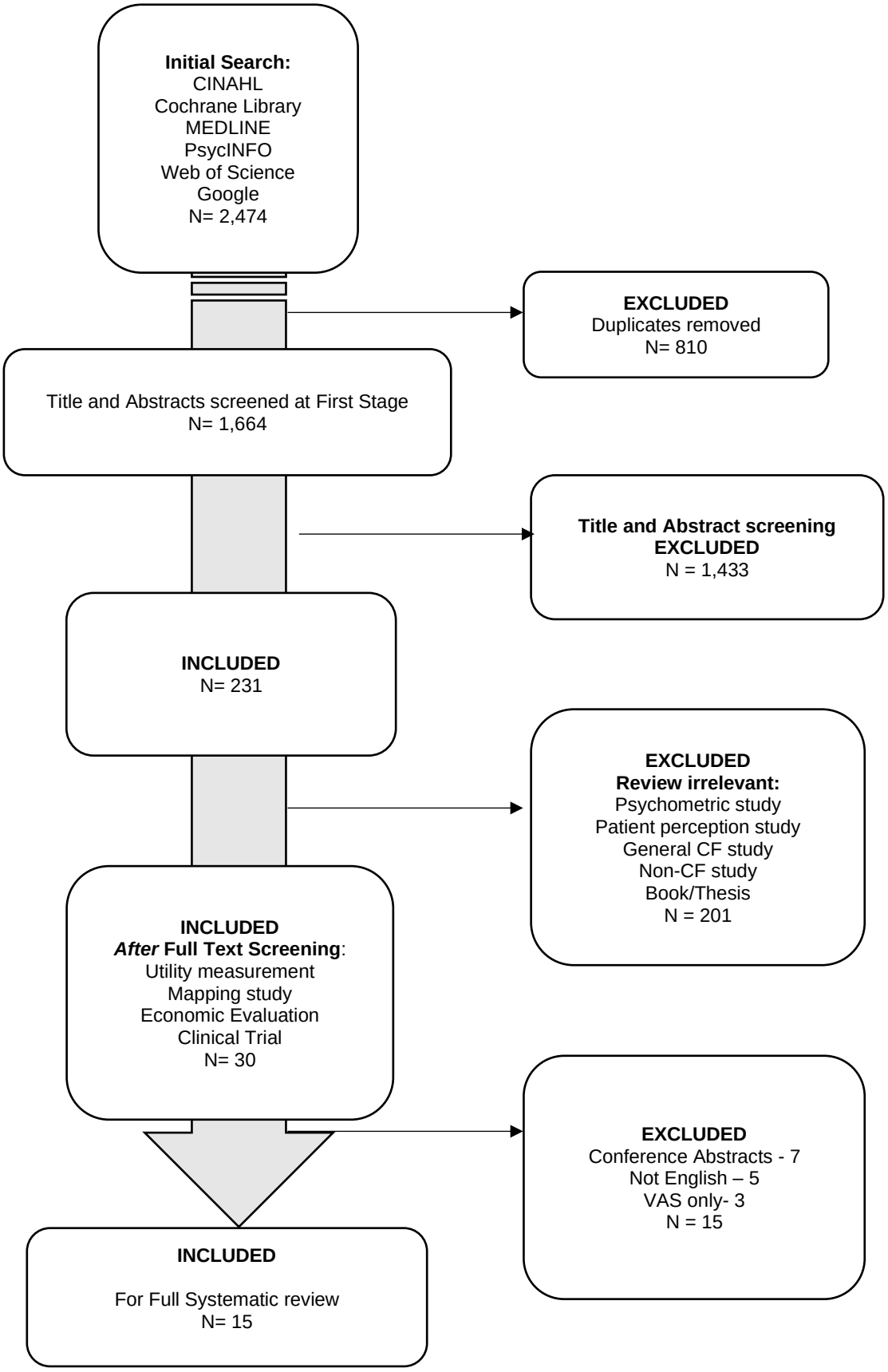


Table 7: Summary characteristics of included studies (by descending publication date)

AUTHOR	YEAR	COUNTRY	SUBJECTS	TYPE OF STUDY	SAMPLE SIZE TOTAL
SOLEM ET AL [139]	2016	USA	Patients (Adults) 12 +/> (Ivacaftor therapy in CF ptx with G551D mutation)	HRQOL study	161
CHEVREUL ET AL [140]	2016	Multiple	Patients (Adults and Children) (or Proxy/carer) and carers	HRQOL study	920
ISKROV ET AL [141]	2015	Bulgaria	Patients (Adults and Children) and carers	HRQOL study	40
CHEVREUL ET AL [142]	2015	France	Patients (Adults and Children) (or Proxy/carer) and carers	HRQOL study	166

AUTHOR	Year	Country	Subjects	Type of study	Sample size total
ANGELIS ET AL [80]	2015	UK	Adults, Children and Caregiver (Adults, Children and Caregiver)	HRQOL study	74
ACASTER ET AL [143]	2015	USA	Patients. (Adults) 18 + >	Mapping study	401
BRADLEY ET AL [48]	2013	UK	Patients (Adults) >16 years, +bacterial infection, + antibiotics medication	HRQOL study	94
DEWITT ET AL [144]	2012	USA	Patients with mild lung impairment (FEV1:75 or more) and carers	Clinical trial	328

AUTHOR	Year	Country	Subjects	Type of study	Sample size total
FITZGERALD ET AL [145]	2005	Australia	Children, Adolescents and Adults (5-18 years)	Clinical trial	50
YI ET AL [146]	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 [147]	2001	UK	Children only	Clinical trial	40
SELVADURAI ET AL [148]	2001	Australia	Patients (8-16 years), admitted to hospital for infective PEx	HRQOL study	66

AUTHOR	Year	Country	Subjects	Type of study	Sample size total
CZYZEWSKI ET AL [149]	1994	USA	Patients and carers (Children and Adolescents and Caregiver)	HRQOL study	254
BUSSCHBACH ET AL [114]	1994	Netherlands	Patients (Adults)waiting for and having received and lung transplant	HRQOL study	6
OREINSTEIN ET AL [150]	1990	USA	CF individuals older than 10 years, positive for bacterial infection and treated with a new antibiotic (proxy: examiner)	HRQOL study	28

3.6 Study Characteristics

Table 7 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 [142] 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 [145, 148].

In Table 7, I 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 [80, 140-142, 149], some of whom were also assessed for their health utility [80, 140-142].

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 [140]. The population age varied across studies, with the youngest mean age of the participant being approximately 9 years [149] and the oldest mean age being 30 years [143].

Completion of the questionnaires was undertaken with no proxy on 6 occasions [48, 114, 139, 141, 143, 147]. The remaining studies utilised proxies in some patient groups to complete the instruments [80, 140, 142, 144, 150]. Dewitt et al [144] 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 [145, 148] and one study interviewed the participants and subsequently allowed them to complete the questionnaire at home [149]. Lastly, one study collected information through face -to- face interviews [146].

Table 8: Summary of utility data collection (by descending publication date)

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 [139]	2016		✓		EQ-5D-3L	✓	Dolan et al [151]	Ivacaftor
CHEVREUL ET AL [140]	2016		✓		EQ-5D-5L (mapping to 3L value set)	x	Multiple countries	-
ISKROV ET AL [141]	2015		✓		EQ-5D-3L	x	Dolan et al [151]	-
CHEVREUL ET AL [142]	2015		✓		EQ-5D-5L (mapping to 3L value set)	x	Perneger et al [152]	-
ANGELIS ET AL [80]	2015		✓		EQ-5D-5L> EQ-5D-3L ^{2}+ VAS	x	Kind et al [153] & Dolan et al [151]	-

AUTHOR	Date	Method of obtaining utilities				Utility for health states	Value set utilised	Intervention
		Direct Utility	Multi-attribute	Mapping study	Instrument/Technique			
ACASTER ET AL [143]	2015		✓	✓	CFQ-R to EQ-5D-3L	✓	Dolan et al [151]	-
BRADLEY ET AL [48]	2013		✓		EQ-5D -3L	✓	MVP Group [154]	Pulmonary Exacerbations (PEx)
DEWITT ET AL [144]	2012		✓		Health Utilities index 2/3	x	Unknown	Chloride Channel Activator
FITZGERALD ET AL [145]	2005		✓		Quality of Wellbeing	x	Unknown	rhDNase

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

AUTHOR	Date	Method of obtaining utilities				Utility for health states	Value set utilised	Intervention
		Direct Utility	Multi-attribute	Mapping study	Instrument/Technique			
YI ET AL [146]	2004	✓	✓		Time trade off, Standard gamble & Health Utilities Index 2	✓	Unknown & Direct valuation	-
SURI ET AL [147]	2001		✓		Quality of Wellbeing	x	Unknown	rhDNase
SELVADURAI ET AL [148]	2001		✓		Quality of Wellbeing	x	Unknown	Aerobic vs Resistance training
BUSSCHBACH ET AL [114]	1994	✓			Time trade off & Standard gamble	✓	Unknown & Direct valuation	Lung Transplantation

AUTHOR	Date	Method of obtaining utilities				Utility for health states	Value set utilised	Intervention
		Direct Utility	Multi-attribute	Mapping study	Instrument/Technique			
CZYZEWSKI ET AL [149]	1994		✓		Quality of Wellbeing	x	Unknown	-
ORENSTEIN ET AL [150]	1990		✓		Quality of Wellbeing	x	Unknown	Antibiotic (Abx)

3.7 Utility elicitation

Table 8 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 [48, 80, 139-142]. This included different version of the EQ-5D, the 3L and 5L. Studies that utilised the EQ-5D-5L version of the instrument [80, 140, 142] mapped their results to the 3L instrument due to the lack of a value set at the time, which is what NICE recommends [86]. This method of deriving utilities was followed by utility elicitation through the Quality of Well-being instrument (QWB) [145, 147-150]. Lastly, the Health Utilities Index (HUI), version 2 and 3 were used in two studies [144, 146]. Direct elicitation via TTO and SG was used by two studies [114, 146].

3.8 Converting HRQOL scores into utilities

I 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 [151] 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 [142] who used a French value set [152] for a French study and by Chevreul et al [140] who utilised multiple value sets for different European countries. Chevreul et al [140] 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 [145, 147-150]. There was no clear information about the value set in any study. However, I am aware that the utility scoring algorithm is available from the developers of the instrument [135].

Finally, two studies utilised the HUI, versions 2 and 3 [144, 146]. Neither study provided information around the value sets that were used to calculate their respective utilities.

3.9 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 [143].

3.10 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 [114], PEx events [48, 139] and FEV_1 [143, 146].

3.10.1 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 [114].

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 [114].

3.10.2 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 [139] and mild/ moderate/

severe PEx [48]. 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 [48].

Utility derived by the time since PEx event start and finish was investigated by Solem et al [139] 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.

3.10.3 FEV_1

FEV_1 utility data were separated either by three [143] or four categories [146] of severity. This included the conventional mild, moderate and severe categorisation. Yi et al [146] 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 [143] mapped the CFQ-R instrument to the EQ-5D 3L by 3 FEV_1 severity levels. Yi et al [146] 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 [143] 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 [146]. 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.

3.11 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 [145, 147], antibiotics [150], aerobic vs resistance training [148], education [149] and chloride channel activator [144]. Four additional articles simply observed the mean utility of CF individuals across Europe [80, 140-142]. These studies particularly focus on characterising change in utility pre and post intervention over time.

3.11.1 Recombinant Human DNase (rhDNase)

Recombinant Human DNase (rhDNase) was evaluated in two clinical trials [145, 147]. Each study targeted different population groups, children only [147] or children and adults [145]. Both studies utilised a multi-attribute instrument to obtain utility data, the Quality of Wellbeing instrument (QWB) Although, Suri et al [147] 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 [147] 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 [145] 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.

3.11.2 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 [144]. 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.

3.11.3 Aerobic vs Resistance training

Selvadurai et al [148] 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.

3.11.4 Education intervention

A clinical education intervention was provided to children and adolescents in order to determine QWB derived utility [149]. 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.

3.11.5 Antibiotics

Quality of wellbeing was applied to CF individuals being treated for PEx with oral Ciprofloxacin [150]. 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.

3.12 Cohort studies

Finally, four studies [80, 140-142] 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 [80, 141, 142], whilst the remaining article was a summary of the before mentioned articles with many additional countries which were evaluated as part of the project [140]. 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 [140] matched those figures provided within either Chevreul et al [142], Angelis et al [80] or Iskrov et al [69]. Further evaluation of the number of patients utilised to reflect the EQ-5D-3L utility index data showed for example in Angelis et al [80], 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 [141, 142].

3.13 Discussion

Health economic modelling has become a key component of healthcare decision making and its use is recommended by NICE for technology appraisals [86]. 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 [155]. Previous models have highlighted a lack of health outcomes evidence to inform CF health economic models [107, 120], particularly around the health outcomes data.

Health state derived utility values were only available for 5 studies [48, 114, 139, 143, 146]. 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 [114]. The treatment sample in Busschbach et al [114] 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 [114].

PEx event data presented covered a 16 to 48-week period [48, 139] and has limited application for this particular health state due to the nature of the populations and treatments being investigated. Solem et al [139] evaluated the impact of Ivacaftor on PEx events. Data from Bradley et al [48], 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 [143, 146]. Acaster et al [143] 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 [146] 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 [103]. Due to unconventional nature of categorising the FEV_1 severity into four categories, the model by McGirr et al [103] 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 [102, 104, 120].

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) [86]. From the studies that evaluated health utility with the EQ-5D we can understand that the

population samples in all three studies [80, 141, 142] 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, I 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 [156, 157] and treatment of the condition [25, 158], 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 [101-105, 107, 120] . 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®® [10] and the published literature [139]. 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 [86]. 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 [135].

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 [11, 159]. 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 [143]. 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 [86].

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 [160]. This further emphasises what patients, clinicians, nurses and other healthcare staff consider to be priorities of research in CF.

3.14 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 [161] evaluated EQ-5D-3L derived utility in Spanish patients who had mild or moderate PEx events, L'abbe et al [162] evaluated HRQOL in CF lung transplantation patients and Yarlas et al [163] 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.

3.15 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.

3.15.1 Update of review

The initial search conducted in this chapter was until 15th March 2019. Searches were updated to 31st October 2020. A total of 6 additional studies were found. Of those studies found, study by Ratnayake et al [164] was a review of patient reported outcome measures (PROMs) which included all the studies found from this review chapter except studies which were RCT's as they removed such studies as part of their exclusion criteria. As a result, the studies found in this chapter cover wider sources of information for HSU data. The paper by McLeod et al [165] was a protocol for a proposed study looking at determining HSU from discrete choice experiments (DCEs), a very relevant study. The study proposed to include more than 4,000 CF individuals from the Australian CF Data Registry. As such, this study may prove to be very useful for future health economic analysis for HSU data, particularly in those countries with similar baseline patient characteristics as Australia. The HRQOL study by Bell et al [166] looked at the EQ-5D-5L outcomes of those patients taking Ivacaftor treatment. However, no HSU or utility data is provided in the publication. The study by Gold et al [167] is a validation study which compares a disease specific instrument outcome measures to the EQ-5D 5L. Lastly, a single study was a cost-effectiveness study on Mannitol [128]. As a result, only these two studies [167, 168] were evaluated further. A brief description of Perez et al [168] is given

below (Section 3.15.2). The study by Perez et al [128] has already been evaluated in Chapter 2 (Section 2.12.2) and the source of data on HSU was deemed to not contain any such data, quite possibly not reported by the author in the published manuscript and directly obtained by Perez et al [128].

3.15.2 Summary of study(s)

In summary, the only study which was evaluated [168] was conducted in the U.S. on 23 CF individuals awaiting lung transplantation who were older than 18 years. It is a HRQOL study which evaluated lung transplantation using other instruments alongside the EQ-5D-5L, although the value set used to covert the scores into utilities was not mentioned. The study itself evaluated HRQOL at different time points (baseline, three months post lung transplant and six months post-transplant. The mean (sd) utility values for each time period were 0.56 (+/- 0.29), 0.90 (+/- 0.09), 0.90 (+/- 0.16). The values showed a mean difference of 0.34 (95% CI; 0.23 - 0.46) (post-transplant compared to pre transplant), which was much higher than the minimum clinical important difference (MCID) of 0.06 for the EQ-5D. The study also showed that changes in lung function and frailty were associated with improvements in EQ-5D.

3.16 Summary of chapter

In this Chapter, the availability of health utility data in the literature was evaluated. The studies were assessed under a number of areas (Section 3.6). Overall, the level of data available for use in health economic modelling of CF interventions is lacking and further research by undertaking studies which evaluate health utility, particularly through use of the EQ-5D is recommended. Further studies which evaluate health utility through assessment of CF individuals contributing data to the CF Data Registry is also suggested.

4 Chapter 4: Methods

4.1 Chapter outline and Aims and objectives

The previous chapters (Section 1,2 and 3) focused on introducing CF, health economics and existing technology appraisals in CF for treatments (Chapter 1), followed by a review of existing health economics modelling studies in CF (Chapter 2) and lastly another review looking at the current level of evidence available around health state utility data in the literature (Chapter 3).

Previous chapters highlighted a requirement for better more representative modelling methods for the economic evaluation of CF management interventions. I suggested focusing on significant healthcare events such as PEx or IV antibiotic use which have been related to disease progression in CF in Chapter 1. The model conceptualisation work conducted in this chapter was undertaken as no previous evidence exists on the conceptualisation of a health economic model in CF for management interventions, despite a number of models being identified in Chapter 2. One of the main aims of the Epi-Net project, presented earlier in this thesis, was to utilise data from the CF Data Registry to help improve the lives of those with CF. As a result, a large focus of this chapter will be the CF Data Registry. Particular emphasis is placed on the use of the CF Data Registry to create transition probability estimates for health economic modelling, further presented in Section 4.19.

Lastly, further work on use of cost data from more representative sources such as HES or SAIL data were suggested in Chapter 2. The work conducted in this chapter highlights the use of the CF Data Registry which contains cost banding data is further presented in Section 4.18.2.

This chapter will describe the data, termed ‘Registry Data’ or ‘CF Registry Data’ briefly as the data used in this thesis comes from the UK Cystic Fibrosis Trust Registry. This will be followed by a summary of methods used in conceptualising a De Novo health economic modelling structure for the evaluation of CF interventions. This chapter will cover the methods used in generating model variables from the Registry Data. This will include key assumptions made in relation to the patient population, data cleaning, and variable selection and creation. This will be followed by a description of the statistical methods used to create the data inputs for the health economic modelling of CF interventions. The chapter will conclude with the variables required for the exemplar evaluation of the intervention that will be used to test and validate the De Novo model, namely Orkambi®. The aim of this chapter is to:

1) Give a description of the UK CF Data Registry
2) Give a description of the methods used in the conceptualisation of a De Novo model structure for the health economic modelling of CF interventions.
3) Give a description of the methods used to clean the data and any additional assumption made in this process.
4) Present the statistical methods which were evaluated and subsequently used to generate inputs for the health economic modelling of CF interventions.

4.2 Access to the CF Data Registry

An application to access the Registry Data from its inception to 2016 was submitted to Elaine Gunn (U.K. CF Registry Clinical Data Manager) on July 31st, 2017 and was granted on the 11th September 2017 (NHS research ethics approval – East of England Cambridge East REC Ref: 07/Q0104/2 UK Cystic Fibrosis Registry). Access to Registry

data were obtained through a remote server at the Royal Brompton Hospital (RBH) with a RBH visitor login. The programme called RStudio [169] was used to undertake all data cleaning, preparing new variables and descriptive analysis of the Registry Data. The Registry Data has individual patient data (IPD) from 1996-2016.

4.3 History and overview of the Registry

The U.K. Cystic Fibrosis (CF) Data Registry is a national centralised database which securely holds information for those who have CF and have given their consent for data collection for a range of variables [159]. Established in 1995, the Registry was initially a small dataset of paediatric individuals. In 2005, the UK Cystic Fibrosis Trust began to utilise a web-based portal for electronic patient data collection and now collect longitudinal data from individuals with CF across the United Kingdom (U.K.), with a more than 12,000 individuals currently present in the dataset (2019) which constitutes more than 90% of those with CF in the U.K, further detail is provided in Section 4.4.3. The UK Cystic Fibrosis Registry now represents the largest and most complete data collection in Europe for CF [159]. All individuals with CF in the U.K. are treated at any one of 33 specialist centres, which form further network clinics which number into the 100s. During adolescence (16-18 years old) CF individuals transfer to one of 27 adult specialist centres. Consent for data collection, depending on the age of the CF individual is given by their parent/guardian or themselves [159].

The Cystic Fibrosis Trust Registry is a combination of administrative and clinical data, as a result a powerful resource which can and has been utilised in CF specific research [50, 102, 170-175]. Sister registries, which collect similar data to the CF Trust Registry exist in other countries which also have been used in many avenues of research from epidemiology [176], survival analysis [177] to health economics [81, 107].

4.3.1 Data collected

A standardised web-based system is utilised by all CF centres to collect data from CF individuals. Data collection covers demographics, hospital resource utilisation, treatments, diagnostic tests, nutrition, social deprivation and mortality. Further information about these variables are available from the CF Registry Portal and CF Trust Registry webpage [178]. Data in the Registry is collected in two distinct ways; by annual review and using an encounter-based approach. The annual review comprises regular reviews on a yearly basis at one of the U.K. specialist centres, whereas the encounter-based approach comprises visits which are in addition to those conducted in that same year at annual review. Although data are collected by either of these approaches, I will only discuss and later use annual review data. This is due to annual review data being systematically collected across the CF centres [159].

4.3.2 Coverage

Between 1996 and 2016 there were 12,463 individuals covered in the UK CF Data Registry. Data coverage, defined as the number of complete entries for those who are registered in a particular year, has been above 90% since 2013 [179]. In total there are more than 120,000 annual review entries in the Registry Data.

4.3.3 Data Quality

Data quality can be assessed by accuracy and completeness. The completeness of the data is represented by how well the data actually represents the condition specific population and how comprehensive such data is. Accuracy refers to validity and reliability [180], how valid the data entered and reliable the process of data entry is [180]. The data quality of the Registry is maintained in a number of ways which include: (1) availability of user guides and training videos for accurate data entry; (2) dashboard alerts for data

completeness and information on key clinical variables/indicators and (3) validation checks conducted by software which ensures meaningful values are entered, for example, clinical indicators and dates [159]. The completeness of the Registry is reflected in the CF Trust annual report, which showed that the Registry covered more than 90% of the CF population in the UK for more than 5 years [178].

4.3.4 Health Care Resource use data

Alongside a range of clinical variables, the UK CF Data Registry also collects data around the use of IV antibiotics (Abx) or oral Abx, whether taken at home or hospital and the number of days spent in hospital. This data is used to define the cost banding group the patient is categorised into. Costing banding categories and the banding matrix is further described later in this chapter, section 4.17.2. Additional data around lung transplant and mortality are also collected in the UK CF Data Registry.

4.3.5 Strengths and weaknesses of Registry

The CF Trust Registry allows many aspects of patient treatment to be monitored for improvement in health policy, NHS reimbursement decisions, drug safety reporting to the European Medicines Agency (EMA), drug efficacy and has the potential to allow Registry based clinical trials to be conducted [181]. The high level of patient coverage includes almost all CF patients nationally (>90%). This coupled with high data accuracy enables the UK CF Trust Registry to be utilised in statistical analyses such as diagnostic and prognostic modelling. Weaknesses of the Registry Data include only having, in majority, annual review-based data.

Survival estimation from the Data Registry cohort is also potentially subject to survival bias. This was also highlighted in a NICE technology appraisal [10]. Individuals in the UK CF Data Registry entered the Registry at different time points and would have a range of

ages at Registry entry. This means that individuals in the Registry who are currently older were not receiving treatments which have resulted in big changes in survival for those of a similar age who are now receiving treatment. Therefore, those who are older in the UK CF Data Registry are not representative of mortality or survival in the current treatment climate and may result in some bias. This limits the ability of the data to be utilised to predict survival. Although studies have attempted to this into account [50], this remains a challenge as the availability of newer more effective treatments as time has moved on will impact survival in newer cohorts [159].

4.4 Decision analytical modelling

The role of decision analytical modelling is to bring together a range of evidence and focusing this evidence upon a particular decision problem to aid decision making at a particular point in time and location under uncertainty [83]. The modelling conducted as part of any economic evaluation, is undertaken to fulfil five key aspects, 1) structure, 2) evidence, 3) evaluation, 4) uncertainty and 5) future research. The first two aspects of economic evaluations have been covered in this chapter, structure (Section 4.4.1.1-4.9) and evidence (Section 4.10 onwards). The remaining three, evaluation, uncertainty and future research will be covered in Chapters 6 and 7.

4.4.1.1 Structure

An important element in decision modelling is decision of how the model will be structured. This aspect of the model will be developed and discussed in Sections 4.5 to 4.11 of this chapter. As will be seen in later portions of this chapter, it was decided that due to the nature of existing models and the conventional use of FEV_1 categories in CF, that continuous FEV_1 data would be categorised into 6 respective health states, Mild, Mild IV, Moderate, Moderate IV, Severe and Severe IV (not including mortality, Figure 11 Section

4.10). Due to the nature of the above assumptions and application of the taxonomy of model structures [121, 182], this ultimately defined the type of model that would be used for this thesis, non-homogenous Markovian model with semi Markovian processes. The methods for creating the exemplar cost-effectiveness model are further elaborated on in Section 5.8 and 6.4 in Chapters 5 and 6 respectively.

4.5 Model conceptualisation

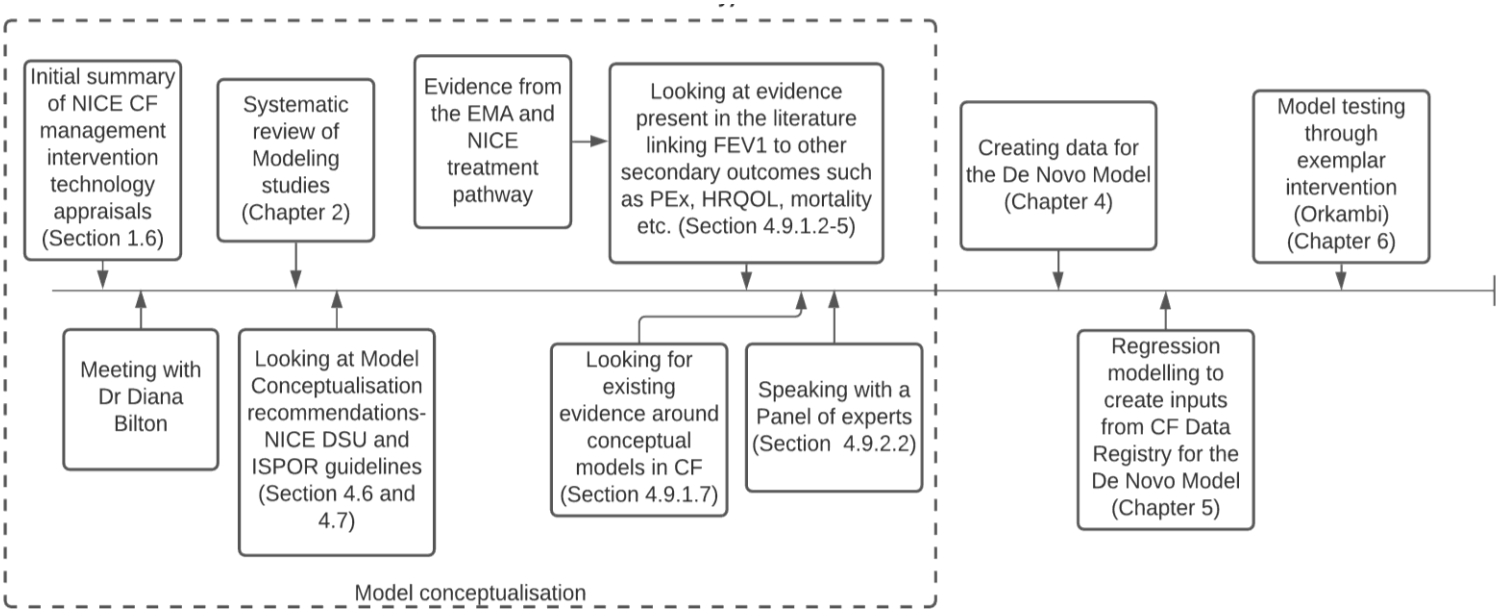
The conceptual model will inform and eventually transform into the De Novo model for the health economic analysis of CF interventions. However, prior to developing a conceptual model it is important to identify that when modelling is referred to herein, it does not include regression models which explain or predict the relationship between inputs and outcomes or infection disease models which look at the epidemiology of infectious diseases. The conceptual model refers to models which are used to simulate the natural process of a disease, in CF for this thesis, and the impact of interventions on this natural disease process and its subsequent impact on both the primary endpoints, incremental costs; outcomes and subsequently the cost-effectiveness.

Figure 4 below presents the model conceptualisation process. It highlights the different levels of evidence used in this chapter to create the final De Novo Model. This includes, an initial meeting with a CF expert (Section 4.9.1.8); the systematic review of health economic models in CF for management interventions; looking at NICE Decision Support Unit (DSU) and ISPOR guidelines around model conceptualisation (Section 4.6); looking at evidence from the literature linking $FEV_{1,}$ the primary outcome measure to other important variables/outcomes in CF (including evidence from the EMA and NICE treatment guidelines (NG78) (Covered in detail in Chapter 1 and Section 4.8.1.2-6); looking for existing conceptual models in CF in the literature through a systematic review

(Section 4.9.1.7) and lastly, discussion with a panel of clinical experts in CF around important health events and proposed model structure before coming to the De Novo model.

Later portions of Figure 4 look at creating data which could populate the De Novo model (Chapter 4 and 5), including health state transition and cost data. Finally, the far-right end of Figure 4 refers to Chapters 6, looking at validating the model (internal and external validity) using an exemplar intervention, Orkambi®.

Figure 4: Model conceptualisation process map (including creation of data for the model and validation of the model (internal and external validity)



4.6 Recommendations in the literature

Prior to creating the model, it was important to define what a conceptual model is and later understand if there were any guidelines on how to do this.

Conceptual modelling is defined as;…"*the abstraction and representation of complex phenomena of interest in some readily expressible form, such that individual stakeholders' understanding of the parts of the actual system, and the mathematical*

representation of that system, may be shared, questioned, tested and ultimately agreed."…[183] page 19.

A conceptual model (CM) can be used to understand disease attributes that lead to disease progression in any condition. It is the crux which allows evidence to underpin a De Novo health economic model. It allows relationships between disease attributes, disease progression and health outcomes to be illustrated, ultimately to understand how some key disease attributes/events can impact the cost-effectiveness of healthcare interventions [184]. Most importantly a CM can help identify relationships that exist between an intervention and a primary outcome which in turn may affect other aspects of the disease in an indirect way which were observed in the literature or clinical trials.

In order to develop a health economic model for CF I first understood the practices which are recommended in the literature. I refer initially to the International Society for Pharmacoeconomics and Outcomes Research (ISPOR) guidelines on conceptualising a model [155]. I move on to looking at other guidance documents; NICE decision support unit (DSU) technical support document 13 [183] and Conceptual modelling (CM) for health economic model development [185]. These informed the essence of my understanding and underlying enquiries in order to develop an implementable De Novo model for CF. Evidence as to what model parameters should be included in a De Novo health economic model also needed to be evaluated which will be covered further in a later portion of this chapter and in Chapter 5.

It is important to note here that the Tappenden et al [185] adapted their discussion paper from the NICE DSU document [183]. As a result, only the NICE DSU discussion paper is used to avoid duplication.

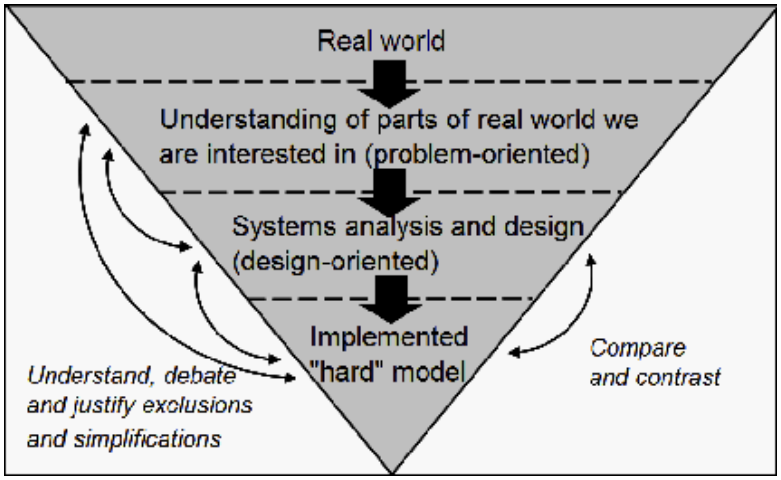
4.6.1 NICE Decision Support Unit (DSU) Model Conceptualisation guidelines

The NICE DSU document explains in considerable detail the process of gathering evidence to inform alternative model structures [183] . The process itself is described as complex and iterative and can be broken into digestible decisions; 1) what should be included in the model? 2) what should be excluded? And 3) how the aspects of the model that are included are conceptualised and mathematically included in a health economic model [183]?

The first aspect of conceptualisation is to determine what is relevant and the NICE DSU document states that such a process should not be dependent on a single person, but rather open to discussion between modellers, decision makers, healthcare professionals and other stakeholders to whom the decision problem is of importance and relevance [183]. This later feeds into the reasons why an initial meeting was held with an expert which was subsequently followed by a discussion with a group of experts. Failure to do so would have introduced bias into the model and would result in a model that is contextually not reflective of the disease or of treatment [183]. A lack of model conceptualisation would lead to lack of model credibility and validity.

A conceptual model can be used to fulfil a number of roles but is classified into two groups 1) problem-orientated and 2) design-orientated [183]. Figure 5 from Kaltenthaler et al [183] shows the process from real world, conceptualisation to the final model design.

Figure 5: Model conceptualisation process [183]



4.6.1.1 Problem orientated models

The problem orientated model looks at primarily seeking input from experts in the disease to determine what should be included and is not governed by what data is available [183]. The aim of this model is to encourage communication and discussion between those who are involved in the informing, building and using the end product, the model [183]. The main focus of this model is the relevance of the disease process and the clinical pathways the patients follow [183].

4.6.1.1.1 Practical model conceptualisation

The problem-orientated conceptual model can be further divided into a 1) Disease process model or 2) Service pathway model [183].

4.6.1.1.1.1 Disease process model

The focus of this type of model is the on relevant disease events and processes and not based on treatments received [183]. As such the model illustrates the disease process. The list of considerations in Table 9 below, adapted from Kaltenthaler et al [183] are useful when developing a disease process model. For those interested in a more in-depth description, please refer to Kaltenthaler et al [183].

Table 9: Disease process model conceptualisation

Consideration/Issue	comments
Inclusion/exclusion of disease related events	Does the conceptual model include all clinically relevant disease events? What metric is the most appropriate to measure progress of disease? Are competing interest considered? E.g. death
Impact of disease on HRQOL or other outcomes	Is there a relationship between disease related events and HRQOL?
Representation of different-risk subgroups	Is the disease process relevant to all patients or a single group or subgroup?
Impact of technologies on the conceptualised disease process	Have all relevant treatments which can be evaluated been identified? Can the model itself account for the impact of technologies used for the treatment of the condition appropriately?

4.6.1.1.1.2 Service pathway model

The focus of this type of model is the treatments received based on what clinical experts or what is known about the disease itself [183]. As such the model illustrates the treatment pathway. For those interested in a more in-depth description, please refer to Kaltenthaler et al [183].

4.6.1.2 Design orientated models

The design orientated model primarily looks, at different potentially acceptable and feasible model designs [183], to identify the evidence that would be required and then have a series of model designs from the beginning to end for comparison and justification of against the final model design [183]. Design orientated models set out clear boundaries around the modelling of pathways and the level of depth contained within the model.

The objective of the design orientated model is defined by the problem-oriented model, but then the design orientated model takes and adds to this step by defining what is feasible based on data availability and available resources (time, expertise etc) for the development of the model itself [183].

Table 10 presents the considerations for the Design orientated model. For those interested in a more in-depth description, please refer to Kaltenthaler et al [183].

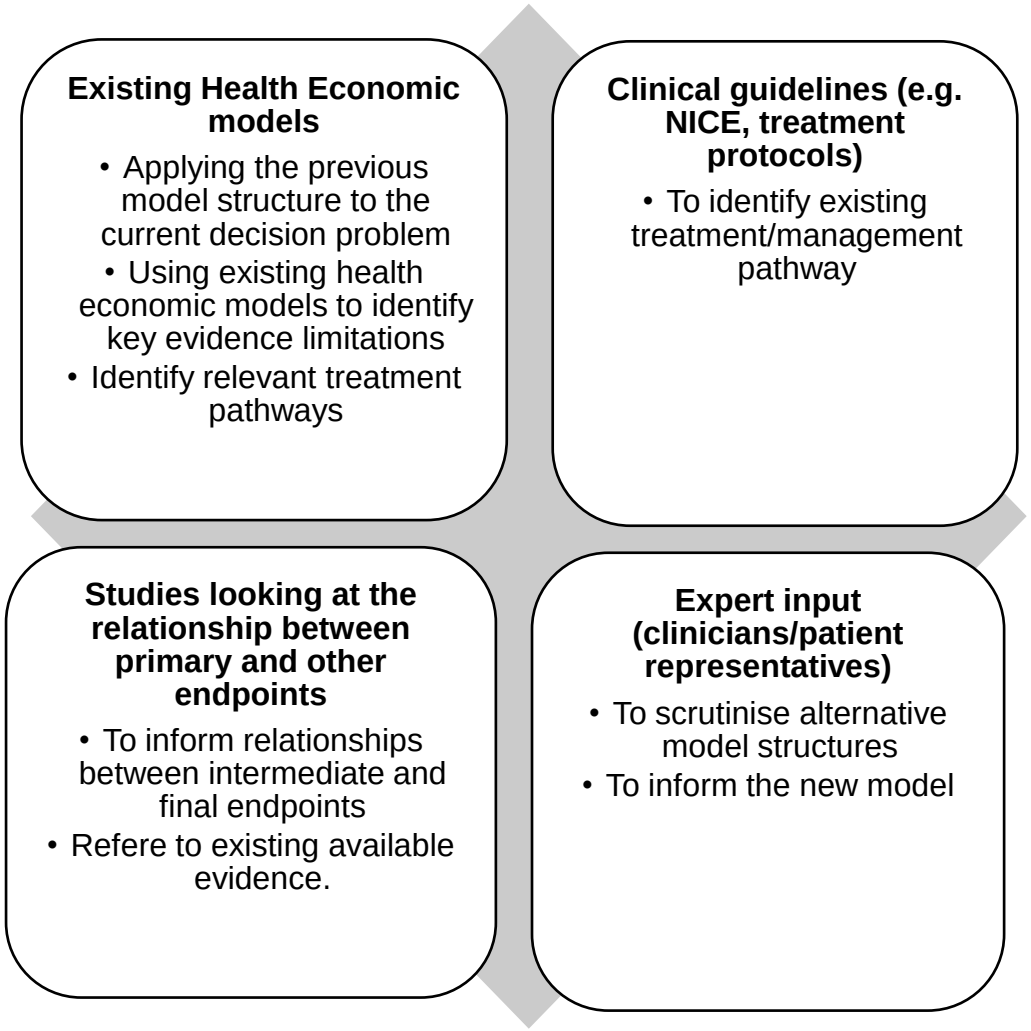
Table 10: Design orientated model conceptualisation

Consideration	comments
Anticipated evidence requirements	What clinical evidence is available to simulate the impact of the new intervention? Is comparison arm most appropriate and does it include all relevant treatments? What other data is required to populate the model? e.g. survival
Modelling clinical outcomes	What outcomes are of interest to the decision maker?

	How will evidence be extrapolated? How will impact of treatment be simulated? How will treatment influence costs and outcomes?
Modelling approach	What is the most appropriate modelling approach? E.g. state transition or patient level simulation? Is the proposed modelling approach feasible given the available resources?
Adherence to economic reference case	Will the proposed model meet the reference case e.g. NICE reference case [86]
Simplifications and abstractions	Has anything been omitted from the model and is this appropriate? Have any aspects of the disease been excluded? How do the problem and design orientated models differ and are these differences appropriate?

In summary, when conceptualising a model, the NICE DSU states that either a problem or design orientated approach may be taken. A list of consideration for either approach have been highlighted above. The NICE DSU further goes on to state that there are a number of evidence sources which can be utilised in support of developing such a conceptual model and are presented in Figure 6. These sources of evidence will be drawn on for the model conceptualisation process in this chapter. Previous work from Chapter 2, the review of models is also a key piece of evidence which will be utilised in the development of the De Novo Model.

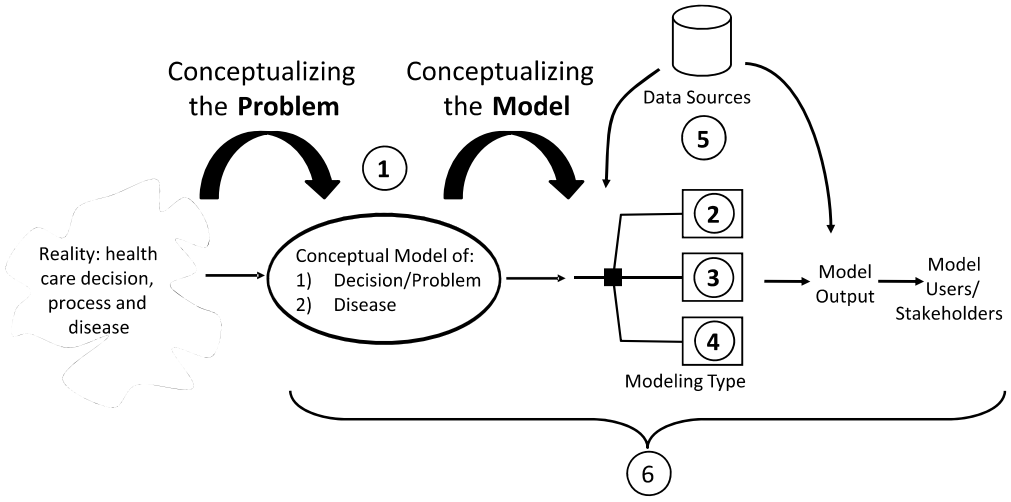
Figure 6: Model conceptualisation: sources of evidence



4.6.2 ISPOR Model Conceptualisation guidelines

When starting the conceptualisation process, Roberts et al [155] defined the process in two parts, 1) Problem Conceptualisation and 2) Model Conceptualisation. In reference to Figure 7, these steps are represented by the number 1.

Figure 7: Model Conceptualisation process, taken from Roberts et al [155].



4.6.2.1 Problem Conceptualisation

The Problem Conceptualisation, in summary, looks at the statement of the problem and the objectives to be achieved from addressing this problem [155]. These could include the development of a De Novo model to 1) guide clinical practice, 2) Informing the reimbursement or funding of an intervention, 3) Optimising use of scarce resources and lastly, 4) Guide public health practice [155]. The problem could fit in any one or multiple categories listed above. Table 11 below defines the objectives, scope and context of the model being developed in this thesis through use of the guidelines presented in the ISPOR guidelines [155]. Table 11 presents a range of recommended best practices by Roberts el al [155] and addresses how they will be achieved in this chapter, (best practice II-1,2, 2a, 2b, 2c, 2d, 2e, 3, 3a, 3b).

Table 11: Defining the Objective, scope and policy context of a novel model.

Decision problem/decision objective	Advancing the Health Economic evidence available to inform economic models and decisions about appropriate care 1) To develop a De Novo model which incorporates significant health events which impact disease progression (Best practices II-1 [155]) a. Review existing health economic modelling practices 2) Use more reflective data sources as input parameters in a De Novo health economic model (Best practices II-3 [155]). a. Review of utility data 3) Employ clinical experts to understand clinical practice (Best practices II-1 [155])
Policy context	Advance the understanding of the health economic evaluation of CF interventions in the UK
Funding source	UK Cystic Fibrosis Trust
Disease	Cystic Fibrosis
Perspective	NHS only (does not include PSS; no such data available in CF Data Registry)
Target population	Cystic Fibrosis; high or low risk mutation groups using a closed approach (patients enter model only at the beginning) [155].
Health outcomes	QALYs and life years gained
Strategies/comparators	Best available care/Standard care (Best practices II-3a [155])
Resources/costs	Reduction in costs from changes in treatment use, reduction in costs from changes in disease progression
Time horizon	Remaining life-time if data is available to support this (Best practices II-3b [155])

4.6.2.2 Model Conceptualisation

The subsequent process of model conceptualisation focuses on the best practice guidelines II-6 to 7 presented by Roberts et al [155]. These involve an explicit conceptualisation process and the use of concept mapping and expert consultations, with the aim to ensure that the final model structure reflects current disease knowledge and how this process is modelled (Best practices II-6 [155]), [155]. It also focuses on the selection of model type which would be suitable to achieve the set objective. There are a number of modelling types that can be used, decision trees are useful for shorter time horizons, state transition models for longer time frames or when transition probabilities vary over time and the population can be considered homogenous in nature and discrete event simulation (DES) which is useful for evaluating outcomes at the individual level while taking into account interaction among individuals [155]. The type of model selected depends on the above characteristics. More detail achieved through DES does not necessarily mean greater accuracy [155], cohort models can achieve detail or accuracy through subgroups characteristics and analysis [155]. Further disadvantages of cohort models such as the lack of patient history can be addressed through the use of tunnel health states/semi-Markov processes [155]. Advantages of cohort models include being simple to; develop, debug, communicate, analyse, accommodate for parameter sensitivity analysis and easier for decision makers to understand [155]. However, the level of detail required for the model is a difficult decision to consider, lack of detail can result in a failure of the model to have any face validity whereas models that are complex will be more difficult to develop, debug, communicate, analyse and accommodate for parameter sensitivity analysis [155].

4.7 Using the Model Conceptualisation evidence from the literature

The modelling conceptualisation process has demonstrated some overlap in the guidelines above, particularly around discussion with stakeholders which include modellers, clinicians and other individuals that would know more about the disease, in this case CF. Further overlap exists around what is the best modelling approach and the evidence required for modelling the disease process itself and the outcomes that were of interest in this thesis.

The guidance presented by Roberts et al [155] was used to define the objective, scope and policy context of a novel model (Table 11). The evidence was also used to understand the advantage and disadvantages of various types of health economic model types available. It also helped form an understanding of what outcomes were considered important as well as the perspective taken.

The guidance presented by the NICE DSU [183] was used to understand what would be the best possible model for use in this chapter, presented as the initial model in Figure 10 (Section 4.8.2.1), using the problem orientated approach. This was followed by what was feasible based on discussion with experts, clinical criteria and data availability, presented as the De Novo Model, Figure 11 (Section 4.9), using the design orientated approach. Furthermore, subsequent to discussions a clear communication on the disease process and treatment available is also mentioned in detail (Section 4.8.1.6), NICE treatment pathway (Figure 9). Taking into consideration the treatment pathway, the ideal model, discussion with experts and data availability the NICE DSU guidelines were also used to support the model conceptualisation process.

Lastly, Figure 8 provides a good visual depiction of the types of evidence that could be utilised in the model conceptualisation process and was used to determine the different types of evidence that could be drawn on to develop a CM.

In this Chapter, due to the overlapping nature and the similarities in the different guidelines [155, 183]. I amalgamated these guidelines to reach the De Novo Model design.

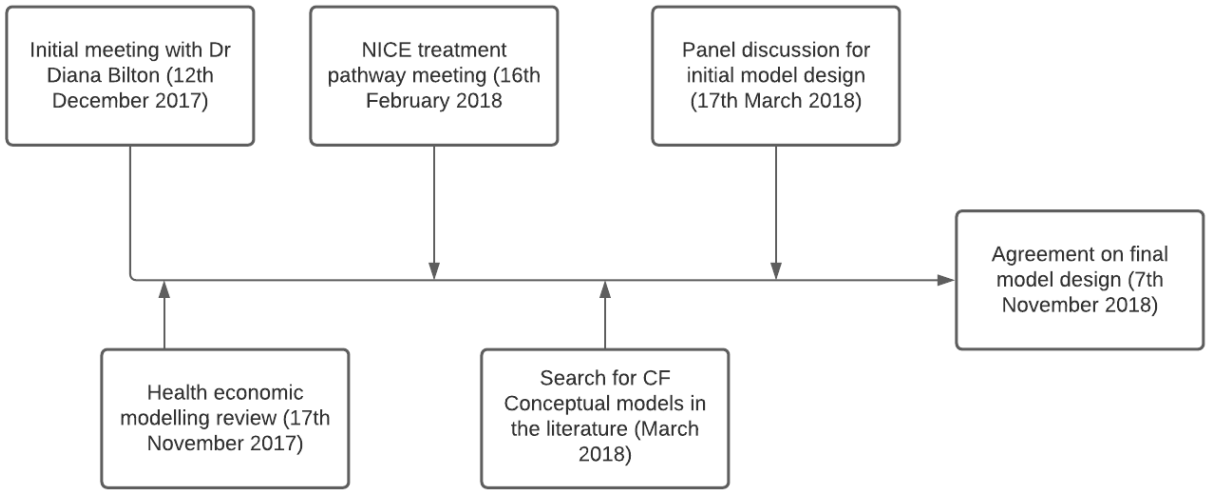
This process of conceptualisation will included looking at the existing evidence in the health economic modelling of CF management interventions, NICE guidance of CF treatment (NG78) [36], literature linking primary to other endpoints, systematic review of CMs and finally taking into account expert opinion (Figure 8), all which are described further in the sections that follow. The different sources of evidence are also discussed.

4.8 Model conceptualisation process taken for De Novo model

The below sections start with a description of evidence found from Chapter 2, review of CF models, followed by the importance of FEV_1 as a primary outcome measure for modelling disease progression (which is linked to Chapter 1, Section 1.3.5-8), evidence from NICE guidelines around CF treatment [36], review of existing health economics model conceptualisation literature in CF and discussion with experts (Epi-Net team). Subsequent to initial investigations, an initial model design was presented to a panel of experts as part of the conceptualisation process to understand whether changes in the model design was required. Result of this panel discussion are presented alongside the

final De Novo Model design in later sections. Figure 8 below shows the Model conceptualisation timeline.

Figure 8: Model Conceptualisation timeline



4.8.1 Gathering the evidence

In the model conceptualisation process, the primary endpoints currently used in CF health economic modelling are linked to disease progression and other additional factors that are associated with disease progression are also identified. In the following sections I look at the existing evidence which links primary endpoints to endpoints of interest to decision makers and health economics. This is followed by a review of the evidence in the literature which links such outcomes to disease progression in CF.

4.8.1.1 Previous health economic modelling in CF

In Chapter 2, a systematic review of health economics modelling used on CF interventions for the management of the condition was undertaken. The aim of the review was to evaluate CF health economic modelling as newer treatments in CF, such as Orkambi®, have effects on IV treatment, PEx and most importantly FEV_1. Among the primary findings, those around the model structure identified a lack of health states which

accounted for significant health events linked to disease progression, particularly PEx events. Some models accounted for such health events indirectly through inclusion of cost and their impact on outcomes, such as utilities. Other models did exist which incorporated PEx as a health state but failed to incorporate other health states such as lung transplantation and post lung transplantation. Other findings highlighted the need for better costing data such as data from Secure Anonymised Information Linkage (SAIL), Hospital Episode Statistics (HES) or the UK CF Data Registry.

For direction of future research, the review highlighted the need for the development of a single model which could be used to evaluate all CF interventions and one which incorporates health states such as PEx events, lung transplantation as well as post lung transplantation alongside mortality. Previous models failed to holistically include all significant health events as highlighted in Section 2.9.5 in Chapter 2.

In accordance with the recommendations in Figure 6 from the NICE DSU document, it recommends looking at existing evidence around model structure which could be applied to the current decision problem (Section 4.1.6.2). The model which followed the most appropriate model structure from the systematic review in Chapter 2 was identified. The criteria used to assess the model structure was, the evidence in the literature; how primary outcomes such as FEV_1 are linked to disease progression (which are further discussed below in Sections 4.8.1.2-6); as well as the quality of the study measured through the QHES instrument (Section 2.8) and the inclusion of evidence in their articles (in Chapter 2) around a model conceptualisation process [120]. The Tappenden et al [102] model reflected disease progression in terms of the health states except for inclusion of specific health state for PEx events. Additional health states such as post lung transplant and

death were also included. Although the model could not be applied to my current decision problem, it could be used as a consideration point for the conceptualisation of the De Novo model.

4.8.1.2 The importance of FEV_1

The importance of FEV_1 is clearly outlined in the introduction of this thesis in Chapter 1. The importance of this outcome measure is linked to its reproducible and repeatable nature [40] and to the strong association of low FEV_1 and increased mortality [40, 186, 187] and decrease in quality of life (QOL) [40]. FEV_1 is also very influential, clinically, in defining disease severity, for comparison between treatment nationally and globally and in regulatory approval of therapeutic CF interventions [41, 187] and has been used in all models reviewed in Chapter 2. The importance of FEV_1 is linked to model conceptualisation through the above-mentioned factors and including it as the primary measure of disease progression will allow the appropriate modelling of disease progression whilst taking into account the impact of disease progression on HRQOL (Chapter 3 and Section 4.9.1.5 below) and cost of care, of which cost is further discussed below in relation to PEx events. This reaffirms that the use of FEV_1 for the modelling need not be changed, but rather should be maintained as the primary outcome measure which determines disease progression.

4.8.1.3 FEV_1 linked to PEx

As FEV_1 is linked to long term survival in CF individuals, it is important to understand the impact of the frequency of PEx on overall pulmonary function, FEV_1 [56, 57]. As stated in Section 1.38 PEx events lead to a reduction in quality of life (QOL), higher costs, increased mortality, lower baseline FEV_1, faster decline in FEV_1, greater risk of lung transplant and increased clinical burden among patients [54, 56, 57].

In terms of cost of PEx events, only a single study exists which evaluated this [122]. The study split the cost of PEx into three treatment administration categories, PEx with intravenous treatment with antibiotics (IV-Abx)., PEx-Inpatient stay (IP) and PEx-Oral Abx (O), which respectively cost US $36,319, $45,361 and $3,265[3]. The study also categorised PEx by stage of pulmonary disease which cost US $30,066 to $119,862[4] for mild and severe FEV_1 respectively. Increase in cost of treatment were attributable to increases in PEx-IV in each FEV_1 severity state. The overall average cost for PEx events was US $37,025 per patient[5] [122].

4.8.1.4 Regulatory authority advice on outcomes in CF

The European Medicine Agency (EMA) have demonstrated that FEV_1 be recommended as a primary endpoint to measure disease progression [91]. The rate of decline in FEV_1 is correlated with survival and is the strongest clinical predictor of survival [91]. The justification of using such an outcome was that is it allows demonstrable change when assessing patients for disease status. However, the EMA also stressed that number of infections with bacteria and resultant pulmonary exacerbations are also important measurable outcomes [91]. A further initiative from the EMA has resulted in PEx being earmarked as important CF related events which should be included for collection in all CF patient registries across Europe [188].

[3] Cost year 2013

[4] Cost year 2013

[5] Cost year 2013

4.8.1.5 FEV1 and Quality of life

Further to the mention of impact of FEV_1 on HRQOL in Section 1.2.6 the systematic review conducted in Chapter 3 demonstrated the link of FEV_1 to QOL. Two studies evaluated FEV_1 state (mild, moderate or severe) and subsequent health utility [143, 146]. The evidence showed a clear link between FEV_1 severity and a decrease in health utility [143], although this was not always so clear in other studies [146].

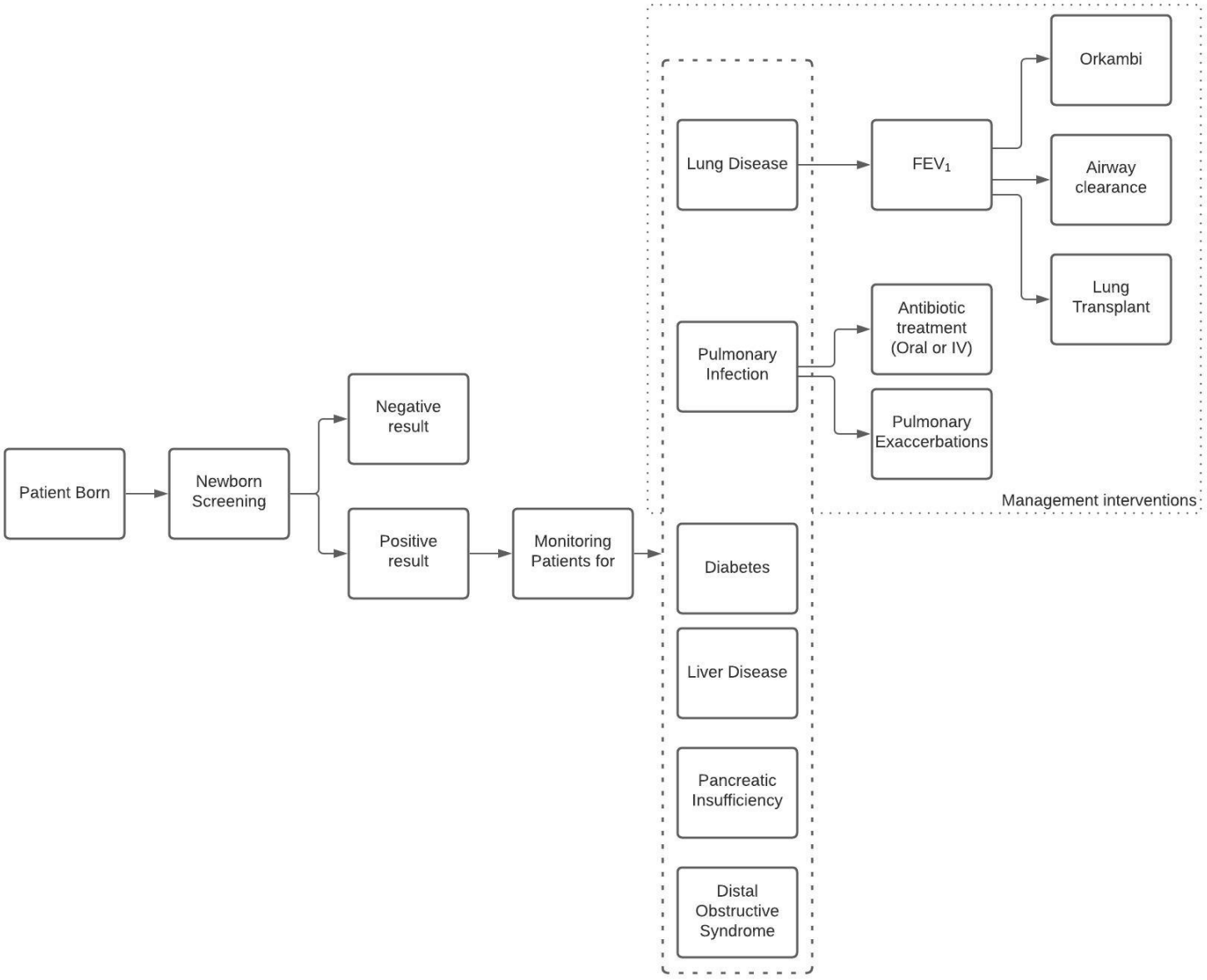
4.8.1.6 NICE treatment guidance for CF

Base on the NICE CF diagnosis and management document (NG78) [36] the treatment pathway for those with CF is shown in Figure 9. The NICE guidance document outlines how CF individuals can be treated for a range of complications from having been initially identified as positive for CF. There is lifelong monitoring of the individual and a range of complication have been highlighted such as liver disease and diabetes in addition to the impact of CF on FEV_1/lung function and the treatment of pulmonary infection with a range of antibiotics (Abx). Additional avenues for treating CF such as modulators and physiotherapy/lung clearance techniques have been identified. Lastly, lung transplant is also available as an intervention to improve the long-term survival of the CF individual. Subsequent to creating Figure 9 from the NG78 NICE guidance document [36], the treatment pathway was further validated through a meeting with clinical experts in CF (Dr Siobhan Carr and Dr Diana Bilton, 16th February 2018). A discussion was had in regard to the validity of the treatment pathway and both clinicians agreed with pathway. We also discussed that although CF individuals are monitored for a range conditions/symptom the primary aim of the model being developed was to look at lung disease and pulmonary infection. This is highlighted by the dotted box in Figure 9 (management interventions) and although only some arrows are shown to link to lung disease or pulmonary infection,

it is important to note that these areas in the dotted line for management interventions are intertwined and affect each other.

The focus of the existing health economic modelling of CF management interventions, as identified in Chapter 2, exists subsequent to screening. Here the CF individuals are evaluated in terms of disease progression through FEV_1. However only a few models take into account the impact of pulmonary infection and subsequent PEx events whilst all models use FEV_1 as the primary avenue to record improvement in disease from treatment (Chapter 2). Although pulmonary infections are often treated with oral Abx, PEx events as a result of such infections are treated with IV antibiotics which can take place either at home or at hospital. This further highlights the importance of FEV_1 and of PEx events.

Figure 9: NICE treatment pathway



4.8.1.7 Rapid review of literature for CM models

A part of developing an understanding of the how to develop a conceptual model for CF, a rapid review of the literature was conducted in order to identify any existing conceptual models for CF which could be used in the conceptualisation process or which could support the conceptualisation of the De Novo model.

As advised by the NICE DSU technical document, I searched two databases which are considered important sources, Medline and Embase [183].

Searches were performed in the two databases, limited to English language articles only from 2007 to March 2018. Date restrictions were applied to reflect the development in understanding of CF disease in the past decade. Due to the nature of disease understanding any literature older than 10 years would be unreflective. The search strategies were designed with one objective, 1) To Identify CMs.

The terms used to identify any existing CMs included: Conceptual Model, Model, Conceptual Framework and CF/Cystic Fibrosis and are based on an existing conceptualisation document by Tabberer et al [184] for Chronic Obstructive Pulmonary Disease (COPD). Results of the search did not identify any existing CMs for CF beyond the health economic models already identified in Chapter 2.

4.8.1.8 Speaking with a clinical expert

Subsequent to conducting the review of health economic models (Chapter 2), looking at the evidence in the literature linking outcomes to disease progression in CF and conducting the rapid review of CM further discussion was sought with a clinical expert in CF. Dr Diana Bilton (Honorary Clinical Senior Lecturer and Director of the Adult Cystic Fibrosis Service at Royal Brompton Hospital) was contacted and a meeting was held on 12th December 2017. The proposed relationships between the different variables discussed above in sections 4.9.1.2 to 4.9.1.3 were presented. Further discussion was had around PEx events and IV treatment data in the CF Data Registry. Dr Diana Bilton stated that markers for PEx events were receipt of IV treatment but severity of IV treatment is difficult to identify as there is no record of severity of PEx events. Only after

2016 would information in regard to PEx being linked to hospital admissions which would not be available in the data I would be sent which is further highlighted in Section 4.13 below. Additional co-morbidities such as CF related Diabetes (CFRD) and CF Liver Disease (CFLD) were also discussed for possible inclusion in the De Novo model to account for changes in long term survival of patients as a result of improve survival. Further discussion around inclusion of such co-morbidities is mentioned in Section 4.8.3.

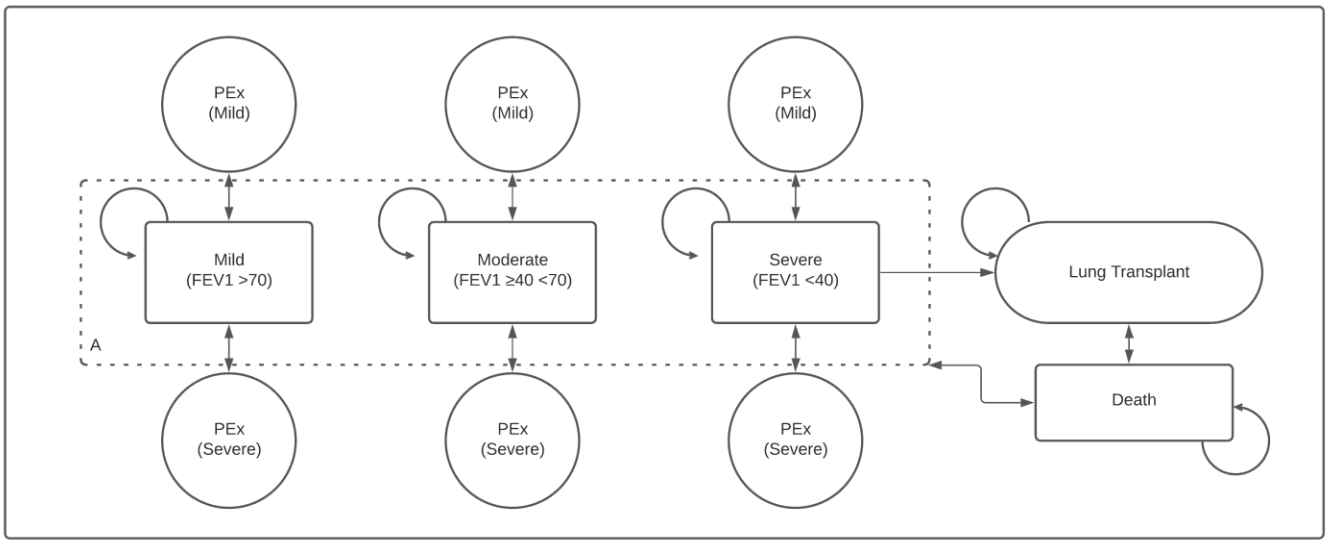
4.8.2 Conceptualised model structure

4.8.2.1 Initial model design

Subsequent to understanding the NICE treatment pathway, looking at existing CF health economic models [102] and looking for existing CM for and discussion with an expert, a novel model structure was proposed which included PEx as a health state for every FEV_1 category and also included two types of PEx, Mild and Severe. The model also included lung transplant and death health states, Figure 10. FEV_1 categories were designated as the following: >70 as Mild, ≥40 <70 as Moderate and <40 as Severe. These classifications were used in subsequent models.

Transition were allowed from any health state (box A) to death and lung transplant could only occur from the Severe health state. Any PEx events that occurred would result in a cohort spending a cycle in that health state followed by returning to their previous health state.

Figure 10: Initial planned CF model



4.8.2.2 Panel discussion

In order to determine the structure of the new health economic model, a panel discussion was held with other Epi-Net members (17th March 2018). This included clinicians (Dr Siobhan Carr and Dr Diana Bilton), statisticians (Professor David Taylor Robinson, Miss Amy MacDougall, Dr Daniela Schlueter and Professor Ruth Keogh) and health economists (Professor Jennifer Whitty and Mr David Turner) who have expertise in, understanding disease progression in CF, the U.K. CF Data Registry and health economic modelling. The aim of the panel discussion was to convene and discuss whether the conceptualised model, Figure 10, met the criteria for disease progression in CF and data were available to populate the model. The points raised during this panel discussion shaped the final structure of the De Novo model.

4.8.3 Findings of Panel discussion

The results of the discussion were that IV treatment was considered to be a more appropriate health state rather than PEx event. This was primarily due to the lack of

definitive guidelines on the definition of what constitutes an PEx event. It was brought to my attention that EuroCareCF Working Group highlighted the difference in the definition of an PEx event in a number of trials [59] and that the Fuch's criteria was best applied to clinical trials [59]. Additionally, the criteria's being applied to signify an PEx have not been prospectively validated [189]. As a result, this criteria for PEx cannot be applied on the UK Registry Data. More recently, the poor application of criteria for PEx in Registry Data has been highlighted, where Registry definitions rather than clinical definitions were applied to such events in a longitudinal analysis of a CF intervention [190].

The common proxy of 14 days of IV-day treatment has been applied in the past in health economic models to signify an PEx event [106]. However, the data on the severity of an PEx event in the CF Registry Data is not recorded. Furthermore, evidence suggests that the duration of PEx event treatment had no particular consistent pattern across countries like United States (U.S.) and Canada, with some lasting 22-50 days [191] or 18-29 days [122] depending on whether they were managed in hospital or community [191] and what type of treatment was required, IV or oral Abx [122]. Duration of treatment has been recorded to be as low as 1 day [192]. Furthermore, when looking at the UK CF Data Registry report for 2016, the results show that over all age groups the number of IV days received were between 14- 45 but could also vary by age groups. Similarly, there was a 45 to 55 % split in the Registry Data between those who did and did not receive IV treatment in that year. Due to these reasons IV days was considered to be a proxy for PEx rather than vice versa. No health states were included which signified the number of IV days but only to identify whether an individual received IV treatment in any given year. This in turn would reduce the complexity of the model structure. The number of IV days

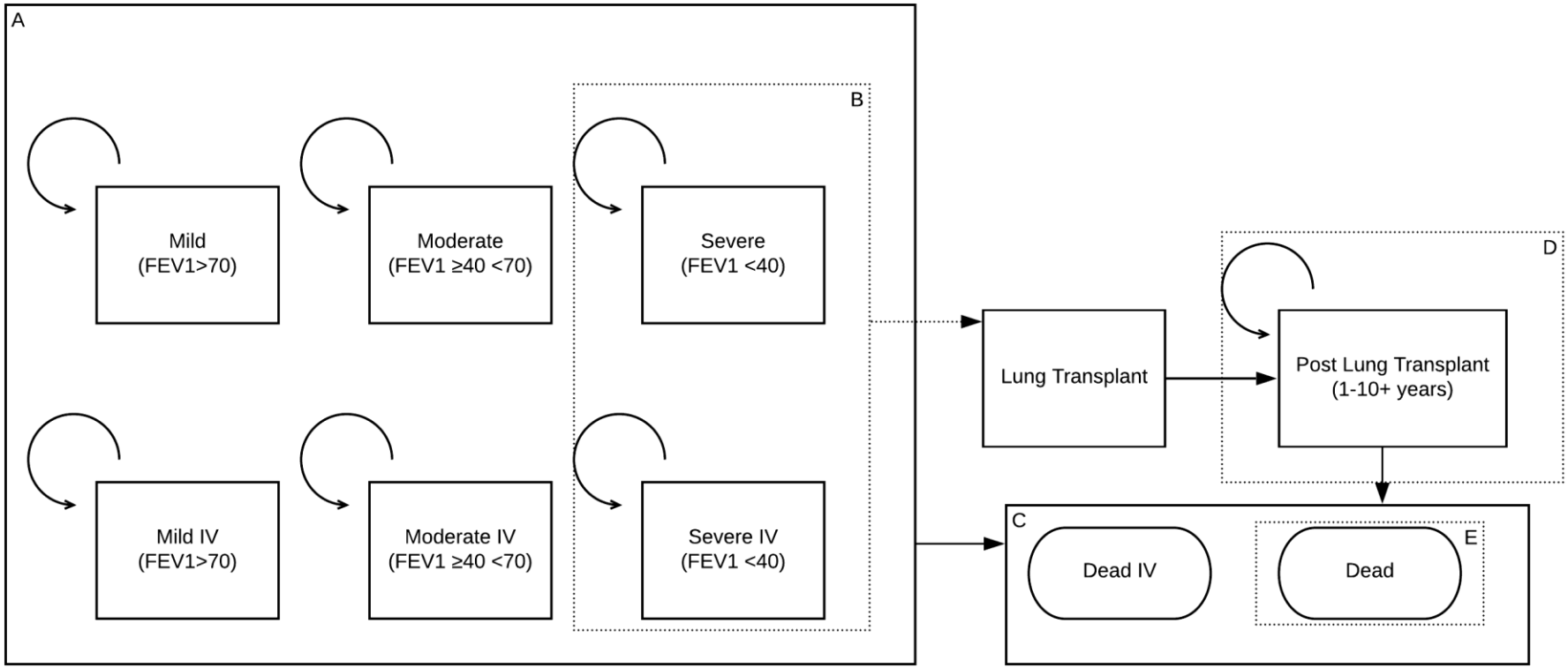
is included in the cost banding matrix (section 4.25) alongside hospital days and additional standard care provided to the CF individual in that year such as physiotherapy and clinical visits to the hospital.

4.9 De Novo model structure

The De Novo model diagram presented in Figure 11 shows a total of 10 health states. All those in box A can transition back and forth into any health state in that box or stay in their respective health states. Similarly, all those in box A can transitions into box C, i.e. CF individuals can die from any health state and can die either subsequent to receiving IV treatment or not. Only those in box B, in either the Severe or Severe IV health state can transition into the lung transplant health state. Subsequent to receiving a transplant only those in box D, surviving from 1 to 10+ years Post Transplant remain in box D or enter box E, Dead subsequent to not receiving any IV treatment. Two dead states were created out of interest if the treatment would lead to difference in outcomes in terms of the number of deaths with or without IV treatment in any given year.

This final model structure was presented at a subsequent Epi-Net group meeting and all those on the panel agreed that they were in agreement with this Final De Novo model design (7th November 2018).

Figure 11: De Novo Model Structure



4.10 Model structural assumptions

The model structure presented in Figure 11 is based on a number of assumptions, outlined in Table 12.

Table 12: Structural assumptions

Patients in any FEV_1 health state IV or No IV, can get either better or worse
Only those in the Severe health state can receive a transplant
Subsequent to having a lung transplant, patients can only progress into the post-transplant health state or die
Every health state has an assigned HRQOL and IV treatment results in a permanent reduction in HRQOL for that cycle

4.11 Preparing the data for De Novo Model

The model was populated largely through the use of individual patient data (IPD) from the UK CF Data Registry, literature and expert opinion. Data from a total of 12,494 CF patients, from 1996 to 2016, were evaluated for use in the De Novo model. Patients could have multiple data points, corresponding to different annual reviews. An initial dataset was created using the master data provided by the UK CF Data Registry. Table 13 below lists included variables and their description. A total of 126,574 observation data entry points across 16 selected variables existed at the beginning of the analysis. The data initially available from the Registry Data were also used to create other variables which were used to create the data inputs for the De Novo model, I will be describing these in more detail later, in Section 4.18.1.1-4 of this chapter.

Table 13: Variables from master dataset

Variable	Description
Patient ID	Unique identifier for a patient
Created Time	This gives the date of when the annual review entry was made.
Annual Year of Review	Year the patient review took place. This helps us calculate the cut-off point of the longitudinal data analysis is required
Age	Patients age at time of review.
Date of birth	-
Sex	Male or Female
Genotyped and Mutation class	Was the patient genotyped? Yes or No mutation class if Yes
FEV_1	Measured yearly at annual review
Has the patient died? / Death date	Did the patient die? Date if Yes
IV treatment in hospital /at home	Whether patient received IV treatment in that year or not (0 or 1)

4.12 Data descriptive

4.12.1 Key Variables

4.12.1.1 FEV_1

In the introduction to this thesis, how FEV_1 is calculated and what it measures was described in more detail (Section 1.2.5). As also explained in that section, FEV_1 is the

primary outcome measure which is used to measure disease progression in CF. In the UK CF Data Registry FEV_1 is taken at every annual review in order to assess the health of the individual. For the proposed De Novo model, FEV_1 was used as the main measure of disease progression from the different health states. FEV_1 was categorised in to three different states, Mild, Moderate and Severe which correspond to FEV_1 >70, ≥40 ≤70 and <40 respectively.

Figure 12 below shows the FEV_1 values from 1996-2016 for those in the CF Registry Data by age and sex. The violin plot demonstrates the distribution of the FEV_1 within the two, male and female, populations. We can see that the two sexes are quite similar, with small differences in the FEV_1 above and below around 23 to 30 years old. The plot has been truncated at the lower end of the x-axis. This shows that a majority of the missing data removed when creating this plot is located in those age groups. This further reflects that those under the age of 6 years old do not provide FEV_1 as such individuals find it difficult to do the manoeuvres to provide FEV_1 values [39].

Figure 12: FEV1 by Age and sex

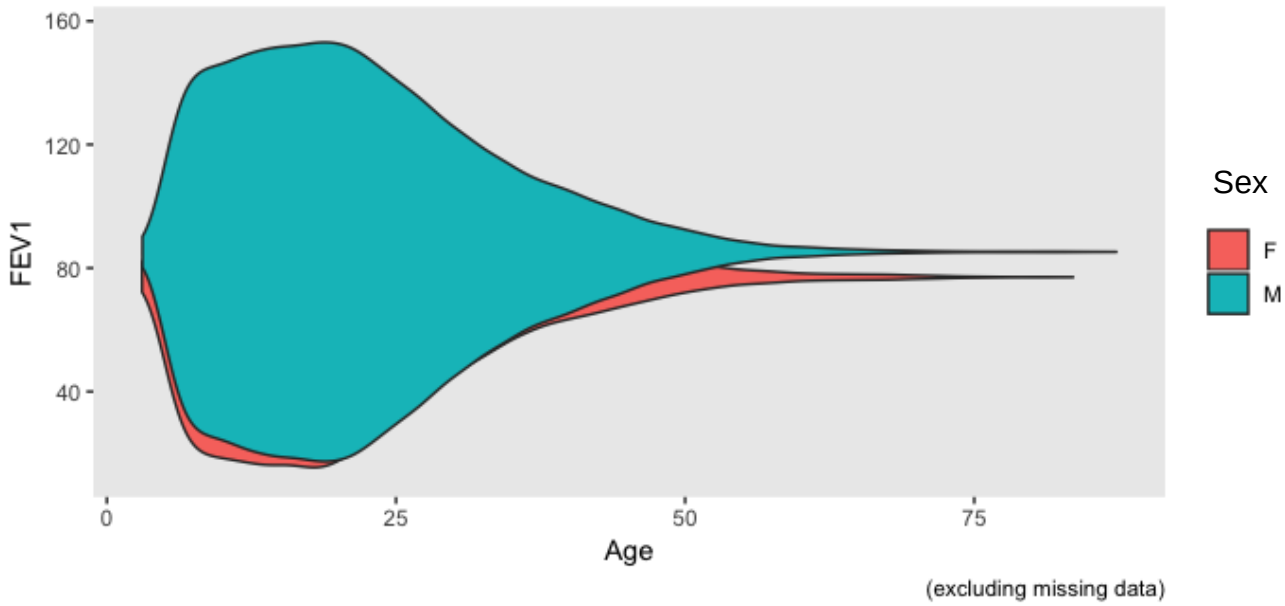


Table 14 shows the FEV_1 by sex in the registry between 1996-2016. We can see again that males have a better FEV_1 compared to females. This follows the observed differences between males and females in CF in general. In the De Novo Model, FEV_1 is not used directly, rather FEV_1 is used to define related health states as explained previously (Section 4.10).

Table 14: FEV_1 by sex (1996-2016) median (SD)

Sex	FEV_1
Female	72 (24)
Male	73 (25)

4.12.1.2 IV days

In the CF Data Registry, data is collected on where the IV treatment, when provided, is taken. It is important to note here that whether an individual receives IV treatment at home or at the hospital is not dependent on disease severity. Evaluation of the variable showed

that the mean number of IV days received at home was 9, whereas the number of IV days received at hospital were 10. However, further evaluation of the data showed a number of outliers in both variables which showed unrealistic number of IV days. These included -346 and on four occasions more than 365 days of IV days at home. For IV days at hospital, these included 36,000 days. As a result, the mean values presented are likely to be skewed from the errors in data entry in the data.

The De Novo model structure has health states which identify whether the individuals in the cohort receive IV treatment in the last cycle. This is possible for any health state; Mild, Moderate and Severe.

4.12.1.3 Mortality

Mortality estimates from the model were also taken from the CF Data Registry. Although there are three variables that identify mortality in the dataset, date of death was used as the primary measure by all Epi-Net team members utilising such data. As a result, the same variable was used in my data analysis.

Out of the total population (12,494) in the dataset, 1,895 (15%) died between the years 1996-2016. Of these, 52% were females and 48% males. Although this mortality is not age adjusted, this signifies that there may be a difference in survival between either sex. This is further supported by reports from the UK CF Data Registry and recent evaluation of the CF Data Registry for survival bias between males and females [11, 193].

4.13 Patient characteristics

4.13.1 Sex

In terms of sex, there were more males (6,546) in the dataset compared to females (5,917), 53% and 47% respectively. The De Novo model will include two separate cohorts for either sex. This approach was taken as there was already some indication of difference

in long-term outcomes between males and females from the UK CF Data Registry [11, 193]. This could potentially highlight difference in treatment effect in the two groups, male and female.

4.13.2 Genotype

In the introduction (section 1.2.1), the different genotypes and their classifications were identified. Variables for genotype selected from the UK CF Data Registry included: whether the individual had been genotyped, what class their genotype was (high, low or none assigned (Section 1.2.1) and in the case the genotype mutation was F508del, whether it was homozygous, heterozygous or other. For the data required in this thesis, I selected only those who had been genotyped. Also, to allow future sub-group analysis of the data, genotype class was also used. Only 84% of those in the UK CF Data Registry were classified as high or low, the remainder were missing (3%) and not assigned (13%). Further looking at genotype, the sex distribution of those who had been assessed for genotype classification was determined. A total of 99% of the female CF Data Registry population had been assessed, compared to 98% of the males.

Looking at the mean FEV_1 value by genotype class showed that those in the high compared to low genotype class had worse values, Table 15. Those whose genotype data were missing had the worst FEV_1 value overall. This was closely followed by those who were in the High-risk group, which includes those with the F508Del mutation.

Table 15: Genotype class by mean (SD) FEV_1

Genotype	Mean FEV_1
High	69 (24)
Low	75 (23)
Missing	65 (28)
None assigned	71 (25)

Similarly, the average number of IV treatment days received by genotype class showed those in the missing genotype class received, on average, more IV treatment days, closely follow by the higher risk genotype group, Table 16.

Table 16: Mean number of IV days (home and hospital) by Genotype class

Genotype	Mean IV days
High	10
Low	4
Missing	11
None assigned	9

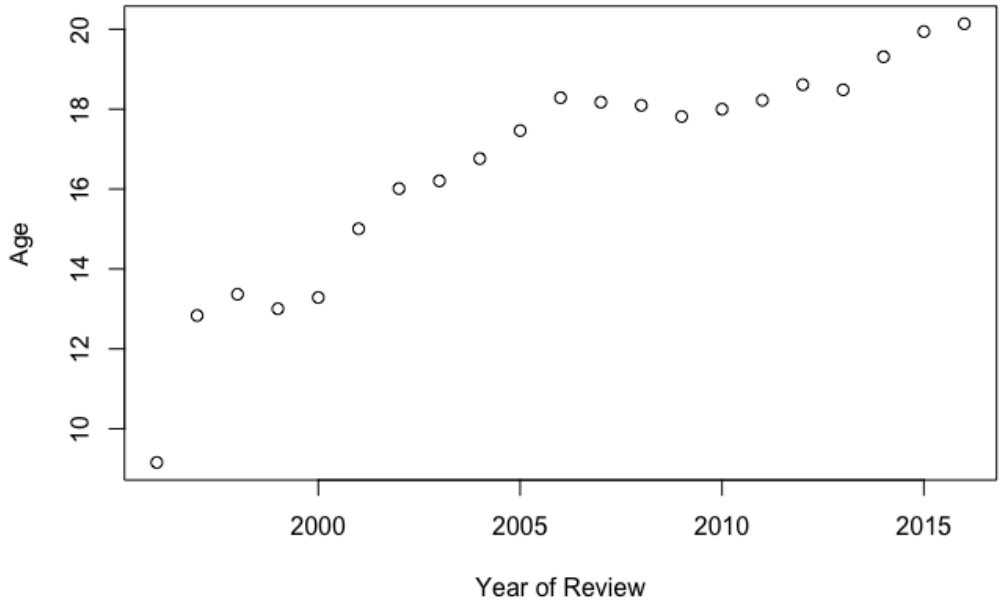
Of those individuals in the High genotype class, 52% were F508del Homozygous and 21% Heterozygous. Knowing this is particularly important as modulator CF interventions available for treatment are only given to those individuals who are Homozygous while others are also available to Heterozygous patients.

4.13.3 Age

The mean age of the cohort in the dataset was 19 years, maximum was 87 and the youngest individual in the dataset was assumed to be 0 days. For the age variable a total

of 20 data point entries, had an age lower than 0 (-0.83) at the date of their review. Figure 13 shows that the median age of the cohort by review year, not including missing data, increased over time between 1996 up until 2016, this shows that there is a clear increase in survival over time in the dataset linked to improvement in the treatment and management of CF in the UK.

Figure 13: Median age by year in the UK CF Data Registry (1996-2016)

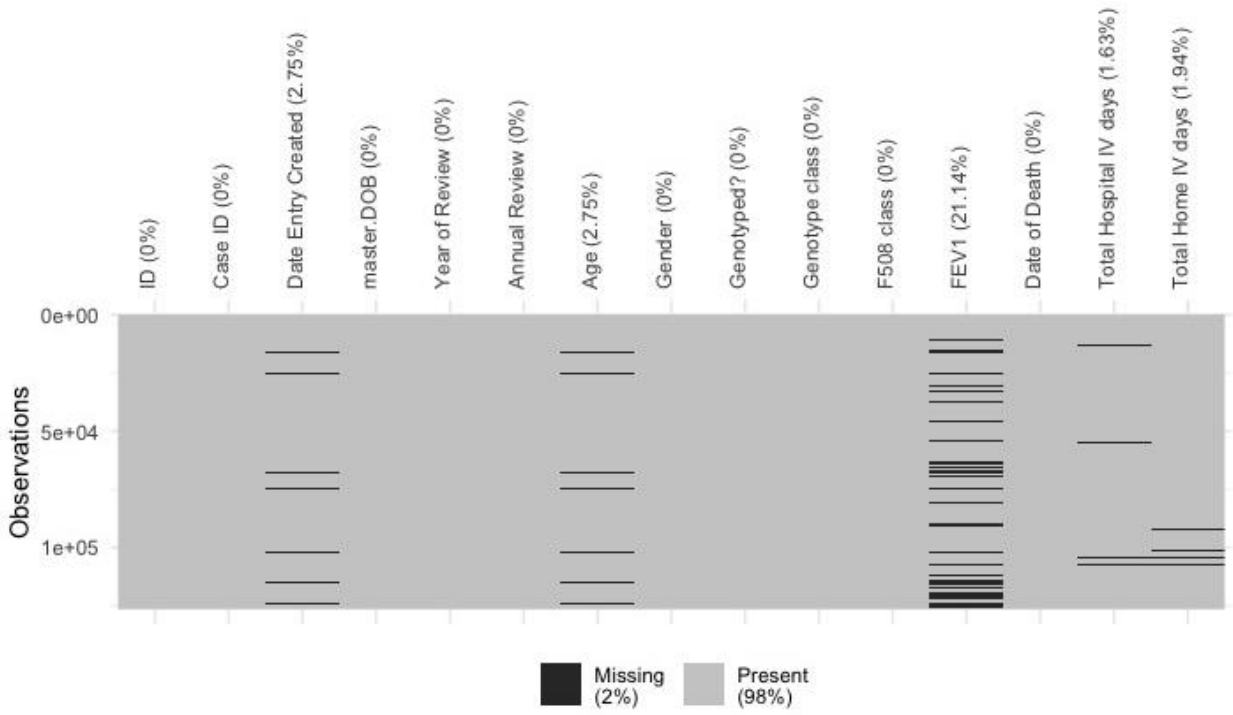


4.14 Missing data

Overall, in the UK CF Registry Data, there was a small proportion of the overall data that was missing, around 2% for data between 1996-2016. This meant that overall, there was only a small proportion of missingness from the total number of participants in the Registry Data. Figure 13 also shows the percentage of missing data for each variable across all observations in the dataset. We can see that the largest percentage of missingness exists in the FEV_1 variable, 22%. This is followed by both age and date of data entry. Lastly, either home or hospital IV treatment was missing in less than 2% of total observations

within those variables. So, both collectively as a dataset and per variable missingness information is provided in Figure 14.

Figure 14: Missingness across all observations (1996-2016)

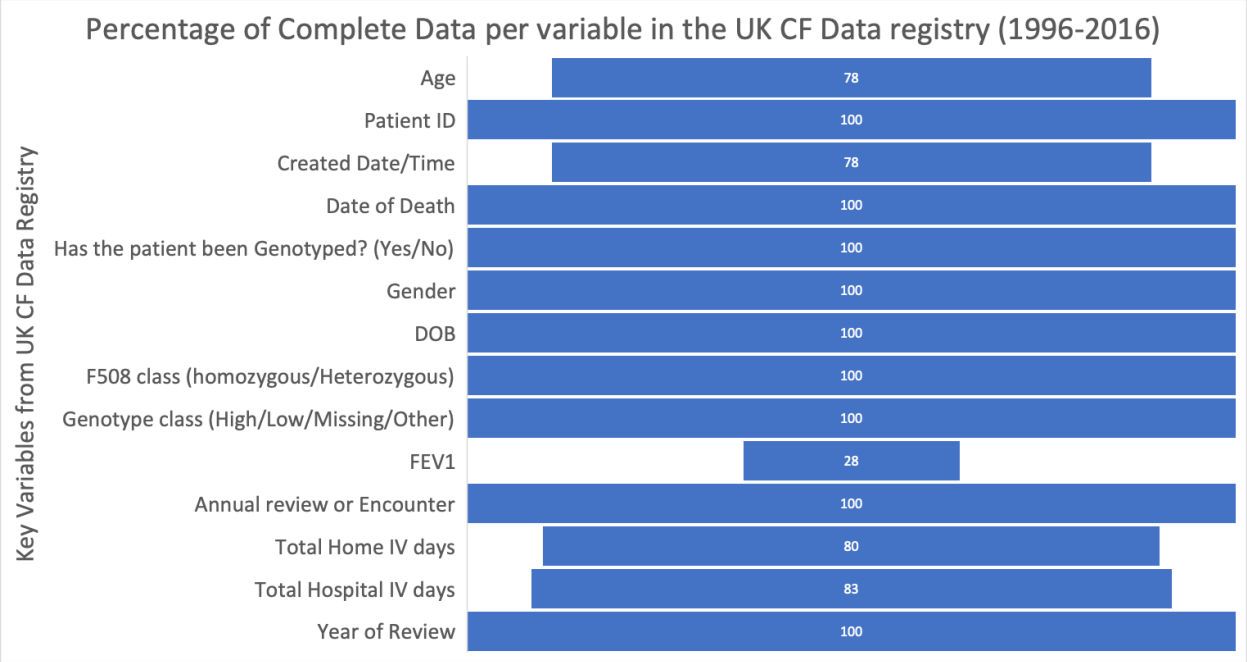


Looking at the completeness of data per variable in the CF Data Registry, Figure 14 shows the percentage of complete data per variable in the Data Registry from 12,464 individuals. Again, we can see that the majority of missing data exists in the FEV_1 variable followed by age, date of entry for the data and IV days. Variable such as genotype class have options to account for missingness from within the classification of the data itself.

From Figure 14 we can see that only 28% of the 12,464 had all entries for FEV_1 between 1996 to 2016, which equates to 3,490 individuals with no missing information for the FEV_1 between 1996-2016. Similarly, the completeness of each of the other variables can be assessed by looking at Figure 15. Furthermore, a detailed breakdown of the percentage of individuals missing between 1-24 entries in their longitudinal data values out of the

whole cohort of 12,463 for each variable are also provided in Table 17. The only variable which had up to 24 missing entries was for FEV_1, where a single individual did not have FEV_1 for the whole duration of the longitudinal data, 1996-2016.

Figure 15: Percentage of complete data per individual in the Registry Data



Variable such as, sex, date of birth (DOB), year of review, death date, whether the patient has been genotyped, F508Del classification and annual review encounter are all complete across the longitudinal period of the data (1996-2016). The Genotype variables already accounted for missingness within the variables.

Figure 16 demonstrates the number of missing entries in the master dataset by variable and any patterns in missingness between the variables. We can see that only 5 variables have missing data, which has already been identified in Figure 14. But in addition to this we can see there missingness linked between variables. For example, age missingness is linked to missingness in FEV_1 and the date the data entry was created.

Figure 16: Missingness by variable and patterns of missingness

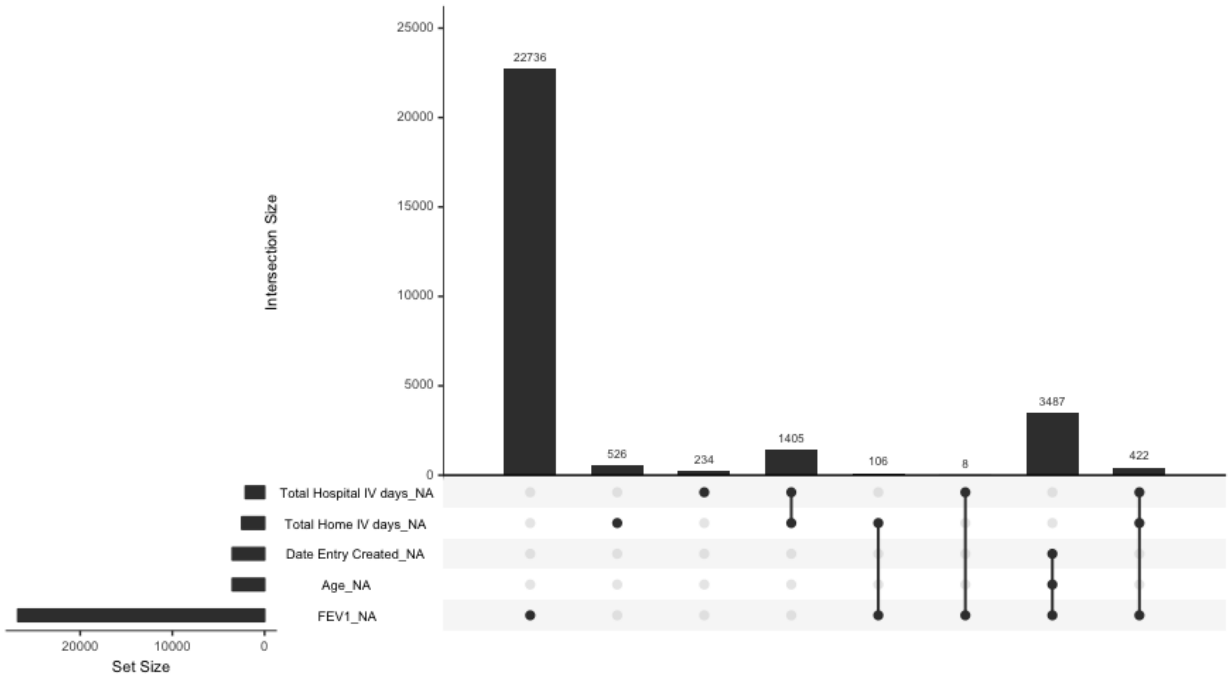

Intersection Size
25000
20000
15000
10000
5000
0
22736
526
234
1405
106
8
3487
422
Total Hospital IV days_NA
Total Home IV days_NA
Date Entry Created_NA
Age_NA
FEV1_NA
20000
10000
0
Set Size

Table 17: Number of missing entries shown by overall population percentage (1996-2016)

	Number of Missing entries															
Percentage missing (%, out of total population; 12,463)	1	2	3	4	5	6	7	8	9	10	11	12	14	15	16	24
Age	17	3	1	0	0	0	0	0	0	0	0	0	0	0	0	0
Patient ID	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
Created Date/Time	17	3	1	0	0	0	0	0	0	0	0	0	0	0	0	0
Date of Death	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
Has the patient been Genotyped? (Yes/No)	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
Sex	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
DOB	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
F508 class (homozygous/Heterozygous)	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
Genotype class (High/Low/Missing/Other)	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
FEV_1	20	14	12	11	8	4	2	1	0	0	0	0	0	0	0	0
Annual review or Encounter	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
Total Home IV days	20	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0

Total Hospital IV days	17	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
Year of Review	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0

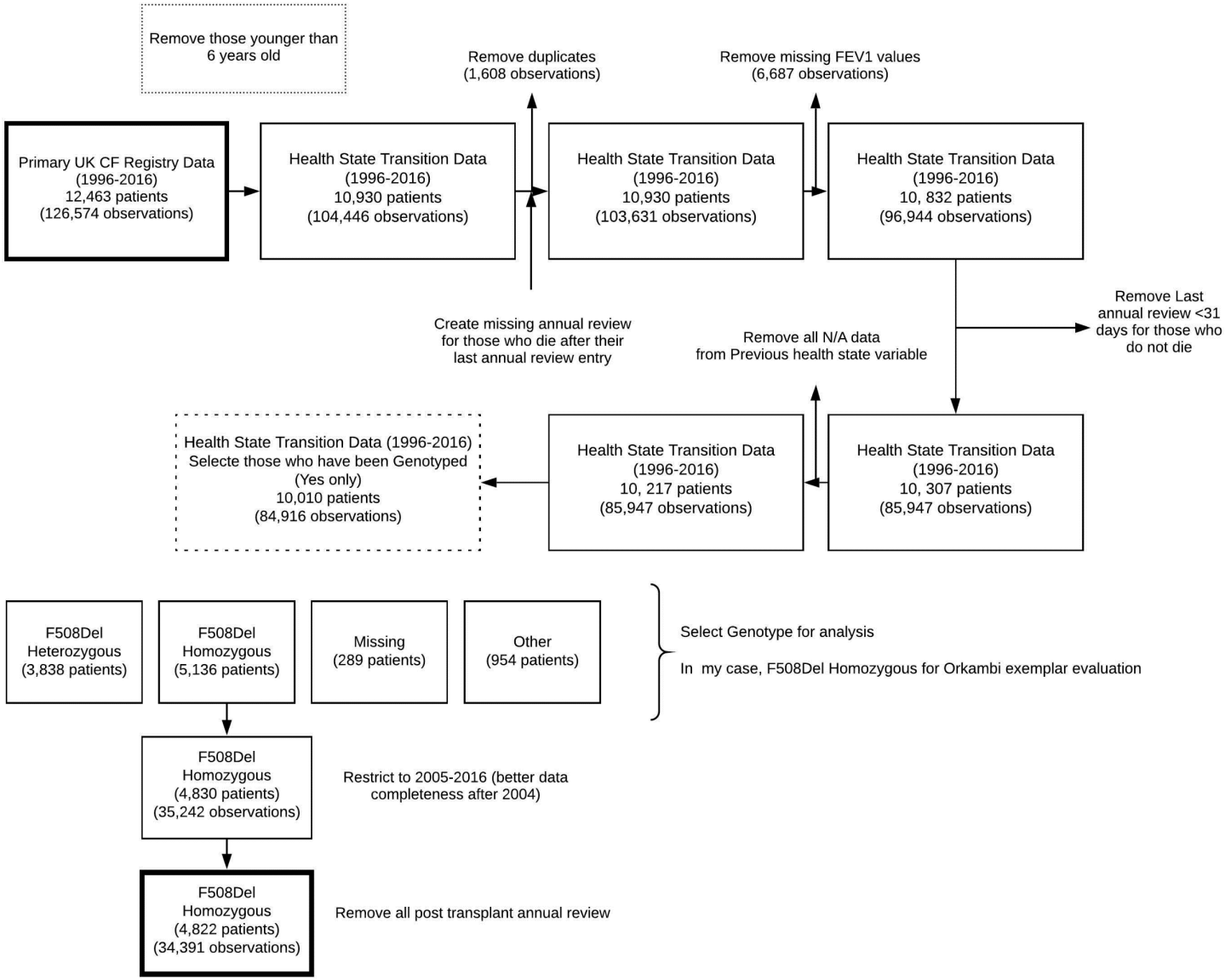
Subsequent Sections within this Section (4.16) further look at the missingness within each variable and subsequent actions taken as a result of this. In summary, it was assumed that the information was missing completely at random (MCAR) and there were no patterns in missingness. This assumption was similar to the assumption taken by other Epi-Net analyses taken as part of the wider group of work. Detailed descriptions of assumptions taken for each variable are provided in subsequent Sections 4.16.1-7.

4.15 Summary of Data Cleaning and Assumptions

A number of variables were cleaned and assumptions applied on the primary dataset to reach the final 34,391 number of observations for 4,822 individuals who were F508Del Homozygous between 2005-2016 in the UK CF Data Registry. F508Del Homozygous individuals were selected as those in this genotype class receive Orkambi®.

Figure 17 below provides a summary of the steps taken to clean/apply assumptions to the data and the number of patients and observations remaining at each step. At the last stage of the cleaning and applying assumptions, the dataset was split into 6 distinct datasets based on the previous health state, which fit the specifications of the regression modelling which is discussed in sections 4.19 and in Chapter 5 sections 5.9 to 5.10.

Figure 17: Summary diagram of Data cleaning



4.15.1 Age and FEV_1

There was a total of 3,487 missing values for the age variable, this belonged to a total of 2,734 CF individuals. For those missing the age variable, additional variables were also evaluated for missingness in the same row of patient annual review entry. The analysis showed that for those whose age was missing, 100% of observations for FEV_1 and 4% of genotype for that review year were also missing. As a result, all individuals with missing age data were removed from the dataset prior to use for deriving input values for the De Novo model, primarily because the primary outcome measure to assess disease progression, FEV_1, was missing entirely.

In Figure 18, a large majority of missing FEV_1 exist in those younger than 6 years old. This is due to FEV_1 data not being collected frequently from those under the age of 6, this is primarily due to the inability of the patient to give a reliable reading, which has already been identified in Section 14.13.1.1.

Figure 18: Density of missing FEV_1 values by Age (1996-2016)

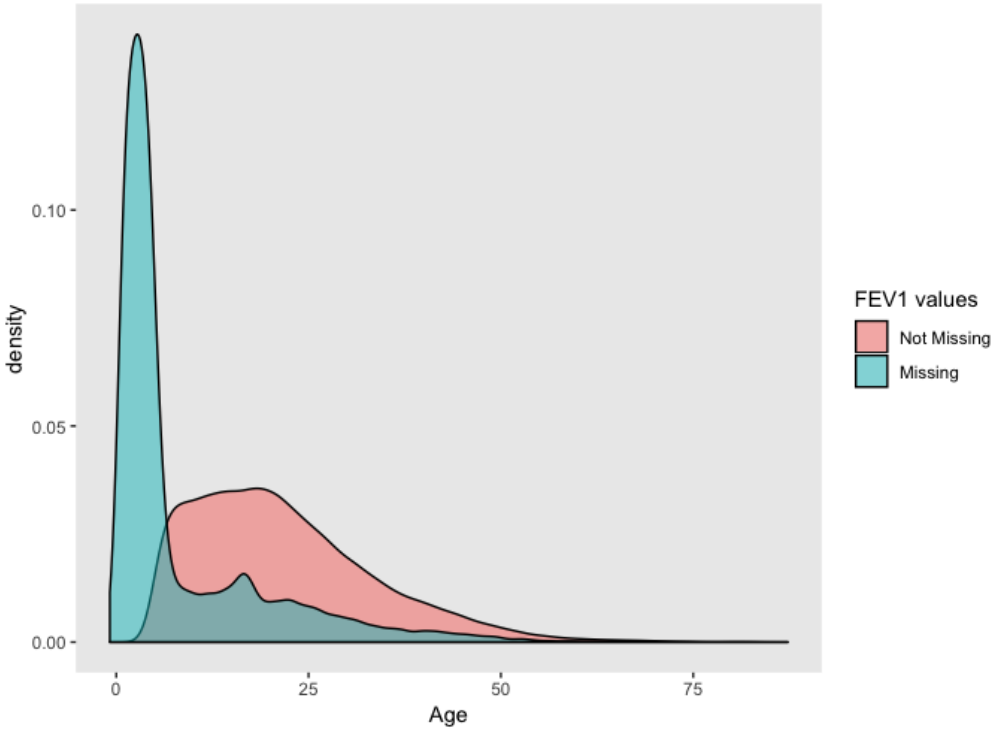


Figure 19 below shows the missingness of data in both FEV_1 and Age variables. The black line across the y-axis highlights those at age 6. This again shows that there are a number of missing FEV_1 values below 6 years old. As a result of these findings, only values for those older than 6 will be used to create the data inputs for the De Novo model. This approach has been used in other studies which use the CF Trust Registry Data as part of Epi-Net (Amy Macdougall, unpublished). This subsequently reduced the missingness of the age and created date variable to 0 and the FEV_1 from 26,759 to 7,589 observations. This reduced the overall missingness in the dataset from 2 to 0.7%.

Figure 19: Missingness of FEV_1 and Age

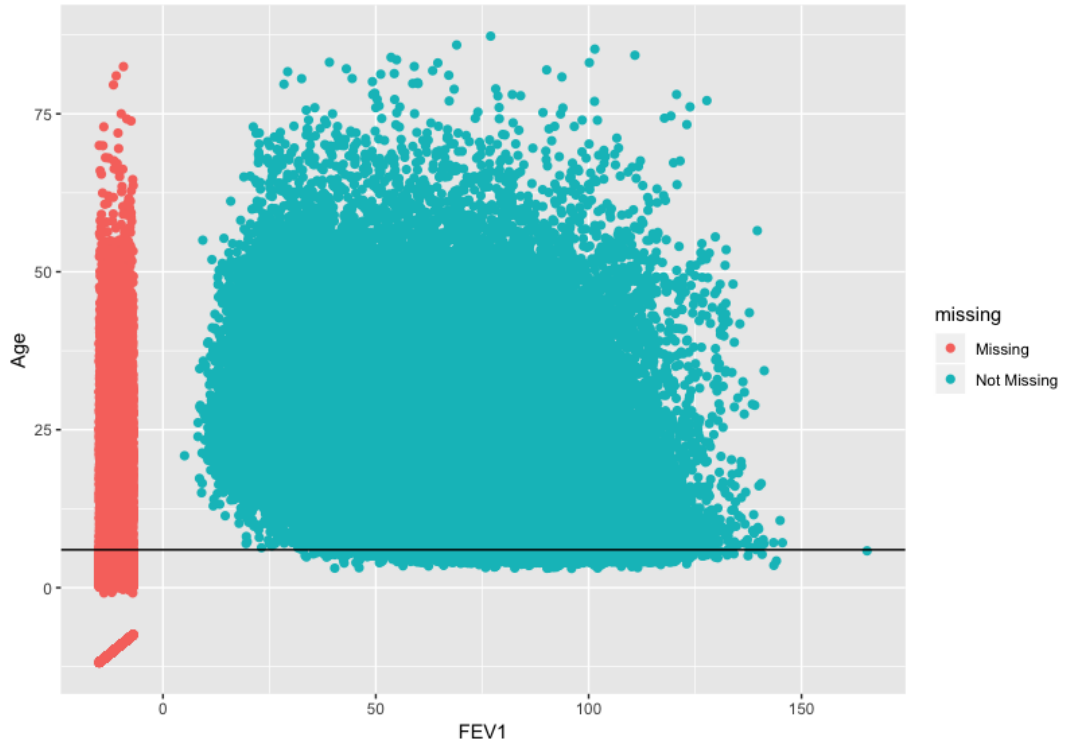


Figure 20 below shows that the missingness in the FEV_1 was reduced considerably, from 72% to 41%. Figure 21 shows the interquartile range (IQR) of the FEV_1 data prior to it being cleaned and after. We can see that the mean is largely unchanged and any differences in the upper and lower interquartile between the datasets are very small.

Figure 20: Completeness of data: after excluding <6 years old

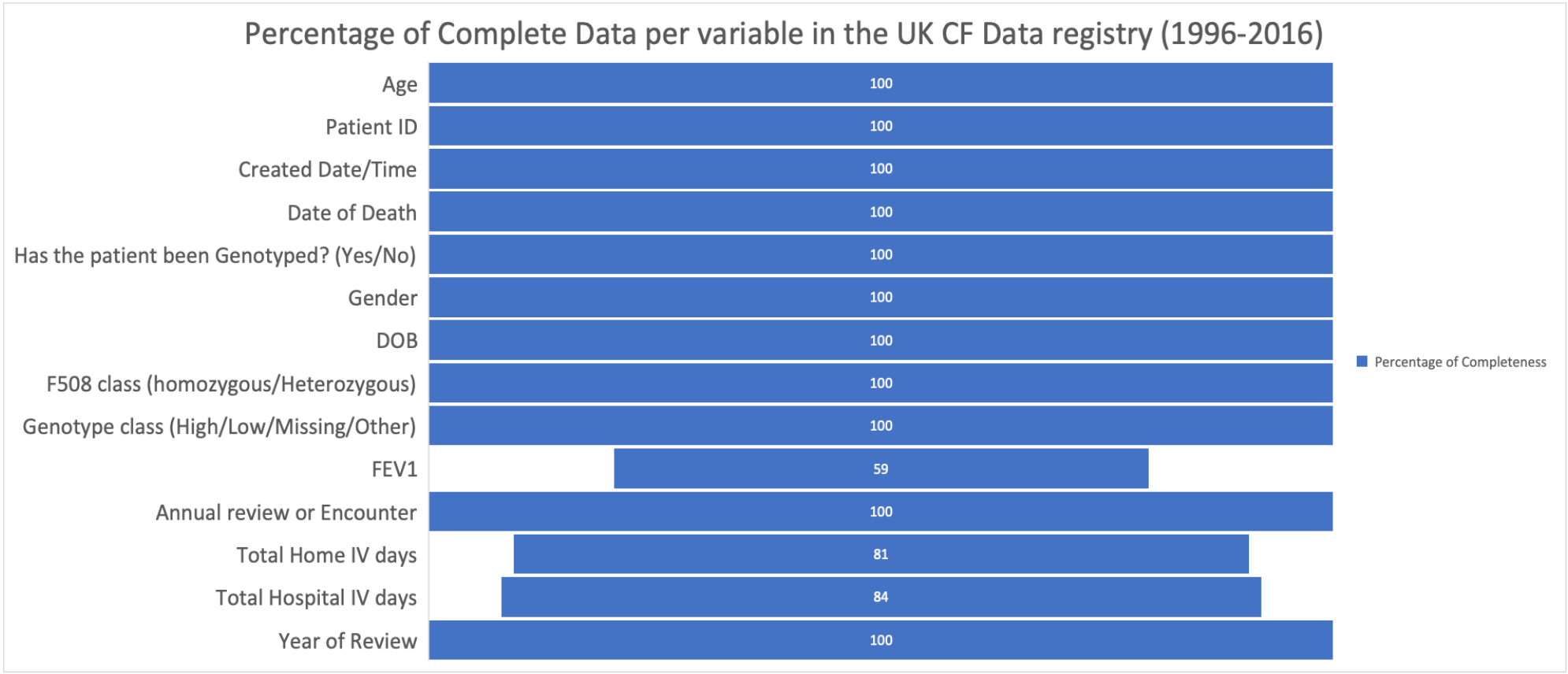
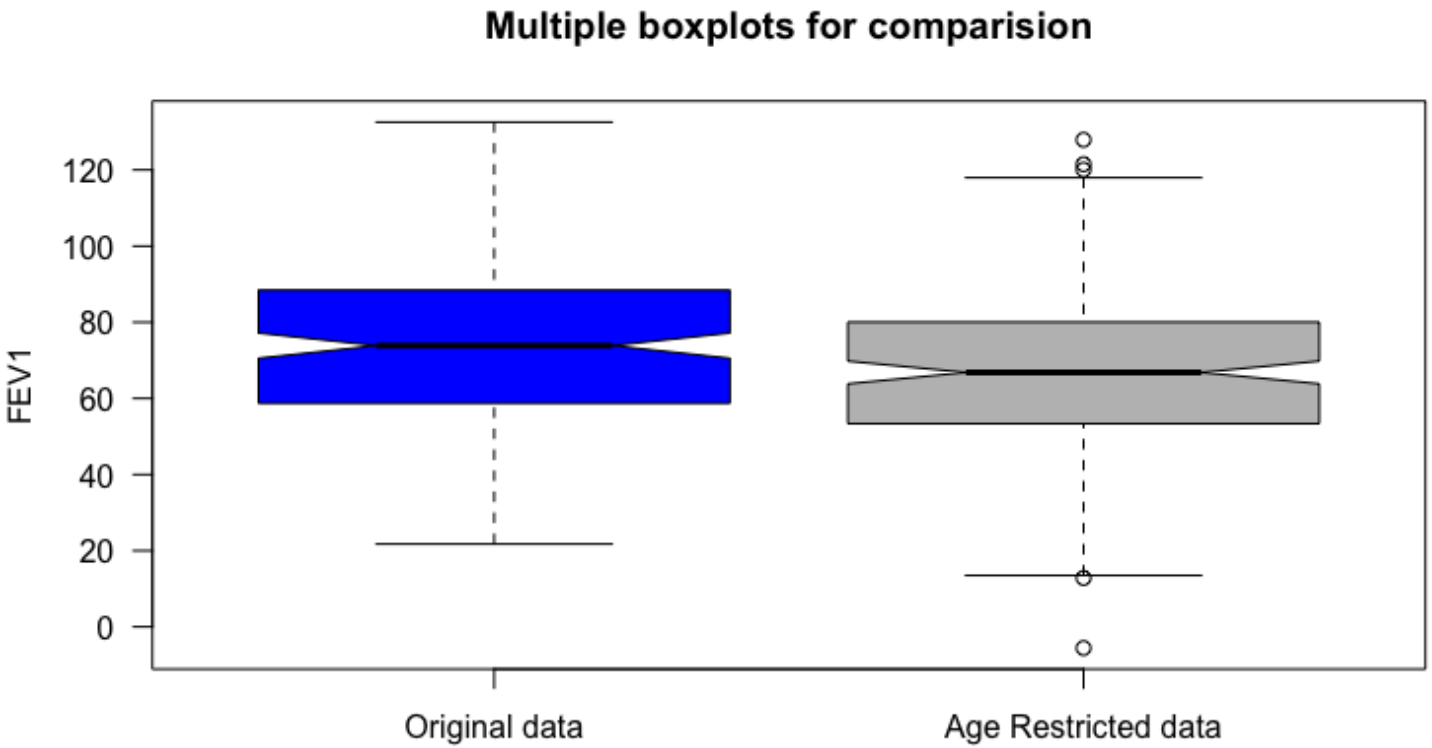


Figure 21: Comparison of data distribution (IQR): before/after excluding <6 years old



However, it is important to note here that prior to restricting the data, assumptions were applied to the mortality variable. It was assumed that those with no FEV_1 value in instances of mortality, would carry their last entry forward. This resulted in a reduction of the missingness in FEV_1, from 7,589 to 6,687 missing FEV_1 observations. Subsequent to removing these missing values, no further missing FEV_1 existed in the dataset. However, a number of other variables were cleaned prior to reaching the final complete dataset.

4.15.2 Duplicate Data

Prior to cleaning the data there were a total of 3,452 duplicate entries in the UK CF Data Registry. These duplicates had at least two reviews for the same year within a short period of time. Subsequent to restricting the dataset to those aged over 6 years old, this was reduced to 1,608 duplicates.

4.15.3 Mortality

Mortality was included in the health state transition input estimation methods further described in Section 4.18.1. After the data were restricted to those who were 6 or older, the overall number of individuals who died in the UK CF Data Registry between 1996-2016 were 1865. In the dataset a number of patients were identified who died but did not have an annual review for the year in which they died. A total of 793 individuals of the 1865 died in the subsequent year after having their review. As a result, I assumed that the last observation was carried forward for all included variables.

The days since last review was determine by subtracting the death date from the date of data entry for the previous year. Similarly, the age at review was determined by subtracting the death date by the date of birth. Additionally, there were individuals in the dataset who provided only a single annual review entry, of these 90 died in the same year. In order to ensure that mortality data for individuals with genotype data were not

removed from the dataset, it was assumed that the FEV_1 for the current year was the same as the previous year. Similarly, it was assumed in the previous year the IV treatment received was the same and the last annual review was conducted exactly a year ago (365 days).

4.15.4 IV days (Home or Hospital)/ IV treatment (Yes or No)

IV treatment, home or hospital were cleaned. Number of days across both variables were added together to create a single IV days variable. Based on this, another variable was created to identify whether the individual received any IV treatment in a given year. If the total number of IV days across both variables exceeded 365 days, it was assumed that only a total of 365 days of IV treatment was possible. Due to there being no discernible difference in terms of severity being identified by whether an individual has IV treatment at hospital or at home, these two variables were added together to create a single variable, IV treatment (yes or no).

4.15.5 Genotype

The primary dataset contained 12,463 individuals. Of these individuals only 84% of those in the UK CF Data Registry were classified as high or low, the remainder were missing (3%) and not assigned (13%). Subsequent to applying assumption or cleaning the variables, those who were genotyped (10,010 patient) were selected of which those who were F508Del (5,136 patients) were identified for inclusion in the analysis and regression modelling discussed in Sections 4.25.

4.15.6 Year of Birth

Over time the treatments available in CF have changed considerably. The treatments available today were unavailable 10 years ago, especially more novel Abx treatments such as dry powder inhaled (DPI) antibiotic treatments. As a result, in order to take into

account any differences in health state transitions by age, the year of birth variable was created. This would enable distinction between those aged for example 7 being born in 2009 and those aged 7 being born more than a decade ago. The resultant transitions are likely to be different for such groups primarily due to changes in treatment availability and resultant improved survival also.

4.15.7 Days since last review

The number of days since the last review was created as an additional variable in the dataset in order to take into account any gaps between annual review. The previous date of data entry was subtracted from the current date of data entry. This allowed large decreases in FEV_1 over time to be explained by large gaps in annual review.

A number of entries existed in the dataset which had an annual review less than a year ago. For example, the individual has their review in December 2015 and then 30 days later, they have another review entry for January 2016. Although having a clinical review earlier than 365 days is possible in clinical care, I assumed that those who had their last review less than 31 days ago were errors in the dataset. This was the case for 241 individuals. However, those who had their annual review entry less than 31 days ago but also died in that annual review period, were kept in the dataset in order to avoid losing mortality data. This was the case for a total of 24 individuals.

4.16 Methodology for calculating transition probabilities

4.16.1.1 Evidence

The evidence that can be applied to any health economic model depends on data availability and the structure of the model itself [83]. Probabilities reflect the possibility of an event occurring in clinical decision making and/or disease progression, such events impact both costs and health outcomes. One aspect of probabilities in decision analytical

modelling are transition probabilities. These form the core functioning of the analytical model [83]. Based on transitions to health states that occur within the model, each transition has a cost and outcomes attached to it [5]. Transition probabilities govern the direction of movement of a cohort in a given model. Transitions can be fixed with respect to time or can change as the model progresses through time and/or based on cohort subgroups (e.g. sex or genotype). Such models are called a homogenous Markov chains model and non-homogenous Markov chains model, respectively [194, 195].

The following sections will look at the data cleaning and assumptions performed on the U.K. CF Data Registry followed by the regression methods applied to the data subsequent to this process. The regression modelling process will be used to derive the majority of the inputs utilised for the De Novo health economic model.

4.17 Data cleaning for regression modelling

Each subsequent dataset created from the above-described data were created as an adjunct to the primary health state transition data. This is primarily because the health state transition dataset, utilised FEV_1 and the above additional variables. Health state transition data is the input information required for state transition modelling, in this case Markov modelling, described above where a cohort of individuals transition between various health states over a predefined time horizon. Any missingness of these variables in this dataset would subsequently impact the missingness in the lung transplantation and cost banding dataset.

As the cost data were only available between 2013-2016, such data were merged with the existing health state transition data between that period. Similarly, the lung transplantation data were also merged with the complete health state transitions data. These are described further in each respective Section (4.18.1, 4.18.2 and 4.18.3).

4.17.1 Health State Transition Dataset

As a result of the missingness identified in the primary dataset between 1996-2016, above, a number of steps were taken to clean the data in order for it to be used in creating the input data for the De Novo model.

4.17.1.1 Health State Previous/Current health state

The current and previous health state variables were created based on the categorisation of the FEV_1 values and whether the annual review entry included IV treatment for that year. Table 18 below shows the FEV_1 for the various current and previous health states and the values given to those FEV_1 categories. Creation of the previous health state variable was based on the FEV_1 value for the patient in the previous year. This meant that the first year an individual patient contributed data to the Registry would have no previous FEV_1 value, hence a missing value would be present for the initial year. Subsequent entries from the same individual would have the previous as well as the current years FEV_1 value. This would be the case until the last available annual review entry.

Table 18: Categorisation of Current and Previous health state

Current health state categories (with or without IV) based on FEV_1	Name of Health state	Previous health state categories (with or without IV) based on FEV_1	Name of Health state
≥ 70 No IV	Mild	≥ 70 No IV	Mild
≥ 70 IV	Mild IV	≥ 70 IV	Mild IV
≥40 <70 No IV	Moderate	≥40 <70 No IV	Moderate
≥40 <70 IV	Moderate IV	≥40 <70 IV	Moderate IV
<40 No IV	Severe	<40 No IV	Severe
<40 IV	Severe IV	<40 IV	Severe IV
Na	Dead		
Na	Dead IV		

4.17.2 Cost Band Data

The cost banding is a system used by the UK CF Data Registry to assign a cost of care to those with CF in the UK. A set of criteria are applied to each individual in the UK CF Data Registry to determine which cost band they are assigned to any given year. Table 19 below shows that different criteria used to assign cost bands. The cost per band themselves, 2016, are given in Chapter 6 Section 6.18.2 Table 71. It is important to note that cost of care includes treatment but also includes cost of other services such as appointments, physiotherapy and additional services. The cost banding system also included information on the number of IV days received and hospital of days in hospital for those who receive IV treatment in any given year. In instances where individuals do not receive any IV treatment in the year, they are still assigned a cost band, but these costs do not include any IV treatment. The cost banding system does not include High-Cost drugs which are treatments that are reimbursed through other avenues. This is described further in Chapter 6, section 6.18.3.

Table 19: UK CF Banding Matrix

Banding definitions		Band						
Therapies		1	1A	2	2A	3	4	5
	Maximum number of total days of IV antibiotics	0	14	28	56	84	112	>/=113
	Nebulised antibiotics (Pseudomonas infection)		Yes					
	Long-term (>3 months) nebulised antibiotics or DNase			Yes				
	Long-term (>3 months) nebulised antibiotics and DNase				Yes			
Hospitalisations	Maximum numbers of days in hospital	0	7	14	14	57	112	>/=113
Supplemental feeding	Nasogastric feeds				Yes			
	Gastrostomy					Yes		
Complications	CF Related Diabetes or ABPA w/o other complications				Yes			
	CF Related Diabetes and ABPA					Yes and (FEV1 ≥60%)	Yes and (FEV1 <60%)	

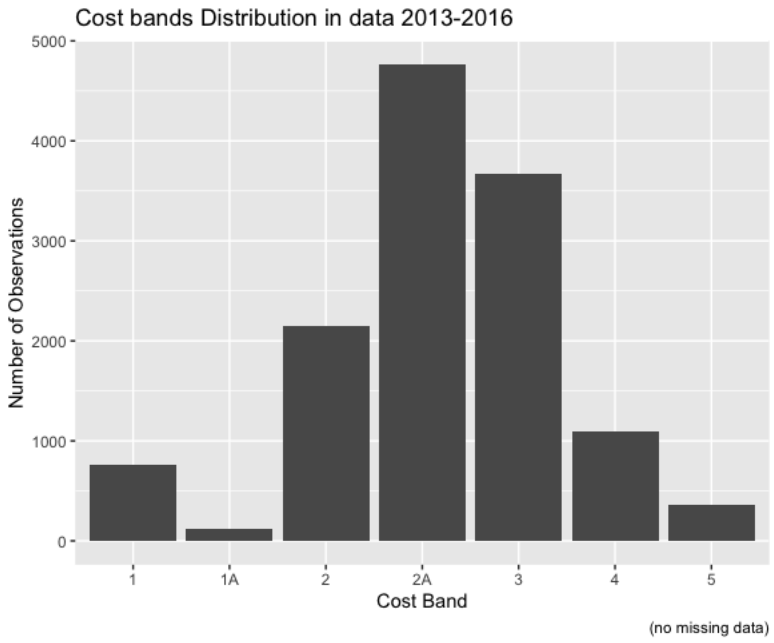
	Massive Haemoptysis or Pneumothorax	Yes and (FEV1 ≥60%)	Yes and (FEV1 <60%)
	CF Related Diabetes and Gastrostomy	Yes and (FEV1 ≥60%)	Yes and (FEV1 <60%)
	Non Tuberculous mycobacterium treated or difficult to treat infections (eg MRSA or Cepacia) requiring other nebulised antibiotics eg Meropenem, Cayston , Vancomycin.	Yes	

A data request was submitted to the UK CF Data Registry for cost banding data between 1996-2016. This request was submitted on 30th May 2018. The request was completed and data alongside information on the cost band of each individual in the Data Registry for each annual review was provide. The data were received on 5th June 2018, only data between 2013-2016 was provided.

The primary dataset contained 31,693 observations with no missing data and belonged to 8,769 patients from the UK CF Data Registry. The data were merged with the primary health state transition data. The cost banding data were cleaned alongside this data to ensure information on additional variables required for the regression modelling were available as well as the cost band for each data entry. The total number of patients who were F508Del Homozygous with annual review between 2013-2016 were 3,740 and totalled 12,919 observations over this period.

We can see from Figure 22 below, that a majority of the data entries in the Cost band dataset are in cost band 2A followed by cost band 3, with very few in cost bands 1a and 5. The time point at which the cost banding was assigned was at the end of each annual review, based on the criteria in the Banding Matrix, Table 19.

Figure 22: Cost band Distribution



4.17.3 Lung Transplant Data

Prior to receiving the lung transplant data, Prof Ruth Keogh (Professor of Biostatistics and Epidemiology at London School of Hygiene and Tropical Medicine) and Dr Sanja Stanojevic (Assistant Professor in Community Health and Epidemiology at University of Toronto), both evaluated the primary UK CF Data Registry Lung transplant data. Any differences or miscellaneous results were cleaned and subsequently the file was sent across for further evaluation and use in this thesis. The data were received on the 20th May 2019.

The lung transplant data were created simultaneously to the health state transition data which was later used to calculate health state transition inputs for the model. Subsequent to the health state transition data being cleaned, the lung transplant data were merged to the data in order to identify all patients who received a transplant and in which year. As a result of identifying all those who received a transplant, data for such individuals was

removed from the health state transition dataset subsequent to receiving a transplant. This was in order to determine the probability of receiving a transplant separately to calculating the health state transitions and is conducted in Chapter 5 Section 5.10. Additionally, annual review entries after the transplant year were removed. This is because the FEV_1 of individuals improved over time subsequent to receiving a transplant, removing annual review entries for subsequent years reduced any possibility or errors in the health state transitions inputs calculated from such data.

A series of assumptions were made when creating the lung transplant data. The first date of transplant was considered the only time the patient received a transplant. All those who received a transplant prior to joining the UK CF Data Registry were removed.

A total of 732 individuals were in the primary lung transplant date. These include those who had a transplant since their last annual review between 1996 - 2016. After restricting the dataset to the period set in the health state transitions dataset, 2005-2016, the number of patients dropped to 554 and reduced further down to 408 after removing duplicates and those who received a transplant prior to entering the UK CF Data Registry. Subsequently, restricting the population of the dataset to those who were F508dDel Homozygous and had sex/sex and age information resulted in data with 211 patients who received a transplant during 2005-2016 who also had complete data for the health state transition analysis.

4.17.4 Post Lung Transplant Data

The post-lung transplant data were cleaned by Prof Ruth Keogh (Professor of Biostatistics and Epidemiology at London School of Hygiene and Tropical Medicine). The input parameters were sent on 18th September 2019. These are further described in Chapter 6, Section 6.16.

4.18 Regression methods

Herein the regression methods are discussed based on the characteristics of the data discussed in above section of this Chapter. A small number of available regression methods which could be used were evaluated (Sections 4.19.2-3) and only a single method was selected to carry out the statistical analyses.

4.18.1 Regression models

Regression modelling is a statistical method by which one variable, response variable, can be explained through its relationship with a single or more variables [196]. When the response variable is continuous the model is linear, when it takes the value between 0 or 1 it becomes logistic [196] and is often termed logistic model [196]. This also means that the error term in the model also takes a value between 0 or 1 [196]. In logistic regression models the outcome is not predicted directly from a series of relationships between other variables but by applying an inverse of any one link functions available to a series of linear explanatory variables [197]. In instances where a logistic regression model is utilised, a logit link function is the only model that can produce odd ratios as the response variable. Other link functions which are capable of handling binary response variables include probit, complementary loglog (C-loglog) and loglog [196]. Both the logit and probit are symmetric link functions with a probability interval of 0-1 and a mean of 0.5 [198]. Although the results of either logit and probit models are most often very similar [196], the choice of the link function is important as it relates the response to the explanatory variables. Both the logit and probit link functions convert the binomial response variable into a continuous scale between 0 and 1. However, as explained already, the logit link function is the only one that allows results to be presented as odds ratios. On the other hand, the probit link corresponds to a standard normal cumulative density function (CDF) and is

most often used when one is interested in the predictive value of a model [198]. When the response variable is assumed to take a normal distribution, this is another justification for use of the probit link function [198].

4.18.2 Health State and Cost band transitions

Often, survival models are modelled as a function of time. However, health is a multifaceted variable which can be associated with many different factors such as age, sex, weight, height, socioeconomic status and genotype. Similarly, cost can be associated with a number of different factors when it comes to healthcare utilisation, such as age, sex, socioeconomic status and disease severity by genotype. In the Whiting et al [107] study, cost for CF by health state/FEV_1 was associated with factors such as age and FEV_1. However, how such variables were selected were not described in the work.

As previously highlighted in this Chapter, due to the nature of the variables in the CF Data Registry and the categorisation of FEV_1 into health states, statistical models which used categorical variables as the response variable would be most appropriate. Similarly, due to the nature of the lung transplant data in the UK CF Data Registry statistical methods which use binary responses for the response variable would be most appropriate.

Two regression modelling methods fit the requirements of the data for health state transitions between the Mild and Dead IV health states, Ordered Logistic and Multinomial Logistic Regression. For determining the probability of lung transplantation, Generalised Linear Regression and Mixed or Random Effects models were evaluated. The probability of survival post-lung transplant was estimated in a separate study using the UK CF Data Registry by the Epi-Net statistician (Prof Ruth Keogh, unpublished), which is described further in Chapter 6, Section 6.16.

4.18.3 Generalised linear regression

Generalised linear regression brings together linear regression and nonlinear regression, where the response variable can take a range of distributions [199]. The key assumptions of the generalised linear regression model (GLMs) is that the response variable can have an exponential distribution, which includes normal and binomial, the explanatory variables form linear combination called a linear predictor and that the link function models the log of odds for binomial data which are used for values between 0 and 1, or probabilities [13] such as lung transplant and no lung transplant in the case of the data in used in this chapter. However, as many GLM make the additional assumption that individual subjects are independent, this will be violated when data is correlated by repeated entries of patient data [198]. Although the above GLM model would meet the requirements of our decision problem and data, models known as Generalised Estimating Equations (GEE) would mean I do not violate the independence assumption and result in probability estimates which take into account repeated measures [196]. Also, the distribution of the response variable, transplant or no transplant was not normal and GEE models are flexible for analysis of such variables [200]. GEE models are primarily used to model correlated data which would otherwise be modelled using GLMs [196]. Such models allow clustering of the data based on observation from the same patient. This is particularly important as estimates can be positively correlated within clusters [201]. However, not taking account of correlation within measurements from the same patient I would still be able to model parameter estimates well but results in biased standard errors [201, 202]. GEE based models are a population averaging method, which differs to subject specific models such as mixed effects or random effects models [196]. Population averaging used in standard logistic regression is similar to that used in GEE based models, where for example

predicted probabilities refer to the average of measure within a cluster [196]. This is largely different to mixed effects or random effects models which employ subject specific effects and the resultant predicted probabilities estimated would be related to individual subjects [196].

As the population in the lung transplant dataset represented a smaller subsample of those with the F508Del Homozygous genotype, it was decided that a population averaging method would suffice for our analysis compared to a subject specific method. The potential gain of using a more complex regression methodology may have not been realised at the opportunity cost of employing more simpler methods. Additionally, the GEE models have been applied in similar healthcare datasets [203], they relax the distribution assumption for the response variable, model fitting is easier to conduct compared to mixed or random effects model and the model is robust to some misspecification around the correlation structure of the data [203]. Therefore, a decision was made to use GEE modelling to calculate the probability of receiving a transplant.

4.18.4 Ordered Logistic regression models

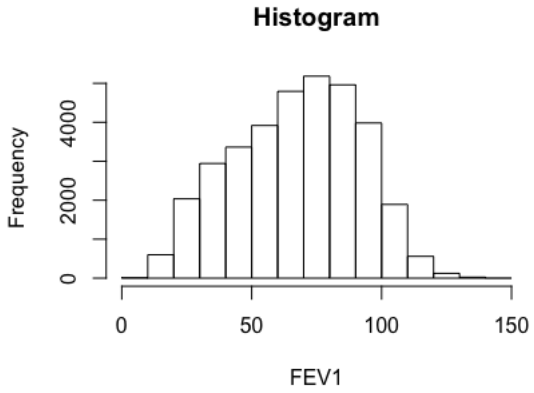
Ordered logistic regression is similar to the binomial logistic regression model and can be used for binary response variables as well [196]. However, the ordered logistic regression model is most often used when there are more than two levels in the response variable. The model structure presented in Chapter 4 has 8 levels (Figure 11), not including lung transplant and post lung transplant. Ordered logistic regression models also include, as the name suggests, an ordering of the response variables, from Mild to Dead IV for example, the prior being a better health state than the later. Additionally, the response variable takes the form of a series of mutually exclusive and exhaustive values [204]. In

the case of my data, this would take the form of the 8 mutually exclusive and exhaustive health states mentioned in Chapter 4; Figure 11.

When the categories in the variable are ranked the distance between adjacent categories is unknown, but it is assumed that the distance between the categories are equal [204]. However, this assumption can be relaxed within the model specification to include different threshold values for the response variable and result in flexible distances between the intervals, mentioned further in model specification, section 5.9.1.

One of the key assumptions for an ordered logistic model is the proportional odds assumption. This means that the model assumes for each covariate the co-efficient value for each response or ordered category is the same [196]. For example, it assumes that age would affect the response category Mild and Severe IV the in the same way. Additionally, another assumption of ordered logistic regression is that the model is based on a normally distributed latent response variable. The latent continuous variable is then divided into a number of categories, similar to the categories generated in the previous models in CF [92]. As can be seen in Figure 23, the distribution of FEV_1, the primary response variable, in the prepared datasets is approximately normally distributed and continuous in nature.

Figure 23: Latent response variable, FEV_1



The underlying continuous range of severity is common in disease progression predictors, so it is difficult to argue against such ordering of categories. Especially given the structure of my primary response variable. If no underlying continuous latent variable exists, then the categories cannot be ordered, the ordered logistic model can no longer be used. The alternative model used in such cases in the multinomial logistic model.

4.18.5 Multinomial logistic regression models

Multinomial logistic regression models are an extension of generalised linear models [196].

The estimation of unordered categories if clear ordering is present in the response variable is lost due to using this regression modelling method [196] and can result in a serious loss of power in the model [201]. One of key assumptions of a multinomial model is the independence of irrelevant alternative (IIA) [196]. This assumption means that the presence of one response category is not affected by the presence of another response category [196]. For example, the chance of an individual to be in Mild health state is not different from the chance of being in Severe. This is also not affected when another response category is added, for example Dead IV.

4.19 Summary

In summary, this chapter outlines the conceptualisation and structure of the De Novo model which will be used to evaluate an exemplar CF intervention, Orkambi®. The overall UK CF Data Registry is described as well as the assumptions and steps used to clean the data for it to be used to create the model inputs for the De Novo Markov Model. The final datasets include those used to determine health state transitions, cost banding and lung transplantation of individuals in the UK with CF who are F508Del Homozygous. The proposed regression methods used to calculate input parameters for the De Novo model are also described in detail. The next chapter will focus on deriving input parameters for the De Novo model using regression methods that are appropriate for the final datasets developed in this chapter. Of the different regression models that could be utilised to generate the inputs, in the next chapter only one will be selected for each data set, health state transitions, cost band probabilities and lung transplantation probabilities respectively.

5 Chapter 5: Using the U.K. CF Data Registry for the development of parameters to inform health economic modelling in the context of Cystic Fibrosis management interventions

5.1 Introduction

In Chapter 4, the UK CF Data Registry was discussed with descriptions of the data along with the assumptions made in order to prepare the dataset for use is this chapter. This chapter focuses on determining health state transition probabilities, cost band probabilities and lung transplant probabilities. Regression models will be selected and specified. Inputs generated in this chapter will be used to fill the requirements of the data in order for the De Novo model developed in Chapter 4 to function.

This chapter initially discusses the regression modelling methods paying attention to selecting a regression modelling approach from Chapter 4, specification of the selected regression models and the results of the chosen models. Following this, the chapter presents the transition probabilities data for the three areas mentioned above. The chapter later looks at the validation of the resultant transition probability data, for both costs and health state transitions including lung transplant. The validity is considered from a statistical and graphical perspective, later turning to the validity through comparison against the existing evidence.

The remainder of the introduction section will focus on previous statistical or other methods used for longitudinal cost and clinical events data in CF. This will be followed by a description of the regression methods used in this chapter in the methods section. In

the previous chapter, the data were described in detail as well as the regression models that could be utilised on such data. Subsequently in this chapter only the methods selected to develop the health economic model inputs parameters are described further.

5.2 Previous findings from the CF Data Registry in Health Economics

5.2.1 Health State transitions

Previous studies which have used the U.K. CF Data Registry for health state transition probability analysis were identified through the review conducted in Chapter 2. No studies exist which have utilised the U.K. CF Data Registry to determine health state transitions for F508Del Homozygous patients. A study was identified which utilised the U.K. CF Data Registry for other genotype group analysis in a cost-effectiveness study [102]. The study was evaluating an adherence intervention [102]. The overall statistical method that was utilised to determine the transition probabilities was an ordered probit regression method. The range of covariates included in the regression models were time since last annual review, rate of being admitted to hospital for IV antibiotic treatment and the individual's age. Although age was included in their regression analysis, it was not used to predict the probabilities for transitioning to different health states for use in their cost effectiveness model. The mean transition probability estimates are presented in Table 20 below.

Table 20: Mean probability of transition by health state; Tappenden et al [102].

FEV_1 transition	Mean Probability value
≥70 to ≥70% - Mild to Mild	0.87
≥70 to 40–69% - Mild to Moderate	0.13
≥ 70 to < 40% - Mild to Severe	0.00
40–69 to ≥70% - Moderate to Mild	0.13

40–69 to 40–69% - Moderate to Moderate	0.76
40–69 to<40% - Moderate to Severe	0.10
< 40 to ≥70% - Severe to Mild	0.03
< 40 to 40–69% - Severe to Moderate	0.14
< 40 to < 40% - Severe to Severe	0.84

Other studies which used CF Data Registries to calculate transition probabilities for a non-UK population were, Van Gool et al [81] and Sharma et al [126]. Van Gool et al [81] utilised three years of data from the Australian CF Registry to determine transition probabilities. Transition probabilities were stratified by age and sex, these are presented in Table 19. Three consecutive years of data were used to calculate transition probabilities. No regression modelling methods were used [81], a simple counting method to determine probabilities by health state and age group was utilised. Sharma et al [126] utilised the American Cystic Fibrosis Foundation to look at overall survival in the model looking at the cost-effectiveness analysis of Orkambi®.

Table 21: Probability of transition by Health State (1 (Mild) to 5 (Death)) and Age groups; Van Gool et al [81]

	From Health State 1 to Health State 1 to 5				
Age group (years)	**Mild| Mild**	**Moderate| Mild**	**Severe| Mild**	**Lung Transplant| Mild**	**Dead| Mild**
0–2	1			0	0
3–5	1			0	0
6–7	0.997			0	0.003
8–10	0.973	0.027	0	0	0
11–13	0.966	0.031	0	0.003	0
14–16	0.952	0.045	0	0.003	0
17–19	0.885	0.109	0	0	0.005
20–22	0.879	0.121	0	0	0
23–25	0.904	0.096	0	0	0
26–28	0.917	0.083	0	0	0
29–31	0.857	0.143	0	0	0
32–34	0.839	0.161	0	0	0
35–37	0.788	0.212	0	0	0
>37	0.884	0.116	0	0	0

	From Health State 2 to Health State 2 to 5			
Age group (years)	**Moderate| Moderate**	**Severe| Moderate**	**Lung transplant| Moderate**	**Death| Moderate**
0–2				
3–5				
6–7				
8–10	1	0	0	0
11–13	0.935	0.065	0	0
14–16	0.9	0.075	0	0.025
17–19	0.947	0.053	0	0
20–22	0.92	0.08	0	0
23–25	0.897	0.09	0	0.013
26–28	0.902	0.082	0.016	0
29–31	0.986	0	0	0.014
32–34	0.911	0.054	0.018	0.018
35–37	0.9	0.1	0	0
>37	0.914	0.057	0.014	0.014

From Health State 3 to Health State 3 to 5			
Age group (years)	**Severe| Severe**	**Lung Transplant |Severe**	**Death| Severe**
0–2			
3–5			
6–7			
8–10	1	0	0
11–13	0.5	0	0.5
14–16	0.5	0.167	0.333
17–19	0.8	0.2	0
20–22	0.806	0.032	0.161
23–25	0.769	0	0.231
26–28	0.765	0	0.235
29–31	0.75	0.05	0.2
32–34	0.667	0.167	0.167
35–37	0.783	0	0.217
>37	0.844	0.044	0.111

From Health State 4 to Health State 4 or 5		
Age group (years)	**Lung Transplant| Lung Transplant**	**Death| Lung transplant**
0–2	1	0
3–5	1	0
6–7	1	0
8–10	1	0
11–13	1	0
14–16	0.833	0.167
17–19	1	0
20–22	1	0
23–25	0.909	0.091
26–28	0.95	0.05
29–31	1	0
32–34	0.933	0.067
35–37	0.944	0.056
>37	0.94	0.06

Absorbing state	
Age group (years)	**Death| Death**
0–2	1
3–5	1
6–7	1
8–10	1
11–13	1
14–16	1
17–19	1
20–22	1
23–25	1
26–28	1
29–31	1
32–34	1
35–37	1
>37	1

5.2.2 Costs

Similar to the health state transitions, studies which used the U.K. CF Data Registry for cost analysis were identified through the review conducted in Chapter 2. Whiting et al [107] used 2011 cross sectional data from the CF Data Registry with CF Banding matrix (presented in Chapter 4, section 4.18.2) categories. They also requested a list of variables in order to determine annual costs for treatments not included for reimbursement within the CF Banding matrix, also known as 'High-Cost' drugs, described further in Chapter 6, Section 6.17.3. Subsequently, costs for care in the cost band (PbR tariff) and non-reimbursed tariff (High-Host drugs) were summed per patient. A linear regression modelling method was used to explore the relationship between age, FEV_1 and costs. Results from their analysis are presented in Table 22, below.

Table 22: Cost regression analysis results by Whiting et al [107]

Variable	ß	SE
Constant	41084	588
Age	–101	12
pp FEV_1	–254	6

Other studies which used CF Data Registry information included a study by Tappenden et al [102]. The data were used to present proportion figures of being in a particular cost band whilst being in a particular health state or FEV_1 category (as described in Chapter 4, Section 4.10) at the time. These values are presented in Table 23 below.

Table 23: Probability of Cost Band Transition by Health state

FEV_1 transition	Mean Probability value
Mild - Proportion band 1	0.20
Mild - Proportion band 1a	0.02
Mild - Proportion band 2	0.24
Mild Proportion band 2a	0.34
Mild - Proportion band 3	0.18
Mild - Proportion band 4	0.02
Mild - Proportion band 5	0.00
Moderate - Proportion band 1	0.05
Moderate - Proportion band 1a	0.01
Moderate - Proportion band 2	0.11
Moderate - Proportion band 2a	0.35
Moderate - Proportion band 3	0.34
Moderate - Proportion band 4	0.11
Moderate - Proportion band 5	0.02
Severe - Proportion band 1	0.02
Severe - Proportion band 1a	0.01
Severe - Proportion band 2	0.06
Severe - Proportion band 2a	0.25
Severe - Proportion band 3	0.33
Severe - Proportion band 4	0.24
Severe - Proportion band 5	0.10

Another study which used CF Data Registry to calculate transition probabilities for a non-U.K. population was, Van Gool et al [81]. Van Gool et al [81] utilised three years of data from the Australian CF Data Registry to determine the cost of being in particular health state by age groups and health states. Table 24 presents the total cost overall costs per health state, mean and median. Although the mean cost is highest for lung transplant, the median costs show that disease severity, worsening health state, resulting in an increase in costs.

Table 24: Costs (US$) by health state and Age groups; Van Gool et al [8]

	Health state			
	Mild	**Moderate**	**Severe**	**Lung Transplant**
Total (mean)	£ 10,151	£ 25,647	£ 33,691	£ 38,344
Total (median)	£ 4,331	£ 18,230	£ 27,108	£ 22,915

5.2.3 Lung Transplant

Similar to the health state transitions and costs, studies which could have utilised the UK CF Data Registry to determine the likelihood of lung transplant were identified via Chapter 2. The review did not identify any studies which used the UK CF Data Registry to determine probability of lung transplant over time. In terms of costs of lung transplantation, Whiting et al [107] used NHS reference cost data, whereas Tappenden et al [102] used personal communication with NHS England.

Other studies which used CF Data Registries for a non-UK population were Van Gool et al [81] and Sharma et al [126]. Van Gool et al [81] utilised three years of data from the Australian CF Registry to determine the probability of transitioning into a lung transplant health state as well as the cost associated with this health state. Sharma et al [126]

utilised the American Cystic Fibrosis Foundation to look at lung transplant and survival post lung transplant of the cost-effectiveness analysis of Orkambi®.

The above summary of existing studies highlights the existing evidence in the literature which has been utilised in the cost effectiveness assessment of CF interventions. It highlights existing practices and the scope for potential future improvement.

5.3 Aims and objectives

The aim of this chapter was to use the best available evidence from the U.K. CF Data Registry and robust statistical methods to:

1. Generate new U.K. based health state transition (including mortality) probabilities for those who are F508Del Homozygous based on data from the U.K. CF Trust Data Registry.
2. Generate new U.K. based Cost band probabilities by health state from the U.K. CF Trust Data Registry to allow best possible estimates of cost
3. Generate new U.K. based Lung transplant probabilities from the U.K. CF Trust Data Registry
4. Compare the probabilities against existing evidence (where available) and data from the U.K. CF Data Registry.

The transition probabilities calculated in this chapter will be used to populate the De Novo model developed in Chapter 4 (Section 4.10).

5.4 Methodology

5.5 Data

The UK CF Data Registry contains longitudinal data with repeated measures over time for a number of patients. The primary outcome of CF, FEV_1, was presented as a continuous numerical value. However, this was changed into a categorical variable to match the model requirements. Additional variables in the dataset used were discrete and binomial in nature. For instance, the probability of lung transplant was binomial. Considering the high quality of CF Data Registry dataset and the coverage of >90% of the UK CF population [178], constructing a health state transition probability matrix based on this data would prove to be a great resource for the health economic modelling analysis of CF interventions. Prior to making a decision on which regression method to use on the data, I understood the nature of the variables that were in the UK CF Data Registry. A list of the variables and patient characteristics are presented in Chapter 4 Section 4.13 and 4.14.

5.5.1 Study design

The work undertaken in this chapter uses longitudinal U.K. CF Registry Data to calculate the probability of transitioning between health states as well as cost banding categories and lung transplant probabilities. Such estimates were produced whilst taking into account a range of variables presented in the statistical regression modelling section, later in this chapter (Sections 5.8.1 and 5.9.1 respectively).

5.5.2 Study Population

The patient population used to calculate the health state transition, cost band and lung transplantation in this chapter were selected from the overall patient population in the CF Data Registry. The CF Data Registry is described in detail in Chapter 4. Figure 16, from

Chapter 4, shows an inclusion/exclusion flow diagram of the patient population for each analysis in this chapter. The diagram shows that the population used in this chapter were those aged above 6 years, who are F508Del Homozygous. This equated to 4,822 patients across 34,391 observations. The population was restricted to this genotype as the exemplar intervention, Orkambi® is provided to those who are of this class. Subsequent population used for cost band and lung transplantation are defined in Chapter 4 under their respective sections (4.18.2 and 4.18.3-4 respectively).

5.6 Statistical regression modelling

5.6.1 Estimating Markov transition probabilities using the UK CF Data Registry

Using a combination of existing health economic modelling practices, expert opinion (Epi-Net) and existing research, I proposed a new Markov model structure in Chapter 4 to evaluate the cost-effectiveness of a treatment option. Subsequent sections discuss the regression methods applied to the data to derive inputs for the De Novo Markov Model. The regression methods were initially described in Chapter 4 Section 4.19.

5.7 Regression model selection

Given the characteristics of the data, that the response variable is categorical and ordered based on severity, the previous use of the regression modelling method in CF [102] and the possibility to adjust for the proportional odds assumptions in the model, it was decided that the ordered probit regression model would be used. The probabilities for transitioning to different health states and the probability of being in a particular cost band in the model were calculated using an ordered multinomial, specifically an ordered probit methodology specified by Jung [205]. An ordinal regression model with a probit link function was selected as I am interested in producing predictive probabilities of categorical responses as outcomes of the regression model. Additionally, a probit link was used as it is assumed

that the underlying distribution of the response variable, FEV_1, although separated into categories is normal and that the error term in the regression equation was normally distributed. Although in most application of ordinal regression models the choice of logit or probit link function does not make much of a difference in the outcomes [204].

The model specification also uses previous health states (Mild to Severe IV) observations as predictors for the model. Such transitional models also include observations from the current year. Also called a Markov chain model or regressive logistic model, the model treats repeated observations from the same individual as independent [201] and the model can be specified to treat each individual separately [201].

Further model specifications and methods are provided in the model specification section which follows for health state transition probabilities, cost band probabilities, lung transplant probabilities and post-lung transplant survival.

5.8 Ordered Probit Model

5.8.1 Specification of the ordered probit models

5.8.2 Health state transition

The models specification presented by Jung et al [205] was followed in order to calculate the probabilities of health state transition. The parameters were selected based on the requirements of the health state transitions within the Markov model, rather than a backward/forward stepwise regression approach. Due to the non-homogenous nature of the model age was selected for inclusion. Similarly, sex was selected as sex gaps in terms of survival and healthcare resource utilisation have been eluded to in CF [11, 178, 206-208]. Additional variables, time since last annual review allowed for the estimation of annual transition probabilities regardless of whether this was different in the actual dataset, the median time between annual review was 366 days. Lastly, year of birth

accounted for treatment trends in the dataset and would allow for selection of probability estimates which reflected more current treatment patterns in CF. Similar variable selection was undertaken by Tappenden et al [102], although their probability estimates were not, in the end, based on those covariates. It is not apparent from their publication why their work did not differentiate the transition probabilities by age when age was a significant variable in the model variable selection process.

In order to create transitional data and to account for the parallel slope assumption the dataset, as explained in Chapter 4, was separated into 6 distinct sets. Each accounting for the previous health states Mild, Mild IV, Moderate, Moderate IV, Severe, Severe IV. As such I state $Pi(k^{t}|j^{t-1})$ as the probability of individual *i* draws health state *k* in time period (*t*), is conditional on having been in health state *j* in time period *t-1*. Where time periods *t* and *t-1* represent the current health state and previous health states respectively. In simple terms, the probability of being in a future health state is dependent on the health state at a previous point in time, a year before. Such probabilities of transitioning were allowed to vary by the afore mentioned covariates in the model. Lastly, a cross-sectional output of predicted probabilities were taken to reflect predicted probabilities for those in 2016 at the various ages and for either sex. For further information on the specifications and statistical equations please see Jung et al [205].

5.8.3 Cost band probability

Similar specification and assumptions used for health state transition models were also used to determine the probability of being in the particular cost bands. The purpose of calculating transition probability estimates of being placed in a particular cost band based on the current health state is to be able to appropriately cost the cohort in any health state through their distribution amongst the 7 different costs bands alluded to in Chapter 4,

Table 17 (Section 4.18.2). This would allow more accurate costing for each health state by age and sex, whilst taking into account similar variables used in the health state transition model specification. As a result, the costs can be calculated by age, sex, and health state, which has not been done before using regression modelling methods in CF. Here the probability of being in a particular cost band was based on an individual existing in a particular health state at time (*t*) 0, the health state the cohort is in at the start of the model. Therefore, I state $Pi(k^t|j^t)$ as the probability of individual *i* draws cost band *k* in time period (*t*), is conditional on having health state *j* in time period *t*. In simple terms, the probability of being in a cost band is dependent on the health state at the same point in time, at the start of the model. I also allow the probability to differ based on a range of explanatory variables which include age, sex, year of birth and last review.

5.8.4 Further specification of the Ordered Probit models

Additional adjustment to the models were made to account for, the requirement of predicted probabilities as the outcome measure from the regression models (a probit link function) and the cut-off threshold of the categorical response variable (equidistant or flexible).

Ordinal regression models can be used to produce a number of outcome variables in the regression outputs [204], these include Odd Ratio and predicted probabilities, based on the link functions used. Due to the nature of the data required for the Markov modelling in Chapter 6, it was decided that predicted probabilities would be the primary outcome measure of the models. Similarly, the assumption of ordered probit regression models is that the distance between the threshold points of the different response health states is equally spaced. This assumption can be relaxed to change the threshold points or value to be flexible [209]. This was done as the categorisation of the different FEV_1 values (i.e.

Mild, Moderate and Severe health states) is not equally distributed but varied in the Markov model health state categories. Lastly, in cases where the proportional odds assumption was violated, adjustments were made to the model using scale effects. This has been recommended, in many instances, as a better alternative to using nominal effect (partial-proportional odds) [209]. Scale effects allow for the scale of the latent variable to differ based on the levels in the covariate within the model [209], rather than changing the threshold of the latent variable based on the different levels of the covariate which is violating the assumptions of parallel slopes [209].

5.8.5 Interpretation of model coefficients

Regression coefficients produced from regression analyses estimate unknown parameters within the population of interest. As such the coefficient estimates describe the relationship between the independent and dependent variable. A positive coefficient value indicates that as the independent variables increase the dependent variable is also increased and vice versa for negative coefficient values. This applied for cases where the dependent variable is continuous. However, for an ordered probit model, the conventional practice of coefficient value representing the mean change in the dependent variable given a one unit increase in the explanatory variable does not apply [204]. The interpretation of the coefficients provides an indication whether the explanatory variable has a negative or positive association of being in a better health state or being in a less costly band.

5.9 Generalised Estimating Equations

5.9.1 Specification of Generalised Estimating Equations model

Due to the specification of the models used to calculate the transition probabilities for both health states and costs, it was decided that the same covariates alongside age^2 would be

used to specify the relationship between the dependent variables and the independent variables for lung transplant. The variable age^2 was included to account for any non-linear relationship between the dependent and independent variable over time. Due to the nature of the data used for lung transplantation, a complementary log-log (C-loglog) binomial link function was used in the model to account for the fact that there would be more 0 values in the model compared to 1s, i.e., more individuals would not have a transplant compared to those who would. This skewed nature of the data would be mimicked by the asymmetric C-loglog link function. This would allow for better specification of the model and better link the explanatory variables to the response variable [198].

5.9.2 Probability of receiving a transplant

The regression used to model the hazard of receiving a transplant is described below. As described in Chapter 4, a GEE model was selected, to account for clustering at the level of the individual. The complementary log-log link function was used.

The covariates included in the model were: age; the square of age; gender, last review, year of birth.

Equation 1

$$Y_{ij} = g(\boldsymbol{\beta X_{ij}})$$

Y_{ij} = a vector representing whether the individual, *i*, receives a transplant or not at time *j*, $i = 1, ..., n$, $j = 1, ..., n_i$

g(.) = link function (c log-log)

$\mathbf{X}_{ij}$ = covariates (age/age^2, gender, last review and year of birth) for individual *i* at time *j* as well as an intercept term.

5.9.3 Interpretation of model coefficients

In reference to the equation above (Equation 1), the β represent weights assigned to the explanatory variables in the equation, i.e. β_1*Age_1. The initial β is a constant, also known as an intercept, which means that this is the same for all explanatory variables. It represents the value of Y when all explanatory variables are equal to 0. The remaining β are associated with a single variable, 1 – 6. These β are multiplied by each explanatory variable and indirectly influences the importance of each variable, the larger the β value the more the associated explanatory variable influences the outcome [210]. Ultimately, the β value gives the change in Y for every in unit increase one the explanatory variable [210].

5.10 Software and packages used to build regression models and calculate probabilities

This section describes the different software packages that were used to calculate the probability estimates which will feed into the model structure presented in Chapter 4.

R Studio was the primary software environment and language used to conduct the analysis to calculate the transition probabilities [169]. A range of packages and commands were used as part of the analysis.

5.11 Health state transition and cost band probabilities

As well as the assumptions taken in the model specification, additional assumptions that could be taken as part of the packages used to calculate transition probabilities are presented. The package, ordinal, from R was used for the cumulative linked models function, CLM [209]. The CLM function provides the option of changing the thresholds of the latent response variable, which forms the categories of the response variable i.e. health states. The threshold selected for the health state transitions model in this chapter

was flexible, this is to reflect that the space between the categories is not assumed to be equal but flexible. Alternatively, due to the nature of the cost bands, as structure of the latent variable, costs, is unknown, the threshold was kept equidistant.

As part of predicting the probabilities for the health state transitions or cost bands, the predict function was used in association with the expand.grid function. The predict function can be used to predict values or probabilities of being in particular health states or cost band for a series of predictors from the fitted models [211].

The expand.grid function creates a series of observations with the characteristics which I specify from the predictors in the regression equation. These were age ranging from 6-65, sex (males/females), year of birth, last annual health review (365 days). Further information on how to calculate the predicted probabilities without the predict function is available on page 360 of Hilbe [196].

5.12 Lung Transplantation probabilities

As well as the assumptions taken in the model specification, additional assumptions that could be taken as part of the packages used to calculate transition probabilities are presented. The main package, geepack, was used for the geeglm function in order to fit Generalized Estimating Equations (GEE) [212]. Due to the nature of the binary lung transplant data, a C-loglog link was used which has an asymmetric distribution and accounts for the skewed distribution of the Y or outcome variable. As above, the predict and expand.grid functions were used to determine the predicted probabilities for specified age range, sex distribution, year of birth and last annual health review (365 days).

5.13 Multicollinearity

Multicollinearity is a term used to describe the interdependence between predictors to the response variable in a regression model [213]. Also termed correlation, high values of

correlation between variables in a model can lead to a range of problems. These are unexpected signs on parameter estimates; no independent variable with statistically significant relationship with the response variable and lastly; increases in the estimated standard errors [213]. To assess the correlation between variables in the regression equations for all probabilities estimates, health state and cost band transition, the calculation of the variance inflation factor (VIF) was used alongside correlation estimates from the packages, clm; ordinal, used to run the regression models. Although there is no overall consensus on what value the VIF need to take in order to indicate collinearity, there are suggestions that value above 10 indicates this [213]. It is important to note here that in instances where variables are correlated does not reduce the ability of the model to be a good fit, affect the ability of the model to make inferences about the mean response or predictions of new responses as long as the inferences are made within the realms of the observed data [214]. The probabilities produced from the different models, particularly the ordered probit model does not look to predict future outcomes but predict existing outcomes on the observational data already available, i.e., the models look to predict probabilities within the realm of the data and not beyond 2016.

5.14 Model goodness of fit

When building the regression models for the health state transitions, cost band probabilities and lung transplantation probabilities it was assumed that the model covariates that were selected were appropriate for the model based on evidence in the literature (as above) and previous studies [102, 107]. Following on from this, I looked to understand how accurately the probabilities predicted from the models reflects the experience in the observed dataset. This understanding is called goodness of fit [215]. It is important to note here that goodness of fit is not a relative but absolute comparison of

the model. Relative model comparisons when selecting covariates and comparing outcome statistics such as R^2 is not a measure of absolute model fit [215]. Absolute goodness of fit is a comparison of the observed values against the fitted values, where the observed values are considered the best possible model [215].

The approaches used to assess model fit and adequacy in this Chapter will cover 2 areas, 1) assessment of absolute goodness of fit via statistical measures and 2) graphical examination of the difference in the observed and predicted values.

5.14.1 Statistical measures of goodness of fit

A number of tests have been identified for the assessment of fit for each of the regression methods used. For instance, for a binary logistic model, the Hosmer and Lemeshow goodness of fit (GOF) test is used to assess the goodness of fit, where a p-value >0.05 shows that model is a good fit [216]. For ordered probit models, an extension of the Hosmer and Lemeshow GOF test is used which can be applied to ordinal data and two additional tests are recommended to assess absolute goodness of fit [217]. They are the Pulkstenis and Robinson (PR) and Lipsitz test [217]. These allow for the model to be tested against the alternate hypothesis, that the model fits the data well. Similar to the Hosmer and Lemeshow GOF test, a p value <0.05 indicates that there is something wrong with the model [217] in either of these tests. For both the health state transitions and cost band probabilities, one of the above goodness of fit assessments was applied. For lung transplantation the Hosmer and Lemeshow goodness of fit (GOF) test was applied. These were applied in order to assess whether the probability estimates that were obtained from the regression models could be used with confidence.

5.15 Graphical examination

Graphical examination was undertaken to assess the outcomes presented in all regression model based predicted transition probabilities. This was done in a number of ways; results were compared to the data from the actual UK CF Registry for the year 2016 and later compared to the existing literature which was described in section 5.2 subsequent to the Introduction of this Chapter. This enabled assessment of the goodness of fit of the results, the expected results in the UK CF Data Registry against those observed and estimated from the regression methods in this thesis. This was primarily undertaken as the models were also stratified by age, (Appendix 1,2,3 and 4, section 8.1-4 for health state transition, cost band probabilities and lung transplant respectively). This graphical examination of the observed and expected probabilities could identify if the models were performing at different success rates across age as well as sex.

I now describe how the count-based estimates for, health state transition probabilities, cost band probabilities and lung transplantation probabilities were calculated for use in comparison against the estimates generated from the regression models for the graphical examination.

Chapter 4 describe the methods used to create the overall dataset for health state transition, cost band and lung transplant regression models. These datasets were used to simply count the number of transitions made in the year 2016. The year 2016 was selected as this would account for the most current treatment trends in CF for ages ranging from 6-65 and for either sex group. Variables selected to stratify the data by included only age, sex and the previous health state of the individual, where relevant. Last review and year of birth were not taken into account, although by restricting to the year 2016 the dataset would reflect the assumption of estimating transition probabilities

for 2016 from the regression models. Due to the nature of the fluctuation in transitions over time when age was used as a continuous variable, age was categorised into groups in brackets of 10 and 5 years from 5-65 years old, for health state transition and cost band proportion estimates respectively. For lung transplantation, age was left as continuous due to the small number of individuals who received a transplant compared to those who did not.

5.16 Health State transition count

Based on the previous health state, transitions to any one of the eight current health states were counted and then divided by the total number of transitions for each age group stratified by sex. This gave the proportion of individuals which made a transition from one health state to another. These proportion estimates were used as probabilities for validating the estimates from the actual dataset. Section 8.2.1 in Appendix 2 show the proportion value for those transitioning from the already described health states to a future health state by age group and sex.

5.17 Cost band count

Based on the current health state the number of individuals in any one of seven band categories, as shown in Chapter 4, were counted and then divided by the total number of transitions for each age group stratified by sex. This gave the proportion of individuals in one of the seven cost bands. These proportion estimates were used as probabilities for validating the estimates from the actual dataset. Section 8.3.1, in Appendix 3, show the proportion value for those in the different cost bands based on their current health state. As, explained, these figures were stratified by age group and sex.

5.18 Lung Transplant count

As described in Chapter 4, it was assumed that lung transplantation would only occur while in any one of the severe health states. Although transplants do occur from other, better, health states it is rare. As a result, proportion of individuals receiving a transplant were calculated from the UK Registry Data by age and sex only. Section 8.4.1 in Appendix 4 shows a graphical representation of proportion of individual receiving a transplant by age and sex.

5.19 Results

5.19.1 Health state transitions

The models fitted to calculate the health state transition probabilities showed that they all converged successfully and were able to make accurate likelihood estimates. The models also showed that the conditional hessian, which was suggested to be lower than between 10^4 and 10^6 [209], were at these values. This shows that a well-defined optimum for the model was reached [209]. Table 25 presents the convergence summaries and conditional Hessian values for each model.

Table 25: Model convergence and parameter accuracy

	Model Previous health state					
	Mild	Mild IV	Moderate	Moderate IV	Severe	Severe IV
Hessian value	8.4e+04	4.3e+04	3.5e+04	3.1e+04	4.2e+04	5.3e+04
Convergence	successful convergence					
outcome	In addition: Absolute and relative convergence criteria were met					

The ordered probit regression summaries for all health states described in Chapter 4 are provided in Table 26. These are the regression outputs from the 6 different ordered probit models that were ran based on the previous health state. The table shows the co-efficient estimates produced through the regression analyses. The estimates show whether the variables selected in the model have a positive or negative association on the probability of being in a better health state. Statistical significance of each covariate is also explained in the Table.

The number of observations available for each regression model are also presented and vary from 10,460 to 935. The variance in observational entries size exist due to the initial distribution of patients who were in the different previous health states in the prior year. There were more individuals in the Mild health state, as they represent a healthier population. Alternatively, there were only 935 entries for those in the Severe health state in the previous year. Additionally, those in the Severe health state are more likely, clinically, to be needing IV antibiotic treatment in the previous year.

Table 26: Regression output for Health state transition models, with confidence interval 95% (Note: *p<0.1; **p<0.05; ***p<0.01)

Previous Health State	Mild	Mild IV	Moderate	Moderate IV	Severe	Severe IV
Number of observations	10,460	7,190	3,941	8,022	935	3,843
	Co-efficient values					
age	- 0.005 (-0.01, 0.003)	-0.002 (-0.01, 0.04)	-0.02*** (-0.02, -0.01)	-0.01*** (-0.01, -0.01)	-0.02*** (-0.03, -0.01)	-0.02*** (-0.02, -0.01)
Time since last review	0.03*** (0.01, 0.1)	0.1*** (0.04, 0.1)	-0.2*** (-0.2, -0.1)	0.1*** (0.04, 0.1)	0.1*** (0.1, 0.2)	0.1*** (0.05, 0.1)
sex (Male)	0.1** (0.01, 0.1)	0.1*** (0.1, 0.2)	0.1*** (0.1, 0.2)	0.1*** (0.03, 0.1)	0.3*** (0.1, 0.4)	0.1** (0.01, 0.1)
year birth	-0.02*** (-0.02, -0.01)	- 0.01 (-0.01, 0.000)	-0.01** (-0.01, 0.001)	-0.01*** (-0.01, 0.004)	-0.02* (-0.03, 0.002)	- 0.02*** (-0.02, -0.01)

The results of the regression analyses show that age is a contributor to increasing severity of disease in any health state, with increasing age having a negative association on the probability in being in a better current health state, with all but two (Mild and Mild IV), being significant ($p<0.01$). In all instances a longer last annual review period demonstrates a very significant ($p<0.01$) positive association of being in a better health state. Although, there is negative association on the probability of being in a better current health state for those in the Moderate health state. Sex, being male, resulted in a higher positive association on the probability of being in a better health state compared to females. This was demonstrated in all regression models with high significance ($p<0.01$ & <0.05). This reflects the differences seen in sex survival and additional outcomes mentioned in the specification of the ordered probit model, section 5.9.1.

Lastly, year of birth, which was placed in the regression equation as an integer and accounted for the treatment trends in the Data Registry. Two models were not significant (Mild IV and Severe), the remaining models were significant at the $p<0.01$ & <0.05 levels for year of birth. The coefficient values for this variable showed that having been born closer to 2016 had a negative association on probability of moving to a better health state in the following year.

5.19.1.1 Model goodness of fit

As specified in the model goodness of fit section (5.14) of this chapter, ordered probit models could be assessed for absolute goodness of fit up to three tests. The Lipsitz test [218] was applied to the models and the results for each of the 6 regression models are presented in Table 27. The results show that only two models reject the null hypothesis, that the model predicted values are different from those that exist in the observed dataset. This means that the transition estimates produced in all models except either severe

health state can be used with reasonable confidence in the appropriate specification of the model. The remaining two models, Severe and Severe IV show a lack of fit, especially the Severe ordered probit model. This means that the transition estimates produced should be used with caution. That being said, the clinical characteristics of those in such health states are replicated in the model transition probability results, i.e., difference existing in males vs. females and increasing probability of transitioning to a more severe health state with poorer survival over time. The goodness of fit statistics for the Severe health state model was poorest, this is likely due to the much smaller numbers of patients in these health states. This is also reflected in the p-values for both models, with Severe IV having a much higher p-value than Severe health state model.

Table 27: Health State transition regression models Goodness of fit (GOF)

Health State	p value
Mild	0.02
Mild IV	0.003
Moderate	0.003
Moderate IV	2^{E-08}
Severe	**0.4**
Severe IV	**0.1**

5.19.1.2 Multicollinearity

In order to assess the multicollinearity of variables in the datasets for each health state transition the VIF was calculated. Table 28-33 presents the correlation of co-efficient results from the CLM package for each model by previous health state. Table 34 presents

the VIF values for each variable by previous health state. The results of the correlation estimations show that year of birth was correlated with age in all models. Similarly, in the VIF analysis results showed correlation existed due to the age and year of birth variables. However, this was under the value of 10 for all except the Moderate previous health state model. This VIF was conducted on the primary data utilised in the regression models. So as age was increasing the year of birth was decreasing, so there would be an expected linear relationship between the two variables. As a result, there would be an expected relationship in the VIF to be high for both these variables. We can see that the VIF is almost identical for both variables. Similarly, the correlation co-efficient values of close to 1 for the above-named variable demonstrated a high correlation, values close to one. This is mainly a structural multicollinearity in the model equation.

Table 28: Correlation of Coefficients: Mild

	age	Last review	sex Male	year of birth
age	1			
Last review	0.069	1		
sex Male	-0.034	0.009	1	
year of birth	**0.936**	0.097	-0.005	1

Table 29: Correlation of Coefficients: Mild IV

	age	Last review	sex Male	year of birth
age	1			
Last review	0.082	1		
sex Male	0.008	0.014	1	
year of birth	**0.922**	0.114	0.025	1

Table 30: Correlation of Coefficients: Moderate

	age	Last review	sex Male	year of birth
age	1			
Last review	0.081	1		
sex Male	-0.041	-0.008	1	
year of birth	**0.955**	0.081	-0.015	1

Table 31: Correlation of Coefficients: Moderate IV

	age	Last review	sex Male	year of birth
age	1			
Last review	0.1	1		
sex Male	-0.026	-0.027	1	
year of birth	**0.931**	0.101	-0.004	1

Table 32: Correlation of Coefficients: Severe

	age	Last review	sex Male	year of birth
age	1			
Last review	0.049	1		
sex Male	-0.117	0.028	1	
year of birth	**0.939**	0.047	-0.086	1

Table 33: Correlation of Coefficients: Severe IV

	age	Last review	sex Male	year of birth
age	1			
Last review	0.089	1		
sex Male	0.014	0.034	1	
year of birth	**0.934**	0.105	0.025	1

Table 34: Variance inflation factor by variable and model

Previous health state	Variance inflation factor (by variable)			
	age	Last review	sex	Year of birth
Mild	8.401202	1.01697	1.008274	8.440526
Mild IV	7.178861	1.016694	1.001007	7.220044
Moderate	10.656262	1.006025	1.00987	10.641385
Moderate IV	7.826937	1.012725	1.001199	7.842121
Severe	8.507593	1.004156	1.027378	8.424221
Severe IV	7.587763	1.011821	1.00167	7.609391

5.19.1.3 Graphical examination

As another avenue for the assessment of model fit and adequacy, graphical examination of the predicted and observed data were undertaken. The methods used to calculate the proportions of individuals transitioning to the various health states is described in the earlier methods section. Results are presented in Figures 1-96 in Appendix 2 (Section 8.2.1).

Examination of the plots across the different previous health state, Mild to Severe IV, showed that there were large variations in the observed and expected results in some instances and in others both followed similar trajectories and were within the probability interval (PI) limits of the predicted probabilities derived from the regression models. This means that although the data may be different, these differences could be explained by the use of a strict 365-day annual review period in the regression model derived predicted probabilities. In the primary dataset there are large variations in days since last review

which could lead to difference in raw transition probabilities compared to the predicted transition probabilities. This is evident through the significance of the last review variable in all specified models (Table 26, section 5.19.1).

5.19.1.4 Transition matrix

The following section provides the predicted probabilities which were estimates from the above regression models using the, expand.grid and predict function in R, which have been described in the software and packages section (5.11) of this chapter.

A summary of the results are presented in Tables 35-40. The results show the annual probability (mean) of transition stratified by sex/previous health state and being reviewed on a strict annual basis (365 days) to any one of the health states (Mild to Severe IV). Probability intervals (95% PI) (lower/upper) for each mean estimate are also provided.

Table 35: Aggregate Transition probabilities (All| Mild) (including PIs)

Sex	**Female**	**Male**
Current Health State from Mild Health State	**Mild**	**Mild**
Mild (PI)	0.649 (0.622-0.676)	0.666 (0.641-0.69)
Mild IV (PI)	0.201 (0.183-0.221)	0.194 (0.177-0.213)
Moderate (PI)	0.07 (0.063-0.079)	0.066 (0.059-0.074)
Moderate IV (PI)	0.061 (0.052-0.071)	0.056 (0.048-0.066)
Severe (PI)	0.002 (0.001-0.004)	0.002 (0.001-0.004)
Severe IV (PI)	0.005 (0.003-0.009)	0.005 (0.003-0.008)
Dead (PI)	0.005 (0.003-0.01)	0.005 (0.002-0.009)
Dead IV (PI)	0.002 (0.001-0.006)	0.002 (0-0.006)

Table 36: Aggregate Transition probabilities (All| Mild IV) (including PIs)

Sex	**Female**	**Male**
Current health state from Mild IV Health State	**Mild IV**	**Mild IV**
Mild (PI)	0.21 (0.186-0.238)	0.247 (0.221-0.276)
Mild IV (PI)	0.505 (0.476-0.533)	0.507 (0.478-0.535)
Moderate (PI)	0.053 (0.047-0.06)	0.049 (0.043-0.055)
Moderate IV (PI)	0.213 (0.191-0.237)	0.183 (0.162-0.206)
Severe (PI)	0.001 (0-0.003)	0 (0-0.002)
Severe IV (PI)	0.006 (0.003-0.01)	0.004 (0.002-0.008)
Dead (PI)	0.001 (0-0.004)	0.001 (0-0.003)
Dead IV (PI)	0.007 (0.003-0.014)	0.005 (0.002-0.011)

Table 37: Aggregate Transition probabilities (All| Moderate) (including PIs)

Sex	Female	Male
Current health state from Moderate Health State	**Moderate**	**Moderate**
Mild (PI)	0.06 (0.048-0.074)	0.077 (0.064-0.094)
Mild IV (PI)	0.05 (0.041-0.06)	0.061 (0.051-0.072)
Moderate (PI)	0.443 (0.41-0.476)	0.476 (0.445-0.508)
Moderate IV (PI)	0.348 (0.32-0.376)	0.311 (0.286-0.337)
Severe (PI)	0.042 (0.034-0.053)	0.033 (0.026-0.042)
Severe IV (PI)	0.049 (0.037-0.066)	0.035 (0.026-0.048)
Dead (PI)	0.004 (0.002-0.009)	0.003 (0.001-0.006)
Dead IV (PI)	0 (0-0.002)	0 (0-0.001)

Table 38: Aggregate Transition probabilities (All| Moderate IV) (including PIs)

Sex	Female	Male
Current health state from Moderate IV Health State	**Moderate IV**	**Moderate IV**
Mild (PI)	0.009 (0.006-0.012)	0.018 (0.014-0.024)
Mild IV (PI)	0.049 (0.042-0.059)	0.074 (0.065-0.085)
Moderate (PI)	0.087 (0.077-0.097)	0.109 (0.099-0.12)
Moderate IV (PI)	0.66 (0.633-0.686)	0.637 (0.612-0.662)
Severe (PI)	0.017 (0.014-0.021)	0.014 (0.011-0.017)
Severe IV (PI)	0.157 (0.138-0.178)	0.129 (0.112-0.148)
Dead (PI)	0.001 (0-0.002)	0.001 (0-0.002)
Dead IV (PI)	0.017 (0.011-0.025)	0.014 (0.009-0.021)

Table 39: Aggregate Transition probabilities (All| Severe) (including PIs)

Sex	Female	Male
Current health state from Severe Health State	**Severe**	**Severe**
Mild (PI)	0.002 (0-0.01)	0.005 (0.001-0.017)
Mild IV (PI)	0.003 (0.001-0.01)	0.006 (0.002-0.016)
Moderate (PI)	0.038 (0.021-0.07)	0.063 (0.04-0.099)
Moderate IV (PI)	0.048 (0.031-0.075)	0.07 (0.05-0.098)
Severe (PI)	0.36 (0.298-0.426)	0.412 (0.354-0.471)

Severe IV (PI)	0.486 (0.409-0.563)	0.405 (0.34-0.475)
Dead (PI)	0.05 (0.028-0.088)	0.031 (0.016-0.059)
Dead IV (PI)	0.01 (0.003-0.03)	0.005 (0.001-0.018)

Table 40: Aggregate Transition probabilities (All| Severe IV) (including PIs)

Sex	**Female**	**Male**
Current health state from Severe IV Health State	**Severe IV**	**Severe IV**
Mild (PI)	0.001 (0-0.003)	0.002 (0.001-0.004)
Mild IV (PI)	0.002 (0.001-0.004)	0.002 (0.001-0.005)
Moderate (PI)	0.011 (0.008-0.017)	0.014 (0.009-0.02)
Moderate IV (PI)	0.082 (0.067-0.1)	0.093 (0.077-0.112)
Severe (PI)	0.077 (0.066-0.09)	0.084 (0.072-0.097)
Severe IV (PI)	0.721 (0.688-0.751)	0.713 (0.681-0.743)
Dead (PI)	0.008 (0.006-0.012)	0.008 (0.005-0.011)
Dead IV (PI)	0.094 (0.071-0.123)	0.081 (0.061-0.108)

The transition matrices (Tables 35-40) show that males compared to females are more likely to stay in better health state which is confirmed by the significance of the sex variable in the regression model. This is clearly evident in the best health state, Mild (males; 0.666 vs. females; 0.649). Similarly, males are more likely to transition back towards a better health state compared to females. This is evident in multiple health states but clearly so in the Severe IV to Moderate IV transition, males; 0.093 vs. females; 0.082.

This sex-based effect also continues within mortality probabilities across all health states, most evident in the Severe IV to Dead IV transition, males; 0.081 vs. females; 0.094. We can also see that the probability of dying increases subsequent to existing in a worse previous health state. For example, the probability of dying is lower for those in the Mild health state (Dead; 0.005, Dead IV; 0.002) compared to those in the Severe health state (Dead; 0.05, Dead IV; 0.068).

We can see that those who do not receive IV treatment in the previous year have a lower probability to transition to health states which involves IV treatment in that current year and vice versa. This could also mean that those who did not have IV treatment in the previous year are less likely to require it in the following year.

The disaggregated results which also stratify the above probability estimates by age (6-65 year), in the Supplementary Material (Markov Model), which will be used for the exemplar health economic cost utility analysis (Chapter 6), shows the same pattern.

5.19.1.5 Comparison against literature

Existing data on health state transition probabilities produced by Tappenden et al [102] were available and based on the U.K CF Data Registry and used for external validity assessment, although such probabilities were not stratified by age or sex. Additional probabilities for health state transitions, although not U.K. based [81, 126], were also compared against using my results.

Regression model outputs were also compared to those available in the literature, where possible. Age being significant is consistent with another study which used U.K CF Data Registry [102]. This study used similar regression methods as presented in this chapter [102] and also used similar variables for their analyses. But the study did not state why probabilities were not based on such estimates of age for their health economic

modelling. Such studies also did not provide details of model accuracy/goodness of fit [102]. The coefficients produced from the health state transitions model showed that males were better off overall. This is reflective of the sex gap present in mortality particularly as seen in the UK CF Data Registry [179] and more recently in survival modelling using the UK CF Data Registry [193].

Table 41 shows the health states transitions produced in this chapter in comparison to those generated by Tappenden et al [102]. It is important to note here that the transitions that were calculated in this chapter also included death subsequent to receiving no IV treatment in the current year and also subsequent to receiving IV treatment in the current year. Whereas Tappenden et al [102] calculated mortality separately to health state transitions. As result the transitions in Table 41 may not sum to 1 exactly. Additionally, probabilities across no IV and IV health states and both sex (male and female) were added together by health state for comparison purposes. The results show that the probability estimates generated from the models in this chapter are very similar to those which were generated from the same ordered probit methods, albeit different genotypes, by Tappenden et al [102]. This supports the face validity of the estimates produced from the regression methods used in this thesis. This is despite the lack of goodness of fit which could be due to use of annual review at exactly 365 days to derive predicted probabilities.

Table 41: Model derived transition probability comparison

FEV_1 transition	Tappenden et al [102] Mean Probability value	Estimates from this chapter Mean Probability value
≥70 to ≥70% - Mild to Mild	0.87	0.80
≥70 to 40–60% - Mild to Moderate	0.13	0.19
≥ 70 to < 40% - Mild to Severe	0.00	0.01
40–60 to ≥70% - Moderate to Mild	0.13	0.10
40–60 to 40–60% - Moderate to Moderate	0.76	0.77
40–60to<40% - Moderate to Severe	0.10	0.12
< 40 to ≥70% - Severe to Mild	0.03	0.01
< 40 to 40–60% - Severe to Moderate	0.14	0.11
< 40 to < 40% - Severe to Severe	0.84	0.82

Additional comparison of the estimates against data from Van gool et al [81] are presented in Table 42, and Sharma et al [126] is discussed further below.

It can be see that the mortality-based estimates when averaged across the age groups present in Table 42 result in transition probabilities that are comparable, even though the data utilised is from the Australian CF Data Registry [81]. Van gool et al [81] also assume that transition to a better health state is not possible, whereas I do allow such transitions, as a result the transitions may differ based on this assumption. But the transitions to better health states in my dataset is based on existing evidence of such occurrences in the Data Registry and CF in general. It is also important to note here that the transition probabilities generated by Van gool et al [81] are based on 2004-2005 data, when more novel treatments were not available, whereas this thesis utilises more recent data. Lastly, Sharma et al [126] used data from the Cystic Fibrosis Foundation Patient Registry in the U.S [34] to look at mortality from the health states presented in Chapter 4. However, percentage annual mortality, by age for F508Del Homozygous patients, are presented in a graphical format and are difficult to quantify. However, it is clear from the graphs that females had a high annual mortality by age compared to males. This pattern is clearly seen in this chapter, with mortality probabilities presented in Tables 35-40.

Table 42: Model derived Transition probability comparison

FEV_1 transition	Van gool et al [81]	Estimates from this chapter
	Mean Probability value	Mean Probability value
≥70 to ≥70% - Mild to Mild	0.92	0.80
≥70 to 40–60% - Mild to Moderate	0.10	0.19
≥ 70 to < 40% - Mild to Severe	0.00	0.01
≥ 70 to N/A - Mild to Dead	0.004	0.004
40–60 to ≥70% - Moderate to Mild	N/A	0.10
40–60 to 40–60% - Moderate to Moderate	0.93	0.77
40–60 to <40% - Moderate to Severe	0.07	0.12
40–60 to N/A - Moderate to Dead	0.017	0.01
< 40 to ≥70% - Severe to Mild	N/A	0.01
< 40 to 40–60% - Severe to Moderate	N/A	0.11
< 40 to < 40% - Severe to Severe	0.74	0.82
< 40 to N/A - Severe to Dead	0.23	0.07

5.19.2 Cost band probabilities

Here I describe the results of the regression modelling methods used to calculate the probability of being in one of the seven cost bands based on the current health state of the individual which was determined in the above section.

The models fitted to calculate the probabilities showed that they all converged successfully and were able to make accurate likelihood estimates. The models also showed that the conditional hessian, which was suggested to be lower than 10^4 and 10^6 [209], were at these values and shows that a well-defined optimum for the model was reached [209]. Table 43 presents the convergence summaries and conditional Hessian values for each model.

Table 43: Model convergence and parameter accuracy

	Model Cost band probabilities					
	Mild	Mild IV	Moderate	Moderate IV	Severe	Severe IV
Hessian value	5.00E+04	4.70E+04	3.00E+04	4.10E+04	2.40E+04	6.20E+04
Convergence outcome	successful convergence In addition: Absolute and relative convergence criteria were met					

The ordered probit regression summaries for all cost bands are provided in Table 44. The table shows the co-efficient estimates produced through the regression analyses. The estimates show whether the variables selected in the model have a positive or negative association on the probability of being in a particular cost band. Statistical significance of each covariate is also explained in the table.

The number of observations available for each regression model are also presented and vary from 2,610 to 191. The variance in observational entries size exist due to the initial distribution of patients who were in the current health states in the current year. There were more individuals in the Mild health state, as they represent a healthier population. Alternatively, there were only 191 entries for those in the Severe health state.

Table 44: Regression output for cost band probability models with confidence interval 95% (Note: *p<0.1; **p<0.05; ***p<0.01).

Current Health State	Regression output					
	Mild	**Mild IV**	**Moderate**	**Moderate IV**	**Severe**	**Severe IV**
Number of observations	2,610	1,867	883	2,221	191	1,130
	Co-efficient values					
age	0.1*** (0.1, 0.2)	-0.003 (-0.1, 0.1)	0.1 (-0.01, 0.1)	-0.04* (-0.1, -0.004)	-0.02 (-0.2, 0.1)	-0.1*** (-0.1, -0.02)
Time since last review	-0.01 (-0.2, 0.1)	0.3*** (0.1, 0.4)	-0.2 (-0.4, 0.1)	0.2* (0.000, 0.3)	-0.7*** (-1.1, -0.3)	0.2** (0.1, 0.4)
sex (Male)	0.1 (-0.01, 0.1)	-0.2*** (-0.3, -0.1)	-0.1* (-0.3, -0.01)	-0.04 (-0.1, 0.03)	-0.3* (-0.6, -0.02)	-0.1** (-0.2, -0.04)
year birth	0.1*** (0.1, 0.1)	-0.01 (-0.1, 0.05)	0.1 (-0.02, 0.1)	-0.03 (-0.1, 0.001)	0.003 (-0.2, 0.2)	-0.1* (-0.1, -0.01)

The results of the regression analyses show that age is a contributor to the increasing probability of being in a higher cost band for those in Severe IV health state as it was associated with a negative co-efficient value, this was significant, Severe IV, -0.1***, ($p<0.01$). Alternatively, on one occasion, Mild (0.1***), the regression model demonstrates a very significant association of age, ($p<0.01$) of being in a better, less costly, cost band. In other instances, Moderate, age continues to demonstrate a positive association although not significant ($p>0.05$). It is also important to note here that current health states with no IV treatment show positive co-efficient values for the better health states, which shows that healthier individuals with increasing age may have a higher probability of being in the less costly band for those health states, as this is not significant ($p>0.05$).

In one instance (Severe), a longer last annual review period demonstrates a very significant ($p<0.01$) association. The co-efficient shows that a larger gap since the last annual review resulted in a lower probability of being in a cheaper cost band (-0.7). This pattern also exists in other No IV health states (Mild (-0.01), Moderate (-0.2)). Alternatively, it is clear from the co-efficient values for IV health states (Mild IV 0.1, Moderate IV 0.2 and Severe IV 0.2) that larger gaps between annual review results in a higher probability of being in a less costly band. Clinically, this make sense as those who have entered an IV based health state in the current year since their last annual review and have not been seen for some time, are less likely to be sicker compared to those who have not entered an IV treatment health state and have a short last annual review period, i.e. needing to see a specialist earlier.

Being male resulted in a higher probability of being in a less costly band, compared to females, in the Mild health state (0.1 (95% CI: -0.01, 0.1), although not at a significant level. In contrast, being male resulted in the higher probability of being in a high-cost band for the remainder of the health states (Mild IV, Moderate, Moderate IV, Severe, Severe IV). Significantly so for those in the Mild IV and Severe IV health states ($p<0.05$).

Lastly, year of birth, which was placed in the regression equation as an integer. The coefficient values for this variable showed that having been born closer to 2016 resulted in a higher probability of being in a more costly band for all the IV health states. Alternatively, being born closer to 2016 and being in the No IV health states meant that there was a higher probability of being in the less costly bands and this was significant for the Mild health state (0.1*** (95% CI: 0.1, 0.1), ($p<0.01$)).

5.19.2.1 Model goodness of fit

As specified in the methods section of this chapter, ordered probit models could be accessed for absolute goodness of fit up to three tests. The Lipsitz test [218] was applied to the models and the results for each regression model are presented in Table 45. The results show that only one model, Mild, does reject the null hypothesis, that the model predicted values are different from those that exist in the observed dataset.

Table 45: Cost band probability regression models; Goodness of fit (GOF)

Health State	p value
Mild	3^{E-10}
Mild IV	**0.3**
Moderate	**0.6**
Moderate IV	**0.4**
Severe	**0.06**
Severe IV	**0.3**

5.19.2.2 Multicollinearity

In order to assess the multicollinearity of variables in the datasets for each current health state and subsequent cost band probabilities, the VIF was calculated. Table 46-51 presents the correlation of co-efficient results from the CLM package for each model by current health state. Table 52 present the VIF values for each variable by previous health state. This VIF was conducted on the primary data utilised in the regression models. So as age was increasing the year of birth was decreasing, so there would be an expected linear relationship between the two variables, this is known as a structural multicollinearity. As a result, there would be an expected relationship in the VIF to be high for both these variables. We can see that the VIF is almost identical for both variables, this is mainly a structural multicollinearity in the model equation. Similarly, the correlation co-efficient values of close to 1 for the above-named variable demonstrated a high correlation, values close to one. The remainder of the variables do show very weak or weak levels of correlations which shows that there is a low risk of bias present in the

model. Similarly, due to the lack of multicollinearity in the remainder of the variables and the presence of significant regression co-efficient values of independent variables in relationship to the dependent variable, it is likely that the specified models are producing reliable relationships between the independent and dependent (health state) variable and any significance shown for any variable is likely to be correct.

Table 46: correlation by variable and health state

Correlation of Coefficients: Mild				
	age	**Last review**	**sex Male**	**year of birth**
age	1			
Last review	-0.1555	1		
sex Male	0.0069	0.0379	1	
year of birth	0.9965	-0.1537	0.0105	1

Table 47: correlation by variable and health state

Correlation of Coefficients: Mild IV				
	age	**Last review**	**sex Male**	**year of birth**
age	1			
Last review	-0.1382	1		
sex Male	0.007	-0.0294	1	
year of birth	0.9954	-0.1398	0.0156	1

Table 48: correlation by variable and health state

Correlation of Coefficients: Moderate				
	age	**Last review**	**sex Male**	**year of birth**
age	1			
Last review	-0.1069	1		
sex Male	-0.0701	-0.0258	1	
year of birth	0.9971	-0.1082	-0.0615	1

Table 49: correlation by variable and health state

Correlation of Coefficients: Moderate IV				
	age	**Last review**	**sex Male**	**year of birth**
age	1			
Last review	-0.1857	1		
sex Male	0.0063	0.0055	1	
year of birth	0.9959	-0.1875	0.0104	1

Table 50: correlation by variable and health state

Correlation of Coefficients: Severe				
	age	**Last review**	**sex Male**	**year of birth**
age	1			
Last review	-0.1557	1		
sex Male	-0.0303	0.1478	1	
year of birth	0.9972	-0.1575	-0.0297	1

Table 51: correlation by variable and health state

Correlation of Coefficients: Severe IV				
	age	**Last review**	**sex Male**	**year of birth**
age	1			
Last review	-0.122	1		
sex Male	0.0175	-0.2101	1	
year of birth	0.9944	-0.0908	0.0117	1

Table 52: Variance inflation factor by variable and model

Current health state	age	Last review	sex	Year of birth
Mild	149	1	1	149
Mild IV	114	1	1	114
Moderate	174	1	1	174
Moderate IV	117	1	1	117
Severe	187	1	1	187
Severe IV	112	1	1	112

5.19.2.3 Graphical examination

As another avenue for the assessment of model fit and adequacy, graphical examination of the predicted and observed data were undertaken. The methods used to calculate the proportions of individuals transitioning to the various health states is described in the earlier methods section. Results are presented in section 8.3.1 in Appendix 3.

Examination of the plots across the different current health states, Mild to Severe IV, showed that there were large variations in the observed and expected results in some instances and in others both followed similar trajectories and were within the PI interval limits of the predicted probabilities derived from the regression models. Most notably, the estimates produced from the ordered probit method were a better fit for the cost band probabilities than for the health state transitions when compared graphically, despite the goodness of fit statistics presenting data showing otherwise. It is also important to note here that the predicted probabilities for being in any given cost band based on being in a

particular health state were based on strict annual review (365 days). This could have influenced the goodness of fit results.

5.19.2.4 Transition matrix

The following section provides the predicted probabilities which were estimates from the above regression models using the, expand.grid and predict function in R, which have been described in the software and packages section of this chapter.

A summary of the results are presented in Table 53-57. The results show a mean annual average probability of being in a particular cost band stratified by sex/current health state and being reviewed on a strict annual basis (365 days). Probability intervals (95% PI) (lower/upper) for each mean estimate are also provided. The tables show that males compared to females are more likely, overall, to stay in lower cost bands. Although this is not evident in the Mild health state, it is in the remainder of the health states. We can also see that those in the No IV compared to the IV based health states have a higher probability of being placed into lower cost band categories. Clinically, this makes sense as those not receiving IV treatment based on health state are less likely be in high-cost bands even within the same current health state. This is most likely due to no costs being incurred in those No IV health states for IV treatment and reduced costs for additional resources for any given band compared to those in IV based health states.

Table 53: Aggregate Cost band probabilities Mild

Sex	Female	Male
Cost band/Current Health State	**Mild Female**	**Mild Male**
1 (PI)	0.059 (0.048-0.073)	0.052 (0.043-0.064)
1a (PI)	0.008 (0.006-0.012)	0.007 (0.005-0.011)
2 (PI)	0.222 (0.197-0.25)	0.209 (0.186-0.235)
2a (PI)	0.506 (0.477-0.535)	0.509 (0.48-0.537)
3 (PI)	0.185 (0.154-0.219)	0.199 (0.169-0.233)
4 (PI)	0.014 (0.006-0.028)	0.016 (0.008-0.032)
5 (PI)	0.003 (0-0.017)	0.004 (0-0.02)

Table 54: Aggregate Cost band probabilities Mild IV

Sex	Female	Male
Cost band/Current Health State	**Mild IV Female**	**Mild IV Male**
1 (PI)	0.002 (0.001-0.005)	0.004 (0.001-0.009)
1a (PI)	0.003 (0.001-0.007)	0.005 (0.002-0.01)
2 (PI)	0.106 (0.082-0.136)	0.139 (0.111-0.174)
2a (PI)	0.377 (0.34-0.415)	0.41 (0.377-0.444)
3 (PI)	0.464 (0.417-0.511)	0.408 (0.361-0.457)
4 (PI)	0.036 (0.024-0.053)	0.025 (0.016-0.038)
5 (PI)	0.01 (0.005-0.02)	0.006 (0.003-0.012)

Table 55: Aggregate Cost band probabilities Moderate

Sex	Female	Male
Cost band/Current Health State	**Moderate Female**	**Moderate Male**
1 (PI)	0.045 (0.03-0.068)	0.059 (0.042-0.084)
1a (PI)	0.004 (0.001-0.011)	0.005 (0.002-0.013)
2 (PI)	0.127 (0.099-0.162)	0.15 (0.121-0.184)
2a (PI)	0.555 (0.519-0.591)	0.56 (0.526-0.594)
3 (PI)	0.215 (0.175-0.262)	0.185 (0.151-0.225)
4 (PI)	0.042 (0.026-0.065)	0.032 (0.02-0.05)
5 (PI)	0.008 (0.003-0.021)	0.005 (0.002-0.015)

Table 56: Aggregate Cost band probabilities Moderate IV

Sex	Female	Male
Cost band/Current Health State	**Moderate IV Female**	**Moderate IV Male**
1 (PI)	0.003 (0.001-0.008)	0.003 (0.001-0.01)
1a (PI)	0.002 (0.001-0.006)	0.002 (0.001-0.007)
2 (PI)	0.041 (0.028-0.061)	0.045 (0.031-0.066)
2a (PI)	0.326 (0.288-0.367)	0.34 (0.3-0.381)
3 (PI)	0.475 (0.436-0.515)	0.468 (0.428-0.508)
4 (PI)	0.126 (0.102-0.158)	0.118 (0.095-0.149)
5 (PI)	0.022 (0.014-0.036)	0.02 (0.013-0.032)

Table 57: Aggregate Cost band probabilities Severe

Sex	Female	Male
Cost band/Current Health State	**Severe Female**	**Severe Male**
1 (PI)	0.013 (0.003-0.056)	0.028 (0.009-0.082)
1a (PI)	0 (0-0)	0 (0-0)
2 (PI)	0.065 (0.027-0.145)	0.104 (0.056-0.185)
2a (PI)	0.449 (0.338-0.569)	0.511 (0.421-0.602)
3 (PI)	0.336 (0.242-0.45)	0.275 (0.196-0.376)
4 (PI)	0.124 (0.06-0.242)	0.076 (0.037-0.149)
5 (PI)	0.01 (0.001-0.075)	0.004 (0-0.037)

Table 58: Aggregate Cost band probabilities Severe IV

Sex	Female	Male
Cost band/Current Health State	**Severe IV Female**	**Severe IV Male**
1 (PI)	0.003 (0-0.013)	0.002 (0-0.012)
1a (PI)	0.002 (0-0.01)	0.002 (0-0.01)
2 (PI)	0.021 (0.01-0.043)	0.024 (0.011-0.049)
2a (PI)	0.167 (0.128-0.215)	0.213 (0.165-0.269)
3 (PI)	0.412 (0.359-0.466)	0.459 (0.401-0.518)
4 (PI)	0.284 (0.236-0.34)	0.236 (0.193-0.292)
5 (PI)	0.108 (0.08-0.15)	0.06 (0.04-0.091)

The disaggregate results which also stratify the above probability estimates by age (6-65 year), in the Supplementary Material (Markov Model), which will be used for the exemplar health economic cost utility analysis (Chapter 6), shows the same above sex, no IV/IV treatment-based patterns.

5.19.2.5 Comparison against literature

Existing data on costs produced by Tappenden et al [102] and Whiting et al [107] were available and based on the U.K CF Data Registry. However, only the data from Whiting et al [107] were used for external validity assessment. This was primarily because I did not have any estimate of cost per health state in this chapter. Similarly, proportion data from Tappenden et al [102] was based on a different genotype of CF patients in the U.K Data Registry. As a result, only the regression coefficients from the linear regression model output were compared against [107]. Although, it is important to note here that the variables selected for the regression modelling conducted in this chapter were different to those used by Whiting et al [107]. Similarly, Whiting et al [107] included data on high-cost drug use in their analysis, whereas I did not and the costs for Whiting et al [107] were based on the total CF population in the U.K. Data Registry for 2015. As a result, differences between the two could be explained by the above.

An existing study on the U.K CF Data Registry shows that females cost more during the later years of their lives compared to males [219]. The coefficients in the regression model show that males are associated with a higher probability to be in a lower cost band than females for all except the Mild health state. The probability estimates generated from the regression model reflect the literature and show that males are less likely to be placed in the high-cost bands compared to females.

Additional data, although not U.K. based [81], was available but not compared against, for the same reason as above, I did not produce any estimate of cost per health state. This will be further evaluated in Chapter 6 Section 6.26.2.4.

Whiting et al [107] showed the cost of treating CF in the UK for the total CF population was £41,084 (SE: £588) per person per year and that this value changes based on age (-£100.78 SE; 12) and FEV_1 (-£254.34, SE; 6). As a result, the baseline cost of £41,084 (SE: £588) decreased with increasing age as well of from higher FEV_1 values. This pattern was compared to the estimates produced in this chapter. The regression estimates from each model in Table 40 showed that as age was associated with an increase the probability of being in a cheaper band for those in the No IV health state and vice versa for those in the IV based health states. This age effect of Whiting et al [107] on costs is similar to that which is seen in our estimates. Similarly, those in better FEV_1 health states have lower negative co-efficient values compared to those with FEV_1 values which correspond to worse health states. For example, an individual in the Mild IV health state has a lower negative co-efficient value (-0.003 ($p>0.01$)), than those in the Severe IV health state (-0.1 ($p<0.01$)).

5.19.2.5.1 Comparison against the observed data

Additional comparisons were made against the data used to generate the regression models. This was done in order to determine if the underlying patterns in the derived datasets are similar to what already exists. This can help me further validate the model.

Evaluation of the dataset utilised to estimate the probabilities of costs showed that the better/healthier states often occupied the band 2A more than any other cost banding category (Mild, Mild IV, Moderate), this was followed by high-cost bands (4 and 5) being

occupied in more severe current health states (Moderate IV, Severe, Severe IV). This is clearly shown in Table 59, below which shows the distribution of CF individuals in particular bands but sex and health state (current). Furthermore, the sex-based difference shows that males were more likely to be placed in less costly bands compared to females overall. This is similar to what is seen in the probability estimates generated from the regression models.

Table 59: Distribution of individuals in cost bands by health state (current) 2013-2016

Band	Sex	Current Health state					
		Severe IV	Severe	Moderate IV	Moderate	Mild IV	Mild
1	Female	4	1	7	17	2	141
	Male	2	4	7	36	7	185
1A	Female	2	0	6	0	1	17
	Male	3	0	3	5	10	24
2	Female	14	3	63	47	124	333
	Male	16	15	50	86	145	507
2A	Female	83	23	351	178	362	440
	Male	106	72	349	317	407	740
3	Female	199	14	572	70	389	77
	Male	243	42	435	94	360	138
4	Female	179	7	164	11	27	3
	Male	152	9	149	17	20	4
5	Female	84	0	38	1	9	1
	Male	43	1	27	4	4	0

Table 59 shows that males compared to females have a higher probability to stay in a better cost band. We can see that males in any health state, except Mild, have a lower probability, compared to females, of being in either cost bands 4 or 5, which are the most expensive, £33,224 and £40,054 respectively. We can also see that those who do not receive IV treatment in the current year have a lower probability of being placed in a higher cost band than those who do. These patterns are also evident in the predicted probabilities estimates looking at the probability of being in a particular cost band by current health state.

In comparing the existing studies which have data which could be utilised the validate the estimates from the methods used in this chapter, the results show that the estimates produced have similar patterns and probability estimates. This strengthens the validity of the estimates produced in this chapter, despite the lack of model fit, especially for the cost band probability estimates. In conducting the work presented in this chapter the work improves the data available in the literature to allow for more accurate estimates of cost-effectiveness in future cost effectiveness analyses in Cystic Fibrosis.

5.19.3 Lung Transplant probabilities

Here I describe the results of the regression modelling methods used to calculate the probabilities of receiving a lung transplant using the data described in Chapter 4 (Section 4.18.3).

5.19.3.1 Model goodness of fit

Model goodness of fit as specified in the goodness of fit section above, specified that I would be using the Hosmer and Lemeshow goodness of fit (GOF) test to see if the observed data and expected data produce similar results for lung transplantation. Table

55 below, shows the output from the test, which shows that the model was a good fit when comparing the observed and expected results. The p value shows that I can reject the alternative hypothesis that the expected and observed values are different. Table 61 presents the observed and expected number of transplants generated compared to the model against the actual dataset based on the number of groups specified in the goodness of fit calculation, G, which is most commonly selected to be 10 [196]. For larger datasets high values of G are set [196]. However, it is also suggested that the groups be changed and the goodness of fit test be re-evaluated at different levels to test for consistency in results [196]. As a result, the grouping was changed to 8 and 12 to see whether the p-value fell below 0.05. The results show that change in the groupings did not change the result to a value below 0.05, Table 62.

Table 60: Hosmer and Lemeshow goodness of fit (GOF) test

X-squared	9
df	8
p-value	0.3

Table 61: Observed and expected number of transplants by different group specified

G	Observed: No Lung Transplant	Observed: Lung Transplant	Expected: No Lung Transplant	Expected: Lung Transplant
1	3459	2	3461	0
2	3457	3	3457	3
3	3454	6	3455	5
4	3450	10	3449	11
5	3445	15	3450	10
6	3439	21	3431	29
7	3433	27	3437	23
8	3426	34	3419	41
9	3419	41	3424	36
10	3,408	53	3408	53

Table 62: Hosmer and Lemeshow goodness of fit (GOF) test with changed grouping

Groups		
8	X-squared	9
	df	6
	p-value	**0.2**
12	X-squared	9
	df	10
	p-value	**0.5**

5.19.3.2 Graphical examination

As another avenue for the assessment of model fit and adequacy, graphical examination of the predicted and observed data were undertaken. The methods used to calculate the proportions of individuals transitioning to the various health states is described in the earlier methods section. Results are presented in Section 8.4.1 in Appendix 4.

Examination of the plots across age and sex showed that there were large variations in the observed and expected results in some instances and in others both followed similar trajectories.

5.19.3.3 Multicollinearity

In order to assess the multicollinearity of variables in the dataset the VIF was calculated. Table 63 present the VIF values for each variable.

Table 63: Variance inflation factor for lung transplantation variables

	Variance inflation factor (by variable)				
Transplant	age	age^2	sex	Last review	year of birth
	28.48	26.32	1.05	1.06	5.99

The VIF analysis results showed correlation existed due to the age and age^2 and year of birth variables. The VIF values showed that only the two variables, age and age^2 were highly correlated. However, this is expected as changes in age while holding other covariates in the model constant is also expected to change the age^2 covariate as they are related, a structural collinearity. On the other hand, the year of birth variable, although shows signs of correlation, this is below 10. As previously encountered, year of birth and age are likely to be correlated due to structural collinearity. The value is lower, most likely due to repeated measures having been used in the regression model.

Table 64: Lung Transplantation regression output

	Transplant		
	Risk Ratio	**CI**	**p**
(Intercept)	0.00	-	.279
age	1.45	1.33 – 1.59	**<.001**
age^2	0.99	0.99 – 1.00	**<.001**
sex (Male)	0.78	0.59 – 1.02	.070
Last review	1.00	1.00 – 1.00	**<.001**
Year of birth	1.02	0.98 – 1.06	.411

The results of the regression analyses, Table 64, show that an increase in age increases the probability or risk of receiving a transplant. The age^2 variable shows a decreased risk of receiving a transplant ($p<0.01$), possibly hinting to a bell-shaped distribution, most likely due to survival bias. Although this does show no effect based on the confidence interval (0.99 – 1.00). The results also show that there is no difference in the probability or risk of receiving a transplant when there is a change in the number of days since the patient had their annual review, also statistically significant ($p<0.01$). The relative risk of receiving a transplant was lower for males (0.78 (95%CI 0.59-1.02) compared to females, although not statistically significant. However, such a pattern also exists in the CF Data Registry observed data which shows that females are more likely to require a lung transplant compared to males.

5.19.3.4 Transition matrix

The following section provides the predicted probabilities which were estimates from the above regression models using the, expand.grid and predict function in R, which have been described in the software and packages section of this chapter (Section 5.10).

In summary, Figure 24, shows the probability of receiving a transplant based on sex and age. We can see that females are more likely to receive a transplant compared to males. This is also the case in the observed dataset, Table 65, where overall a higher percentage of females receive a transplant compared to the males. We can also see that the probability of receiving a transplant increases until around 34 years for both sex groups. Subsequently, the probability decreases near enough to 65 years for both groups which according to the age^2 variable is some survival bias present in the data due it being significant.

Figure 24: Probability of receiving a transplant

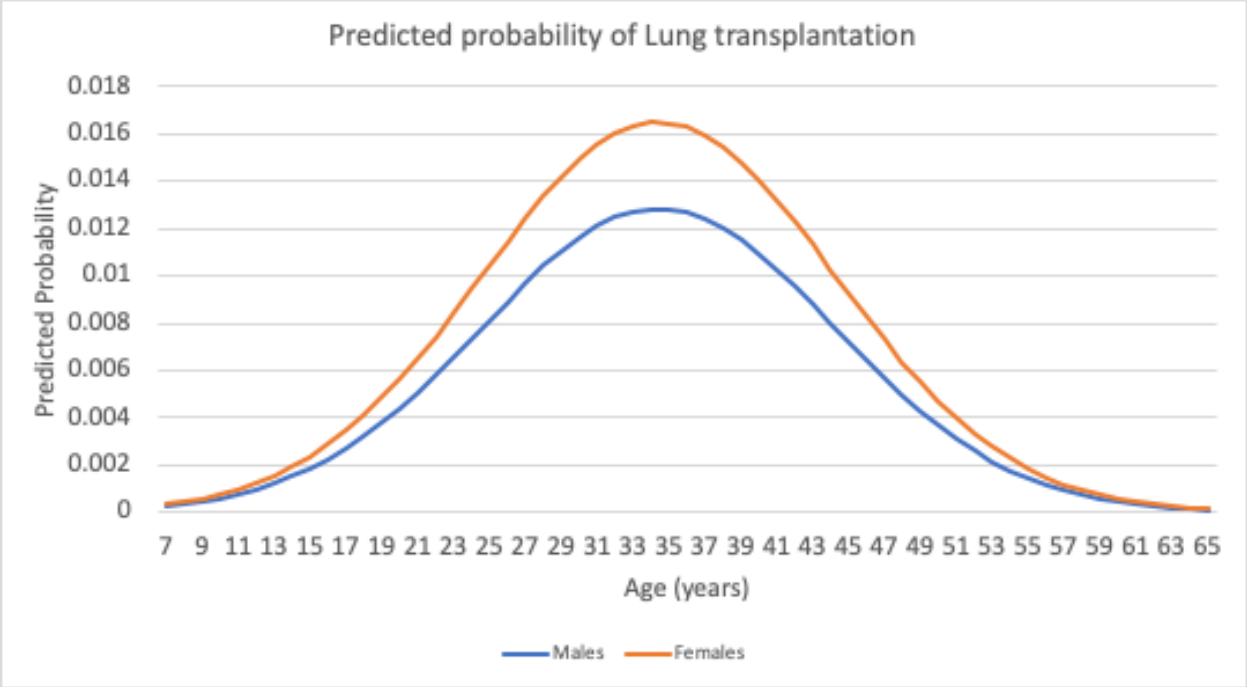


Table 65: Observed lung transplants by sex

	Number of individuals who received a transplant	
Sex	**Female**	**Male**
Transplant		
No	15,495	18,896
Yes	104	107
%	0.671	0.566

5.19.3.5 Comparison against literature

Existing data on lung transplant produced by Van gool et al [81] available and based on the Australian CF Data Registry between 2002-2005. These were used for external

validity assessment of the probabilities generated in this chapter. Evaluation of the data presented by Van gool et al [81], also presented in Section 5.2.3 of this Chapter showed that a large majority of lung transplants occurred while the CF individual was in the Severe health state, although very few occurred in better health states. Figure 25 below shows the probability of receiving a transplant based on the health states which was taken from Van gool et al [81].

Figure 25: Probability of Lung transplant by Health state [81].

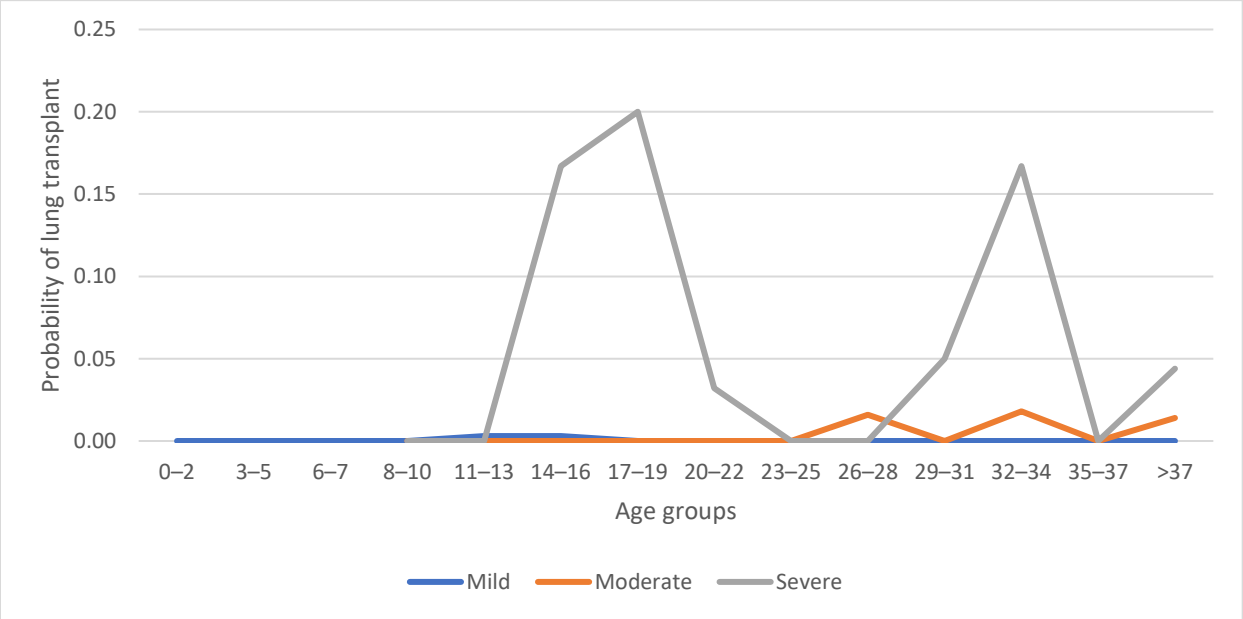
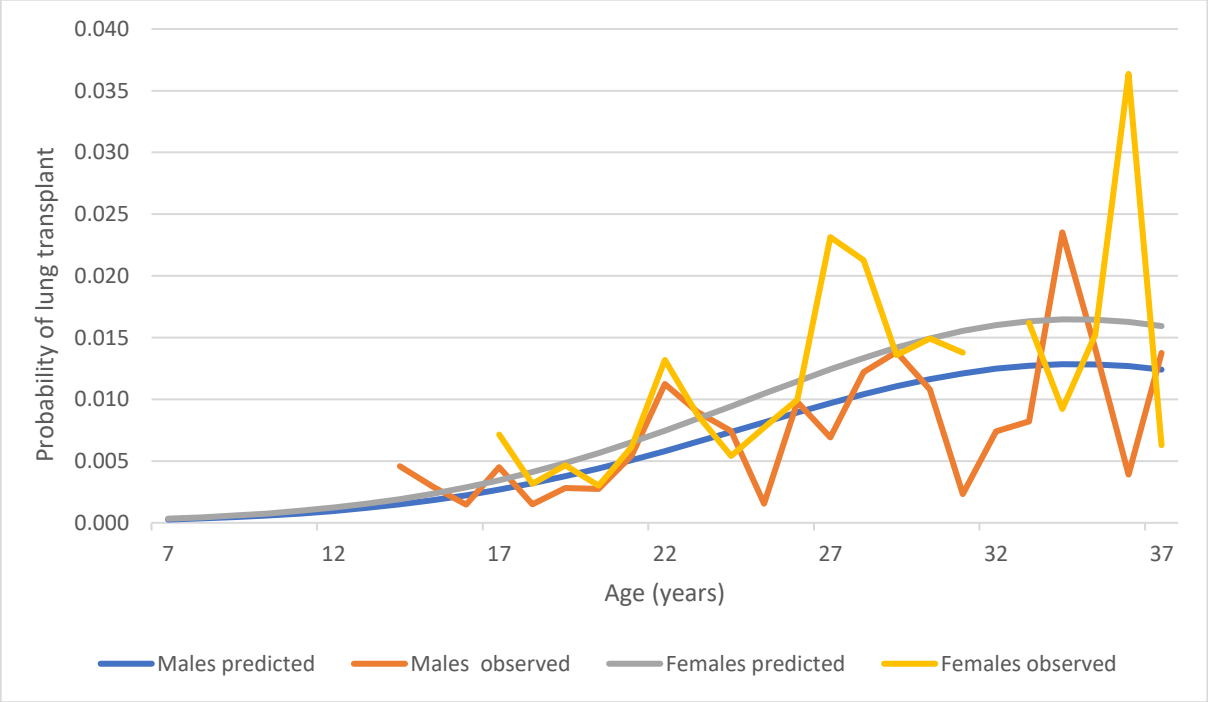


Figure 26 below shows the predicted and observed probabilities of receiving a lung transplant based on the U.K. CF Data Registry from the regression model and the raw count data (males and females). A comparison of Figure 25 and 26 shows that the observed estimates from the raw data for both differ in terms of probability of receiving a lung transplant. The most immediate explanation for this difference may be that the two datasets represent different countries and two different time periods, 2002-2005 [81] and

2016. The change in available treatments and improvement in survival over time could have changed the likelihood of receiving a transplant. However, the overall increase in probability over time, as age increases, is present in both Figures.

Figure 26: Probability of Lung transplant by sex



5.20 Discussion

5.20.1 Summary

5.20.1.1 Principle findings

The aim of this chapter was to, 1) develop probability estimates for health state transitions, 2) cost banding probabilities and 3) lung transplantation probabilities for use in the De Novo health economic model developed in Chapter 4. Two different types of regression modelling methods were utilised, ordered probit regression (health state transitions and costs) and GEEGLM regression (lung transplantation).

This is the first study to provide transition probabilities based on age and sex. This allows for more accurate cost effectiveness estimates from decision modelling of CF interventions. All models included age, sex, last annual review and year of birth and the majority of these were statistically significant for transition between health states, costs and lung transplantation.

Compared to existing approaches [102, 107] utilised for the health state transition probabilities estimates, this is the first U.K. based study to provide estimates by age, sex and time since last annual review for F508del Homozygous patients. Although conventional counting methods could be utilised to estimate such probabilities, they are not able to provide detailed breakdown. These include individual age units and the time since last annual review which have a statistically significant association with probability of transitioning to a worse or better health states (Section 5.19.1). The GoF statistic presented in Section 5.19.1 also show that the observed and predicted estimates are a good match, in a majority of models. The estimates are further validated through comparisons with the literature which show good face validity of the data. Any differences in the observed and predicted estimates presented in the graphs in Appendix 8.2.1 could be explained by the large variations in time since last annual review in the raw data compared to the predicted probabilities which was selected as 365 days.

In terms of costs, compared to existing approaches [102, 107] utilised for the cost band probability or costs in general, this is the first U.K. based study to provide estimates by age, sex, last annual review for F508del Homozygous patients. As such this means that costs are provided based on the probability of occupying a particular PbR cost band when

in a particular health state. Although other studies exist which used regression modelling for costs and these include age and FEV_1. This study provides probabilities based on gender in addition to the current health state, age and time since last annual review. This study also takes into account treatment trends through inclusion of year of birth variable to ensure that costs reflect the current treatments that are utilised in CF care, 2016. The regression outputs in Section 5.19.2 show that age, time since last review and sex are significant predictors in some of the specified models. Although, the GoF statistic presented in Section 5.19.2 shows that only the Mild model predicted probabilities reflect the observed data, comparison of against the observed data (Section 8.3.1) shows good face validity of the predicted cost band probabilities. Lack of GoF could be due to a strict time since last review of 365 days used to predict probabilities from the model as in the observed data, there is large variation in time since last annual review.

Lastly, this is the only study to provide probabilities of receiving a lung transplant based on age and sex through use of the U.K. CF Data Registry. The regression outputs show that age was a significant contribution to the probability of receiving a transplant. Previous studies highlighted lung transplant probabilities for Australian CF individuals between 2002-2005. The data in this chapter presents probabilities based on gender and age with more recent data (2005-2016) using a regression method which takes into account repeated measures from the same CF individual which is novel. As such this provides a better, more detailed, breakdown of lung transplant probabilities.

5.21 Strengths and limitation of the study

The study utilised a very generalisable and large dataset which covered >90% of the CF population in the U.K and as such is the largest primary resource available for the analysis of CF related outcomes. A range of statistical methods were applied to the datasets in order to determine input parameter for use as input parameters in the De Novo model from Chapter 4. This is also the first study to be conducted to look at the health state transitions, cost band and lung transplantation probabilities using the U.K. CF Data Registry which also provide a thorough breakdown of model outcomes in terms of goodness of fit, accuracy and probabilities values stratified by age and sex for F508Del Homozygous individuals in the U.K. CF Data Registry. Given the recent increase in the evaluation of potentiators such as Ivacaftor and other drugs such as Lumacaftor, these probability estimates could prove useful for the cost effectiveness analysis of such interventions or similar interventions.

Furthermore, the internal and external validity of the results were compared where data were available and in a majority of the cases the data were comparable to the observed data and the evidence present in the literature. This further highlights the usefulness of this data. Similarly, as mentioned in Lioa et al [220], the correctness of the model equations can be verified through the method of appropriate sum of probability values. All probability values were equal to 1 for all health state transitions and cost band probabilities. This further increases the validity of the data.

However, there were also a number of limitations in this study. Variable selection processes were not undertaken to identify the best variables which could predict disease

progression in CF. The variable selected were based on the existing evidence in the literature, expert opinion and existing practices for the health economic modelling of CF interventions. Other models exist which have used other variables and utilised model selection processes to determine survival for example Keogh et al [50] and Liou et al [42]. However, these were used for survival prediction not for disease progression or cost estimation.

Repeated measures methods were used to calculate the probability of receiving a transplant. However, they were not used to determine health state transitions or cost band probabilities. Attempts were made to use functions available in the ordinal package [38], which accounted for repeated measures, such as the clmm function. However, I was unable to estimate the models using repeated measures because the model failed to converge. Further attempts were made to fit models including repeated measures, with support from statisticians in the Epi-Net team as well as the author of the ordinal package [221], but they failed. The data published by Tappenden et al [102] may or may not have used repeated measures. It is unclear from the article. However, the results from the chapter show similar transition probabilities to that of Tappenden et al [102] which have been used in a number of cost-effectiveness analyses presented in Chapter 2.

In this analysis, where the violation of the parallel slope assumption occurred the models were adjusted for this using the scale effects mentioned by Christiansen [221]. Subsequent testing for the assumption showed that it was no longer violated, and the model took into account the scale effects of the independent variables.

Lastly, it is important to note that the probabilities produced were generated to reflect U.K CF patients who were F508Del Homozygous (male and female) who were seen on a strict annual basis, i.e. 365 days. However, this assumption around annual review period may not be reflective of what happens in reality as the mean annual review gap was 408 days in the Registry Data but ranged up to 4524 days. As a result, this could have reduced the comparability of the derived data to the observed data in the U.K. CF Data Registry. This may explain why in a number of cases, the derived probabilities did not reflect exactly those which were observed in the Data Registry. However, it is important to understand that the derived results were comparable to the existing evidence in the literature and those in the Data Registry.

5.22 Further work

In this study, I used rigorous regression modelling methods to estimate transition probabilities that can be used as inputs to the De Novo model in CF in Chapter 6. These regression models are appropriate because they are designed for use with outcome measures which are ordered and categorical as well as binomial in nature. Nevertheless, further work to explore the impact of using different modelling approaches to calculate health state transitions and cost estimates would be useful for comparison. An example of such a comparison is presented in the case of Whiting et al [107] where the model outcomes produced similar patterns in costs as a result of the explanatory variables used. Such an exercise would expand our understanding of the impact, if any, of using alternative regression approaches with differing related assumptions on the input parameters produced for health economic modelling of CF interventions.

Further work could also explore the options for using repeated measures approaches to estimate the transition probabilities and compare the repeated measure estimates to those produced by the Ordinal Probit models in this chapter. Lastly, this thesis focuses on using data from the U.K, additional work in the future could look at utilising other Registry Data sources in CF or outside of CF and the application of such methods on such Data Registries. Utilisation of similar method in other registries would provide useful insight into whether different registries produce different results in terms of health state transitions, costing and lung transplantation probabilities.

To the researcher's knowledge, this is one of the first studies to use Registry Data to determine input parameters for health state transitions, costs and lung transplant whilst providing transparent information around the methods, model fit and subsequently, in Chapter 6, utilise this data to undertake an exemplar cost effectiveness analysis of a relevant CF treatment. The transparency provided in this thesis could be a step towards better reporting of methods for calculating data inputs for health economic models from large observational data registries.

5.23 Conclusion

This chapter as well as Chapter 2 and 3 look at the existing evidence availability for the health economic modelling of CF interventions. Chapter 4 used existing evidence and expert opinion to develop a De Novo model structure. However, this chapter is the main body of work by which the aims of this thesis are achieved, to advance the health economic evidence available to inform a De Novo health economic model and decisions about appropriate reimbursement of CF interventions. Through use of robust regression

methods, the evidence available for the health economic modelling of CF interventions is being improved. This is primarily achieved through data which is derived from the longitudinal Data Registry which covers more than 90% of the CF population in the U.K. Furthermore, data is not only provided for health state transitions including lung transplant and post lung transplant (Chapter 6) but also for costs as well as high-cost drugs (Chapter 6). Such data is also available by sex and different age integers. The model structure as well as the estimates generated are validated by experts. Lastly, a number of comparisons are made of the derived probabilities against the existing evidence (where available) and the observed data within the Data Registry as the best real-world model. Although the results do not show findings that are exactly the same, they show that the results are very close to the observed probabilities as well as those which exist in the literature. The estimates improved on the existing evidence by providing a better detailed breakdown of inputs based on sex and age as well as novel data inputs around lung transplantation and post lung transplantation. The subsequent chapter will look to further validate the input parameters and particularly the De Novo model structure through the evaluation of the cost effectiveness of an exemplar intervention, Orkambi®. Orkambi® will be used to compare the outcomes generated in the De Novo model against those from existing published models looking at the economic evaluation of Orkambi®.

6 Chapter 6: Extending the cost-effectiveness modelling of CF interventions using a different model structure and real-world data from the CF Data Registry.

6.1 Introduction

In the previous chapter, regression methods were utilised in order to generate transition probabilities with the aim to use such data in the De Novo model developed in Chapter 4. The De Novo model structure was developed to include IV based health states and, in this chapter, will be populated with novel data streams generated in Chapter 5. This will be done in order to evaluate whether the cost effectiveness modelling of CF interventions can be extended by changing the structure and through use of new data streams.

In order to evaluate whether the cost effectiveness of CF interventions can be extended, an exemplar intervention was selected. Orkambi® was chosen as the CF Registry Data had very few individuals who were currently on the treatment at the time of the data analysis, this would reduce any chance of bias of treatment effect being incorporated into the control group of the intervention as data were utilised from the CF Registry (Section 6.12). Additionally, there were no published U.K. based studies of the cost-effectiveness of Orkambi® using novel data from the U.K. CF Data Registry and existing studies, both technology appraisals and published studies, on the cost effectiveness of Orkambi® would allow for in-between model consistency validation.

What follows is a review of existing cost effectiveness studies, which include technology appraisals. This is primarily presented here, rather than in Chapter 2 (Section 2.12.1) to

summarise the different aspects of the health economic modelling of Orkambi® which will prove vital for the validation of the model and outcomes presented in this Chapter. This is then followed by the methods and results of the exemplar cost-effectiveness evaluation of Orkambi®. Lastly, the model outcomes are validated using information from Section 6.3.

6.2 Aims and objectives

The methods used in this Chapter illustrates how statistical techniques, from Chapter 5, can be utilised to inform and extend the De Novo health economic modelling of CF interventions.

The aims of this chapter are to:

a) Utilise a novel model structure based on disease progression, data availability and clinical expert opinion in the U.K.
b) Incorporate the estimates generated in Chapter 5 to evaluate an exemplar intervention, Orkambi®.
c) Validate the De Novo model structure, through in between model consistency by evaluating exemplar intervention Orkambi®.

6.3 Cost-effectiveness models for Orkambi®

A number of economic evaluations or health technology assessments have been conducted for Orkambi®. Two published model based economic evaluations [126, 127], four technology appraisals [7-10] and a single review report looking at the cost-effectiveness of Orkambi® were identified [94]. Of the four technology appraisals that were found, two were conducted by the Canadian Agency for Drugs and Technologies in

Health (CADTH), and the National Centre of Pharmacoeconomics (NCPE) and NICE both conducted one study each. Lastly, the review of a range of modulator treatments including Orkambi® was conducted by the Institute for Clinical and Economic Review [94]. The two economics evaluations, four technology appraisals and single review were evaluated further in a range of areas which are discussed further in the proceeding sections.

6.3.1.1 Evaluation type

Of the two economic evaluations conducted on Orkambi®, one was a cost-utility analysis [126] and the other a cost-effectiveness and budget impact analysis [127]. The technology appraisals by NCPE, NICE and CADTH were all cost-utility analyses [7-10]. Similarly, the Institute for Clinical and Economic Review conducted a cost-utility analysis in their review of Orkambi® treatment in CF.

6.3.1.2 Time horizon

The time horizon used in the models varied. All technology appraisals used a lifetime horizon [7-10], Sharma et al [126] adopted a 10 year time horizon owing to the lack of effectiveness data and a likely change in the future availability of novel treatments which could surmount the effectiveness of Orkambi®. Lastly, the study by Vadagam et al [127] had a single year time horizon due to the model being a static decision model. Again, this was decided based on the limited effectiveness of Orkambi®, clinical trial data and matched control patients.

6.3.1.3 Discounting

A 3% discount was applied clearly on both costs and outcomes for economic evaluation study by Sharma et al [126], whereas Vadagam et al [127] did not apply any discounting due to their model only having a time horizon of a year. In terms of the technology

appraisals, the NCPE did not state the discount rate or whether it was applied to both costs and outcomes [9], NICE stated the discount rate of 3.5% to both costs and outcomes, CADTH stated that Vertex Pharmaceuticals applied different discount rate in each submission, 5% in the 2016 submission [7] and 1.5% in the most recent [8]. Lastly, the Institute for Clinical and Economic Review applied a 3% discount to costs and outcomes.

6.3.1.4 Model structure

The only study which provided information on their model structure used the conventional 5-health state model discussed in Chapter 2 (Section 2.7.3) with additional states for pulmonary exacerbation and post lung transplant [126]. The technology appraisals by the NCPE [126] states that they used an individual patient simulation model but did not elaborate on the actual structure of the model, as was the case the with NICE [10] and CADTH [7]. However, the most recent technology appraisal by CADTH provided a diagram of the individual patient simulation model [8]. Lastly, Vadagam et al [127] did not describe their model structure.

6.3.1.5 Country

The country for which the analysis was conducted was either the United States (U.S) [126, 127], Ireland [9], Canada [7, 8] or the U.K [10].

6.3.1.6 Perspective

The studies were conducted from a U.S third party payer [126, 127] and Health Service Executive (HSE) [9], Canadian public health care payer [7, 8] and NHS and personal social services perspective [10].

6.3.1.7 Data sources

6.3.1.8 Treatment efficacy

Clinical trial data utilised in all of the studies were sourced from a range of publications [46, 222, 223]. The two economic evaluations of Orkambi®[126, 127] used pooled absolute change in the FEV_1 as their efficacy measure. However, this varied based on the treatment dose. Vadagam et al [127] used the mean absolute change in FEV_1 across two clinical trials based on a single dose of Orkambi®(400mg Lumacaftor with Ivacaftor (250mg) every 12 hours), presented as a mean absolute change in FEV_1 of 2.8 (CI:1.8-3.8). On the hand, Sharma et al [126] used the mean absolute change in FEV_1 across two dose groups of Orkambi®(600mg/400mg Lumacaftor with Ivacaftor (250mg) every 12 hours), which was presented as a range and not a mean improvement with a distribution. The technology appraisal by CADTH [7] used treatment efficacy values similar to Vadagam et al [127]. The most recent submission from Vertex pharmaceuticals to CADTH [8] used a range of sources for the clinical efficacy of Orkambi®[222-226], to reflect the population in their model. The technology appraisal by NICE used treatment efficacy values similar to Vadagam et al [127]. Lastly, Institute for Clinical and Economic Review [94] used two different efficacy values based on the age of the population, with those between 6-11 having a mean absolute increase in percentage FEV_1 of 2.4 (CI:0.4-4.4) [227] and those older than 12 having a mean absolute increase in percentage FEV_1 of 2.8 (1.8-3.8) from Orkambi®(400mg Lumacaftor with Ivacaftor (250mg) every 12 hours) [46].

The effectiveness data, although the same, was used differently particularly when applying treatment effect on the costs and outcomes. Sharma et al [126] applied a 100%

sustained efficacy of Orkambi®throughout the model time horizon as their base case analysis. In the, worst case scenario analysis, the treatment efficacy was only allowed to occur in the first year of the model cycle. Vadagam et al [127] used the efficacy data for one year to match the time horizon of their model. The technology appraisal conducted by NICE [10], applied the effectiveness of Orkambi® up to week 24 in the model.

The NCPE [9] and CADTH [7, 8] did not provide much detail about how treatment efficacy data were utilised.

6.3.1.9 Costs

These were calculated through a variety of routes. Sharma et al [126] estimated the cost of Orkambi® through manufacture listing price and subsequent insurer reimbursement. Vadagam et al [127] obtained the cost of Orkambi® from the RED BOOK [228]. The models submitted by Vertex Pharmaceuticals to the NCPE [9], CADTH [7] and NICE [10] only provided a direct price of Orkambi® and no further breakdown of costs. However, the most recent Vertex pharmaceuticals submission [8] appraised by CADTH does state that annual costs for managing CF was adjusted for FEV_1, exacerbations, adverse events and lung transplantation. Furthermore, the report shows that resource use related to the management of CF, lung transplantation and exacerbations were derived from both unpublished work by Vertex and unpublished data from the Canadian CF Data Registry and clinical opinion. These were weighted by figures from the literature around laboratory testing, staff wages and yearly costs of CF treatment, but do not clearly state what these were. The review by Institute for Clinical and Economic Review of the cost-effectiveness

of different modulators provide a very detailed breakdown of how costs were derived for PEx, age and FEV_1 distributions [94].

Vadagam et al [127] costs included clinic/hospital visits, laboratory/monitoring tests among others and were taken from CF care guidelines published by the CF Foundation (U.S). Sharma et al [126] used a study by Lieu et al [116] to account for the cost of being in the various, mild/moderate/severe PEx events. These costs were inflated using the Personal Consumption Expenditure health component price index. Lung transplant cost were taken from the Millennium report.

6.3.1.10 Utilities

No detail was provided in the technology appraisals by the NCPE [9], CADTH[7] on the sources of utility data, although the report does mention that quality of life (QOL) is taken into account. Information on where utility data were derived in the most recent appraisal by CADTH [8] was taken from two clinical trials [222, 223] and a single study around PEx events [139]. The Institute for Clinical and Economic Review used utility values from a single study [105] where the utility of being in a FEV_1 health state was taken from Tappenden et al [106] but were originally derived from another study [229]. The NICE technology appraisal showed that Vertex pharmaceuticals used values from two clinical trials [222, 223] and a HTA submission for Ivacaftor® [107]. However, sensitivity analyses subsequently changed these to those derived from other studies [106, 143]. Sharma et al [126] obtained utility data from a previous economic evaluation by Tappenden et al [106], who derived these from another study [229]. Vadagam et al [127] did not conduct any

QOL assessment/impact as part of their health economic model. This shows clear paucity in available utility data as identified in Chapter 3.

6.3.2 Primary outcome measures

Vadagam et al [127] used the efficacy data to determine the cost per 1-unit increase in the FEV% predicted per patient as their ICER. However, they also included a non-conventional, average cost-effectiveness ratio (ACER) as the cost per FEV% predicted per patient. The technology appraisals submitted by Vertex Pharmaceuticals to the NCPE [9], CADTH [7, 8] and NICE [10] looked at the cost per QALY. The Institute for Clinical and Economic Reviews primary simulated outcomes were cost per year, life years accumulated and cost per QALY [94].

6.3.3 Model assumptions

The assumptions taken in the base-case analysis for each published paper or technology appraisal are presented in Table 66.

Table 66: Assumption taken

Study author	Assumptions
NCPE [9]	Starting age: 12 years Patient distribution: based on clinical trials [222, 223] Treatment effect: ranging between 2.6 - 4% [46]
CADTH [7]	Starting age: 12 years Rate of FEV1 decline: lower for those taking Orkambi® Price reduction in Orkambi®: 82% of original cost after 12 years
CADTH [8]	Starting age: 6 years Patient characteristics: based on clinical trials [222, 223] Price reduction in Orkambi®: 82% of original cost after 12 years
NICE [10]	Starting age: 12 years Patient characteristics: based on clinical trials [222, 223] Treatment effect: 2.8 (1.8-3.8) [46] applied until week 24 only Rate of FEV1 decline: lower for those taking Orkambi® 24.7% of people with a FEV1 below 30% had a lung transplant. Post-lung transplant mortality was assumed to be 15.2% in the first year, and 6.1% for each subsequent year. Price reduction in Orkambi®: 89% of original cost after 12 years

Study author	Assumptions
Institute for Clinical and Economic Review [94]	Starting age: 6 years Patient distribution: based on CF Foundation 2016 No increase in FEV1 over time Standard care is the same in both treatment arms CFTR drugs decrease the annual number of acute pulmonary exacerbations through the increase in FEV1 and through effect of Orkambi® on acute PEx.
Sharma et al [126]	Starting age: 12 years Usual care comprised of treatment with antibiotics, pancreatic enzymes, aminoglycosides (inhaled tobramycin as well as intravenously administered aminoglycosides) and DNase Patient distribution: based on CF Foundation 2015 (87% in mild, 11% in moderate, 2% in severe) Transplant was only received by those in the Severe health states (including post -PEx) Patients do not progress to worse health states while on treatment

6.3.4 Incremental cost-effectiveness estimate ratio (ICER)

The base-case assumptions in each model produced ICER values, Table 67:

Table 67: ICER results and cost year by study

Study author	ICER	Cost year
NCPE [9]	€369,141/QALY	Not stated
CADTH [7]	CAD $485,767 /QALY	Not stated
CADTH [8]	CAD $446,529/ QALY	No Stated
NICE [10]	£218,248/QALY	Not stated
Institute for Clinical and Economic Review [94]	US $890,739/QALY	2017
Sharma et al [126]	US $3,655,352/QALY	2016

6.3.5 Sensitivity analysis

Various forms of sensitivity analysis were conducted in all the above reviewed technology appraisals and publication. These are further mentioned in the discussion of this chapter.

6.4 Methodology

In this chapter, I have carried out a cost-utility analysis which uses Markov processes in combination with semi-Markov processes, as described in Chapter 4. Briefly, Markov processes allude to Markov models which have time-dependent transition probabilities which have no memory of the history of the cohort of patients. i.e. what health state they were in prior to entering the current health state. Semi-Markov processes are a relaxation of the Markov processes memory assumption, whereby memory can be introduced in the form of tunnel health states. The perspective of the study is the National Health Service (NHS) and the comparator standard care. Standard care comprises, usual treatment

based on CF Trust PbR cost banding matrix allocation and provision of High-Cost drugs which are not included in the NHS PbR tariff, a list of which are provided in Table 73, (Section 6.18.3). Standard care also comprises lung transplantation and post lung-transplantation follow up.

6.5 Model design

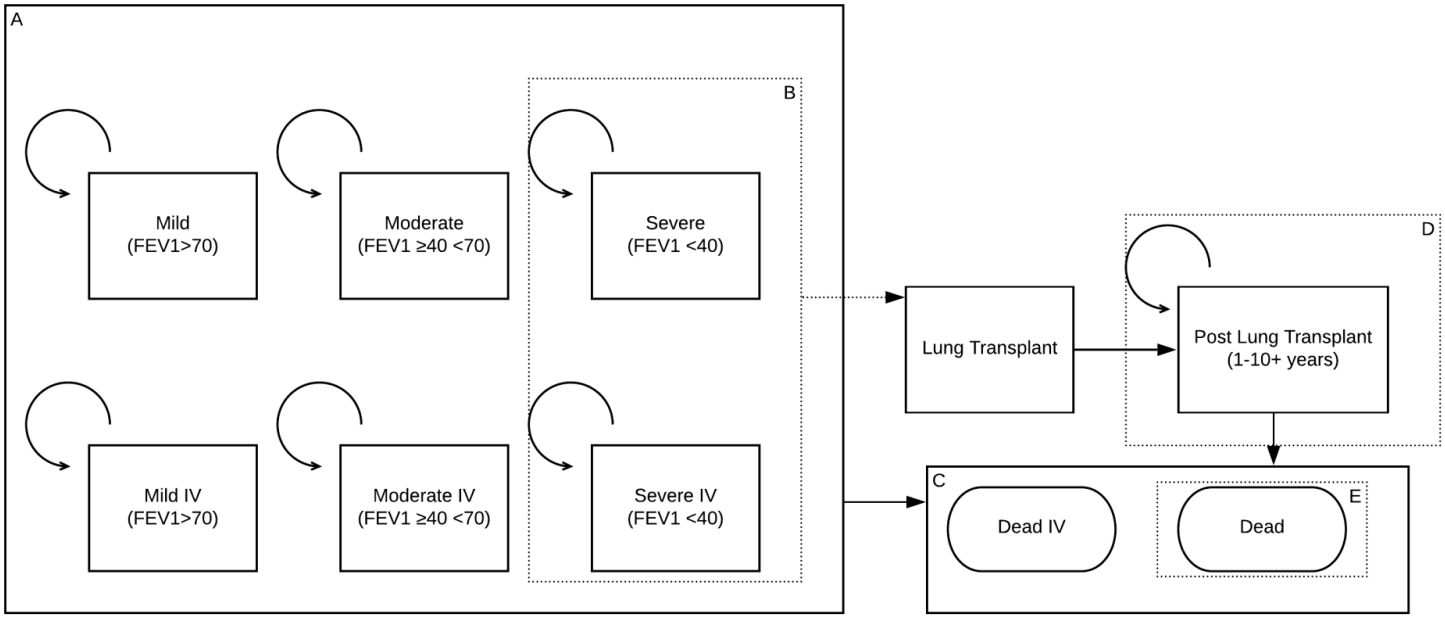
In Chapter 1, a summary of the principles of good practice in decision modelling were highlighted (Section 1.4.2.1). The quality of a model was covered in three areas: structure, data and validation [88]. The proceeding sections will cover these aspects in reference to the cost-effectiveness conducted on Orkambi® as an exemplar.

The model chosen to undertake the evaluation of a number of CF interventions, as explained in Chapter 4, was adapted to look at the exemplar cost-utility analysis of Orkambi®. The model simulates the outcomes of a cohort of individuals with CF with a starting age of 7, based on the use of data from the Chapter 5 and other data from the literature. A starting age of 7 was selected as Orkambi® is provided for those older than 6 years. Chapter 4 covers in detail the De Novo Model design process which includes reference to the advantages of using a Markov Cohort Model as well as the taxonomy of model structures [121]. Additional changes to the model to include tunnel health states was also discussed.

With knowledge that NICE now expect uncertainty around mean outputs due to parameter uncertainty to be quantified [121] and the assumption that the decision maker would be interested in the variability of the results around the mean estimates, both a stochastic and deterministic approach was used in the decision modelling. Additionally, I assumed that there is no interaction between the patients in the dataset, the assumption that all individuals who are F508Del Homozygous are homogenous in the dataset, that modelling relationships and that some occurrences in the patient population (post lung-transplantation) represent non-Markovian time properties. One of the main drawbacks of Markov models is the lack of memory which can be altered through inclusion of tunnel health states which represent semi-Markovian processes to add memory into the model. The cycle length of the model is 1 year, reflecting annual review data of the CF Data Registry. The time horizon is based on the median survival of those in the CF Data Registry in 2016, which is 47.0 (44.7-48.2), with a significant difference in mean predicted survival between males and females, female survival being lower [230]. This time horizon was utilised due to the survival bias present in the U.K. CF Data Registry and resultant predicted probabilities [10]. The discount rate is 3.5% for both costs and outcomes [86]. Half cycle correct was also applied to both costs and outcomes [86].

6.5.1 Model diagram

Figure 27: Diagrammatic representation of the CE/Markov Model Structure



Description of health states

The model structure is presented in Figure 27. There is a total of 10 different health states: Mild, Mild IV, Moderate, Moderate IV, Severe, Severe IV, Dead, Dead IV, Lung transplantation and Post-Lung Transplantation (years 1-10+). The two Dead health states are the same, the only difference between the two is whether the cohort in the model died post IV treatment in that year or not.

Transitions can occur back and forth between all health states in Box A, or to the same health state (circular arrow). Only those enclosed in the dashed line in Box A, Box B, can enter into the Lung Transplant health state. Subsequent to receiving a Lung Transplant, individuals enter into the Post-Lung Transplant health state (Box D) in which they remain until death (Dead) (Box E). Transitions can occur from any health state in Box A to either Dead state in Box C.

The model assumed that individuals who would receive Orkambi® treatment would initially be distributed across the health state from Mild to Severe IV based on the dataset utilised to calculate the transition probabilities in Chapter 5. Table 68 provides the percentage distributed in each health state by sex. Subsequent transitions to other health states were based on the transition probabilities generated in Chapter 5. The initial distribution of patients in the model were based on distribution of 6-year-old CF patients in their respective health states prior (previous health state) to turning 7 years old (current health state). So, this means that although the transition probabilities are based on 7 years onwards the initial cohort distribution is based on those 6 years old, as such the model is described as starting from age 7. The data utilised to calculate initial health state distribution values at 6 years old were the same data used to calculate the health state transition probabilities in Chapter 5. We can see from the below distribution that no patients were in either Severe health state and that a higher majority of females were in the worse health states compared to males.

Table 68: Patient Distribution in model

Health state Previous (sex)	Proportion by sex
MILD (Males)	74%
MILD (Females)	50%
MILD IV (Males)	18%
MILD IV (Females)	35%
MODERATE (Males)	5%
MODERATE (Females)	3%
MODERATE IV (Males)	3%
MODERATE IV (Females)	12%
SEVERE (Males)	0%
SEVERE (Females)	0%
SEVERE IV (Males)	0%
SEVERE IV (Females)	0%

Methods of disease progression are based on changes in the lung function (FEV_1) which have been designated as follows for each health state: Mild; ≥70, Moderate ≥40 <70 and Severe <40. The overall designations, in terms of FEV_1, are based on the most commonly used classification in the health economics modelling of CF interventions [92]. Further description of how health states are defined as not receiving intravenous antibiotics or receiving intravenous antibiotics has been explained in Chapter 4.

6.6 Characteristics of patients in the model

The starting population of the model is the total number of individuals who were F508del Homozygous in the CF Data Annual Report of 2016 [11]. This equated to a total population size of 4,789, males and females [230]. I assumed that these individuals had a sex distribution similar to that of the overall CF Data Registry for 2016, which was 53.2% males and the remaining females [230].

Progression in the model began at the age of 7 and individuals progressed through the model until the age of 47, the median survival age. The median age was selected due to the nature of how the probability estimates were calculated in Chapter 5, survival bias present in the data, treatment trending being very likely to change beyond this period, as well the range of assumptions made when cleaning the data in Chapter 4. The U.K. CF Data Registry calculates their mortality estimates by grouping together several years, using methods proposed by Sykes et al [208], as single year predictions of median survival can have large variations year on year [178]. As a result, estimates of survival could be even more unreliable after the median age of survival.

A summary of these details are in Table 69.

Table 69: Model demographics at baseline

Demographics at baseline		
Characteristics	**Starting value**	**Source**
Population	4,789	UK CF Data Registry annual report 2016 [230]
Age	7	Model assumption
Sex distribution (%) (Males/Females)	53.2/46.8	UK CF Data Registry annual report 2016 [230]
Median survival (years old)	47	UK CF Data Registry annual report 2016 [230]

6.7 Base-case analysis

The base case analysis started with the distribution of the cohort across the different previous health states, Mild to Severe IV, as described earlier in Characteristics of patients in the model section above. Similarly, initial cohort and sex distribution was provided in this section. For those who received treatment, it was assumed that treatment was effective for the entire period during which they were on treatment. As a result, the cost of treatment was also applied to the treatment cohort for the whole-time horizon of the model.

6.8 Scenario analyses

A range of scenario analyses were performed by changing the characteristics of the patients in the model. Table 70 below shows the different scenarios analyses performed.

Table 70: Scenario analyses

Base Case	Treatment effect applied for whole time horizon of model, costs of Orkambi® applied throughout time horizon of model in base-case analysis
Scenario 1	Treatment effect applied for 2 years, costs of Orkambi® applied throughout time horizon of model
Scenario 2	Treatment effect applied for 2 years, cost of Orkambi® applied duration of treatment (2 years)
Scenario 3	Initial cohort patient distribution in analysis replicated RCT for Orkambi® [46]
Scenario 4	Starting of age of cohort in analysis changed to 12 years
Scenario 5	Starting of age of cohort in analysis changed to 25 years
Scenario 6	Change utility data for health states to estimates used by Whiting et al [107]

6.9 One-way sensitivity analysis

A range of one-way sensitivity analyses were used to assess the validity of the model. Furthermore, it was used to look at how the ICER value for Orkambi®'s cost-effectiveness changes in responses to a changes in series of values.

6.10 Threshold analysis

Threshold analysis was performed on the cost of Orkambi® at threshold between £20,000-30,000/QALY and the QALYs generated from treatment at various thresholds of costs per QALY.

6.10.1 Utilities

Looking at how the utility values of each health state in the model would affect the resulting ICER of the base-case scenario. The utility values were individually adjusted to the upper and lower range presented by Sharma et al [126]. It is important to note here that the values for the health states which include IV treatment, a utility decrement of -0.17 was applied to the lower limits.

6.11 Probabilistic sensitivity analysis (PSA)

Uncertainty around the deterministic sensitivity analysis (DSA) results of the modelling conducted in this chapter was explored using the above scenario analyses but also included the above mentioned one-way sensitivity analysis. However, random draws from the distributions of the point estimates can also be used, called probabilistic sensitivity analysis (PSA). Probabilistic sensitivity analysis allows the model to vary the value of each input parameter simultaneously based on a probability distribution selected as most appropriate for each input parameter in the model [1].

The uncertainty around all model parameters were investigated. The model parameters sheet in the included Markov Model (Supplementary material) provides the point estimate for DSA and distribution of the parameters used in the PSA in the model, as well as any assumptions in cases where distributions were not selected (e.g., Cost bands and High-Cost drugs).

6.12 Model Validation

A number of technology appraisals, publications and a review have been identified in the Section 6.3 which look at the cost effectiveness of Orkambi®. In order to assess the credibility of the model produced in this chapter the model was tested to demonstrate

validity. The methods that could be used are analogous to those mentioned by Turner et al [231] which were based on validation methods suggested by Philips et al [232]. Four methods of validation were discussed by Turner et al [231] and these include, internal consistency, external consistency, between model consistency and lastly, predictive validity. Due to the nature of health economic modelling and the variety of sources used to develop the model in this chapter, it was decided that a range of consistency checks would be used. In order the validate the model outcomes, as done by Turner et al [231], between model consistency was also evaluated.

6.12.1 Internal consistency

Internal consistency of the model as described by Philips et al [232] was assessed by changing values in the model, such as health state utilities model to extreme values (Threshold analysis; Section 6.10 and One-way sensitivity analysis; Section 6.9). This was done to ensure that the model behaved as expected when values were changed of the different selected parameters in the model. However, further internal consistency tests such as programming of the model in alternative software was not undertaken as resources were not available to programme the model in an alternative resource.

6.12.2 External consistency

In order to assess the external consistency, clinical expert opinion was used in the consensus of the model structure and the most appropriate information used in the model. Lastly, the results of the model were assessed through comparison for similarities in relation to estimates produced from other studies and well as review of such estimates by clinical experts in CF.

6.12.3 Between model consistency

To validate the model against existing literature, inputs from a number of the studies mentioned in the previous literature section of this thesis were used. These estimates were used in the exemplar Orkambi® cost-effectiveness analysis to determine if there were any substantial difference in model outcomes. These were then elaborated on. This was the main focus of the validation undertaken in this chapter, the methods used follow those, as much as possible, utilised by Turner et al [231].

6.12.4 Predictive validity

This was not undertaken as the model developed in this chapter was not a predictive model, where data were used to predict future outcomes as in epidemiological models.

6.13 Model assumptions

Cost band proportions estimates were taken from Chapter 5. These estimates for each health state did not change for either treatment or intervention group and as a result, cost band proportions per health state were the same across Orkambi® and No Orkambi® cohorts. The main difference between control and treatment groups were driven by change in health state transitions from the treatment.

Lung transplantation, although could occur from better health states as shown in the UK CF Data Registry, this was very rare. As a result, I assumed that lung transplantation would only occur from either Severe health states. This was supported by clinical expert opinion (Siobhan Carr, 31st July 2019).

Patients could transition between any health state, better to worse or worse to better, except for absorbing health states and subsequent to lung transplantation.

6.13.1 Transition probabilities

As already mentioned, a cohort of the patients moved through the model on an annual basis based on the transition probabilities defined in Chapter 5. Transition between different health states were derived from an ordered probit regression model, which included death. A significant difference in the model in this chapter and existing models for Orkambi® [126, 127] or other CF interventions [106] was that transitions were allowed to better health states, from worse health states, regardless of whether the individual was receiving treatment or not. These transitions to better health states were based on predicted probabilities derived from the U.K. CF Data Registry.

6.13.2 Treatment effectiveness

In order to model the long-term effectiveness of Orkambi®, treatment effectiveness was taken from a study by Konstan et al [226]. This study looked at the long term efficacy of Orkambi®, while taking into account the outcomes from the TRAFFIC and TRANSPORT clinical trials [222, 223], extending observation of treatment effectiveness in those who were F508Del Homozygous to 96 weeks. Patients who started treatment with Orkambi® (Lumicaftor 400mg/250mg Ivacaftor every 12 hours) in either the TRAFFIC or TRANSPORT and continued treatment in the extension study (PROGRESS; 96 weeks) [226], the results showed a mean absolute improvement in FEV_1 of 1.1 (95% CI: 0-2.2), $p<0.05$ at 96 weeks compared to baseline levels. Values presented here from the clinical trials are calculated using the Global Lung Function Initiative (GLI) equations [233], which are also used to calculate the FEV_1 values presented in the U.K. CF Data Registry. As a result, this would improve the generalisability of the effectiveness estimates onto the U.K. CF Data Registry FEV_1 values.

To model the treatment effects without introducing any bias, the original population/dataset used to calculate the health state transition probabilities in Chapter 5 were used. The development environment Rstudio® [169] was used in conjunction with the function rnorm in order to create a range of normally distributed values with a mean of 1.1, and upper and lower 95% CI of 2.2 and 0, respectively. The rnorm function equation is rnorm (n, mean, standard deviation (sd)), where n is the number of values that will be simulated with a mean and sd presented in the equation. The sd of the values was calculated using the following equation from Edlin et al [1], (upper – lower CI)/ 3.92, where 3.92 covers the probability density function of a normal distributions 95% CI (1.96 x 2). The standard deviation is equal to (2.2-0)/3.92 = 0.56. A total of 10,000 value were simulated in order for the treatment effect to reflect a mean and CI of 1.1 and 0-2.2 respectively. A larger value would have produced many estimates with these figures due to the central limit theorem.

Subsequent to creating treatment effect values, they were randomly added onto the current FEV_1 of those in the CF Data Registry to account for Orkambi®. Lastly, the ordered probit regression methods used to calculate the health state transition probabilities in Chapter 5 were applied to this dataset to calculate transition probabilities for those receiving treatment.

6.14 Orkambi® status of patients in U.K CF Registry

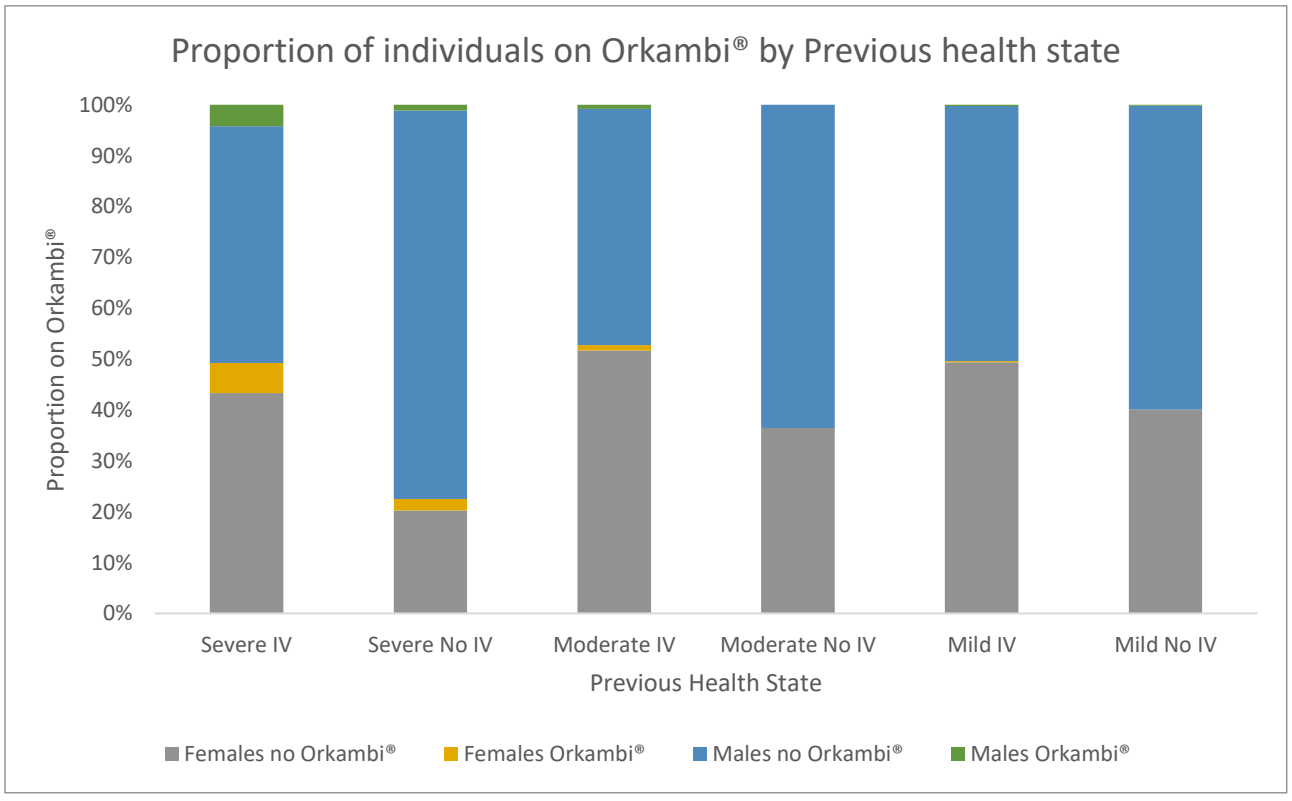
The Orkambi® status of those in the U.K. CF data registry was evaluated and only 77 patients were taking Orkambi® out of the total 12,463 patients in the Registry. Orkambi® status was only provided from 2016, so patients would have only been on the treatment

for a year in my dataset. Of those 77 individuals, the total number in the final dataset utilised to calculate the transitions probabilities, Chapter 5, were 67. Out of the total number of patients in the dataset, those on Orkambi® represented 1.38%.

Figure 28 provides a breakdown of those who were on Orkambi® in 2016 compared to those who were not by sex and their previous health state.

I did not remove these individuals from the data as they were less than 2% of the overall data and that this would not affect the overall estimates generated by the regression modelling for health state transition probabilities. We can see that there were more females on Orkambi® than males and that Orkambi® status was positive more often in the Severe IV health state.

Figure 28: Breakdown of Orkambi® status by sex



6.15 Lung transplant health state

The probability of receiving a transplant was based on the data in the CF Data Registry and are described in detail in Chapter 5. For the exemplar cost utility analysis of Orkambi® I assumed that transplant could be received only whilst in the Severe health states and were age dependent. As part of the PSA, probability of receiving a transplant were varied by adjusting the predicted transition probabilities by up to 10% above or below the mean value. Subsequently, those who received a transplant could either enter into death health state or progress onto post-transplant survival.

6.16 Post-Lung transplant health state

Post-long-transplant survival was estimated using CF Registry Data from 2007 to 2016 by Professor Ruth Keogh. The analysis was restricted to individuals who had no record of a transplant prior to 2007 and who were F508Del Homozygous. Dates of death post-transplant were available up to the end of 2016 and individuals with no date of death were assumed to be alive at the end of 2016. There were 204 individuals included in the analysis who had a lung transplant between 2007 and 2016, of whom 51 died. A Cox regression model including sex and age at transplant (in years) was fitted. Age at transplant ranged from 4 to 60 years and was entered as a linear term in the Cox regression. The estimated hazard ratio of death post-transplant for females versus males was 1.19 (95% confidence interval 0.68,2.10) and a 1-year increase in age at transplant was associated with an estimated hazard ratio of 0.98 (0.94,1.02). Note that neither sex nor age at transplant were associated with post-transplant survival at the 5% significance level. The results from the Cox model were used to obtain estimates of 1-year, 2-year,

and up to 10-year post-transplant survival probabilities for males and females and by age at transplant.

The health states for post-lung transplant were tunnel states/semi-Markovian processes. This allows mortality after lung transplant to vary by time. Without such a state this would not be possible. This meant that patients could only progress from Lung transplant to post transplant survival up to 10+ years and such survival varied by the age at which the cohort received their transplant. The patients in these health states could either enter an absorbing health state or move to subsequent post-transplant survival. After 10 years of post-transplant survival the cohort of individuals could either stay in 10+ survival or enter the absorbing health state, death. Similar to the lung transplant health state, it was assumed in the model that those who received a transplant would only enter into the Death health state post-transplant. This assumption reflects the Payment by Results (PbR) guidance [234]. It states that as soon as a patient receives a transplant payment of the CF PbR tariff will cease at the end of the month the transplant was received. Any further care required post-transplant, although provided at CF specialist centers, would be the responsibility of those managing transplant commissioning arrangements, hence the costs would also be accounted to them. Further discussion with a clinical expert (Dr Siobhan Carr, 2nd February 2021) confirmed that this assumption is in line with current treatment, that Orkambi® is no longer provided to lung transplant patients. Although this may change in the future.

6.17 Perspective of model

The model analysis is based on an NHS perspective. This included only cost born to the healthcare system through direct resource utilisation. A personal and social service perspective was not added to this as no such data were available in the U.K. CF Data Registry.

6.18 Costs in the model

The costs included in the model were those born out of inpatient/outpatient care, drug costs, as well standard care costs based on the cost banding matrix published by the CF Trust Registry. The cost year in the model was 2016/17. This was selected to reflect previous studies conducted on Orkambi®. Methods for adjusting the costs are presented in Section 6.18.3.

6.18.1 Banding matrix

Costs were based on the banding matrix definitions proposed by the UK Cystic Fibrosis Trust, Table 71. The probabilities of being in any cost band based on the current health state of the cohort of the patients in the model are described in Chapter 5 (Section 5.19). In Chapter 4, the cost banding matrix is explained in more detail (Section 4.17.2). However, in summary the cost banding matrix is used alongside an algorithm by the U.K. CF Data Registry to determine, annually, what cost band an individual patient falls into. The cost band probability data allows distribution of the cohort into the various bands by their current health state and allows calculation of cost of CF by current health state as well as by age and sex.

Table 71: Cost banding matrix

Banding definitions		Band						
		1	**1A**	**2**	**2A**	**3**	**4**	**5**
Therapies	Maximum number of total days of IV antibiotics	0	14	28	56	84	112	>/=113
	Nebulised antibiotics (*Pseudomonas* infection)		Yes					
	Long-term (>3 months) nebulised antibiotics or DNase			Yes				
	Long-term (>3 months) nebulised antibiotics and DNase				Yes			
Hospitalisation	Maximum numbers of days in hospital	0	7	14	14	57	112	>/=113
Supplemental feeding	Nasogastric feeds				Yes			
	Gastrostomy					Yes		
Complications	CF Related Diabetes or ABPA w/o 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 (eg MRSA or Cepacia)					Yes		

	requiring other nebulised antibiotics eg Meropenem, Cayston , Vancomycin.							

6.18.2 Cost figures

Table 72 presents the costs of being in any particular banding category in 2016/17 [235] also presented in the Markov Model; sheet Cost_Bands (Supplementary material). This banding category is based on the matrix in Table 71. The predicted probabilities generated in Chapter 5 define how the cohort is distributed between these banding categories whilst in any current health state presented in Figure 27 of this chapter, except lung and post lung transplant. The cost presented in Table 72 are based on the 'year of care tariff', which was first introduced in 2013 to include mandatory payments to CF centres across England for CF related care [178]. The 'year of care tariff' uses the UK CF Data Registry to categorise individuals to particular bands based on their disease severity and only covers CF related care at hospitals [178], as reflected in Table 71. This tariff-based system also excludes charges for High-Cost drugs such as Colistimethate sodium, Tobramycin, Dornase alfa, Aztreonam Lysine, Ivacaftor and Mannitol [234, 236].

Table 72: Cost (annual) by bands [235]

Band	1	1A	2	2A	3	4	5
Costs	£ 5,033	£ 7,447	£ 7,447	£ 12,036	£ 18,422	£ 33,224	£ 40,054

6.18.3 High-Cost Drugs

To determine the proportion of individuals in each health state that were on a range of High-Cost drugs, proportion estimate data were taken from the UK CF Data Registry. These proportions were stratified by age, sex and the current health state of the individual.

So, the proportions for a range of age categories for either sex group would be more reflective of what is observed in U.K CF care for those who are F508Del Homozygous. A full graphical breakdown of these proportions by age and sex are provided in the Markov Model, sheet; High Cost Drugs (Supplementary material). The CF Data Registry only provided an indication of whether the individual in the registry received a drug in that year or not. It did not provide any indication of duration or dose. As a result, clinical expert guidance (Siobhan Carr, 25th July 2019) was taken to determine the doses and duration of treatment for the range of High-Cost drugs based on best clinical practice. Based on the advice, the doses and resultant costs are presented in Tables 73 and 74 respectively.

Table 73: High-Cost drugs, doses and treatment regimen/duration

Drug name	Duration	Type	Dose
Mucolytic	Alone (12 months)	Mannitol Dry Powder (Inhaled) Dnase	2 x day: 400mg 1 x day: 2500 units = 2.5 mg
Colistimethate Sodium	Alone (12 months)	Colistimethate Sodium Solution - Colistin (Colomycin)	No information in the BNF about nebuliser drug option: only injection so will take this as indicative of costs: Colomycin is 2 megaunit 2x a day >8 years/ 1 megaunit 2x a day <8 years
	Combination (6 months)	Colistimethate Sodium Solution - Colistin (Colomycin)	
	Alone (12 months)	Colistimethate Dry Powder Inhaled (Colobreathe)	Colobreathe is twice a day and only 1 strength.
	Combination (6 months)	Colistimethate Dry Powder Inhaled (Colobreathe)	
	Alone (12 months)	Promixin (Colistimethate Sodium Solution)	Promixin is 0.5 megaunits 2x a day until 8 years old/ Promixin is 1 megaunits 2x a day over 8 years old
	Combination (6 months)	Promixin (Colistimethate Sodium Solution)	
Tobramycin	Only used in alternating fashion (i.e. 6 months)	Tobramycin Solution (inhaled)-Bramitob	Tobramycin – is 300mg twice a day every other month – so 6 months use

	Only used in alternating fashion (i.e. 6 months)	Tobramycin Solution (DPI)-TOBI	Tobramycin (DPI) is also twice a day, alternate months
	Only used in alternating fashion (i.e. 6 months)	Aztreonam Lysine (Cayston)	Aztreonam 75 mg single dose 3 times a day and used every other month
Orkambi®	Alone (12 months)		400mg of Lumacaftor in combination with Ivacaftor (250mg) every 12 hours

Table 74 provided the costs for each drug based on figures in the British National Formulary (BNF) [237]. Figures were deflated to 2016 using the NHS drug cost inflation index in the Personal Social Services Resource Unit (PSSRU) cost 2019 report [238]. The table shows the cost of the treatment for those either older, younger than 8 years or whether the treatment is age independent (any). Furthermore, the drug name or type is given followed by the duration (12/6 months) as some treatment cannot be given for more than 6 months at a time if they are given in combination. For example, Colistimethate Sodium Solution - Colistin (Colomycin) and Colistimethate DPI (Colobreathe) can be coupled together.

The inflation index figures are presented in Table 75. In order to deflate the price of the High-Cost drugs, the 2018 index value was divided by the 2016 index value to give an index value of 1.04866. This value was used to calculate the drug cost for 2016.

Table 74: High-Cost drugs (2016)

Drug Name/Type	Take alone or with another drug	Age of individual	< 8 years	> 8 years	Any
		Drug Name	Cost		
Mucolytic (DNase/Hypertonic Saline)	Alone (12 months)	Mannitol Dry Powder (Inhaled)		£5,681	
		Dnase		£5,681	
Colistimethate Sodium	Alone (12 months)	Colistimethate Sodium Solution - Colistin (Colomycin)	£618	£ 1,112	
	Combination (6 months)	Colistimethate Sodium Solution - Colistin (Colomycin)	£ 309	£556	
	Alone (12 months)	Colistimethate DPI[6] (Colobreathe)		£11,086	
	Combination (6 months)	Colistimethate DPI (Colobreathe)		£5,543	

[6] DPI- Dry powder inhalation

	Alone (12 months)	Promixin (Colistimethate Sodium Solution)	£ 2,334	£ 4,669
	Combination (6 months)	Promixin (Colistimethate Sodium Solution)	£1,167	£ 2,334
Tobramycin	Only used in alternating fashion (i.e., 6 months)	Tobramycin Solution (inhaled)-Bramitob	£ 6,792	
	Only used in alternating fashion (i.e., 6 months)	Tobramycin Solution DPI TOBI	£ 7,467	
	Only used in alternating fashion (i.e., 6 months)	Aztreonam Lysine (Cayston)	£ 12,482	
Orkambi®	Alone (12 months)	Lumicaftor/Ivacatfor	£ 91,546	

Table 75: PSSRU inflation indices

Cost were deflated using the PSSRU 2019	**Index values were taken from Drug costs (PSSRU)**	
	2016/17	104
	2017/18	105
	2018/19	109

Although the costs presented in the NHS National Tariff Payment System 2016/17 [239] do not reflect any uncertainty in their cost estimates for the costs bands, for the PSA analysis a 10% variability above and below the mean deterministic value was introduced and no distributional assumption was applied. All costs and outcomes were discounted to present value at 3.5% annually and were presented for the year 2016 in U.K. pounds sterling (GBP).

To reflect uncertainty in the probabilities of being placed in particular cost bands based on the current health state of the cohort in the Markov model. A beta distribution was assumed, which are appropriate for probability values that lie between 0 and 1. Uncertainty was incorporated for each estimate stratified by age and sex. In order for the probabilities to sum to 1, probabilities were weighted by their probability and divided by the sum probability for each age and sex combination.

6.19 Health state utility

A systematic review was conducted to ascertain the availability of health utility data in CF, Chapter 3 [93]. Additionally, the utility values used in a previously published model [102] were obtained and used in my model (personal communication with Paul Tappenden, 22nd February 2018). These estimates, which were also found in the review, were taken from two original studies to determine the utility of being in mild, moderate and severe health states as well as lung transplantation [113, 229]. Changes in the FEV_1 were the main indicator in the changes in utility for any cohort of patients in the model, as well as whether one received a lung transplant. As explained earlier, previous models for CF interventions have assumed that any IV treatment longer than 14 days would signify an exacerbation event. For those who were in the mild, moderate or severe health states in this model, it was assumed that there would be a change in the utility as a result of receiving IV antibiotic treatment. A utility decrement of 0.17 was applied to the model [102], although there is no data in the CF Dats Registry about PEx events or the reason for receiving such IV treatment. As IV days in the Data Registry were assumed to equate an exacerbation, the decrement was applied for the whole year. As a result, treatment with Orkambi® would effect health state transitions but also impact outcomes through utilities. Similarly, the range data provided for the sensitivity analysis, a utility decrement was also applied to the lower bound to reflect utility of the IV health state. Lastly, it was assumed that there would be no variation in utility across either sex group.

For conducting the PSA analysis, the deterministic values were given a beta distribution due to the values for all health states being closer to 1 than 0. Value for alpha and beta

were calculated using the following equations respectively, (((1-utility)*utility/standard error)-1)* utility, alpha*((1- utility)/ utility), where the utility value represents utilities for each respective health state. Standard errors for the alpha value were calculated based on the number of individuals in each respective study, 29 [229] and 79 [113]. The number of individuals were based on the data within the respective studies.

Overall utility for each health state, with or without IV treatment and sex were given the different mean utility values but they were also allowed to vary in the PSA analysis.

Table 76 provides a summary of the utility data used in the deterministic and probabilistic analysis. These values were taken from Tappenden et al [102] (health state specific utilities) and Anyanwu et al [113] (lung transplant utilities).

Table 76: Utility parameters

Current Healthstate	Sex	Health Utility	SE	Variance	SD	alpha	beta
Mild	Male	0.86	0.03	0.00	0.17	109	17
Mild	Female	0.86	0.03	0.00	0.17	109	17
Mild IV	Male	0.69	0.03	0.00	0.17	109	17
Mild IV	Female	0.69	0.03	0.00	0.17	109	17
Moderate	Male	0.81	0.04	0.00	0.22	78	18
Moderate	Female	0.81	0.04	0.00	0.22	78	18
Moderate IV	Male	0.64	0.04	0.00	0.22	78	18
ModerateIV	Female	0.64	0.04	0.00	0.22	78	18
Severe	Male	0.64	0.06	0.00	0.32	42	24
Severe	Female	0.64	0.06	0.00	0.32	42	24
Severe IV	Male	0.47	0.06	0.00	0.32	42	24
Severe IV	Female	0.47	0.06	0.00	0.32	42	24
Dead	Male	0.00	0.00	0.00	0.00	0.00	0.00

Dead	Female	0.00	0.00	0.00	0.00	0.00	0.00
Dead IV	Male	0.00	0.00	0.00	0.00	0.00	0.00
Dead IV	Female	0.00	0.00	0.00	0.00	0.00	0.00
Lung Transplantation	Male	0.83	0.02	0.00	0.17	319	65
Lung Transplantation	Female	0.83	0.02	0.00	0.17	319	65

6.20 Data analysis

6.20.1 Running the model

The model was programmed using Microsoft Excel®. The supplementary material contains the Markov Model. The model contains the macros used to perform the probabilistic sensitivity analysis (PSA) and creation of cost effectiveness acceptability curve (CEAC).

6.20.2 Transition probabilities

In cases where the data were taken from Chapter 5 such information has already been provided in Sections 5.19 of that chapter.

To reflect uncertainty in the probabilities of being placed in particular health states in the Markov model, a beta distribution was assumed, which is appropriate for probability values that lie between 0 and 1. Uncertainty was incorporated for each estimate stratified by age and sex. The following formulae was used, =BETAINV(RAND(), alpha, beta). In order for the probabilities to sum to 1, probabilities were weighted by their probability and divided by the sum probability for each age and sex stratification.

The model was run deterministically after the parameter values were set into their relevant sheets and cells. The deterministic analysis added the respective costs and QALYs for each health state for both the control and intervention cohort of males and females. The outcome of the analysis is presented in various forms; incremental cost effectiveness ratios (ICER), Cost effectiveness plane and incremental net monetary benefit (NMB) at a range of ceiling ratios(λ)/ threshold values for the QALY.

In order to calculate the ICER and NMB outcomes, the formulae (Equations 2 and 3) were used, where C_2 is the cost generated under the intervention arm of the model, C_1

is the cost generated under the control/comparator arm of the model, E_2 is the effectiveness units (QALYs) under the intervention arm of the model and E_1 is the effectiveness units (QALYs) under the control/comparator arm of the model. The ceiling ratio (λ) for the NMB calculation is represented by the threshold value for the QALY, which is between £20-30,000 based on NICE guidance [86] in the base case analysis but was kept at set at £25,000 for the base case analysis but varied to different levels for the creation of the CEAC and the expected value of perfect information (EVPI) (Section 6.24.5).

Equation 2; ICER = C2-C1/ E2-E1 = ΔC/ ΔE

Equation 3; NMB = (Ceiling ratio (λ)*QALYS)-C2

To reflect uncertainty in the model, PSA was performed to generate a cost-utility plane which graphically showed the joint distribution of costs and effectiveness. The ICER from each simulation round was then plotted on this graph, a total of 5000 simulations were ran, which amounted to 5000 estimates of incremental cost and QALY. Each estimate showed the mean incremental difference per person in the cohort, 4,789. The plot provides a visual indication of the uncertainty in the costs and effects around the deterministic ICER result.

Figure 29: Example of Cost-utility plane [1]

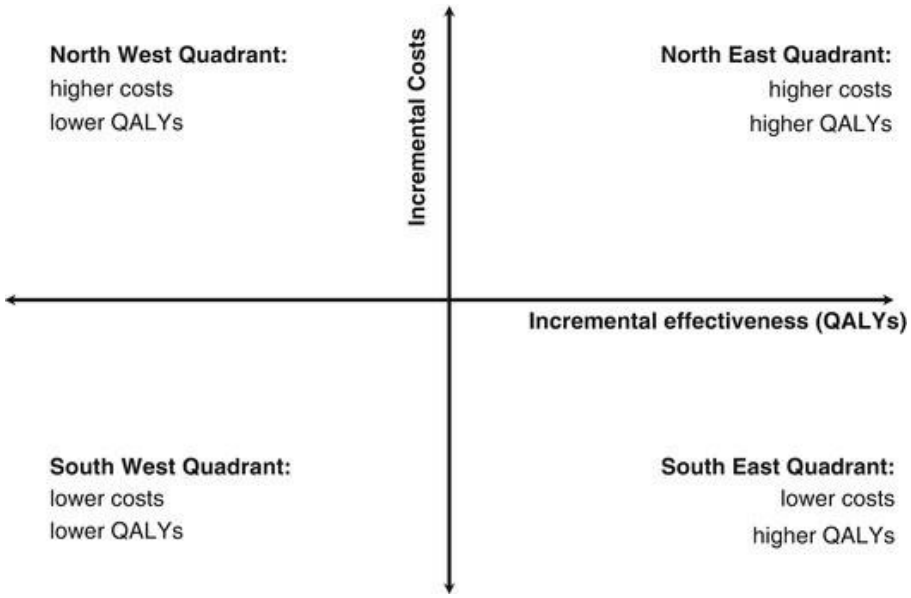
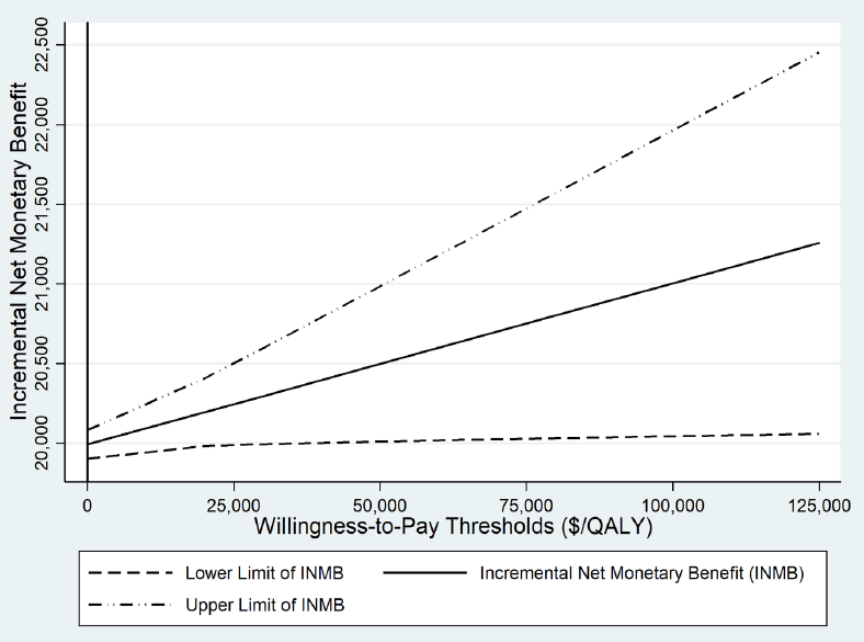


Figure 29 presents an example of the cost-effectiveness plane, where the intervention is presented by incremental change in costs and effects against the comparator or control intervention [1]. It has of four quadrants with incremental costs and effects on the vertical and horizontal axis respectively. Any estimates presenting themselves in the north east (NE) quadrant are more costly but also more effective, whereas those in the south west (SW) quadrant are less costly and less effective. Estimates presenting themselves in the north west (NW) quadrant are more costly and less effective and are often described as being dominated, while those in the south east (SE) quadrant are less costly but more effective and are said to dominate the comparator or control intervention in the model [1]. ICER values that fall into the NW and SE quadrants both generate negative ICER values. This requires caution when interpreting the results especially when presenting uncertainty

around the ICER through PSA as negative ICER value could span across quadrants (for example NW and SE) which could produce similar negative ICER values. The same could be said for positive ICER values which span the NE and SW quadrants of the same magnitude. Any resultant ranking of the ICER values, positive or negative would place similar ICERs from different quadrants together [5]. In turn this makes interpreting the ICER values difficult [83].

A solution, around the ICER value interpretation, is the use of NMB and CEAC. The advantage of using the NMB approach is that it places both costs and effects on the same scale. In NMB, the incremental effect in the model is converted into monetary terms using the ceiling ratio (λ) or willingness to pay threshold of a QALY [83]. In instance where the ceiling ratio of willingness to pay threshold for a QALY is unknown, a range of ceiling ratios can be used to produce a graphical depiction of incremental NMB [83]. Figure 30 shows an example of incremental NMB, on the y-axis, for a range of ceiling ratios on the x-axis with confident intervals (CIs) for each ceiling ratio. The CIs for each threshold value, represented by the dashed line in Figure 30, for lower and upper the CIs respectively. Where, N represents the simulation number ran for the PSA. If the NMB is a positive value, this shows that the value placed on the benefits generated exceeds the cost of generating them, while the opposite, negative NMB, shows that the control is the better option in the evaluation.

Figure 30: Example of Incremental NMB [2]



Taking the concept of NMB further, it is not always easy to interpret an ICER Plane, particularly if there are multiple interventions. However, it is possible to determine the probability of the intervention being cost effective at a range of thresholds similar to the NMB analysis. This is achieved through the CEAC [83], where the average probability of cost effectiveness is calculated over all 5000 simulations of the PSA at a range of threshold/ceiling ratios (λ).

Decision uncertainty surrounding intervention effectiveness, resource use and outcome parameters in the model will introduce a dilemma of whether a health technology should be adopted given existing information. The probability of cost-effectiveness at the various threshold in the CEAC describes the chance that resources will be wasted if a decision is made to commit to the approval of a health technology or vice versa if a decision is made

not to commit [83]. As a result, the consideration of the value of additional research to reduce any uncertainty around the cost effectiveness of an intervention can have important opportunity cost implications. As such, Value of information analysis (VOI) allows analysis of uncertainty on many levels, one of which is Expected Value of Perfect Information (EVPI) [83].

6.21 Expected Value of Perfect Information

Expected Value of perfect information can be calculated from the PSA (Section 6.12) [83]. The EVPI is the difference between the NHB or NMB given current information compared to that which is generated given perfect information [5]. Given the result of the PSA analysis, there is some uncertainty based on the distribution of the CEAC or Cost effectiveness plane. As a result, there is a chance that the wrong decision is made, to either provide a treatment or not and this could lead to an opportunity loss [83, 240] which could have substantial cost implications on health system budgets and also in terms of care not provided to a patient population. By conducting an EVPI analysis, decision makers can decide whether conducting further research on the intervention could lead to less uncertainty and better decision making [240, 241]. As such EVPI looks at the cost of eliminating all uncertainty [242] in the model.

In instances where the EVPI is lower than a particular threshold of willingness to pay for a QALY (e.g., £20,000-£30,000) and the EVPI is not higher than this threshold then this suggests that there is no value in carrying out further research [242]. The EVPI can give the population or per person level monetary gain that could be realised at different thresholds of willingness to pay for conducting further research to eliminate uncertainty.

As such the EVPI uses all the parameters in the model to determine uncertainty, but in instances where the EVPI is higher than the willingness to pay threshold research could be conducted on a single parameter or group of parameters [1], for example utility data. This leads to other forms of value information analysis such as Expected Value of Perfect Parameter Information (EVPPI) [242].

6.22 Results

6.22.1 Health State transitions

Figures 31-32 show the deterministic run of number of patients in each health state by age for males (control/intervention) and females (control/intervention). The starting cohort size was 4,789, in total (2538 males and 2251 females), distribution based on sex is further elaborated upon in Section 6.6. The dotted lines represent the treatment cohort, whereas the solid lines represent the control cohort. We can see that there is a difference in the occupation of the different health states for the cohort on treatment. For mortality there is a difference from the start of the model, for males and females, which is shown by the slight drop and shift to the right for all-cause mortality. For other health states, we can see that there are initial changes which subsequently merge with the control group, as can be seen by the overlapping of control and treatment cohorts, Figure 31-32. Lung transplantation and post-lung transplantation were not included in the graphs due to their small numbers. However, differences can be seen in the model which accompanied this thesis (Supplementary Material; Markov Model). Tables 77-78 below presents the initial distribution of the male and female cohorts across the

different health states in the model based on U.K. CF Data Registry (2016) [11], age 6 and based on the predicted probabilities from Chapter 5 at age 7 respectively.

Table 77: Cohort distribution in Markov Model (6 years old)

Sex	Total	Mild	Mild IV	Moderate	Moderate IV	Severe	Severe IV
Females	2251	1125	794	66	265	0	0
Males	2538	1887	456	130	65	0	0

Table 78: Cohort distribution in Markov Model (7 years old)

Sex	Total	Mild	Mild IV	Moderate	Moderate IV	Severe	Severe IV	Dead
Females	2247	1072	709	147	286	5	27	4
Males	2536	1595	643	155	129	4	10	2

Figure 31: Deterministic run of Males (control) vs, Males (intervention), number of people in each health state over time (Ages 7-47).

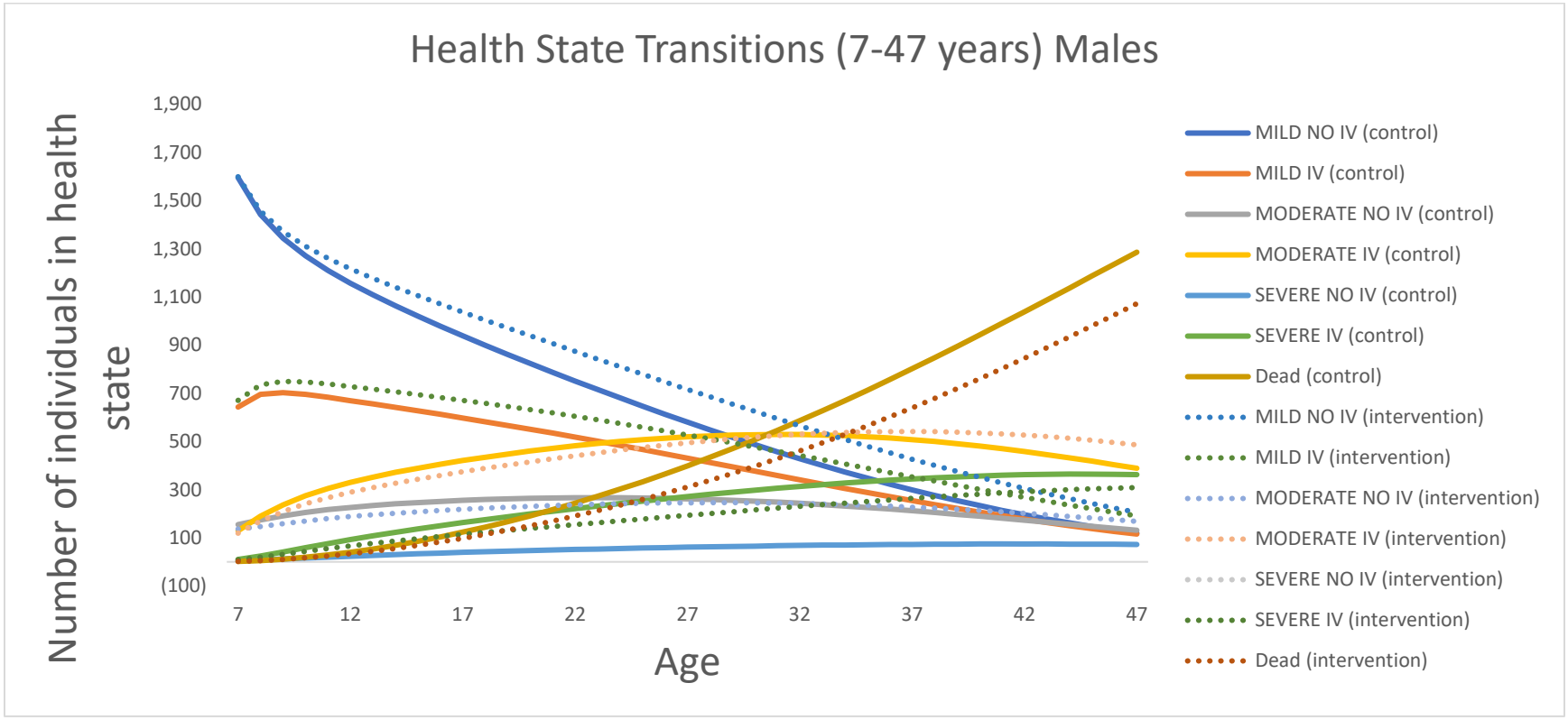
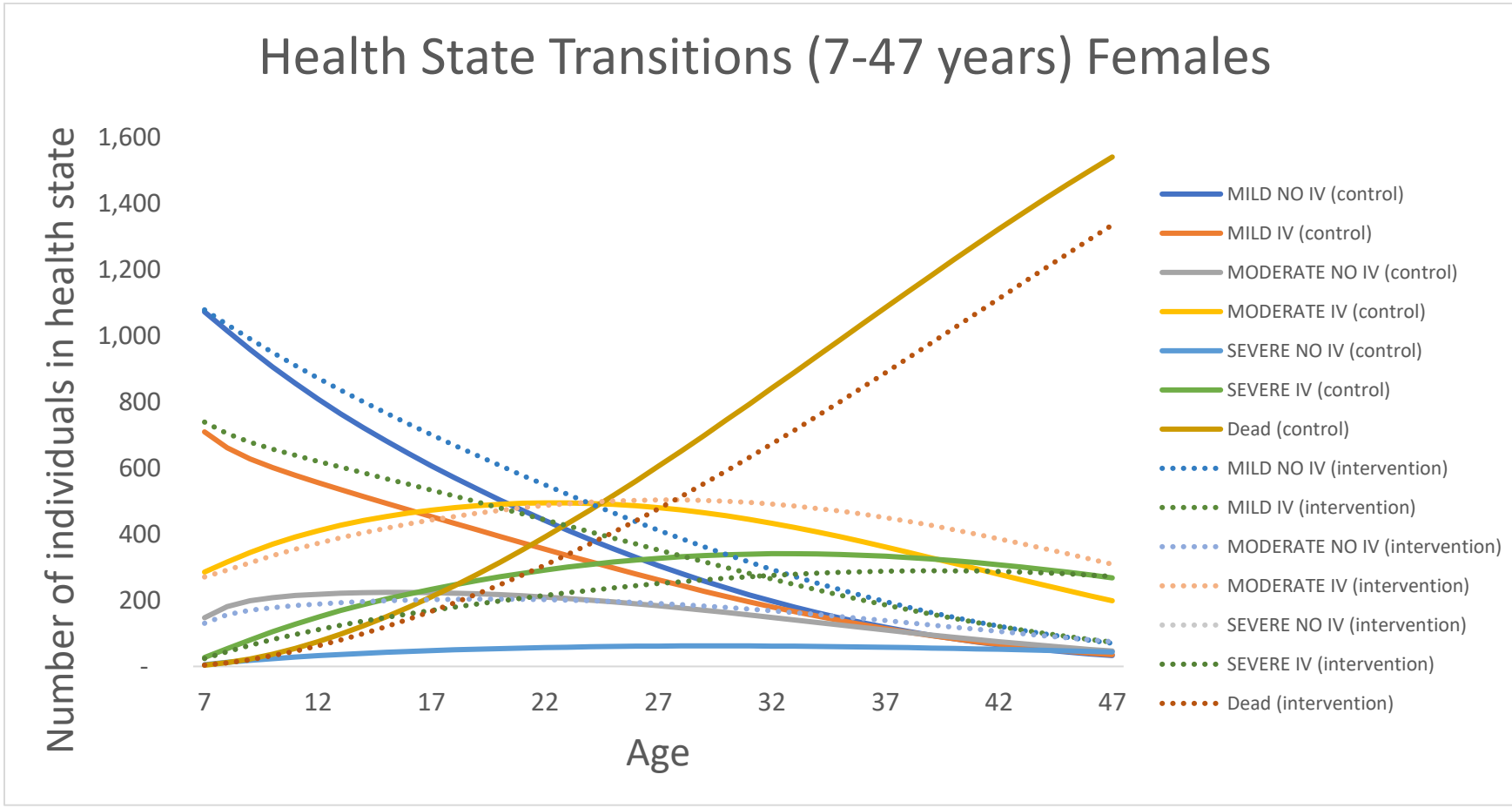


Figure 32: Deterministic run of Females (control) vs, Females (intervention), number of people in each health state over time (Ages 7-47).



6.22.2 Life years gained

Tables 78-79 show the overall, undiscounted and discounted, time in each health state stratified by sex and whether the cohort received the intervention or not.

Overall, the deterministic results show, in Table 79, that the main driver of change due to treatment was the amount of time spent, in life years (LYs), in the Mild and Mild IV health states (total Mild males; 43,928 and 51,555 LYs vs females; 28,008 and 34,080 LYs, for control and intervention respectively). The intervention cohort of males and females also spent fewer years in worse health states and experienced reduced mortality (total deaths; males 19,929 and 16,022 LYs vs females 27,219 and 22,372, for control and intervention respectively). No substantial changes were seen subsequent to receiving a transplant or thereafter for males or females when comparing life years across treatment groups (data not shown).

Table 79: Total life years (undiscounted) in each health state by Sex and treatment

	Life years (undiscounted)			
Health state	**Males (control)**	**Males (Intervention)**	**Female (control)**	**Female (Intervention)**
MILD	26,574	30,834	15,927	19,096
MILD IV	17,354	20,721	12,081	14,984
Total Mild	43,928	51,555	28,008	34,080
MODERATE	9,104	8,749	6,508	6,663
MODERATE IV	17,938	17,915	16,203	17,478
Total Moderate	27,042	26,664	22,711	24,141
SEVERE	2,188	1,564	2,017	1,607
SEVERE IV	9,981	7,534	10,874	8,926
Total Severe	12,170	9,097	12,891	10,533
Dead	19,929	16,022	27,219	22,372

Table 80: Total life years (discounted) in each health state by Sex and treatment

	Life years (discounted)			
Health state	**Males (control)**	**Males (Intervention)**	**Female (control)**	**Female (Intervention)**
MILD	18,069	20,164	11,422	13,111
MILD IV	11,099	12,797	8,358	9,936
Total Mild	29,168	32,962	19,780	23,047
MODERATE	5,062	4,665	3,965	3,853
MODERATE IV	9,147	8,811	9,127	9,359
Total Moderate	14,209	13,476	13,092	13,212
SEVERE	1,005	704	1,008	776
SEVERE IV	4,465	3,310	5,271	4,193
Total Severe	5,470	4,014	6,279	4,969
Dead	7,218	5,765	10,254	8,340

The total number of life years gained, Table 81, across all health states, per person were 2.29 and 2.91 for males and females respectively as a result of taking Orkambi®. We can see that majority of life years were gained in three health states, Mild, Mild IV and Moderate, with females gaining more LYs in the Mild IV health state compared to males. However, males gained more LYs in the Mild No IV and Moderate health states. There was a reduction in the occupation of the more Severe health states due to treatment,

albeit only a small reduction for both sexes. Female experienced smaller reductions in the Moderate and Severe IV health states.

Table 81: Life years gained (per person) by health state and sex from treatment with Orkambi® (base-case)

Health State	Life years gained (discounted)	
	Males	**Female**
MILD	0.83	0.75
MILD IV	0.67	0.70
MODERATE	1.49	1.45
MODERATE IV	-0.16	-0.05
SEVERE	-0.13	0.10
SEVERE IV	-0.29	0.05
Dead	-0.12	-0.10
Total	2.29	2.91

Table 82 shows the life expectancy of those in the model, male and female. We can see that Orkambi® improved the life expectancy of females more than males.

Table 82: Average number of years survived in the Markov model (starting age; 7 years)

Life Expectancy			
Males (control)	**Males (Intervention)**	**Female (control)**	**Female (Intervention)**
33.15	34.69	28.91	31.06

Overall, in the model the lower median survival of females compared to males persisted, as seen in the UK CF data registry [230], regardless of whether on treatment or not. The model showed that around 49% of the cohort of males were still alive at 47 years, whereas only 32% of females were alive at the same age. However, the number of years spent in the model were lower than the median survival estimates produced from the registry [230]. The UK CF Data Registry [230] shows that median survival for males and females was 47.9 years (95% CI: 46.1-51.4) and 44.2 years (95% CI: 40.8-47.1) ($p<0.05$) respectively from UK CF Data Registry between 2012-2016. For females at 44 years of age in the model, 37% of the cohort was still alive, less than the median survival in the UK CF Registry data.

Table 83 shows the number of cycles each person in the cohort spends in each health state for males and females for control and intervention cohorts respectively. We can see that there is an increase in the number of cycles spent in the Mild, Mild IV, Moderate and Moderate IV health states for males and females.

Table 83: Average number of cycles spent in each health state by the cohort (male/female)

Health State	Average Cycles			
	Males (control)	Males (Intervention)	Female (control)	Female (Intervention)
MILD	10.47	12.15	7.08	8.48
MILD IV	6.84	8.16	5.37	6.66
MODERATE	3.59	3.45	2.89	2.96
MODERATE IV	7.07	7.06	7.20	7.77
SEVERE	0.86	0.62	0.90	0.71
SEVERE IV	3.93	2.97	4.83	3.97

6.22.3 Payment by Result costs

Figure 33-34 below presents the cost per person (undiscounted) by health state over the time horizon of the model for males and females respectively (undiscounted). As can be seen from the figure, cost for Mild, Mild IV and Moderate increase over time, whereas the costs decrease over time for Moderate IV, Severe and Severe IV. A similar pattern exists for females.

Figure 33: Cost per person

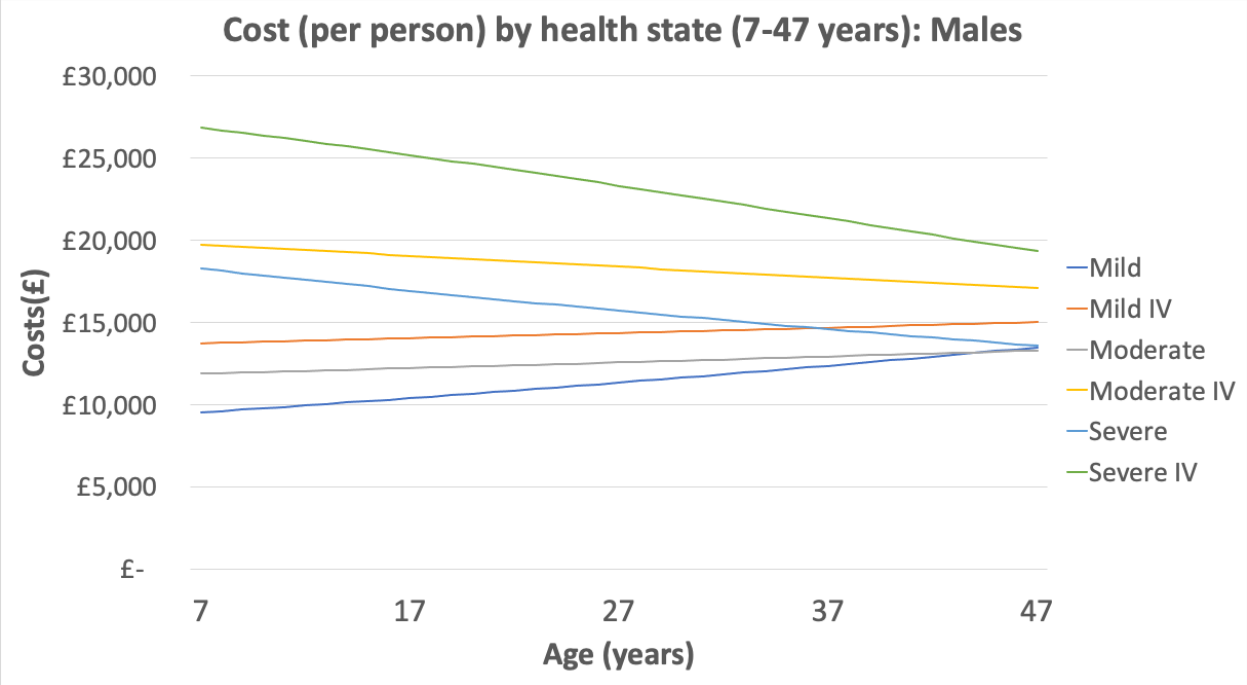
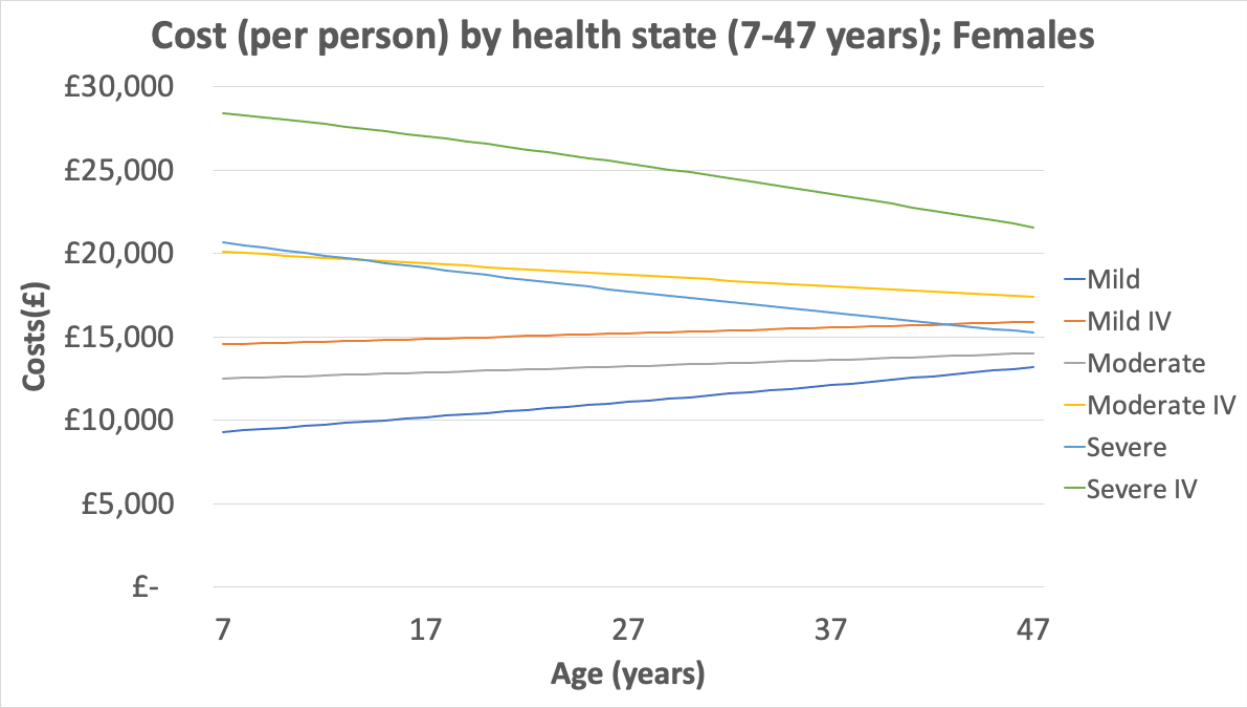


Figure 34: Cost per person



Tables 84-85 show the total PbR banding costs stratified by sex, health state and treatment both undiscounted and discounted. These do not include the cost of Orkambi® for those in the treatment arm.

For males, in Table 84, the undiscounted costs show that treatment increased the overall total cost for the Mild and Mild IV health states. The remainder of the health states, Moderate, Moderate IV, Severe No IV and Severe IV health states show a reduction in costs, especially the Severe IV health state. For females, Table 84, the undiscounted costs show that the cohort on treatment had increased costs for all the Mild and Moderate health states. The Severe health state showed a reduction in costs, especially the Severe IV health state. These above patterns of changes in cost from treatment are also evident

in the discounted costs, Table 85, for males. However, for females discounting costs showed that treatment resulted in a decrease in costs for the Moderate health state, most likely due to discounting effects.

Table 84: PbR Banding Costs by health state, sex and treatment (Undiscounted) over time horizon of model

Health State	PbR banding Costs by health state (undiscounted)			
	Males (control)	Males (Intervention)	Female (control)	Female (Intervention)
MILD	£ 284,252,688	£ 333,753,479	£ 163,924,681	£ 199,212,311
MILD IV	£ 246,400,626	£ 294,968,963	£ 180,644,373	£ 224,783,550
Total Mild	£ 530,653,314	£ 628,722,442	£ 344,569,053	£ 423,995,861
MODERATE	£ 114,208,991	£ 110,166,890	£ 85,255,728	£ 87,706,205
MODERATE IV	£ 328,164,835	£ 326,441,082	£ 304,839,679	£ 326,938,168
Total Moderate	£ 442,373,826	£ 436,607,971	£ 390,095,407	£ 414,644,373
SEVERE	£ 33,396,984	£ 23,758,987	£ 35,335,529	£ 27,925,835
SEVERE IV	£ 222,271,021	£ 166,945,999	£ 269,394,712	£ 219,557,071
Total Severe	£ 255,668,004	£ 190,704,987	£ 304,730,241	£ 247,482,906
Total Cost	£ 1,228,695,144	£ 1,256,035,400	£ 1,039,394,700	£ 1,086,123,141

Table 85: PbR Banding Costs by health state, sex and treatment (Discounted) over time horizon of model

Health State	PBR banding Costs by health state (discounted)			
	Males (control)	Males (Intervention)	Female (control)	Female (Intervention)
MILD	£ 187,989,225	£ 211,618,198	£ 114,964,951	£ 133,246,441
MILD IV	£ 156,388,586	£ 180,668,122	£ 124,205,163	£ 148,002,339
Total Mild	£ 344,377,812	£ 392,286,320	£ 239,170,114	£ 281,248,779
MODERATE	£ 62,807,358	£ 58,057,349	£ 51,439,200	£ 50,180,289
MODERATE IV	£ 169,757,971	£ 162,946,900	£ 174,046,550	£ 177,618,425
Total Moderate	£ 232,565,329	£ 221,004,249	£ 225,485,750	£ 227,798,714
SEVERE	£ 15,769,743	£ 11,003,836	£ 18,156,873	£ 13,880,216
SEVERE IV	£ 102,516,656	£ 75,684,165	£ 133,945,222	£ 105,946,430
Total Severe	£ 118,286,399	£ 86,688,001	£ 152,102,095	£ 119,826,646

The breakdown of cost provided by cost bands for each health state, in Figure 35-36 below, have variation in total costs by age when comparing treatment vs, no treatment with Orkambi®. The total cost per health state generated by in the PbR cost bands alone, in either sex groups, overall followed the above-described pattern stratified by age. For males, Figure 35, we can see that the large variation exists throughout the time horizon of the model. For females, Figure 36, the pattern of variation in PbR costs was similar to that of males.

Figure 35: Breakdown of cost (PbR) control vs intervention (age 7-47) males over time horizon of model

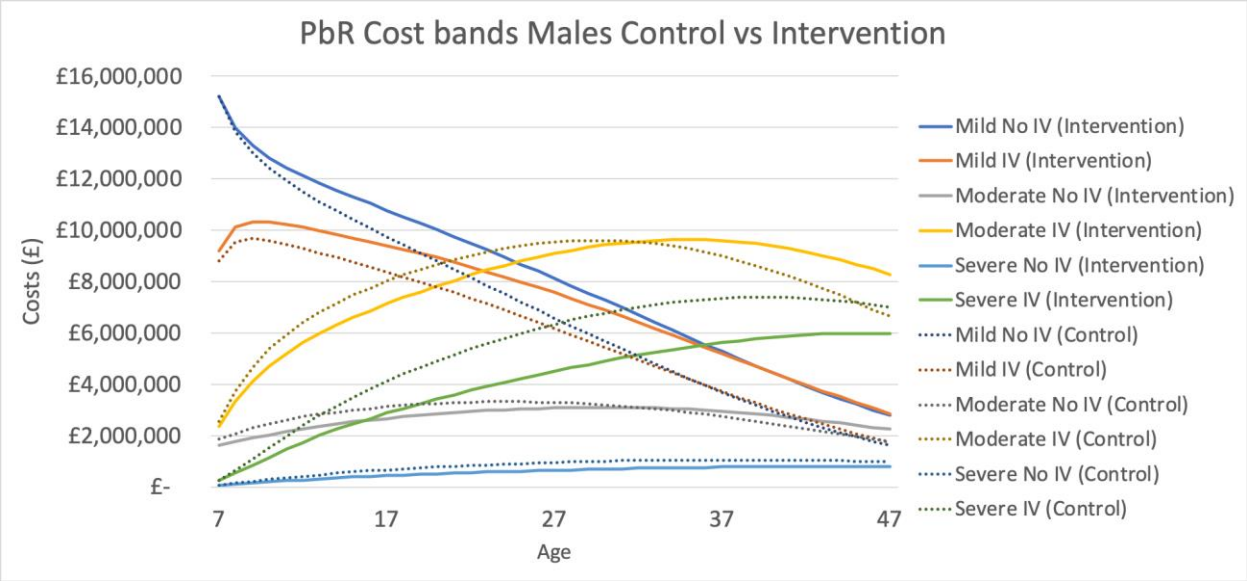


Figure 36: Breakdown of cost (PbR) control vs intervention (age 7-47) Females over time horizon of model

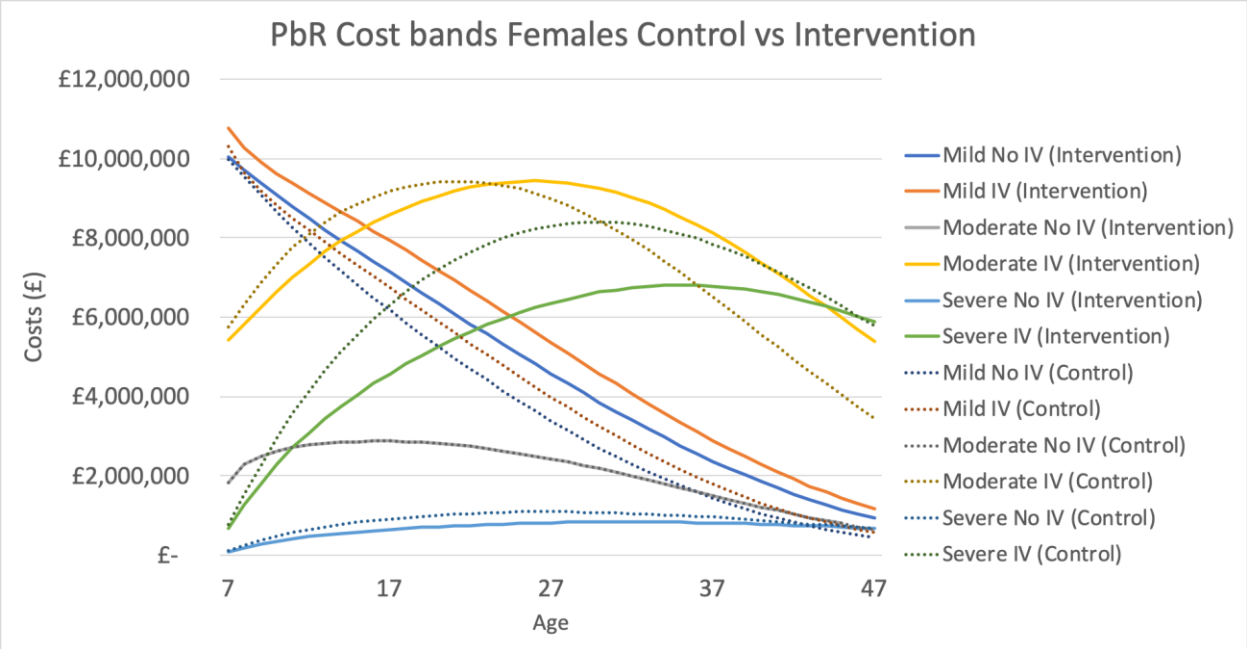


Table 86 shows the discounted costs per person by health state, intervention and sex. This again follows the pattern described above for Table 85. Table 86 shows the discounted PbR banding cost per person in the model by sex and treatment. We can see that males overall, on treatment, cost more than any other category. The female, per person, costs were much lower than males, even after taking treatment. This is most likely due to the overall initial distribution of the patients in the model, the difference in health state transition probabilities between the two sexes where females have a worser outcomes. It was seen in Chapter 5 (Section 5.19.1), that females often were worse off in terms of health than males.

The total undiscounted costs generated by PbR banding were £ £1.229 million, £1.256 million, £1.039 million and £1.086 million for males (no Orkambi®/Orkambi®) and females (no Orkambi®/Orkambi®), respectively (Table 84). This shows that on average females accrued lower costs compared to males in either treatment or no treatment.

Table 86: PbR Banding Costs per person by health state, sex and treatment over time horizon of model (Discounted)

	PBR banding Costs per person by health state (discounted)			
	Males (control)	**Males (Intervention)**	**Female (control)**	**Female (Intervention)**
MILD NO IV	£ 74,065	£ 83,374	£ 45,294	£ 52,497
MILD IV	£ 61,615	£ 71,180	£ 48,935	£ 58,311
Total Mild	£ 135,680	£ 154,555	£ 94,229	£ 110,808
MODERATE NO IV	£ 24,745	£ 22,874	£ 20,266	£ 19,770
MODERATE IV	£ 66,882	£ 64,199	£ 68,572	£ 69,979
Total Moderate	£ 91,627	£ 87,072	£ 88,838	£ 89,749
SEVERE NO IV	£ 6,213	£ 4,335	£ 7,154	£ 5,469
SEVERE IV	£ 40,390	£ 29,818	£ 52,772	£ 41,741
Total Severe	£ 46,603	£ 34,154	£ 59,926	£ 47,210
average	£ 91,303	£ 91,927	£ 80,998	£ 82,589

Table 87: PbR Banding Costs, total, by sex and treatment over time horizon of model (Discounted)

Total cost per person (7- 47 years)			
Males (control)	**Males (Intervention)**	**Female (control)**	**Female (Intervention)**
£ 273,910	£ 275,781	£ 242,993	£ 247,767

A closer look at the results, Figures 31-32, also show that, on average, females spent more time in either of the Severe health states overall, compared to other health states in comparison to males. This is despite both sex groups starting with an initial 0% in either Severe health states at age 6. We can also see this pattern in Figures 35-36, females accrue higher costs in the Severe IV health state at a faster rate than males. This is further evident in the model, where females in either treatment groups were substantially more likely to be placed in a higher cost band (band 4 and 5) compared to males in the same Severe IV health state, regardless of age, Figure 37 (control group only shown).

The same could be said for the Moderate IV health state but this could also be influenced by the difference in initial patient distribution between males and females in the Moderate IV health state, where there were 12% of the initial cohort (females) compared to 3% for males in that health state at age 6, Figure 38 (control group only shown). However, this is unlikely to be purely due to this fact. The large difference in costs could be explained by females transitioning to worse health states and dying, which is already evident through analysis in Chapter 5.

Figure 37: Occupation of PbR cost band by sex for Severe IV health state

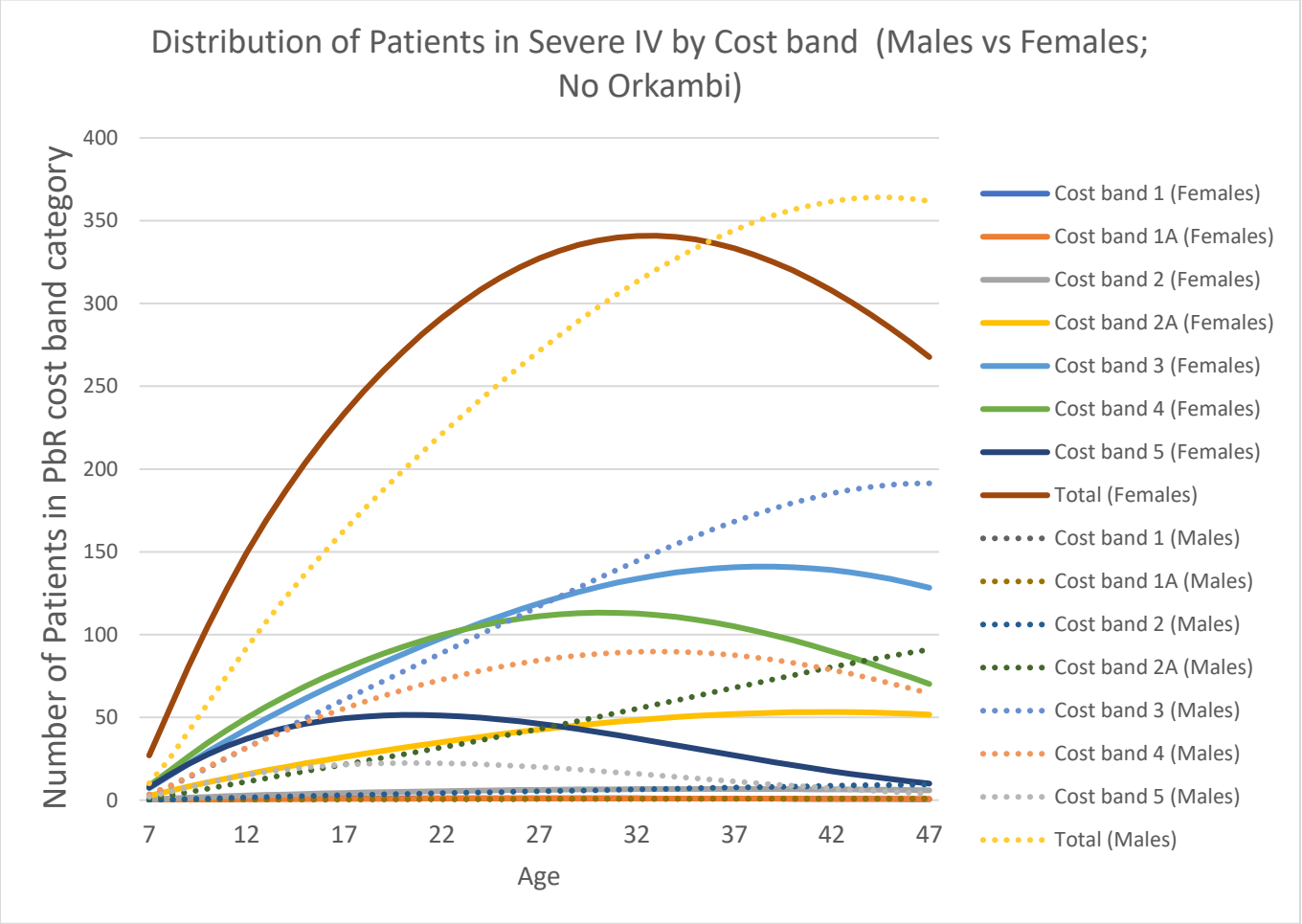
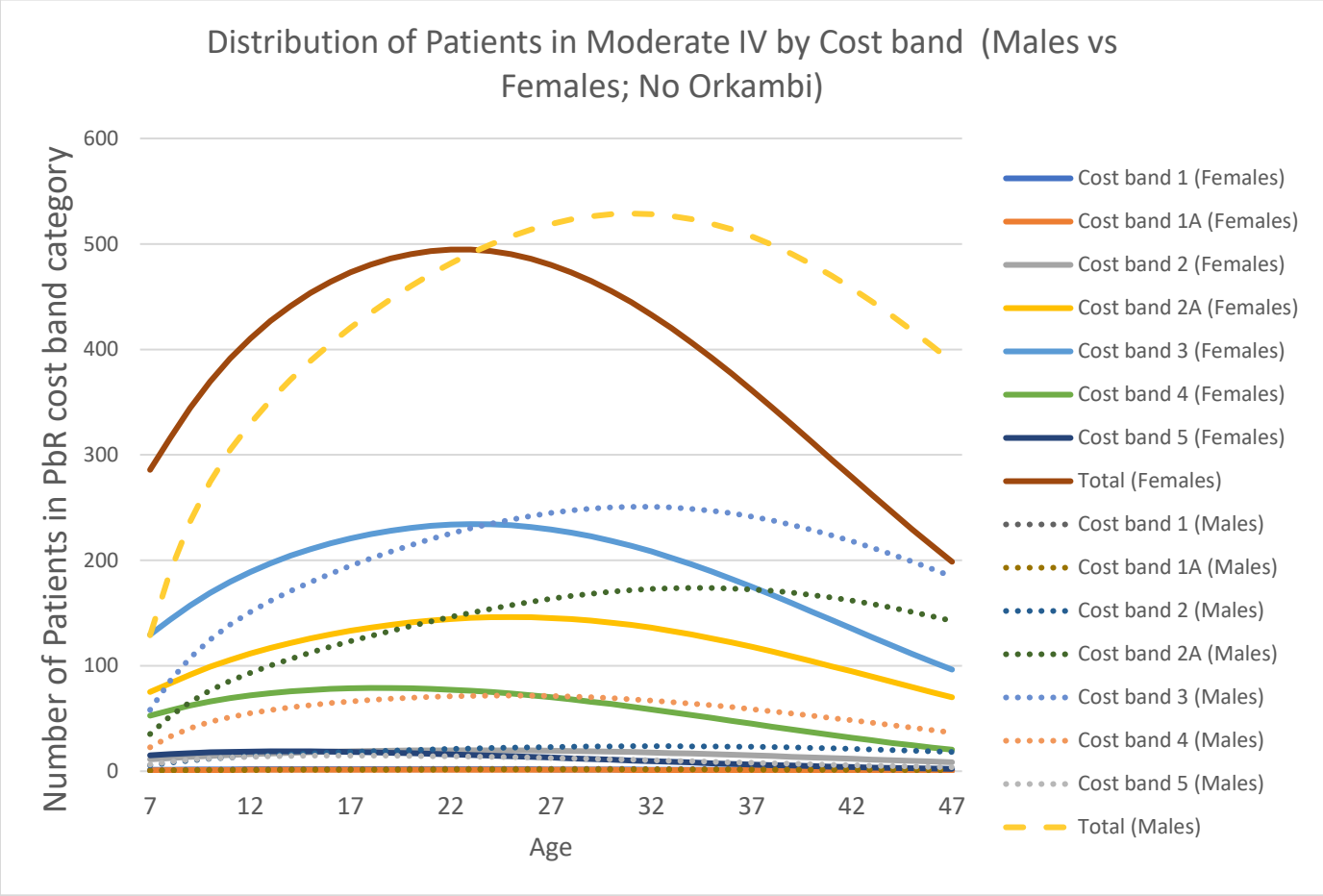


Figure 38: Occupation of PbR cost band by sex for Moderate IV health state



6.22.4 Lung transplantation costs

Table 88: Total Lung transplant costs by sex and treatment (7- 47 years)

	Males-No Orkambi®	Males-Orkambi®	Females-No Orkambi®	Females-Orkambi®
Total Costs (Undiscounted)	£4,747,988	£4,753,030	£6,225,985	£6,245,737
Total Costs (Discounted)	£1,910,813	£1,910,803	£2,617,186	£2,621,487
Per person costs (Discounted)	£753	£753	£1,163	£1,165

In terms of the costs associated with lung transplantation, there is an unexpected marginal increase in costs of lung transplant across treatment groups. Table 88 shows those who received Orkambi® having slightly higher costs than those who were not over the time horizon of the model (undiscounted). The results also show that for males on treatment total costs after discounting were reduced and lower for the treatment group. This was not the case for females on treatment. Table 86 also presents the discounted per person costs in the model for lung transplantation for either sex group whether on treatment or not. We can see there was no difference for males and only a very small marginal increase in costs for females on treatment.

6.22.5 High-Cost drugs

Figure 39-40 below presents the cost per person (undiscounted) by health state over the time horizon of the model for males and females respectively (undiscounted) for High-Cost drugs.

As can be seen from the figure for males, cost for Mild and Moderate remain relatively stable over time, whereas the costs for Mild IV, Moderate IV and Severe IV increases over time. A similar pattern exists for females.

Figure 39: Cost per person (males)

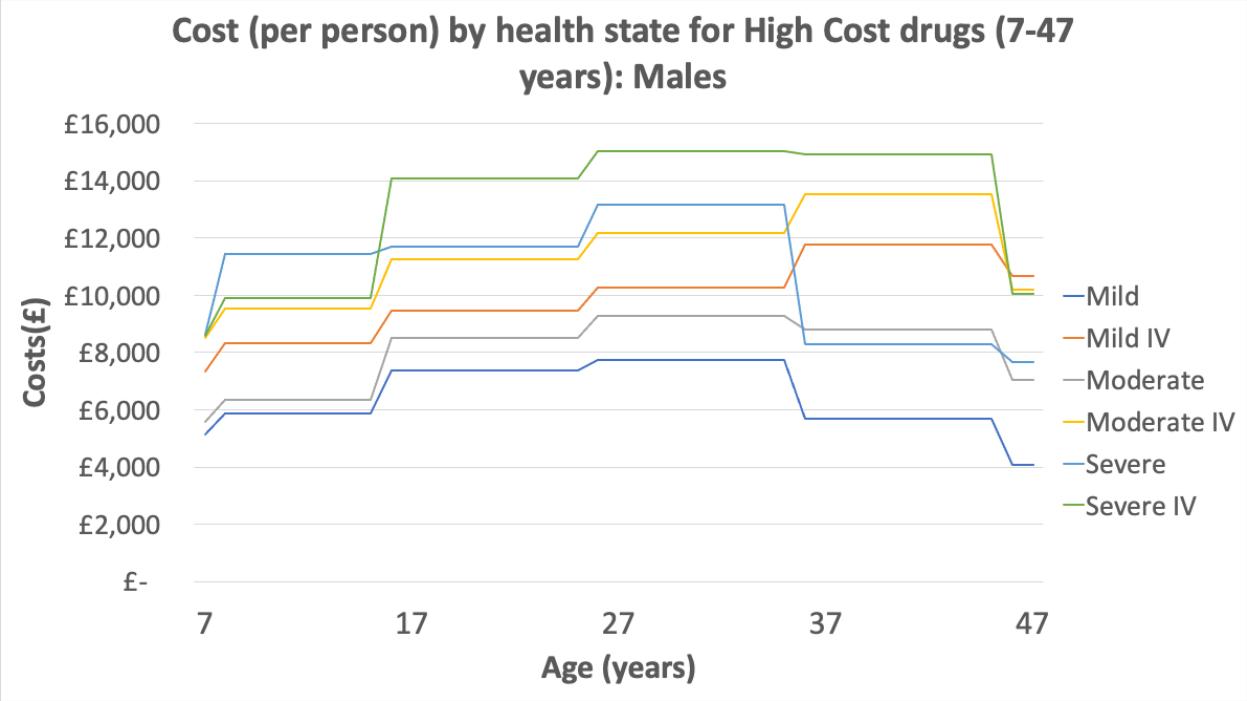
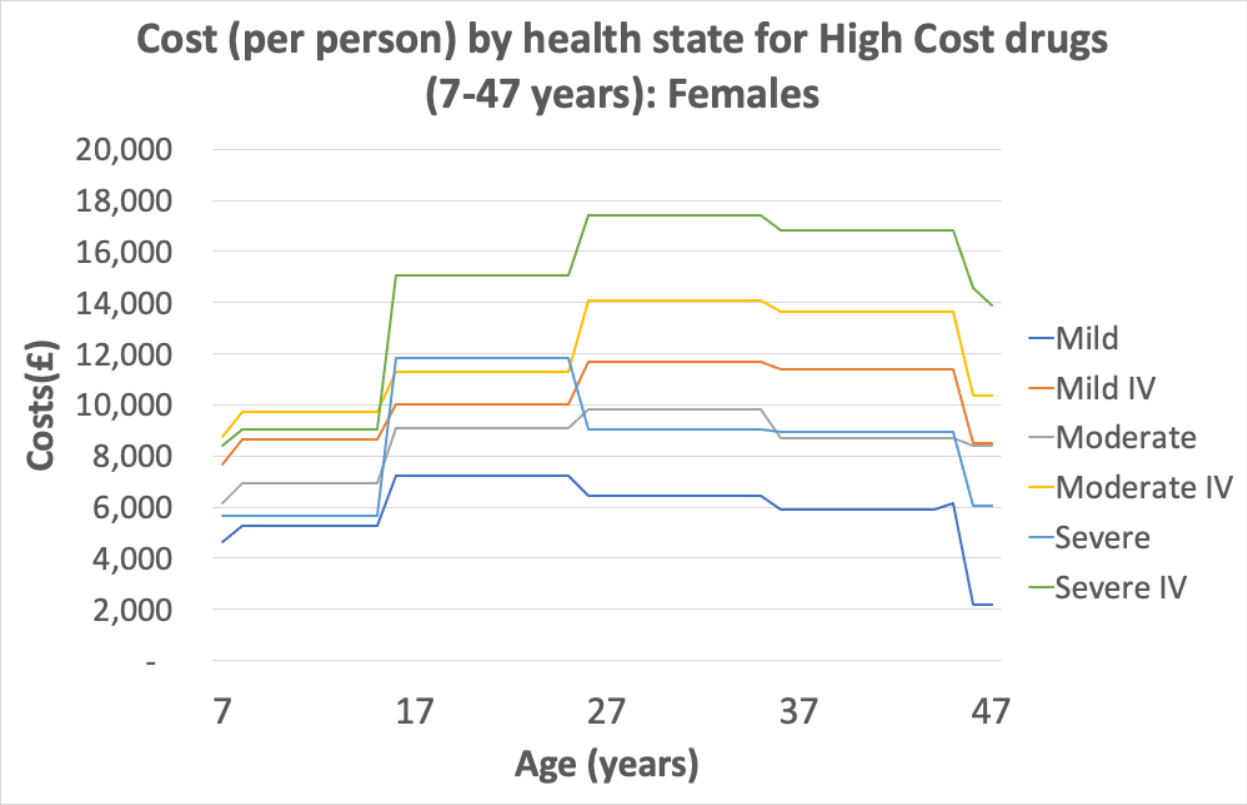


Figure 40: Cost per person (Females)



Tables 89-91 show the High-Cost CF drug costs stratified by sex, health state and treatment. These costs do not include the costs of Orkambi®. Table 89 shows the total costs, discounted, generated by high-cost drugs were £436 million, £441 million, £373 million and £385 million for males (no Orkambi®/Orkambi®) and females (no Orkambi®/Orkambi®), respectively. On average males accrued higher costs for the Mild health states, whether they were on treatment or not, except for those in the remaining health states. Most likely due to the change in the transitions between the health states as a result of receiving Orkambi®.

In the case of females, they accrued higher total costs the Mild, Mild IV and Moderate IV health states. This is most likely due to the change in the transitions between the health states as a result of receiving Orkambi®.

Table 89: High-Cost drug costs by health state, sex and treatment (7- 47 years)

	High-Cost Drug Costs by health state (discounted)			
	Males (control)	**Males (Intervention)**	**Female (control)**	**Female (Intervention)**
MILD	£ 116,366,761	£ 130,721,613	£ 67,067,314	£ 77,832,477
MILD IV	£ 101,276,655	£ 117,938,429	£ 78,456,167	£ 94,492,271
Total Mild	£ 217,643,416	£ 248,660,042	£ 145,523,482	£ 172,324,748
MODERATE	£ 40,363,546	£ 37,534,391	£ 32,880,226	£ 32,332,621
MODERATE IV	£ 104,497,052	£ 101,484,795	£ 105,924,308	£ 110,208,036
Total Moderate	£ 144,860,598	£ 139,019,187	£ 138,804,534	£ 142,540,657
SEVERE	£ 11,203,539	£ 7,782,655	£ 9,306,090	£ 7,126,246
SEVERE IV	£ 62,029,265	£ 45,957,406	£ 78,993,230	£ 63,228,579
Total Severe	£ 73,232,804	£ 53,740,062	£ 88,299,320	£ 70,354,825
Total	£ 435,736,818	£ 441,419,291	£ 372,627,336	£ 385,220,229

Table 90 shows the cost per person (discounted) by health state, sex and treatment. The table shows that treatment with Orkambi® increases the cost per person of being in either of the Mild health states, but also reduced the costs per person of subsequent worse health states. This is also the same for females, except for the Moderate IV health state

which resulted in an increase cost per person on treatment. We can see that females cost more per person for being in the Moderate IV and Severe IV health states compared to males regardless of whether they were on treatment or not.

Table 90: High-Cost drug costs per person by health state, sex and treatment (7-47 years)

	High-Cost Drug Costs per person by health state (discounted)			
	Males (control)	Males (Intervention)	Female (control)	Female (Intervention)
MILD	£ 45,847	£ 51,502	£ 26,423	£ 30,665
MILD IV	£ 39,901	£ 46,466	£ 30,911	£ 37,229
Total Mild	£ 85,748	£ 97,968	£ 57,334	£ 67,893
MODERATE	£ 15,903	£ 14,788	£ 12,954	£ 12,739
MODERATE IV	£ 41,170	£ 39,983	£ 41,733	£ 43,420
Total Moderate	£ 57,073	£ 54,771	£ 54,687	£ 56,159
SEVERE	£ 4,414	£ 3,066	£ 3,666	£ 2,808
SEVERE IV	£ 24,439	£ 18,107	£ 31,122	£ 24,911
Total Severe	£ 28,853	£ 21,173	£ 34,789	£ 27,719
Average	£ 57,225	£ 57,971	£ 48,936	£ 50,590

Further investigation of High-Costs drugs by age, sex and for a cohort on Orkambi®, Figure 41, showed that the higher cost for females in either the Moderate IV or Severe IV health state existed throughout the model, age 7-33 years for Moderate IV and age 7-44

years for Severe IV health state respectively. This could be due to the difference in the initial distribution between the sexs, with double the males in this health state than females. However, this difference in costs would also be due to the difference in High-Cost drug utilisation between the sex groups. Lastly, Table 91 shows the Males were more expensive to treat while on Orkambi® compared to females and that the estimated cost for High-Cost drugs were higher for those on Orkambi®.

Figure 41: High-Cost Drug Costs by sex and health state

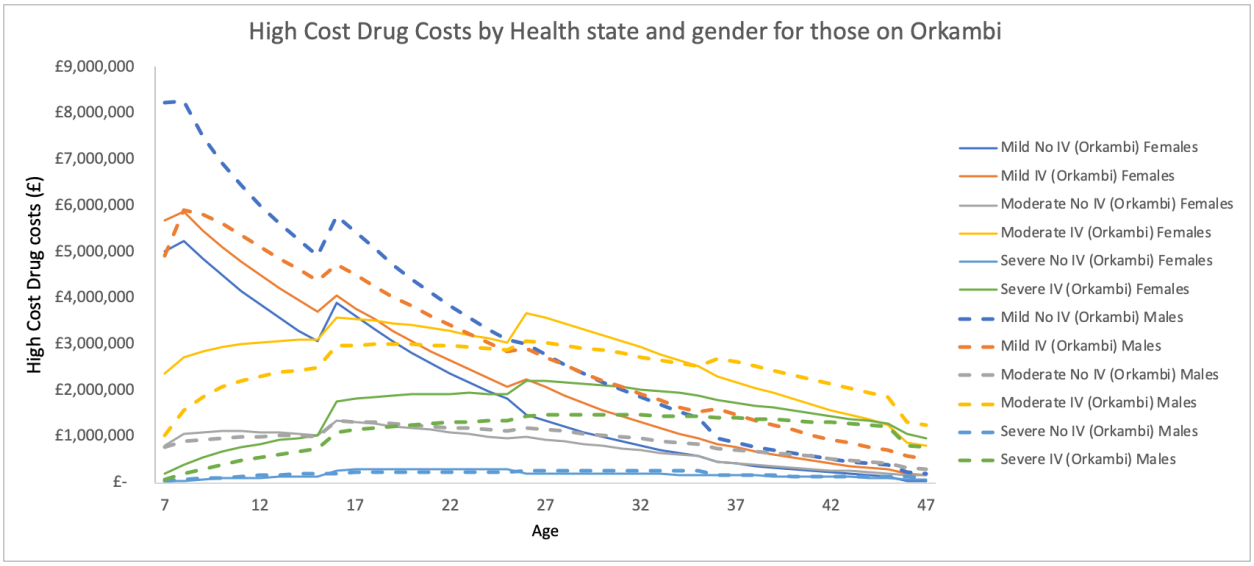


Table 91: High-Cost drug costs by sex and treatment

Total High-Cost Drug Costs per person			
Males (control)	**Males (Intervention)**	**Female (control)**	**Female (Intervention)**
£ 171,674	£ 171,899	£ 146,809	£ 147,252

6.22.6 Costs of Orkambi®

Tables 92-93 show the Orkambi® costs stratified by sex and health state. Table 92 shows the total costs, undiscounted, generated by Orkambi® treatment were £7.993 billion, £6.294 billion for males and females, respectively. Table 93 shows the total costs, discounted, generated by Orkambi® treatment were £4.619 billion and £ 3.774 billion for males and females, respectively. Total discounted lifetime costs per person, Table 94, for males and females was £1.819 million and £1.677 million. The tables showed that treatment with Orkambi® was more costly in males in the Mild and Moderate health states when undiscounted. However, this changed when the costs were discounted, Females became more costly to treat in the moderate IV health state, all else remaining the same. Females were more costly to treat with Orkambi® in the Severe health states, undiscounted or discounted. However overall, Males cost more to treat with Orkambi® than females, undiscounted or discounted.

Table 92: Orkambi® costs stratified by sex and health (undiscounted)

	Orkambi® Costs by health state (undiscounted)			
	Males		Female	
MILD	£	2,822,719,162	£	1,748,176,476
MILD IV	£	1,896,882,785	£	1,371,694,059
Total Mild	£	4,719,601,947	£	3,119,870,536
MODERATE	£	800,924,904	£	609,959,967
MODERATE IV	£	1,640,063,370	£	1,600,036,356
Total Moderate	£	2,440,988,274	£	2,209,996,323
SEVERE	£	143,151,415	£	147,102,090
SEVERE IV	£	689,670,786	£	817,101,694
Total Severe	£	832,822,201	£	964,203,783
Total Cost	£	7,993,412,422	£	6,294,070,642

Table 93:Orkambi®costs stratified by sex and health state (discounted)

	Orkambi® Costs by health state (discounted)			
	Males (control)		Female (control)	
MILD	£	1,845,951,254	£	1,200,246,103
MILD IV	£	1,171,531,645	£	909,574,939
Total Mild	£	3,017,482,899	£	2,109,821,043
MODERATE	£	427,021,346	£	352,747,664
MODERATE IV	£	806,607,539	£	856,727,960
Total Moderate	£	1,233,628,886	£	1,209,475,624
SEVERE	£	64,459,546	£	71,022,813
SEVERE IV	£	302,982,577	£	383,891,035
Total Severe	£	367,442,123	£	454,913,849
Total Cost	£	4,618,553,907	£	3,774,210,515

Table 94:Total cost of Orkamnbi® per person by sex

Total Orkambi® cost per person	
Males	**Female**
£1,819,639	£ 1,676,808

6.22.7 Total Costs summary

Figure 42-43 below presents the total cost per person (undiscounted) by health state over the time horizon of the model for males and females respectively.

As can be seen from the figure for males, cost for less severe health states increases overtime whereas costs for more severe health states decreases overtime. Although overall cost per person is high for those in the severe health states compared to those in the healthier states.

Figure 42: Cost per person (Males)

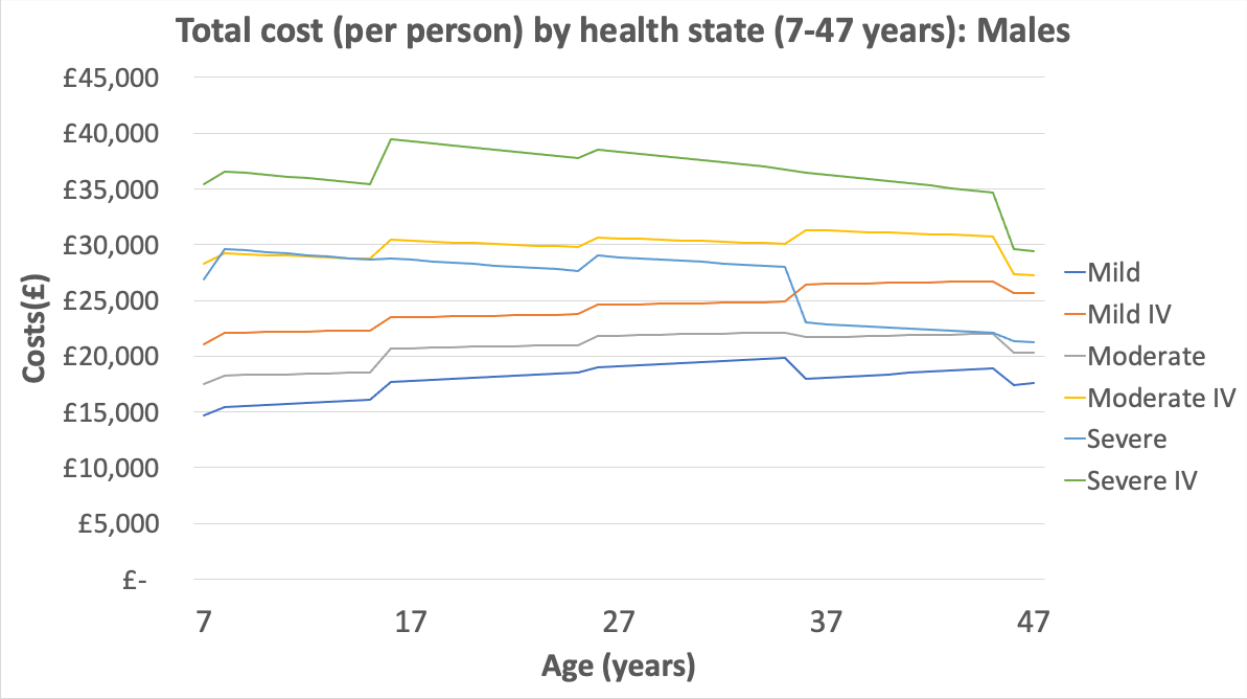
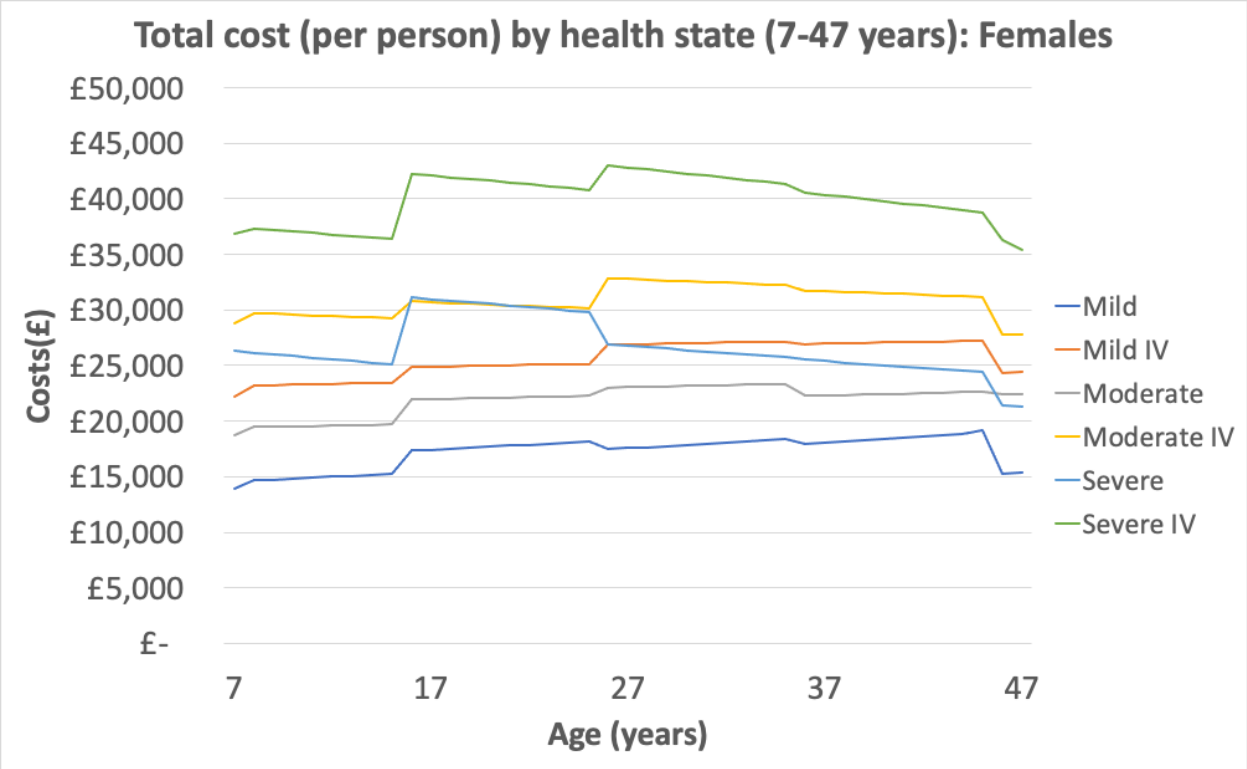


Figure 43: Total Cost per person (Females)



Tables 95-96 show the total costs stratified by sex and health state without half cycle correction being applied. Table 95 shows the total costs, undiscounted, generated by either group, control and treatment by sex and health state (males: £2.019 billion, £10.061 billion vs. females; £1.693 billion, £8.071 billion for males and females control and treatment group, respectively. Table 96 presents the discounted costs as above.

Table 95: Total costs by sex and health state (no half cycle correction)

	Total Costs by health state (undiscounted)			
	Males (control)	Males (Intervention)	Female (control)	Female (Intervention)
MILD	£ 459,086,921	£ 3,360,036,260	£ 259,891,150	£ 2,063,426,179
MILD IV	£ 410,969,543	£ 2,390,824,570	£ 298,067,581	£ 1,744,361,153
Total Mild	£ 870,056,465	£ 5,750,860,830	£ 557,958,731	£ 3,807,787,332
MODERATE	£ 189,524,988	£ 983,979,506	£ 141,079,558	£ 755,384,998
MODERATE IV	£ 540,406,105	£ 2,180,074,192	£ 501,324,638	£ 2,141,831,535
Total Moderate	£ 729,931,094	£ 3,164,053,698	£ 642,404,196	£ 2,897,216,533
SEVERE	£ 56,828,352	£ 183,469,567	£ 53,978,153	£ 189,762,141
SEVERE IV	£ 363,032,127	£ 962,705,279	£ 439,511,440	£ 1,176,955,112
Total Severe	£ 419,860,479	£ 1,146,174,846	£ 493,489,593	£ 1,366,717,253
Total Cost	£ 2,019,848,037	£ 10,061,089,374	£ 1,693,852,521	£ 8,071,721,117

Table 96: Total costs by sex and health state (no half cycle correction)

	Total Costs by health state (discounted)			
	Males (control)	Males (Intervention)	Female (control)	Female (Intervention)
MILD	£ 304,355,986	£ 2,188,291,065	£ 182,032,266	£ 1,411,325,021
MILD IV	£ 257,665,241	£ 1,470,138,196	£ 202,661,330	£ 1,152,069,549
Total Mild	£ 562,021,227	£ 3,658,429,261	£ 384,693,595	£ 2,563,394,570
MODERATE	£ 103,170,905	£ 522,613,087	£ 84,319,425	£ 435,260,574
MODERATE IV	£ 274,255,023	£ 1,071,039,235	£ 279,970,858	£ 1,144,554,421
Total Moderate	£ 377,425,927	£ 1,593,652,322	£ 364,290,283	£ 1,579,814,995
SEVERE	£ 26,973,282	£ 83,246,037	£ 27,462,963	£ 92,029,275
SEVERE IV	£ 164,545,921	£ 424,624,148	£ 212,938,453	£ 553,066,045
Total Severe	£ 191,519,203	£ 507,870,185	£ 240,401,415	£ 645,095,320
Total Cost	£ 1,130,966,358	£ 5,759,951,767	£ 989,385,294	£ 4,788,304,884

Table 97 presents the total costs per person by health state, sex and treatment (discounted). The results show that males cost more in the healthier states such as Mild No IV, Mild IV, Moderate No IV and Moderate IV, whereas females cost more in the more severe health states, Severe No IV and Severe IV. Lastly, Table 98 presented the cost

per person by sex and treatment not taking into account the health state (discounted). The results show that males accrue a High-Cost for either treatment or no treatment compared to females overall.

Table 97: Total costs by sex and health state (no half cycle correction)

	Total Costs per person by health state (discounted)			
	Males (control)	**Males (Intervention)**	**Female (control)**	**Female (Intervention)**
MILD	£ 119,912	£ 862,153	£ 80,873	£ 627,024
MILD IV	£ 101,516	£ 579,212	£ 90,038	£ 511,842
Total Mild	£ 221,428	£ 1,441,365	£ 170,912	£ 1,138,866
MODERATE	£ 40,648	£ 205,902	£ 37,461	£ 193,378
MODERATE IV	£ 108,052	£ 421,973	£ 124,386	£ 508,503
Total Moderate	£ 148,700	£ 627,875	£ 161,847	£ 701,881
SEVERE	£ 10,627	£ 32,798	£ 12,201	£ 40,887
SEVERE IV	£ 64,829	£ 167,295	£ 94,604	£ 245,716
Total Severe	£ 75,456	£ 200,093	£ 106,806	£ 286,603

Table 98: Total Cost per person by sex and treatment

Males (control)	Males (Intervention)	Female (control)	Female (Intervention)
£ 446,336	£ 2,269,887	£ 440,727	£ 2,128,288

6.22.8 QALYs

Tables 99-102 show estimates of QALY generated in the base-case analysis using a deterministic approach without half-cycle correction, although final result provide QALYs with half-cycle correction. Table 99 presented the undiscounted number of QALYs generated from the model across the different health states. For males, we can see that treatment with Orkambi® resulted in an increase in the number of QALYs generated from the Mild health states. Subsequent health states show a decrease in QALYs, mainly due to a shift in transition of individuals to the better Milder health states from receiving Orkambi®. This pattern is also evident in the females in the model, however the increase in QALYs also extends to both Moderate health states. We can also see that Males overall generated more QALYs in the model compared to females, either with or without Orkambi®.

Table 100 shows the same as the above but presented the discounted QALYs and the patterns evident in Table 99 are also evident in Table 100. However, we can see that females in the Moderate IV health state also experienced an increase in the number of QALYs generated subsequent to discounting. Overall, we can see that males over the time horizon of the model generated more QALYs than females, either with or without Orkambi®.

Table 99: Total QALYs generated by health state, sex and treatment

	QALYs generated (undiscounted)			
	Males (control)	**Males (Intervention)**	**Female (control)**	**Female (Intervention)**
MILD	22,853	26,517	13,697	16,423
MILD IV	11,974	14,297	8,336	10,339
Total Mild	34,828	40,815	22,033	26,762
MODERATE	7,374	7,087	5,272	5,397
MODERATE IV	11,480	11,466	10,370	11,186
Total Moderate	18,854	18,552	15,642	16,583
SEVERE	1,400	1,001	1,291	1,028
SEVERE IV	4,691	3,541	5,111	4,195
Total Severe	6,092	4,542	6,402	5,223
Total	59,774	63,909	44,076	48,568

Table 100: Total QALYs generated by health state, sex and treatment

	QALYs generated (discounted)			
	Males (control)	**Males (Intervention)**	**Female (control)**	**Female (Intervention)**
MILD	15,539	17,341	9,823	11,275
MILD IV	7,658	8,830	5,767	6,856
Total Mild	23,198	26,171	15,590	18,131
MODERATE	4,100	3,778	3,212	3,121
MODERATE IV	5,854	5,639	5,842	5,989
Total Moderate	9,954	9,417	9,053	9,111
SEVERE	643	451	645	497
SEVERE IV	2,098	1,556	2,477	1,971
Total Severe	2,742	2,006	3,123	2,467
Total	35,894	37,595	27,765	29,709

Table 101 presented the QALYs generated per person by sex and Orkambi® treatment, whether discounted or not. The results show that Males on Orkambi® produced the most QALYs per person, either discounted or not.

Table 102 shows the QALYs gained per person by health state subsequent to taking Orkambi®. Overall, it shows that females produced more QALYs per person after treatment over the time horizon of the model in the Mild health states, but less QALYs in

the more severe health states. Compared to life years gained in Table 15, above, females gained more life years (2.91) and more QALYs (0.86) per person over the time horizon over the model compared to males. Although males gained more QALYs and LYs in the healthier states compared to females. The overall results also show, when comparing QALYs and LYs gained (Section 6.22.2), that there were more life years gained compared to QALYs which means that a large majority of health benefit comes from an improvement in survival and not an improvement in QOL. This also suggests that gains in LYs are made with very poor QOL.

Table 101: Total QALYs per person by treatment and sex (discounted)

	Total QALYS per person			
	Males (control)	**Males (Intervention)**	**Female (control)**	**Female (Intervention)**
Discounted	14.16	14.82	10.96	11.72
Undiscounted	23.58	25.20	17.41	19.17

Table 102: Total QALYs per person by health state from Orkambi®

Health State	QALYS gained (discounted)	
Sex	**Males**	**Female**
MILD NO IV	0.71	0.65
MILD IV	0.46	0.48
MODERATE NO IV	-0.13	-0.04
MODERATE IV	-0.08	0.07
SEVERE NO IV	-0.08	-0.07
SEVERE IV	-0.21	-0.22
Total	0.67	0.86

These results indicate that both males and females were spending more time in the better health states and less in the more severe health states based on the benefits received from treatment with Orkambi®. The results also show that females produced more QALYs for the Severe IV health state. This could be due to a combination of factors, that there were males in the model to begin with and that males were more likely to remain in and transition to better health states compared to females as shown in Chapter 5

6.23 Deterministic results

Table 103: Results of Deterministic analysis (per person) (WTP threshold: £25,000)

Results (Deterministic)

MALES			
	Cost (£)		QALY
Orkambi	£	2,253,434	14.73
No Orkambi	£	443,290	14.08
Diff	£	1,810,143	0.65
ICER	£	2,792,146	£/QALY
With half-cycle correction			
	Cost (£)		QALY
Orkambi	£	2,207,309	14.38
No Orkambi	£	436,191	13.72
Diff	£	1,771,117	0.66
ICER	£	2,693,202	£/QALY
NMB (with half cycle correction)			
	Cost (£)		QALY
Orkambi	£	2,207,309	14.38
No Orkambi	£	436,191	13.72
NMB(Orkam	**-£**	**1,847,928**	
NMB(No Ork	-£	93,251	

FEMALES			
	Cost (£)		QALY
Orkambi	£	2,116,946	13.16
No Orkambi	£	438,656	12.31
Diff	£	1,678,290	0.84
ICER	£	1,992,402	£/QALY
With half-cycle correction			
	Cost (£)		QALY
Orkambi	£	2,067,432	12.80
No Orkambi	£	430,169	11.95
Diff	£	1,637,263	0.85
ICER	£	1,924,233	£/QALY
NMB (with half cycle correction)			
	Cost (£)		QALY
Orkambi	£	2,067,432	12.80
No Orkambi	£	430,169	11.95
NMB(Orkam	**-£**	**1,747,397**	
NMB(No Ork	-£	131,406	

Total (across Gender)			
	Cost (£)		QALY
Orkambi	£	2,189,284	13.99
No Orkambi	£	441,112	13.25
Diff	£	1,748,172	0.74
ICER	£	2,363,992	£/QALY
With half-cycle correction			
	Cost (£)		QALY
Orkambi	£	2,141,567	13.64
No Orkambi	£	433,361	12.89
Diff	£	1,708,206	0.75
ICER	£	2,282,330	£/QALY
With half-cycle correction			
	Cost (£)		QALY
Orkambi	£	2,141,567	13.64
No Orkambi	£	433,361	12.89
NMB(Orkam	**-£**	**1,800,679**	
NMB(No Ork	-£	111,184	

6.23.1 Incremental cost, outcomes and Overall ICER

Table 103 shows the deterministic results of the ICER calculation for the model per patient, based on sex and with both sexes combined. The results show that treating males was more expensive despite the intervention being more effective for females, (males; £1.810 million, females; £1.678 million (without half cycle correction), (males; £1.771 million females; £1.637 million (with half cycle correction)). The ICER results for females also show that the intervention costs less per QALY for females compared to males. In terms of effectiveness, those receiving Orkambi® treatment show an increase in QALYs, (males; 0.66 vs females; 0.84 and combined 0.74). The QALYs gained across sex are different, as stated females generating 0.19 QALYs more than males. The ICER results show that, per QALY, Orkambi® treatment was substantially more expensive than No Orkambi® treatment, males; £2.693 million vs females; £1.924 million and combined £2.282 million for males, females and both combined respectively, whilst taking in account half-cycle correction. When compared to the NICE threshold cost per QALY guidance, of between £20,000-£30,000/QALY, Orkambi® would not be a cost-effective option.

6.23.2 Net Monetary Benefit

Looking at the NMB, not incremental NMB, produced by the deterministic estimates in the model, we can see that there would an NMB of -£93,251, -£131,406 and -£111,184, for males, females and both combined who were not on Orkambi® at a threshold of £25,000/QALY. Those who received Orkambi® had an even large deficit in NMB of -£1.848 million, -£1,747 million and -£1.801 million for males, females and both at the same threshold per QALY.

6.23.3 Probabilistic results

6.23.3.1 Incremental cost, outcomes and Overall ICER

Table 104 shows the probabilistic results of the ICER calculation for the model per patient, based on both sexes combined. The results show little variability in costs within the Orkambi® or control group, this reflects the 10% variability in the PbR cost bands and no variability around the cost of Orkambi®, other High-Cost drugs and 10% variability in the cost of lung transplant. However, for QALYs, we can see that there is more variability, most likely due to the distribution, normal, given to such parameters for the PSA analysis. An important result to note here is that the QALYs generated from control, upper 95% CI, are higher than the lower 95% CI bound for the Orkambi® group. This shows that there is a plausibility that there would be no difference in QALYs from treatment with Orkambi®.

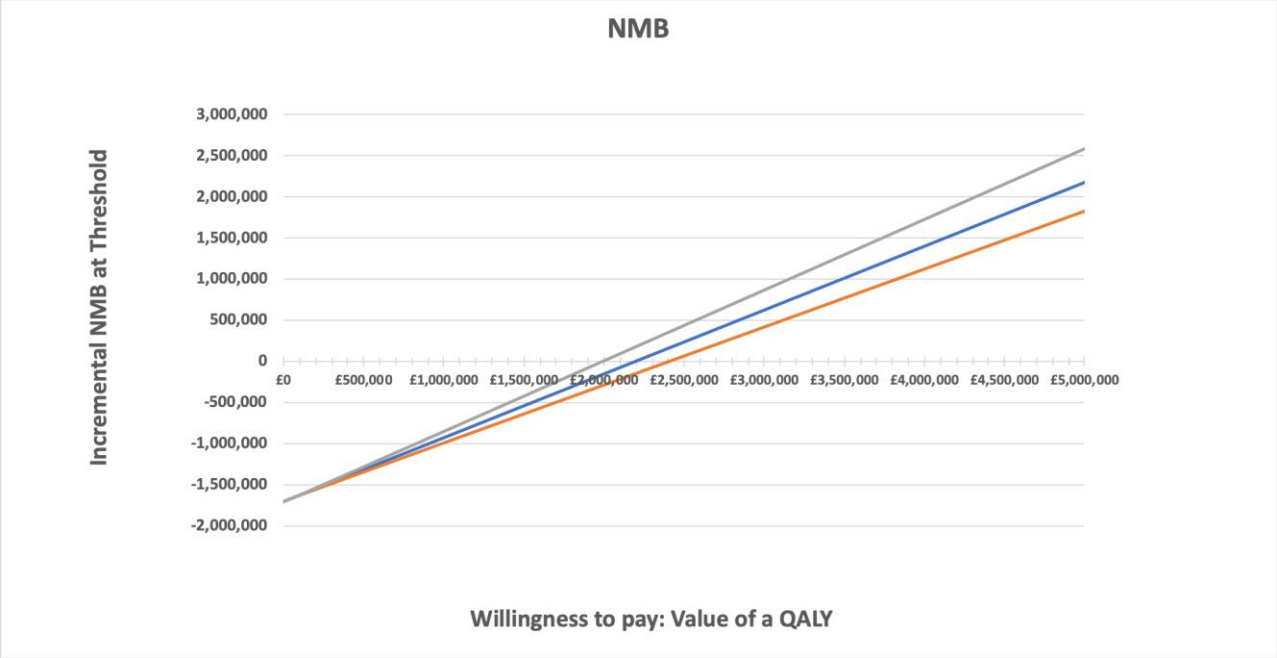
Table 104: Probabilistic results (discounted)

Results (PSA) Combined sex						
(95% CI)						
With half cycle correction						
	Costs (£)			QALYs		
	Lower	Mean	Upper	Lower	Mean	Upper
Orkambi®	£ 2,129,193	£ 2,138,019	£ 2,148,254	14.94	15.32	15.76
No Orkambi ®	£ 421,965	£ 429,196	£ 438,169	14.18	14.55	14.97
Incremental difference						
	£ 1,703,957		£ 1,714,597	0.71		0.86
ICER						
	Lower			Upper		
	£ 2,019,919			£ 2,457,337		

6.23.3.2 Incremental Net Monetary Benefit

Figure 44 shows that at threshold willingness to pay for a QALY of £2.2 million, the mean incremental NMB goes from negative to positive. At a threshold of £2.2 million the incremental NMB also shows the amount of uncertainty around the mean and places the incremental NMB between -£150 thousand and £181 thousand for the 97.5 and 5 percentiles of all estimates. This further reflects the uncertainty in the cost-effectiveness of Orkambi®. However, at a threshold of £20,000 to £30,00 there is a 100% chance that the NMB is negative.

Figure 44: Incremental Net Monetary Benefit

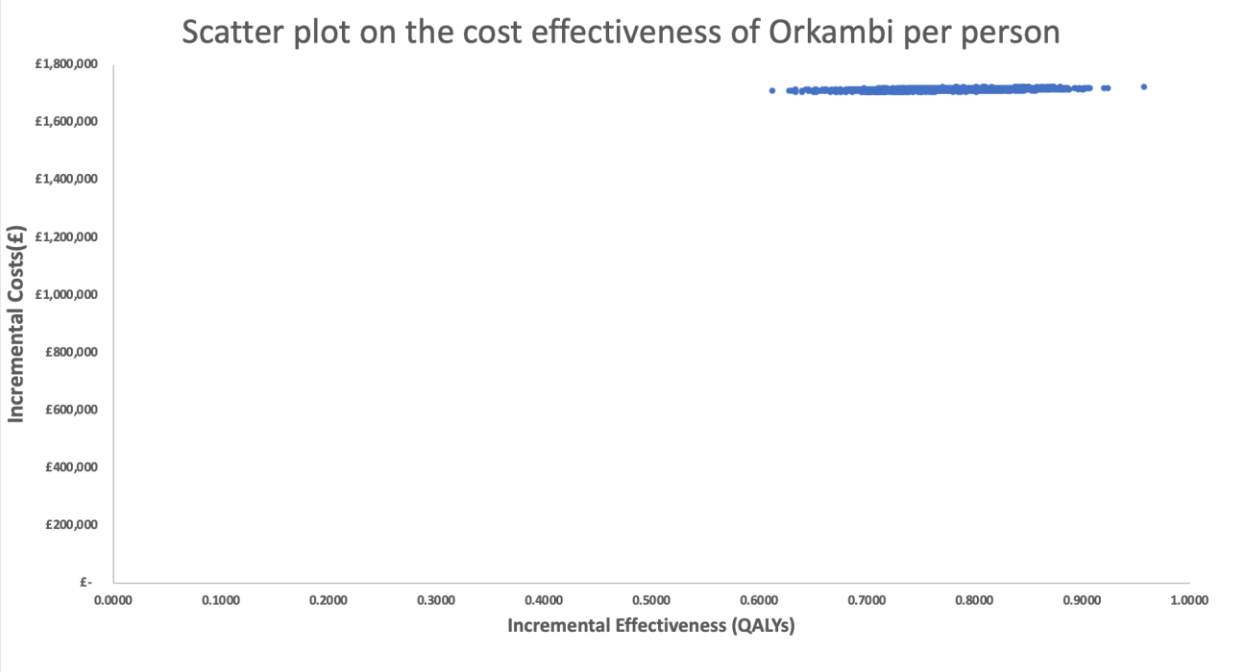


6.23.4 Cost effectiveness plane

As explained in the methods section the cost - effectiveness plane allows the presentation of the uncertainty around the deterministic values (distributions) entered into the model for the exemplar cost-utility analysis. In Figure 45 we can see that all of the point estimates

of costs and QALYs fall into the NE quadrant of the plane which shows that intervention is more effective but also more costly. The cost-utility plane also shows that there was small uncertainty in the incremental costs between treatment groups, with all incremental cost estimates from the PSA falling between £1.69 million and £1.72 million. This reflects the 10% assumed uncertainty in the PbR cost banding, whilst there was no uncertainty in the costs of lung transplantation and high-cost drugs. Similarly, there was no uncertainty in the proportion estimates, calculated through use of the UK CF Data Registry, which were driving the High-Cost drug calculations.

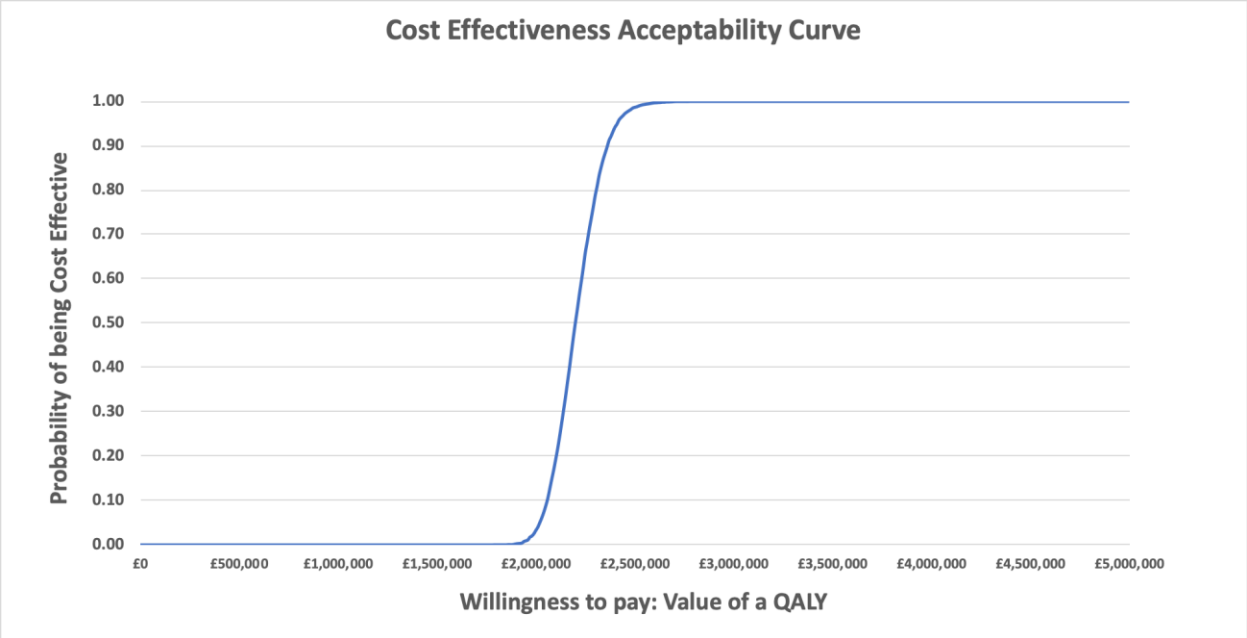
Figure 45: Cost Effectiveness plane



Although the cost-utility uncertainty visually is represented in the cost-effectiveness plane. It is useful to present the magnitude of uncertainty in the outputs of the analysis. The CEAC in Figure 46, is presented to the show the probability of cost effectiveness at a

range of threshold values. Thus, enabling the decision makers to understand the risk of making the wrong decision based on current information, model parameters and their distributions, based on the different willingness to pay for a QALY. Figure 37 shows that, at a threshold of willingness to pay over £2.78 million per QALY the probability of Orkambi® being cost effective is 100%. This shows that at a threshold of between £20,000-£30,000 per QALY, Orkambi® is not a cost-effective option. Even at a threshold of £2.2 million per QALY per person, the CEAC shows that there is a 50% probability of the intervention being cost effective. The shape of the CEAC reflects the placement of estimates in NE quadrants.

Figure 46: CEAC



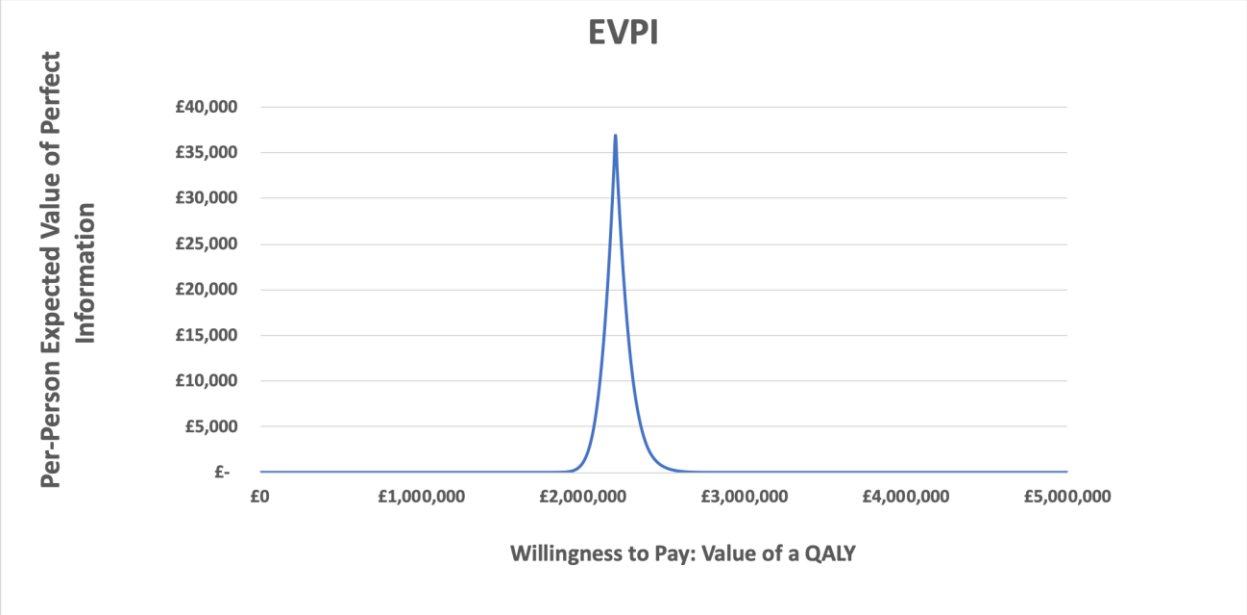
6.23.5 Expected Value of Perfect Information

In order to determine the value of information, particularly the EVPI, the EVPI for a range of threshold values per QALY are presented in Figure 47. Ultimately, the EVPI will provide

the decision maker with information on whether further research should be conducted in order to remove any uncertainty in all parameters represented in the cost-effectiveness of Orkambi®. The EVPI shows that for a willingness to pay threshold of up to £2.2 million, there would be a £36,000 value per person in conducting further research around the uncertainty in all parameters, which does not justify an investment of £2.2 million per person, which is further supported by ISPOR guidelines on VOI analysis [242]. This finding is not surprising considering the very high cost of Orkambi® shown through the disputes between NICE and Vertex Pharmceutical [75] around its cost and previous studies on Orkambi® [126, 129].

If the EVPI presented a value which was higher than the threshold willingness to pay per QALY of £20,000-£30,000 then further investigation using EVPPI could have been conducted to determine which parameters would justify further research in order to remove decision uncertainty [242]. This however is very unlikely to occur in the case of Orkambi®.

Figure 47: EVPI of further research into the cost effectiveness of Orkambi®



6.24 Sensitivity analysis

6.24.1 One-Way sensitivity analysis

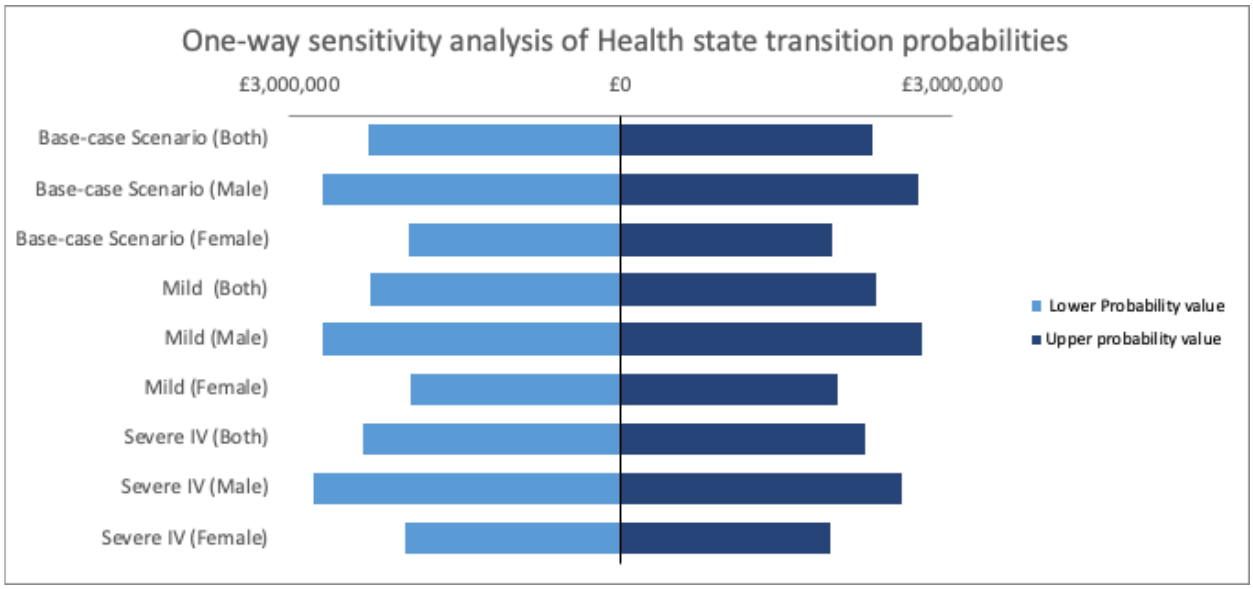
A number of parameters in the model were changed as part of the one-way sensitivity analysis to determine which parameters had the largest influence on the outcomes of the model.

6.24.1.1 Health State transition probabilities

Probability values generated in Chapter 5 for each health state were changed, individually by previous health state to their lower and upper limits. Transition from poorer health states to better health states were also evaluated despite these being considered to be rare, especially those from Severe health states to Mild health states. Only transitions to Mild and Severe IV health states were evaluated to determine what impact they had on the outcomes. Figure 48 shows the impact of changing the health state transition values

to their upper or lower limit for all transitions to the Mild and Severe IV health state respectively. These are further discussed in detail in the sections that follow (Sections 6.24.1.1.1-2).

Figure 48: Impact on ICER value by changing health state transition probabilities



6.24.1.1.1 Mild health state

Changing the transition probabilities to either end of the prediction interval (lower/upper) for all transitions to the Mild health state resulted in a decrease and increase in mortality respectively. Changing the transition probability to the upper limit increased the ICER for both males and females, whereas decreasing the transition probability increase the ICER for males but decreased the ICER value for females by around £30,000/QALY.

In terms of costs, an increase to the Mild health state transitions resulted in a decrease in overall costs for males and a led to a very small increase in these costs for females not receiving Orkambi® respectively. Changing the health state transition to the lower limit resulted in an increase in costs for males and females. Possibly due to more of the cohort

transitioning to more severe health states. Increasing the health state transitions to the Mild health state also resulted in an increase in cost of those receiving Orkambi® treatment whereas decreasing it resulted in a decrease in such costs.

6.24.1.1.2 Severe IV health state

Changing the transition probabilities to either end of the prediction interval (lower/upper) for all transitions to the Severe IV health state resulted in a decrease and increase in mortality respectively. A closer look at the changes in mortality when using the lower transition probability limit showed that this resulted in an increase in male mortality but decreased female mortality. This could be due to less females transitioning to the Severe IV health state, especially considering they already had a higher probability of transitioning to poorer health states.

Changing the transition probability to the upper limit decreased in the ICER for both males and females, whereas decreasing the transition probability increased the ICER for males and females.

In terms of costs, an increase to the Severe IV health state transitions resulted in a decrease in overall costs for males and females. Alternatively, changing the health state transition to the lower limit resulted in an increase in costs for males and females. Possibly due to less of the cohort transitioning to more severe health states and dying. Increasing the health state transitions to the Severe IV health state also resulted in a decrease in cost of those receiving Orkambi® treatment whereas decreasing it resulted in an increase in such costs.

6.24.1.2 Costs

In the one-way sensitivity analysis cost band were evaluated by changing the individuals PbR band costs by increasing and decreasing them by 150% and 50% respectively. In terms of High-Cost drugs, the same approach was used for each drug included in the model (Section 6.22.5).

6.24.1.2.1 Cost bands

When costs for each of the listed bands (Section 6.18.1) were altered to 50 of 150% of the original 2016 costs, there was no large change in the overall ICER values. This shows that such costs had very little influence on the overall costs in the model.

6.24.1.2.2 High-Cost drugs

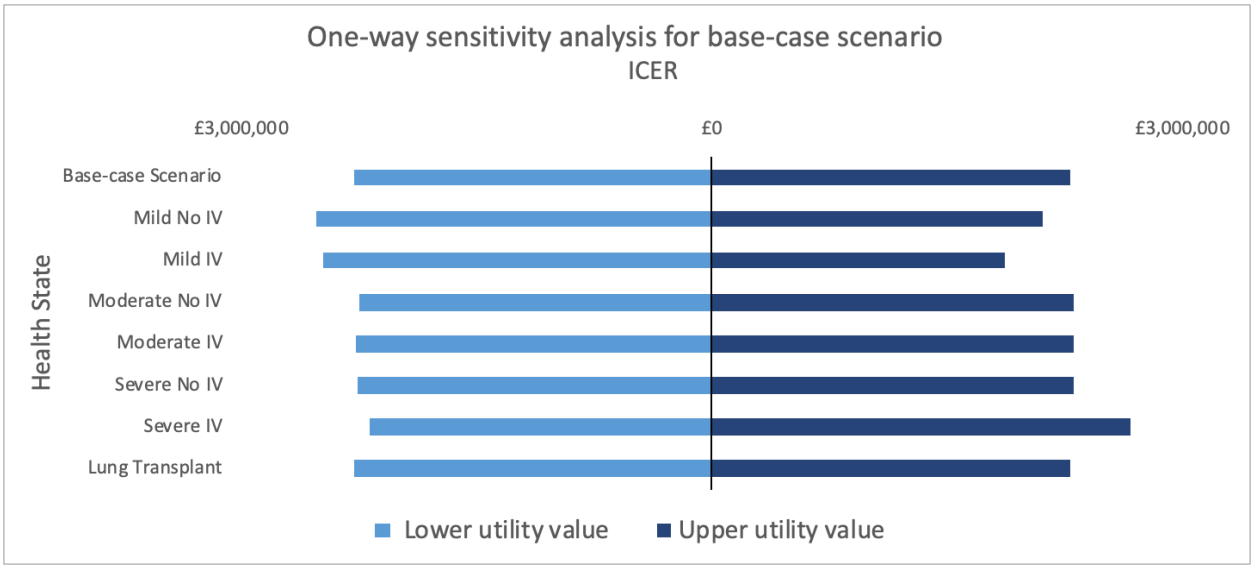
Changes to the cost for each drug to 150% or 50% of the original cost results in a substantial change in the ICER values for male and female individuals but also to the overall ICER across both sexes. This shows that the cost of such treatments had a large influence on the overall cost of treating a CF individual.

6.24.1.3 Utilities

Figure 49, a tornado diagram, shows the resulting ICER values for a change in each health state based on the upper and lower utility values. The base case analysis results are presented alongside for reference purposes.

We can see the largest impact of reducing the ICER value was seen when increasing the utility value of the Severe IV health state to a lower value of 0.70. This was very closely followed by an increase in the ICER by decreasing the utility value of Mild health state to its upper limit of 0.77.

Figure 49: One-way sensitivity analysis of utility data



Lastly, Figures 50 and 51 present tornado diagrams showing the resulting ICER values for changes in the utility values by sex to the upper and lower utility values. As before, the base case analysis results are presented alongside for references purposes. The results of the sensitivity analysis show, for females and males, the largest change to the ICER was from increasing the utility of the Severe IV health state followed by a decrease in the utility of the Mild health state.

Figure 50: One-way sensitivity analysis of utility data (Males)

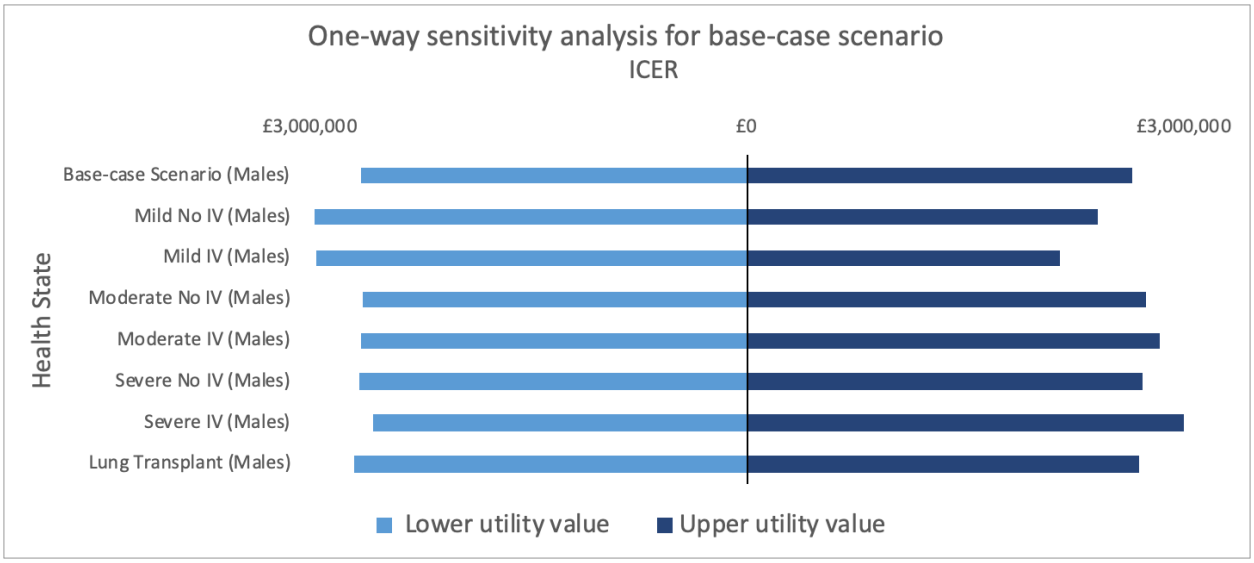
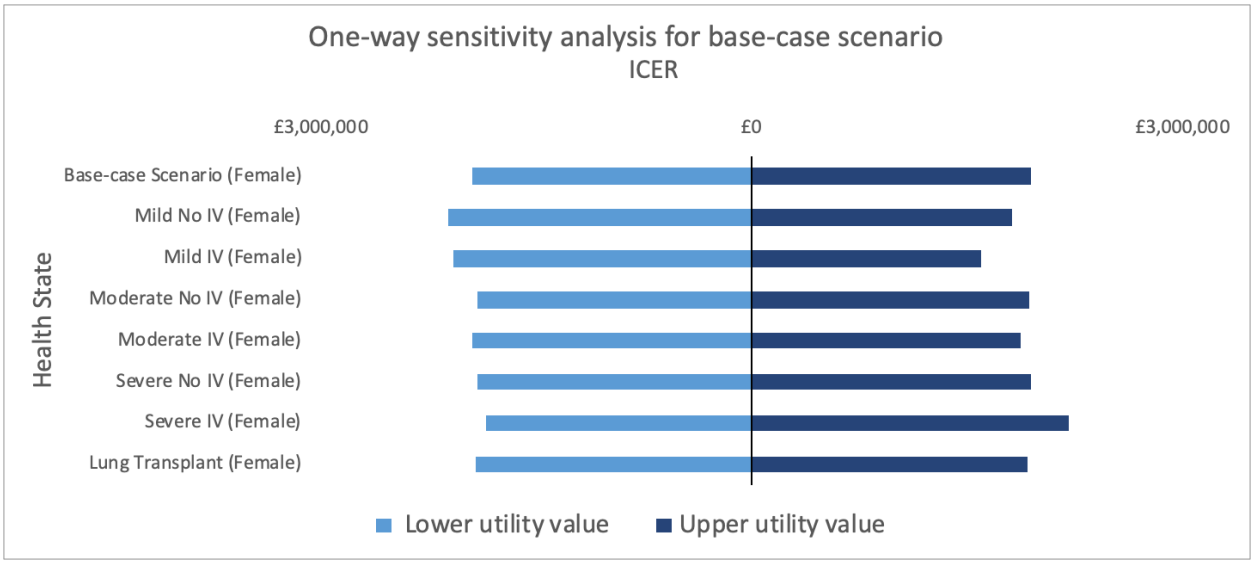


Figure 51: One-way sensitivity analysis of utility data (Females)



6.24.2 Threshold analysis

Similar to one-way sensitivity analysis, threshold analysis was used to determine how adjusting a single value in the model would change the decision around the cost effectiveness of Orkambi®. A threshold analysis of the cost of Orkambi® in Table 105

shows the cost at which Orkambi® would be cost effective at threshold values per QALY between £20,000-£30,000.

Table 105: Changing the cost of Orkambi®

Cost per QALY	Percentage fraction of original Orkambi® cost?	Cost of Orkambi®
£20,000	0.5%	£ 436
£25,000	0.7%	£638
£30,000	0.9%	£ 839

6.24.3 Scenario analysis

A range of scenario analyses were conducted as part of the sensitivity analysis (Section 6.24.3.1-4). Table 70 presented the different assumptions for each scenario (Section 6.8). A summary of the results are presented in Table 106.

Table 106: Scenario analysis deterministic results

Scenario number	Deterministic result		
	Incremental costs	Incremental QALYs	ICER
Scenario 1	£ 1,637,165	0.05	£34,261,418
Scenario 2	£134,346	0.05	£2,811,497
Scenario 3	£1,602,787	0.85	£1,892,719
Scenario 4	£1,490,774	0.82	£1,821,224
Scenario 5	£1,136,986	0.59	£1,942,596
Scenario 6	£1,708,206	0.68	£2,522,681

6.24.3.1 Treatment efficacy

In the base case analysis, it was assumed that treatment effectiveness would last the duration Orkambi® costs were applied. Costs were applied for the whole-time horizon to reflect treatment with Orkambi® until median survival. Changing the treatment efficacy to 2 years (scenario 1) while cost were applied for the whole time horizon resulted in an ICER of £34,261,418. Changing treatment efficacy and cost of Orkambi® to 2 years resulted in an ICER of £2,811,497 (Scenario 2).

6.24.3.2 Cohort distribution

Changing the initial distribution of the cohort (Scenario 3), while keeping all other parameters the same as the base case analysis, to that which is reflected in the clinical trial data of Wainwright et al [46] resulted in an ICER of £1,892,719.

6.24.3.3 Starting age

Changing the starting age of the model to 12 (Scenario 4) and 25 (Scenario 5) until the median age of death, while keeping all other parameters the same as the base case analysis except the initial cohort distribution, which was changed to that similar to the clinical trials data of Wainwright et al [46], resulted in ICER values of £1,821,224 /QALY and £1,942,596/QALY respectively.

6.24.3.4 Utilities

The utilities for the health states was changed to those used by Whiting et al [107] (Scenario 6). The resulted in an ICER of £2,522,681/QALY, from incremental costs and QALYs of £1,708,206 and 0.68 respectively.

6.25 Between model validation

6.25.1 Existing models data

A number of models/technology appraisals which looked at the cost effectiveness of Orkambi® were identified at the start of this chapter [7-10, 94, 126]. In order to compare and validate the health economic model developed in this chapter, attempts were made to replicate their input parameters, where available and where possible, into my model and compare the outcomes from the deterministic analyses only. This was only done for three models, 1) NCPE [9] 2) NICE [10] and 3) Sharma et al [126]. These were selected as both the NCPE and NICE are within the U.K and Sharma et al [126] is the only Orkambi® based cost effectiveness publication which looks at a long-time horizon. Model assumptions, where possible, presented in Table 66 of the introduction were replaced into my model and the outcomes compared. This exercise was conducted in order to clearly identify the similarities and differences in the models [7-10, 94, 126] compared to

the model developed in this chapter. Treatment effect was incorporated into each model using the method explained in the treatment effectiveness section in the introduction (Section 6.3.1.5).

6.25.1.1 NCPE

The model submitted to the NCPE [9] was replicated to match, the initial patient health state distribution, including time horizon, the treatment effect, starting age and sex distribution. Treatment effect duration was not clearly stated in the appraisal, so Orkambi® effectiveness was applied through the whole-time horizon. The model time horizon was assumed to be between 12-57 years old. This approach was taken as it reflected the age range in the clinical trial data [46]. However, treatment effectiveness was applied from Konstan et al [226] estimates and not Wainright et al [46]. The sex distribution was 51/49 % for males and females respectively. With the size of the cohort in the model being 1000. These parameters entered in the model develop in this chapter resulted in an ICER of £1,627,235/QALY.

This is higher than the ICER value presented in the technology appraisal by the NCPE of €369,141/QALY. The costs and QALYs generated over the time horizon of the models were quite different. For costs, the NCPE HTA produced an incremental cost of €903,947 compared to incremental cost £1,572,096 for Orkambi® from the model in this chapter. In terms of the number of QALYs generated across both sex groups, the model presented in this chapter generated 0.97 additional QALYs compared to 2.45 QALYs in the NCPE technology appraisal.

6.25.1.2 Sharma et al al [126]

The modelling data utilised by Sharma et al [126] was also utilised to carry out a between model validation exercise. A number of parameters in the model developed in this chapter were again changed. These include, the initial patient health state distribution, treatment effectiveness of base-case scenario, time horizon, starting age and utility data for health states. However, treatment effectiveness was applied from Konstan et al [226] estimates and not Wainwright et al [46]. Utility data estimates were taken from the same study for both models but additional utility decrements for IV treatment were applied for those in the IV health state to replicate assumptions of Sharma et al [126]. The sex distribution was assumed to be similar to that which was in the clinical trial data. The size of the cohort that was being modelled was 1000.

These parameters in the model resulted in an ICER of £7,193,850 which is just under double than that predicted by Sharma et al [126] in their base-case scenario. The incremental cost and QALYs generated by the model developed in this chapter were £746,572 and 0.10, respectively. The incremental costs are less than half of those of Sharma et al [126], $1,677,901 and the incremental QALYs of 0.45, is higher from Sharma et al [126] compared to those which were produced from the model in this chapter.

6.25.1.3 NICE

The model submitted to NICE [10] was replicated to match, patient health state distribution, sex distribution, health state utility data, time horizon, starting age and discounting value. Treatment effectiveness was applied from Konstan et al [226] estimates and not Wainwright et al [46] for the whole time horizon of the model. This was

to reflect the reduced decline in FEV_1 for those on Orkambi® compared to those in the control cohort.

These parameters in the model resulted in an ICER of £2,282,330/QALY. This is substantially higher than the ICER value of the model technology appraisal conducted by NICE, £218,248/QALY. The incremental costs and QALYs for the model in this chapter were £1,708,206 and 0.75 respectively. However, the incremental costs and QALYs for the NICE technology appraisal were £753,570 and 3.45, more than double the incremental cost difference and more than 4 times lower QALYs.

6.26 Discussion

6.26.1 Summary of main findings

The aim of this chapter was to develop and validate the De Novo novel health economic model conceptualised in Chapter 4 which could be used to conduct the cost-effectiveness analysis of CF interventions. The novel aspects of the model structure were to include IV health states for the three main FEV_1 categories, Mild, Moderate and Severe. In addition, the model included lung transplant and post lung transplant health states. In terms of data, the model included input parameters which were largely exclusively taken from the UK CF Data Registry, this increases the value of the model as it is based on real world data and increases the generalisability to a U.K. CF population context. Although the model generated in this chapter was an exemplar analysis, the exercise undertaken to assess its validity showed whether the model could be used in the cost effectiveness analysis of other CF interventions such as mucolytic agents, antibiotics and further novel combination of modulator treatments. The validity of the model structure itself was

assessed through its ability to take into account significant health events which would have impacts on both costs and outcomes. The disease process of CF was evaluated through the model conceptualisation process through existing evidence in the literature and discussion with experts (Section 4.9). Figure 8 presented in Section 4.9.1.6 showed the evidence of the disease pathway in CF and was developed and agreed to by clinicians (Dr Diana Bilton and Siobhan Carr) based on the evidence presented in the guidance document [36]. This Figure (8), presented the overall disease pathway for CF patients and as such the resultant De Novo model can be used for the evaluation of all treatments available for CF, expect screening interventions. In terms of the model structure, it takes into account significant health events that occur during the life course of the patients, except PEx events which were difficult to include due to limited data and no information being present to classify such events in terms of severity (Section 4.9.1.8). However, this could change with the inclusion of PEx events variable in the CF Data Registry more recently.

Additionally, the probability data in the model which was generated using the CF Data Registry was used for particular sub-populations, however, in future similar methods could be applied for the use of treatments which are available to other subgroups or to CF individuals in general.

The results of the exemplar analysis showed variations in the ICER results in this chapter when compared to the ICER estimates of other studies introduced at the beginning of this chapter. The base-case analysis showed an ICER of £2,282,330 per QALY gained (95%CI: £2,019,919 - £2,457,337). The studies included for comparison and between

model validation were published cost effectiveness analyses and appraisals of submitted health technologies by governing bodies in different countries. The results of the comparison showed that the ICER estimate generated in the De Novo model were always higher than those generated in other models when input parameters were replaced with those from the other studies [10] [126] [9]. An exercise similar to that conducted by David et al (2011) was utilised to assess between model consistency but to also try to understand why, if any, differences existed in the ICERs and their respective cost and QALYs.

As highlighted in Chapter 2, there are a number of practices when it came to the health economic modelling of CF interventions. Both individual patient simulation models were identified [101] [107] and five Markov Cohort models were identified [102] [103] [104] [105] [106]. The same can be said for models that appraise Orkambi® for its cost-effectiveness, different approaches have been utilised, either an individual patient simulation [7-10, 94], Markov cohort model [126] or decision tree [127]. In general, there was no overall consensus on the methods or data inputs utilised in the modelling of Orkambi®. This can reduce the comparison of the results from such models, as is seen by the different ICER results, Table 65 section 6.5.3. An attempt is this chapter was made to compare the cost effectiveness results of evaluating exemplar intervention Orkambi® from the De Novo model to other models present in the literature or on health technology regulatory websites in order to validate the model. Upon closer evaluation of the reasons for such difference a number of inputs, difference in methods and structure were identified. These are discussed further alongside the strengths of the current work below.

6.26.2 Strengths of current work and comparison with existing literate

Six existing studies were identified which look at the cost effectiveness of Orkambi® [7-10, 94, 126]. These were used to compare the results generated from the model developed in this chapter, in the form of between model consistency. Additional studies which look at the costs generated, where available, for treatment of CF [81] were also evaluated for consistency of the results from this chapter.

6.26.2.1 Model Structure

The model conceptualised in Chapter 4 and validated in this chapter is the first which looks at the impact of including IV treatment as a health state for the three main categories of FEV_1; Mild, Moderate and Severe. As a result, the model structure used is particularly relevant for interventions which impact IV abx use. No previous studies exist which employ a conceptualisation process for creating the model which involved clinicians, health economist, statisticians and epidemiologists. This was further highlighted in Chapter 2 when no general reason was demonstrated for having a set model structure in the cost effectiveness studies found.

6.26.2.2 Data

The data used to develop the model were originally based on a more than 90% coverage of those with CF in the U.K. The exemplar CEA in this thesis focuses on F508Del Homozygous patients. However, similar methods to calculate transition probabilities could be utilised for other genotypes. This as well as the ability to change the sex distribution to that which is reflective of age in the U.K CF population improves the usability of the model for assessing the cost effectiveness of CF interventions. The approaches taken to develop input parameters were based on transparent

statistical/regression methods. The CF Data Registry was used to calculate health state transitions probabilities, probabilities for being in PbR cost bands by current health state, probability of being on various high-cost drugs, probability of receiving a lung transplant and lastly, the probability of survival post lung transplant. Again, this is the first study to utilise a CF Data Registry to generate such data for the health economic evaluation of an exemplar intervention.

Additional benefits include the inclusion of a wider team of statisticians involved and clinical experts who supported in the construction of methods and validation of the model outputs further bolster the validity of the model.

6.26.2.3 Treatment efficacy

The treatment efficacy was assumed to be normally distributed between 0-2.2 (95%CI) absolute FEV_1 improvement [24] (mean 1.1) and was randomly applied to F508Del Homozygous patients. Similarly, the model in this chapter applied a treatment effectiveness which was based on the longer-term effectiveness of Orkambi® over 96 weeks [24]. These effects were observed in the same cohort that began treatment at week 0. This is dissimilar to studies which applied an absolute improvement of 2.8 and did not consider any variance around treatment effect, as reflected in the clinical trial data [19]. It is also not clear what assumptions were made when treatment effect was applied by other studies on Orkambi® [126].

The NICE technology appraisal submission [17] based their no Orkambi®FEV_1 population decline on US and Canadian data. The technology appraisal submission also assumed that those on treatment subsequent to 24 weeks would only experience a FEV_1 decline

of -0.68 in any health state compared to the no Orkambi® cohort decline of up to -2.34 ppFEV1. The resultant assumption by Vertex pharmaceuticals would have likely to have overestimated the benefits of Orkambi® in the model as stated by the NICE Evidence Review Group (ERG) in their appraisal [17]. The most recent Orkambi® model appraised by CADTH [16] made the same observations as the NICE ERG when looking at treatment effects over time. Sharma et al [12] in the base-case applied the assumption that treatment effect would be maintained while the cohort was on therapy and there would be no subsequent decline in FEV_1 with the added benefit of constant risk ratio reduction of PEx events. However, they do no state what value of FEV_1 improvement was applied. Lastly, the ICER review of modulator treatments in CF used effectiveness measures for Orkambi® based on clinical trial data. However, they assumed that there was no decline in FEV_1 for the first two years and at a rate of 50% of the no Orkambi® patients in subsequent years. They varied their annual FEV_1 decline, in the no Orkambi® cohort, by age and was based on published literature [49, 50]. In comparison with the model developed in this chapter, the assumption around treatment effect was the FEV_1 was based in UK CF Data Registry derived estimates and that any treatment would be sustained whilst on treatment. If treatment was stopped then subsequent to such a period, there would be no different between treatment groups in terms of health state transitions. The model in this chapter has used the most recent evidence available on the efficacy of Orkambi® [226] and applied treatment effect based on a distribution around a mean absolute improvement. As a result, some individual may or may not show an improvement subsequent to taking Orkambi® which is more reflective of the clinical trials outcomes.

Treatment effect has come from a number of trials already mentioned and sensitivity analyses of treatment efficacy duration has been shown to considerably decrease the number of incremental QALYs generated. For instance, Sharma et al [126] in their base case analysis and assumption of lifetime treatment efficacy generated 0.45 QALYs over a 10-year time horizon. Changing the treatment efficacy to a single year reduced the incremental QALYs to 0.20 over a 10-year time horizon. When looking at the scenario analysis conducted in this chapter, changing the treatment efficacy to 2 years alone (scenarios 1 and 2) resulted in incremental QALYs of 0.05 over the time horizon of the model, which starts at the youngest age compared to any model appraised or published on Orkambi®. The highest number of incremental QALYs generated from the model in this chapter were 0.85 as a result of changing the initial patient distribution of cohort in the model from that of the UK CF Data Registry to that found in the RCT [46]. Similar changes to QALYs were seen in the appraisal by the CADTH [8], where adjustments of the assumptions in the model results in 0.85 QALYs.

6.26.2.4 Costs

Although this is not the first study to use statistical methods to calculate costs for CF individuals in a health economic model [107], the methods used reflected the specification of the data, that the outcome was an ordinal variable across 7 different costs bands. The costs are separated across sex groups as well as age, ranging from 6-65 years for either sex. Similarly, the statistical methods take into account treatment trends of the most recent data available at the time of analysis, 2016. These strengths as well as the

probabilities being based on reviews conducted year to year resulted in transition probabilities which are available for a range of health states. Lastly, this is the first model to calculate per person cost by age and sex for both cost bands and High-Cost drugs for the various health states. These cost probabilities were validated by clinical experts and sense checked for reliability (Dr Siobhan Carr and Dr Diana Bilton).

Costs for the NICE appraisal [10] for treatment took an NHS and personal and social services perspective. Cost were discounted at 3.5% and Orkambi® cost £2,000 per week (£104,000 annually). However, a price reduction was also assumed to take place after 12 years in their base-case analysis which was very high. The model presented in this chapter did not assume any price reduction and this is likely to have resulted in an substantial difference to the ICER value when compared to that which was produced from the appraisal [10]. Cost for Orkambi® in my model were taken from the BNF, 2019, and were deflated to 2016 costs. This resulted in an annual cost of £92,000, which is markedly lower than that used by Vertex for their model. This would affect the resultant ICER value showing a more favourable value for Orkambi®.

Cost for CF in the NICE appraised model [10] were based on FEV_1 and were based on a 2-year U.K retrospective study of 200 F508Del Homozygous patients. Hospitalisation cost were also assumed to be reduced by 61% for those receiving Orkambi®. Albeit, that this assumption was flagged by NICE ERG as possibly double counting health benefits from treatment [10]. Any information or breakdown of costs are not provided. The model in this chapter used data from the UK CF Data Registry which belonged to 3,740 F508Del Homozygous patients in the registry between 2013-2016. Costs were based on health

state, sex and additional variables described in Chapter 5. Hospitalisation costs were assumed to be included in the Cost bands as already defined in the cost banding matrix (section 4.25, Chapter 4). Any reduction in costs associated with IV treatment or hospitalisation were assumed to be accounted for through changes in the health state and the resultant distribution among cost bands in those health states.

Closer evaluation of the costs in the NCPE appraisal [9] does not provide any information about how costs were calculated. The initial [7] and subsequent appraisal [8] by CADTH did not provide any detailed information around costs separate to the cost of Orkambi®. The Institute for Clinical and Economic Review used a detailed costing method which was a combination of personal communication, previous research and weighted averaging methods. This resulted in an annual cost of $77,143 for best supportive care alone [94]. Costs for lung transplantation were taken from a research report from 2017 (Milliman Research Report [243]).

It is clear that there are cases where costing methods are not transparent but where they are a range of assumptions and methods have been used. In this chapter, the methods for costing each health state are presented transparently and are based on the U.K. CF Data Registry. Additionally, the methods used in this chapter present the cost per health state which varies by age and sex and has not been presented in the past studies. When comparing the costs of standard care or best supportive care, the model in this chapter shows that standard care costs £433,361 over the time horizon of the model across both sex groups. This is different to that estimated by Institute for Clinical and Economic Review. However, it is important to take into account that the data used in this model is

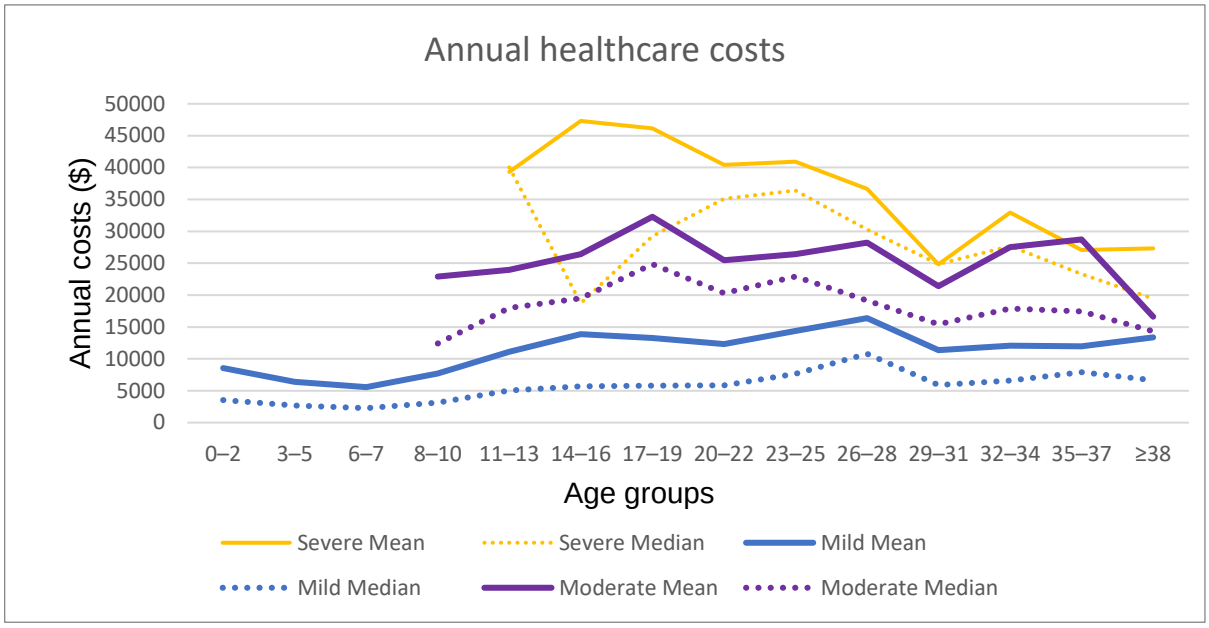
from CF patients who fit the criteria for allocation of treatment, i.e. F508Del Homozygous and is based on more recent data and few assumptions.

I compared the results of this study against others which have looked into the long-term costs and outcomes of Orkambi® [129] alone. Costs for the control/no intervention group were also compared to data present in the literature [81] mentioned in Chapter 5 (Section 5.19.2.5) which presented annual costs by health state, age from the Australian CF Data Registry (2002-2005).

The study by Dilokthornsakul et al [129] utilised a Markov cohort model but did not incorporate an IV health state. The study results showed that the long-term costs of providing Orkambi® was $3,904,539 (95% CI $2,903,682 - $5,354,545). Compared to this chapter, £2,141,567 (95% CI £2,129,193 - £2,148,254) across both sexes the figures for either are very close to each other. However, the start age of the cohort for the Dilokthornsakul et al [129] model was 25 years, whereas the model in this chapter the cohort starts at 6 years old. As a result, we can see that the cost estimates for the Orkambi® cohort are well within the range of the Dilokthornsakul et al [129] study.

Comparing the cost generated from this chapter (Section 6.22.3,6.22.5 and 6.22.7) against those of Van Gool et al [81] showed that the patterns present in the outcomes were similar and the overall costs were withing reasonable range of each other. Figure 52 below shows the mean and median annual cost for those aged between 0->37 years in three different health states. The costs show a steady increase over time for the better health states but a decrease for the poorer health states. This pattern of increasing annual cost per person is also seen in Figures 33,34,39,40,42 and 43.

Figure 52: Annual cost for health state by age [81]



The overall lifetime cost were also compared and were also compared between the two studies. Van Gool et al [81] showed a mean lifetime costs (0-47 years) of $306,332 (95% CI: $256,098-$375,304) discounted at 3.5% and the model in this chapter showed a total lifetime cost (7-47 years) of £446,336/£440,427 for male and females respectively (3.5% discount rate).

The comparison was made despite the data used in this thesis being more current than that which was used by Van Gool et al [81] (2002-2005). This again further increases the validity of the model.

6.26.2.5 Utilities

The review conducted in Chapter 3, showed that there was a dearth of evidence when it came to utility data for health economic modelling of CF interventions. The modelling conducted in this chapter used utility data which was evaluated for purpose and strictly

used data which was generated in a patient population which was being evaluated for IV treatment [229] for the health states specified in the model structure in Chapter 4.

The utilities and resultant QALYs generated in cost-effectiveness appraisals [7-10] except for the cost effectiveness study by Sharma et al [126] were higher than those which were produced from the model in this chapter. The QALYs ranged from 0.45 [126] to 3.45 [10], whereas the QALYs produced in the model from this chapter were 0.75 over the 40-year time horizon. It is very clear that different studies have produced different incremental QALY benefits and the estimate in this chapter fits within these estimates. The key drivers for changes in QALYs seem to be generated from treatment effectiveness and the assumptions around how treatment effect is applied, especially in terms of efficacy duration. This in combination with the initial distribution of the cohort, starting age and the time horizon of the model can change the resultant incremental QALYs.

6.26.2.6 ICER

In the introduction a range of characteristics of these studies were identified. However, a number of additional sensitivity analyses performed in these studies showed large variations in the base case analysis ICER results. In Table 64, the ICER values for the different studies were shown to vary from £218,248/QALY to US $3,655,352/QALY in the base case analyses. The ICER value generated from the base case analysis was £2,282,330 per QALY (95%CI: £2,019,919 - £2,457,337). This is lower than the base case analysis results of Sharma et al [126], but was higher compared to other studies.

The Evidence Review Group (ERG) at NICE applied a number of changes to the model submitted by Vertex pharmaceuticals [10]. The changes in the assumptions in the model

resulted in an ICER that was as high as £459,045/QALY. Similarly, the ERG stated a range of plausible assumptions that Vertex Pharmaceuticals could apply in their base-case analysis which could potentially increase the ICER value. The base-case ICER value for the most recent submission to CADTH [8] was CAD $446,529/QALY based on incremental costs and QALYs of $2,235,590, 5.20 respectively. However, after the common drug review (CDR) adjusted the model assumptions the ICER increased to CAD $ 3,785,432/QALY (12 years or older) based on incremental costs and QALYs of $3,204,133, 0.85 respectively. The economic evaluation conducted by Sharma et al [126] had an ICER of US$3,665,352/QALY. However, change in the assumption around the effectiveness of Orkambi® to one year only and subsequent similar decline in FEV_1 similar to the no Orkambi® cohort resulted in a much higher ICER value, US$8,480,265/QALY. Lastly, the review of CF modulators for the cost effectiveness by Institute for Clinical and Economic Review [94] resulted in an ICER of US $890,739/QALY, but changes to the long term effectiveness assumption of treatment increased the ICER to CAD$1,647,556/QALY.

We can see that changes to base case assumptions in appraisal reports which were subsequently submitted to regulatory authorities such as NICE and CADTH resulted in ICER values that were substantially larger than their initial values. In the case of CADTH, the revised assumptions relating to effectiveness, compliance, and drug costs in both reports resulted in ICER values that were substantially larger than those seen in this chapter. This points out that the ICER value from the model in this chapter fits within the ranges estimated in the literature.

6.26.2.7 Survival bias

Previous health economic modelling in CF has highlighted the possible presence of survival bias in Registry data [10].

Survival bias was initially covered in detail in Section 4.3.5. The model outputs in this chapter also included life years gained and the results presented showed that although males had a median survival similar to that which existing in the CF Data Registry annual report [11], females showed reduced survival (Section 6.22.2). The survival estimates published in the CF Data Registry report were based on the total CF U.K. population, whereas the model in this chapter estimates survival for those who are F508Del Homozygous. This could have resulted in differences in survival due to the more severe nature of the population using Orkambi®. This and the existing difference in survival between males and females in the CF Data Registry [11, 193] could explain the lower median survival for females presented in this chapter.

6.26.3 Limitations of Current work

6.26.3.1 Treatment efficacy

A number of studies exist which demonstrate the efficacy of Orkambi® over time [19-25]. The model developed in this chapter assumed that improvement in CF related outcomes were based on improvements in FEV_1 alone and any additional impacts of reduction of IV days was accounted through costs and utility alone. As such, individuals received IV treatment regardless of improvement in FEV_1 from Orkambi® if they were originally placed in an IV treatment health state prior to treatment i.e. control cohort. This meant that improvements in FEV_1 would result in transition to a better IV based health state. As a result, impact of treatment in IV based health state would only be accounted through

reduction in the cost banding category and improvement in utilities and in terms of the number of IV and hospital days received in those cost bands. This ultimately meant that those who received IV treatment could not go onto not receiving IV treatment as a result of Orkambi® treatment. Although the clinical trial paper [226] used to estimate the effect of treatment showed that there was a reduction in the number of IV days and hospital days received whilst on treatment, the model in this chapter accounted for this through the cost banding system which already identifies, based on the different cost bands, the number of IV and hospital days for each band. A change in the health state transitions as a result of treatment would account for changes in IV and hospital days through this avenue alone. This reduced the possibility of double counting treatment effect through both FEV_1 and IV and hospital days which was also highlighted in a number of appraisals of Orkambi® by CADTH [7, 8] and NICE [10], which are mentioned earlier (Section 6.25.1). But this may also increase the chance of underestimating treatment effect. This would also contribute to higher ICER values as seen in the results from the model in this chapter.

Treatment effect was assumed to lead to an improvement of percent predicted FEV_1 between 0-2.2 in the model. Health states were formed from the categorisation of FEV_1 into health states; Mild, Moderate and Severe, whether on IV or not. As a result, only those individuals in the UK CF Data Registry who were close to the borderline of each FEV_1 based category would be able to benefit from treatment. However, this would also be the case for other models if they categorised patients based on FEV_1 thresholds.

A small proportion of patients in the data used to create the health state transition probabilities were identified as being treated with Orkambi®. Application of treatment effect on such individuals would potentially result in double counting benefits in FEV_1 and subsequent IV and hospital days. However, due to the small size of this population compared to the overall number of individuals in the dataset, the effect of such a situation is negligible. This is another reason why analysis post 2016 of the dataset was not undertaken, as post 2017 a majority of patients were given Orkambi® in the UK CF Data Registry.

6.26.3.2 Costs

Costs were taken from NHS England Monitor report [239] and as such there was no information around the variability of the cost banding figures provided. In the model I assumed a 10% variability around the mean estimate of each band. However, this resulted in little variability in the cost effectiveness results, as can be seen in the cost effectiveness plane (section 6.23.4). Further one-way sensitivity analysis showed that large changes in these costs had little impact on the overall ICER.

Similarly, High-cost drugs were given a point estimate and due to information not being available around the uncertainty of the costs, the costs from the BNF were taken as final. No variability in such costs were introduced in the model due to lack of data to state otherwise. One-way sensitivity analysis showed that changes in High-Cost drug costs had the largest impact on the ICER value. This may result in an underestimation of the ICER variability for Orkambi®.

The costs presented as a result in this chapter reflect the U.K. CF population, but they do not reflect the change in High-Cost Drug use that may be seen when taking Orkambi®. This is primarily due to no such data existing in the Registry Data. The model presented in this chapter does not take into account potential changes in utilisation of High-Cost drugs, only change in PbR cost band as a result of changes in Health state transition. Although research exists which shows that there is no significant change in the utilisation of High-Cost treatments when taking Orkambi® [244], this is based on an Irish national pharmacy claims database. This could have resulted in an overestimation of the ICER values presented in this chapter, which could have resulted in lower ICER values which were further in favour of existing published estimates.

Although due to the high cost of Orkambi®, changes in either the PbR or High-Cost drug costs/use would unlikely change the decision of the modulator treatment being not cost effective.

6.26.3.3 Utilities

There is a lack of evidence around health state utility data in CF as identified by the review conducted in Chapter 3. Although the results showed large variation in the utility estimates in the PSA analysis, the overall incremental difference between the two, control and treatment, groups were very small.

6.27 Future work

Based on the aims of this chapter, the model looked to see whether adding an additional health state of IV treatment for each health state would enable the model to be used conventionally across all CF interventions. This is primarily because previous models

failed to incorporate significant events which impact disease progression in CF, as identified in Chapter 2. Orkambi® was used an exemplar intervention to validate the model develop in Chapter 4. When compared to other model outcomes the results of the analysis showed that they were comparable and differences largely exist due to treatment effect, cohort distributions, starting age of treatment and time horizon. Future work could utilise the same model structure and look to validate it using other existing treatments such as antibiotics and modulators such as Ivacaftor®. However most importantly, the evaluation of Orkambi® as an exemplar intervention has highlighted the different approaches used to assess the cost effectiveness of the intervention. Due to data availability different input datasets were used in the different models that were identified. An important find, in conjunction to Chapter 3, has been the lack of utility data for CF. Future work could look at generating health state utility data alongside other CF Registry-based variables, although difficulties in measuring utility using generic instruments in CF patients have been highlighted. Additionally, work could be conducted on generating more granularity in the Cost Banding matrix in order to identify cost which would separate individuals who receive IV treatment to those who do not. As a finding from the model related to the cost banding was that the banding matrix seemed to generate some instances of IV treatment for those in the No IV treatment health state. Although this was validated as a possible event (Dr Siobhan Carr and Dr Diana Bilton) but was only related to increase in costs other than IV treatment but were classified into particular bands which included IV treatment.

Novel additions to the model in this chapter included data inputs generate from work in Chapter 5 on the UK CF Data Registry, which included health state transitions probabilities, cost banding probabilities, high-cost drug proportions and lung transplant probabilities. The novel additions also included inclusion of IV based health states. These would have most likely resulted in differences between model outcomes, from either costs or QALYs as the model was structurally different and was driven by different data.

It is important to note that only a single model used in the validation exercise was a Markov cohort model (Sharma et al), the remaining model looked at in the technology appraisals were individual patient simulation models [9, 10]. The results from both Markov Models were more comparable than those which used other model types. Differences in results are also likely to be due to this and future research could look at using the data generated in this thesis or similar methods in an individual patient simulation model and to compare the model outcomes again.

The purpose of conducting the EVPI in this study was to highlight that further research into the cost effectiveness of Orkambi® is not justified. However, it is important to note that EVPI is highly influenced by the population at risk and the duration the treatment is being provided for. In the analysis conducted in this chapter, I assumed that there would be no reduction in costs in treatment due to patent expiry and that the population would not change which was eligible for Orkambi®. Additional factors that could be considered in future analyses could be time to patent expiry, availability of biosimilar treatments, changes in number of individuals who are eligible for treatment and additional changes in the price of Orkambi®.

Additional work, in the future, could also include the use of the model to evaluate other CF management interventions in other genotype populations. The model could be adapted for further analysis of the impact of both CFRD and CFLD.

Lastly, I feel that many of the differences generated in the model identify a key element in the decision modelling of CF interventions. That there is no single best approach to modelling CF interventions and future work on coming to an understanding of the best approaches for modelling CF treatment would benefit the evaluation of CF treatments.

6.28 Conclusion

Although this is not the first cost effectiveness analysis conducted on Orkambi®, it is the first cost-utility analysis of a CF modulator intervention in the U.K. using data predominantly from the UK CF Data Registry. The modelling was conducted from the perspective of the NHS and the population of interest were those with F508Del Homozygous mutation. This is the first model that looks at the effect of Orkambi® across either sex or in combination. Also, outcomes in the model can be segregated by age and sex.

Key variables were identified as driving the differences in results of different Orkambi® appraisals or economic evaluations. These included particularly how efficacy was applied to the models and which study was used to determine the effect or Orkambi®. Other drivers included utilities, initial patient distribution in the Markov model and how significant events such as IV treatment as a result of PEx are costed and accounted for in the models. The results showed that the model structure utilised in this chapter produced

similar results to those which exist in the published literature and from agencies which provide guidance on medicine use i.e. NICE, CADTH and NCPE.

7 Discussion

The aim of this chapter is to revisit the original aims of this PhD and demonstrate how each chapter has cumulatively met the objectives set out at the start. The main findings are shown against each chapter, although the strengths and limitations and future work of each chapter are discussed therein. I discuss how this thesis adds to the literature in CF and highlight some avenues how my research has impacted CF research. The final sections provide suggestions for future work in different areas which would give substantial benefit for health economics research in CF. Lastly, the chapter finishes with an overall conclusion of the thesis.

7.1 How the thesis addresses the objectives

The thesis aimed to advance the health economic evidence available to inform economic models and the decisions about appropriate Cystic Fibrosis care. This has been achieved through a series of objectives. These are further described in Table 107 alongside the chapters which meet the objectives in this thesis. A total of two systematic reviews have been conducted as part of this thesis (and published) to cover aims 1a and 1b. Analysis of the CF Data Registry was undertaken and methods presented in 2a were used in order to achieve aims 2b-d. Lastly, the input parameters generated in 2b-d were utilised in a De Novo model structure which was discussed in detail in Chapter 4 to achieve aim 2e.

Table 107: Summary of Aims and objectives

Aims	Objectives	Covered in and findings
1. How are Cystic Fibrosis medications evaluated for their cost-effectiveness?	a) To identify and review the current state of the economic modelling literature for CF with the view to identify potential areas of importance that can be addressed within this PhD.	Chapter 2 presents the systematic review of health economic models and found that modelling did not reflect disease progression in CF
	b) To review and identify health utility data that exists for the health economic modelling of CF.	Chapter 3 showed that research around health utilities for CF, be it health state, FEV_1 or significant health event (PEx) related, requires further work.
2. How Registry Data can be used in the development of parameters to inform health economic	a) Demonstrating how existing statistical methods can be utilised to develop health state transition or other probability estimates	Chapter 4 presents regression modelling methods used to generate transition probabilities. Ordered probit and Generalised Estimating equations were appropriate for the available data.

modelling in the context Cystic Fibrosis treatments.	b) Generating new U.K. based health state transition (including mortality) probabilities based on data from the CF Trust Data Registry.	Chapter 5 presented health state transition probabilities which were comparable to the existing data in the literature
	c) Generating new U.K. based Cost band probabilities from the CF Trust Data Registry	Chapter 5 presents a novel method to calculate costs for being in different health state which were to the existing data in the literature
	d) Generating new U.K. based Lung Transplant probabilities from the CF Trust Data Registry	Chapter 5 presents a novel method to calculate probability for receiving a transplant which were to the existing data in the literature and the observed data in the U.K CF Registry

	e) Developing a novel health economic model structure based on disease progression, data availability and clinical expert opinion in the U.K.	Chapter 4 present the model conceptualisation process used to develop a De Novo health economic model which was validated against the literature and by clinical experts
	f) Developing a health economic model incorporating the estimates generated in objectives a) to d) into objective e) to evaluate an exemplar intervention, Orkambi®.	Chapter 6 presents the exemplar CUA of Orkambi® to validate to the De Novo model and found that the ICER and cost estimates produced were comparable to existing published models

7.2 How this thesis extends knowledge and understanding

In summary, this thesis extends our knowledge and understanding in the health economics of CF in 4 main ways.

7.2.1 Health state transition data for use in CF models

This thesis looked to understand how the use of the UK CF Data Registry could support and further advance the health economic modelling of CF interventions.

One of the key additions to existing evidence is health state transition probabilities based on a national Data Registry which covers more than 90% of the population and this really strengthens the external validity of these estimates. Chapter 5 has provided a very detailed breakdown of probability estimates by age, sex and health state. The new data has been assessed by clinical experts and has been comapred to existing evidence and the estimates are highly comparable and have been said to make clinical sense by experts (Dr Siobhan Carr and Dr Diana Bilton).

7.2.2 Cost band probability data for use in CF models

This thesis looked to understand the current practice of health economic modelling of CF interventions. Existing health economic models were evaluated for different aspects including model structure and data inputs (Section 2.7).

The review highlighted that available cost data were based primarily on multiple external data sources and in some instances were more than a decade old. In cases where count-based estimates were used, these were based on CF Registry Data but were not disaggregated by age, sex and health state together. Only in one instance were costs based on regression methods employed on the CF Registry Data [107] but again, this did not incorporate sex into the cost estimation and the approach used presented costs as a

continuous outcome. However, such cost data is not available in CF. Existing cost banding categories (Section 4.18.2) only exist for CF. Similarly, no variation around the mean cost per band is available in the literature. In this thesis, novel approaches to costing have been demonstrated through regression methods to determine the probability of occupying a cost banding category, which is includes all drugs but High-Cost drugs. Such cost banding categories also include IV treatment days received per year and also the number of hospital days spent as an inpatient in hospital annually. Such probabilities are based on sex, age and current health state. Additional costs for High-Cost drugs have been included as part of Chapter 6. As a result, the work presented in this thesis shows probabilities estimated for cost banding categories by age, sex and current health state, which in not currently available in the literature. Furthermore, costs are based on a national Data Registry which covers at least 90% of the CF population in the U.K, so this really strengthen the external validity of these estimates.

7.2.3 Novel Model Structure

Similarly, existing model structuring practices were evaluated as part of this thesis. The results showed that very few studies incorporated the effects of serious health events such as PEx's But in cases where this was done, impact was indirectly applied through HRQOL and costs [102]. In instances where such events were incorporated as health states, subsequent health states such as lung transplantation and post lung transplantation were not included [101]. The work undertaken in this thesis on the model structure used a detailed conceptualisation process which was supported with contribution by statisticians, epidemiologist, clinicians in CF and health economists. As a

result, a De Novo model structure was created which incorporated significant health events and is reflective of disease progression in CF and can be used for a multitude of interventions in CF in the future.

7.2.4 Gaps in literature for future focus

Subsequent to understanding how CF interventions were evaluated, gaps in evidence were identified. Particularly, health state utility data were identified as needing further enquiry. The review conducted highlighted that there was limited evidence available which could be used in the health economics modelling of CF interventions and requires further research.

A number of strengths and limitations were also discussed and are presented in detail in each chapter.

7.3 Research impact of the work

Overall, this thesis shows how refined use of the CF Trust Data Registry can support the health economic modelling of CF interventions. All input parameters used in the De Novo health economic model in this thesis were generated from the UK CF Data.

Similarly, the reviews conducted in this thesis have highlighted the need for further work on the HRQOL data, particularly, utility data. This had led a research grant being approved to look at the health-related quality of life in CF individuals (personal communication, Professor Jennifer Whitty, 16th Nov 2020).

Furthermore, the review on the health economic modelling studies conducted led to a De Novo model structure which incorporated significant health events which can affect the long-term costs and utilities as a result of receiving a CF treatment, as shown through

Orkambi®in this thesis. The validity of which has been demonstrated through between consistency comparison with published technology appraisals [7-10] and articles [126]. The results showed that the transition probabilities generated in this thesis are comparable to those existing in the literature when averaged by age and sex. Although it may be argued that use of Registry Data may lead to some confounding due to a small proportion of patients in the CF Data Registry receiving Orkambi® treatment. This is unlikely due to the small numbers of such people in the Registry Data.

Furthermore, the development of a De Novo model for the cost-effectiveness analysis of CF interventions was another key aspect of this thesis. The De Novo model could be used for future evaluation of CF treatments, in the UK particularly, as all aspects of costs and outcomes are covered in this model. The model itself allows for inclusion of significant health events and further patient/cohort sub-groups, such as those with CFRD or CFLD, could be included for impact of such treatment on the cost-effectiveness of different treatments.

7.4 Future work

7.4.1 Utility data

Data on the utility of being in particular health states but also experiencing significant health events such as PEx have been highlighted as requiring further study in this thesis. A single study by Bradley et al [48] has been used in a majority of health economic models to demonstrate health state utility and disutility and also in this thesis.

However, other sources of evidence, particularly Solem et al [139] provide information on utilities based on PEx which led to hospitalisation or not and the definition of PEx meets

the defined Fuch's criteria which was highlighted as best for use in clinical trials. However, no utility data is provided based on health state. As a result, Bradley et al [48] alone provide health state-based utility data. But the author, in their study limitations, highlighted that the sample size for the study was small. So, another study looking at the health state related utility for CF patients would provide an additional valuable resource for the health economic modelling of CF interventions. This could be achieved through such data being collected by the CF Data Registry when patients see their physicians for annual review. Additional studies could be carried out which look at HRQOL subsequent to significant health events such as PEx as close as possible to the event data whilst recording their best FEV_1 value that year and follow up the patient prospectively. These later could be linked to the CF Data Registry to determine long term outcomes such as mortality and health state transitions as well as costs and could again be used for the health economic modelling of CF interventions.

7.4.2 Cost data

As explained in this thesis, existing cost data in the literature were estimated using count-based methods and only provided probabilities of being in particular cost bands by health state [102]. Only a single health economic evaluation conducted [107] used regression modelling approach to costing but added cost per band and High-Cost drugs. The cost that were used were not derived from a particular genotype but of those in the overall registry. This may not be appropriate for evaluating interventions which are given to select genotype groups. The costs band probabilities and well as use of High-Cost drugs presented in this thesis are based on a select genotype (F508Del Homozygous) and are

provided by age, sex and current health state. This level is detail is not currently available in the literature. Furthermore, given the nature of F508Del Homozygous mutation, which is a high-risk group, High-cost drug use and probabilities of occupying particular cost bands will most likely to differ compared to those in lower risk groups or in CF on average (mixture of High and Low risk groups). As a result, reductions in IV days, hospital inpatient stay will reflect changes upon receiving treatment for F508Del Homozygous patients and not an average of CF patients in the U.K.

Future work for cost data could focus on linking the U.K. CF Data Registry to Hospital Episode Statistics (HES) or Secure Anonymised Information Linkage (SAIL) data to obtain more refined use of resources to support the calculation of cost per person, by age, sex and current health state. This will support the HTA of novel and existing treatments in CF.

7.4.3 New Data from the CF Trust Registry

The data provided as part of this thesis contained variables only up until 2016, where such data did not contain information on whether an individual in the Data Registry experienced an PEx. However, subsequent years 2017 onwards have data on such events. As a result, future studies could also focus on the number of PEx events experienced whilst on a number of existing or novel CF treatments. Furthermore, the number of individuals in the Registry Data who were receiving Orkambi® as a treatment were very few. However, subsequent to 2019 the number of those receiving this treatment has increased considerably. This could potentially lead to issues with confounding upon use. As a result, methods such as propensity score matching could be used to account

for novel modulator treatment use and comparison in economic evaluations using the CF Data Registry. Existing studies which have looked at the effectiveness of modulator treatments through use of the CF Data Registry have highlighted the impact of such treatments in real world settings and thus increases the external validity of such treatments [245]. As a result, future studies could also use treatment efficacy data from within the Data Registry to evaluate their cost-effectiveness and the EMA have already called for such observational research [246].

7.4.4 Further model adaptations

The work conducted in this thesis also looked at developing a novel model structure. However, as highlighted in Chapter 2, there are other additional areas of CF that require further research. These include the impact of CFRD and CFLD, which are becoming more prevalent as the median survival of those in the CF in the U.K. increases. Future models could look at incorporating the impact of such conditions on the health state transitions, including lung transplantation, as well as costs.

7.4.5 Other registries

This thesis is not the first study which has looked to use Registry Data in the health economic modelling of treatments. However, this is the first study to use the CF Registry Data to provide input parameters to such a refined level. Further studies in the future could also be conducted on additional CF Registry Data from other countries to determine if there are substantial differences in the long-term outcomes of CF patients as well as the cost effectiveness of CF interventions. Such studies could be useful in highlighting key areas of research in CF so that treatment provision could be homogenous across

different countries. The methods used in this thesis have also highlighted that such regression methods could be applied to registry outside CF to generate similar input parameters for the economic evaluation of treatments.

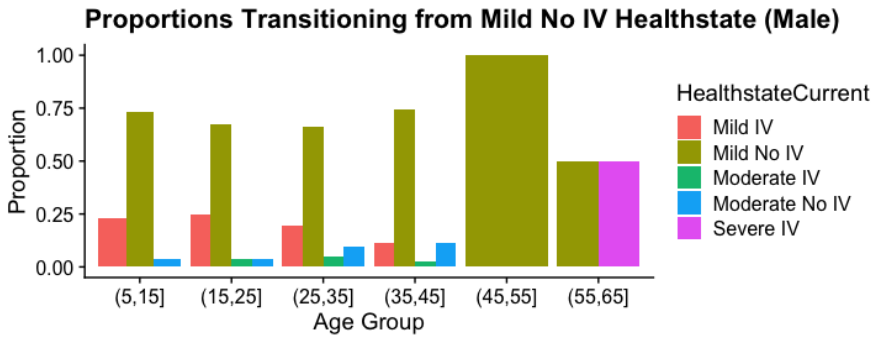
7.5 Conclusion

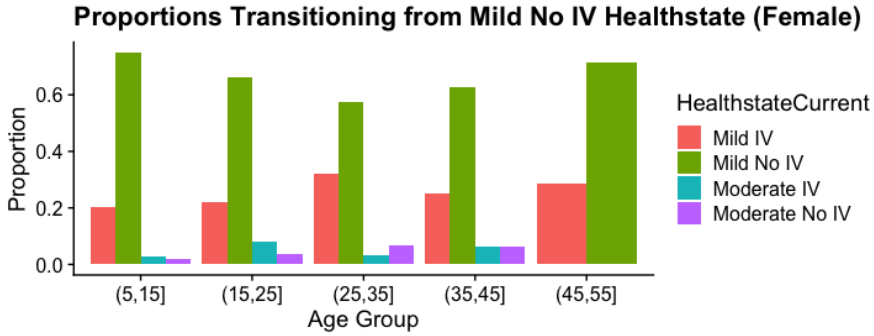
This thesis has developed our understanding of the areas that require further improvement for the health economic modelling of CF interventions to take a step in a direction which allows decision makers to be more confident about drug reimbursement. This thesis has taken an approach to develop a De Novo model to address the lack of reflective disease modelling in CF. It has also developed input parameters from a national Data Registry to show that such databases can prove to be a strong supportive tool which has great potential in supporting the improvement in the cost effectiveness evaluation of existing and novel CF treatments in the future. Most importantly the methods used and resultant evidence developed in this thesis can help support decision makers to allow appropriate access for CF individuals to treatment whilst preserving the sustainability of the NHS, not just today but also in the future.

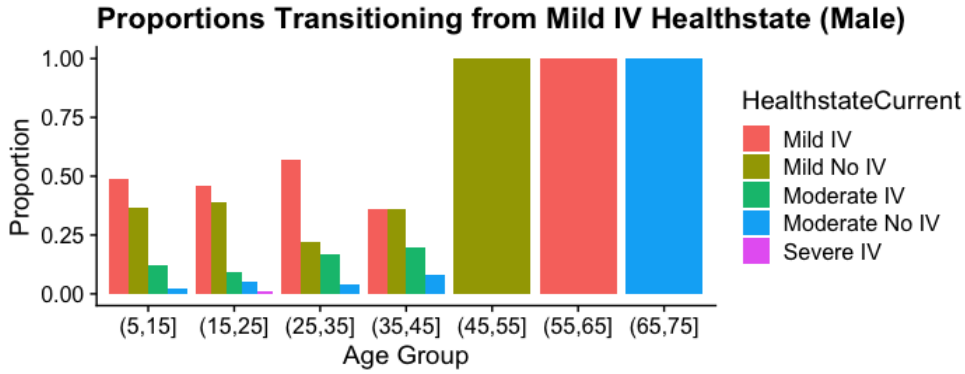
8 Appendix

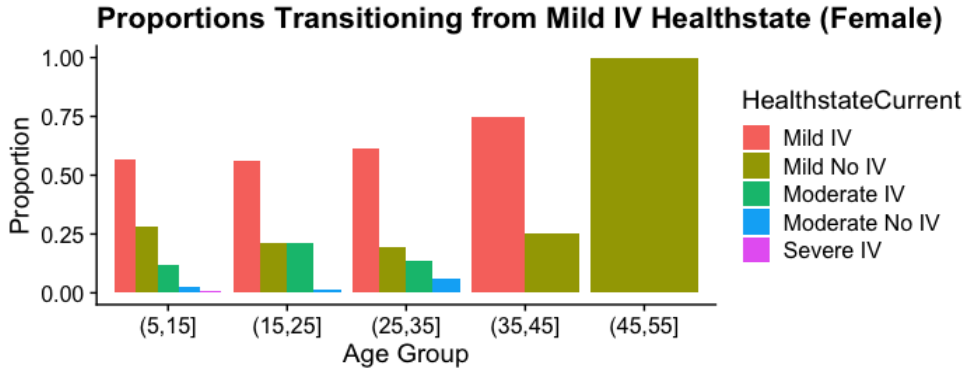
8.1 Appendix 1: Plot of observed proportions in each current health state by previous health state, gender and age groups

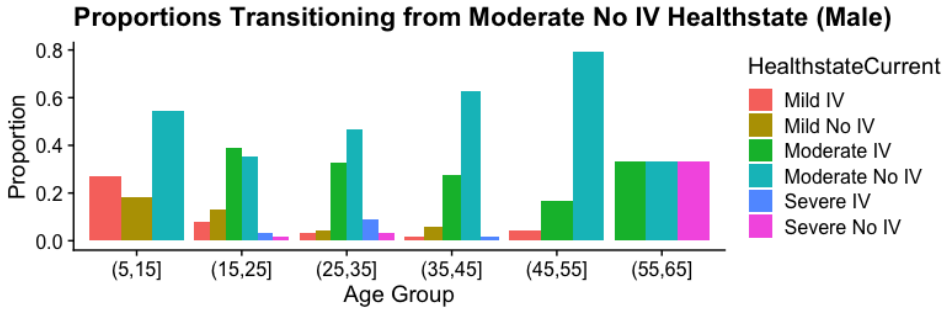
8.1.1 Health State transitions

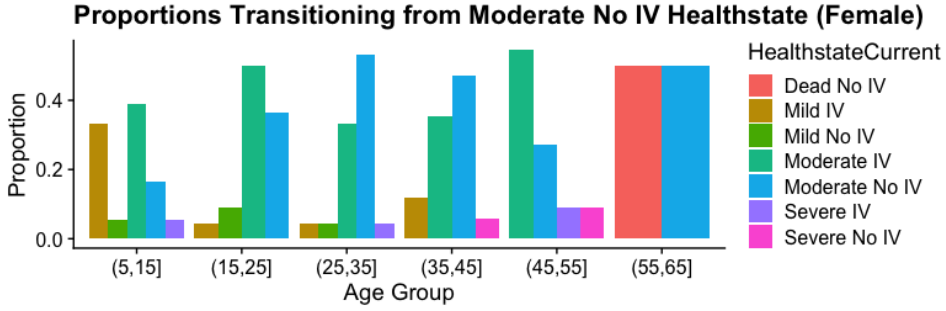


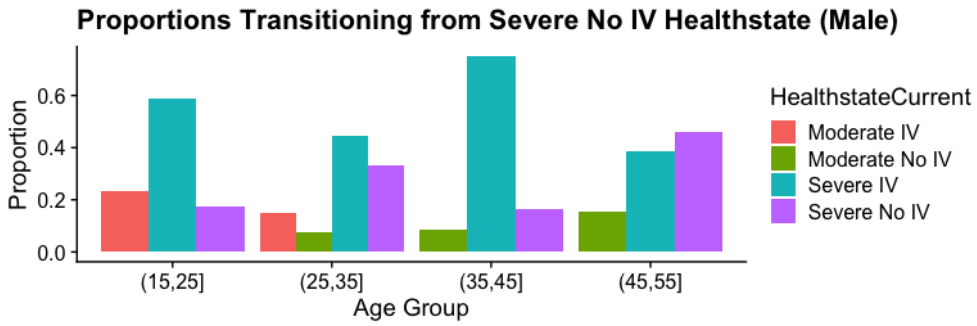


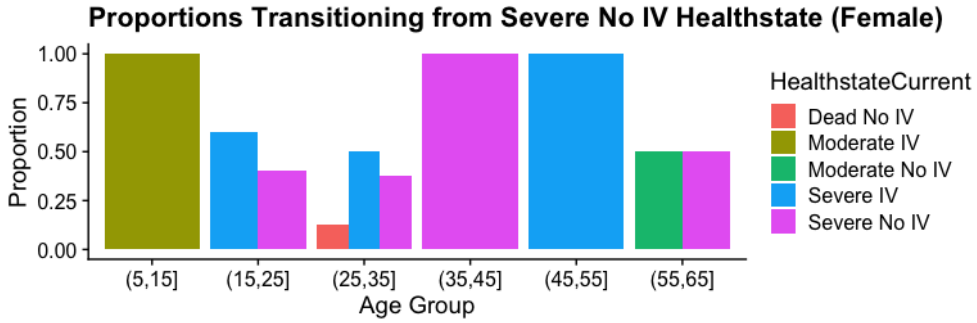

Proportions Transitioning from Mild IV Healthstate (Male)
Proportion
1.00
0.75
0.50
0.25
0.00
(5,15]
(15,25]
(25,35]
(35,45]
(45,55]
(55,65]
(65,75]
Age Group
HealthstateCurrent
Mild IV
Mild No IV
Moderate IV
Moderate No IV
Severe IV

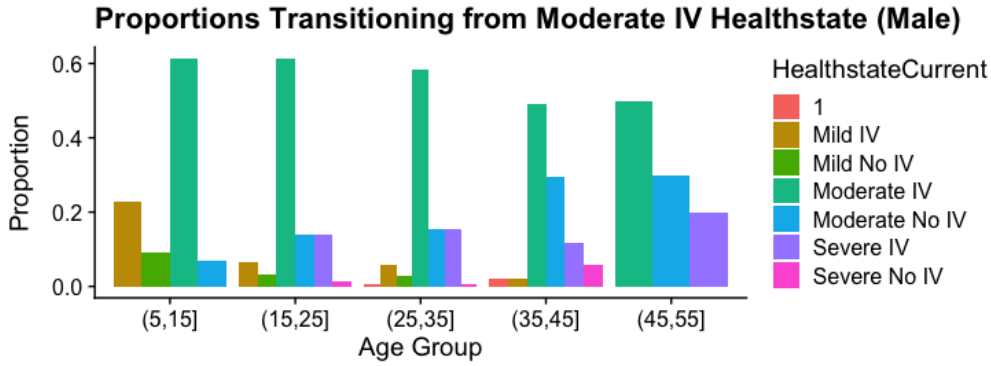

Proportions Transitioning from Mild IV Healthstate (Female)
Proportion
1.00
0.75
0.50
0.25
0.00
(5,15]
(15,25]
(25,35]
(35,45]
(45,55]
Age Group
HealthstateCurrent
Mild IV
Mild No IV
Moderate IV
Moderate No IV
Severe IV

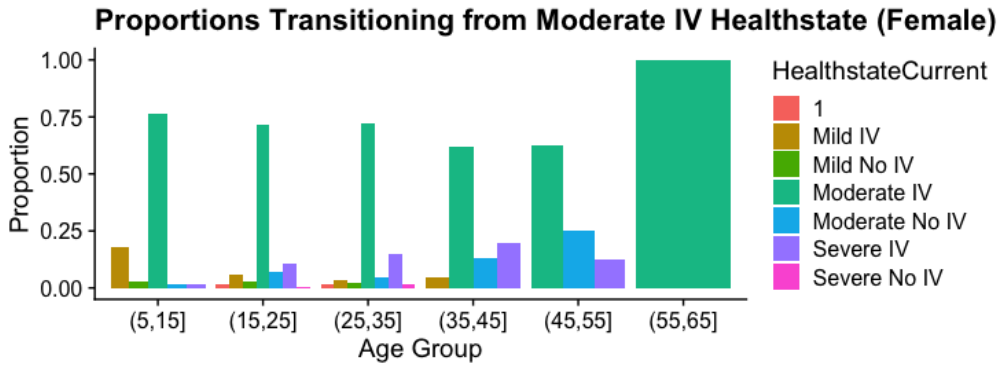

Proportions Transitioning from Moderate No IV Healthstate (Male)
Proportion
0.8
0.6
0.4
0.2
0.0
(5,15]
(15,25]
(25,35]
(35,45]
(45,55]
(55,65]
Age Group
HealthstateCurrent
Mild IV
Mild No IV
Moderate IV
Moderate No IV
Severe IV
Severe No IV

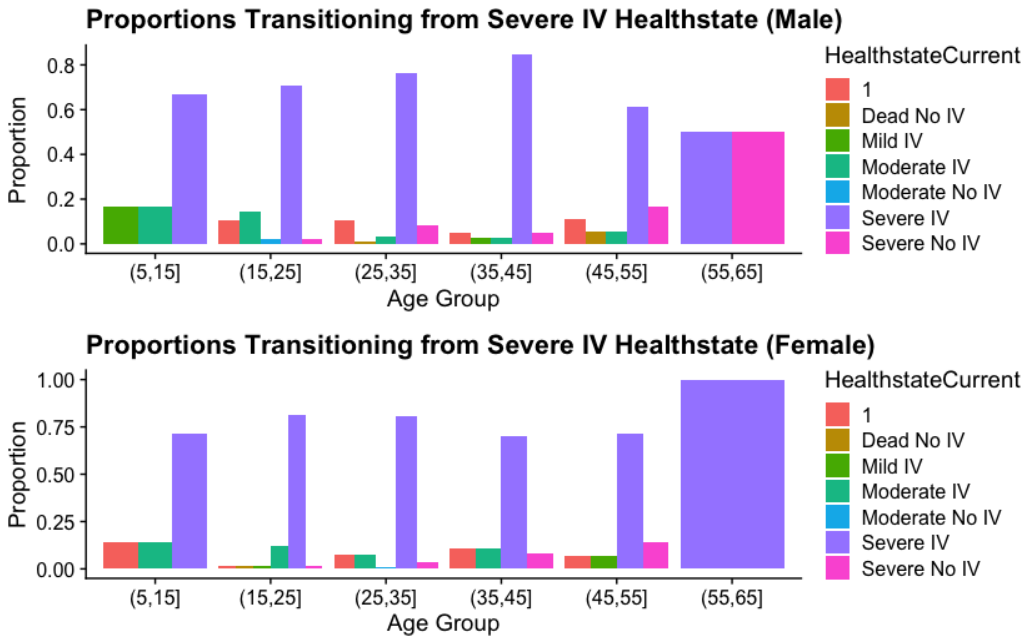

Proportions Transitioning from Moderate No IV Healthstate (Female)
Proportion
0.4
0.2
0.0
(5,15]
(15,25]
(25,35]
(35,45]
(45,55]
(55,65]
Age Group
HealthstateCurrent
Dead No IV
Mild IV
Mild No IV
Moderate IV
Moderate No IV
Severe IV
Severe No IV


Proportions Transitioning from Severe No IV Healthstate (Male)
Proportion
0.0
0.2
0.4
0.6
(15,25]
(25,35]
(35,45]
(45,55]
Age Group
HealthstateCurrent
Moderate IV
Moderate No IV
Severe IV
Severe No IV

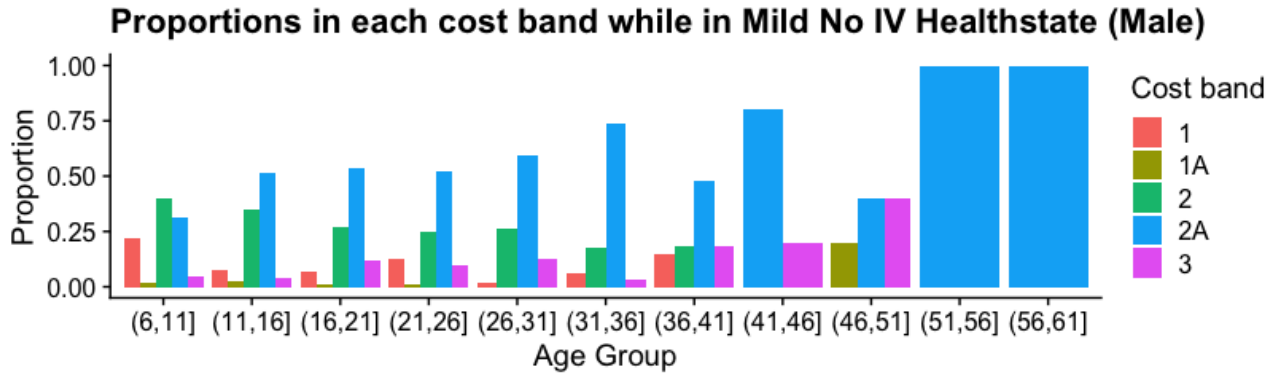

Proportions Transitioning from Severe No IV Healthstate (Female)
Proportion
0.00
0.25
0.50
0.75
1.00
(5,15]
(15,25]
(25,35]
(35,45]
(45,55]
(55,65]
Age Group
HealthstateCurrent
Dead No IV
Moderate IV
Moderate No IV
Severe IV
Severe No IV

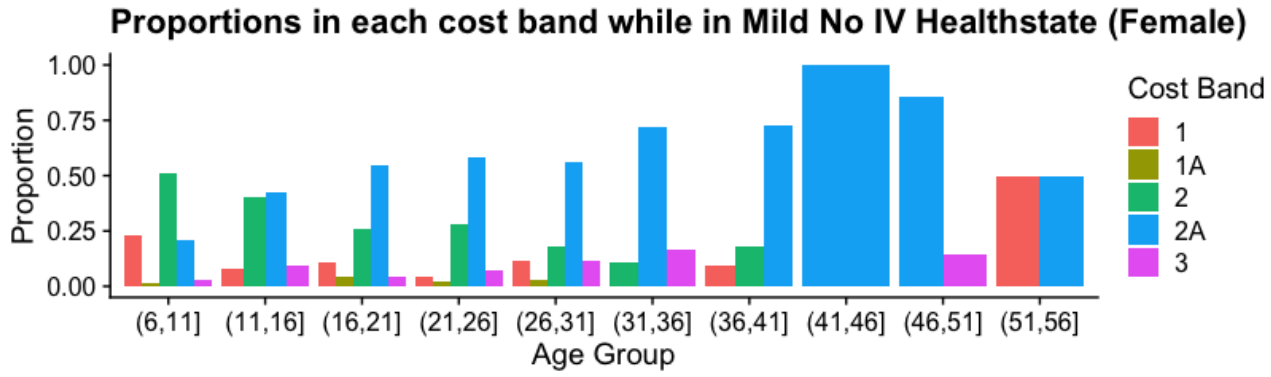

Proportions Transitioning from Moderate IV Healthstate (Male)
Proportion
0.0
0.2
0.4
0.6
(5,15]
(15,25]
(25,35]
(35,45]
(45,55]
Age Group
HealthstateCurrent
1
Mild IV
Mild No IV
Moderate IV
Moderate No IV
Severe IV
Severe No IV

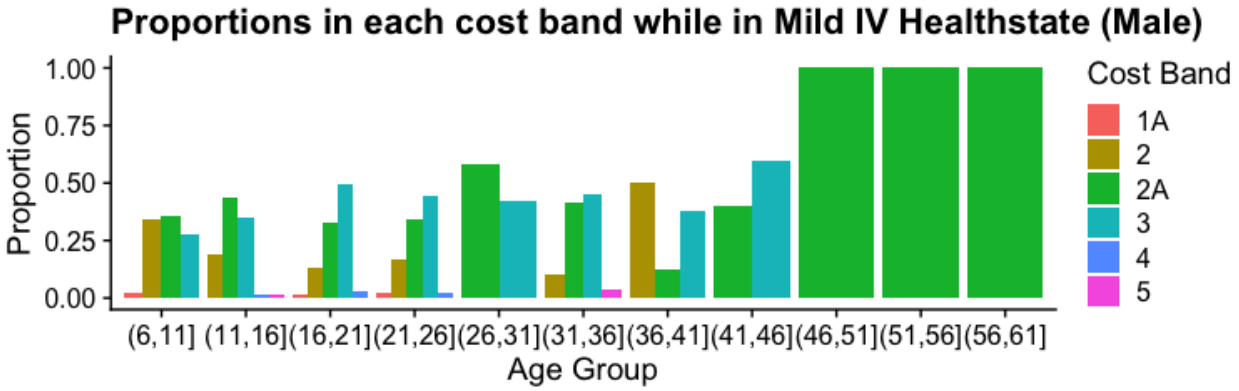

Proportions Transitioning from Moderate IV Healthstate (Female)
Proportion
0.00
0.25
0.50
0.75
1.00
(5,15]
(15,25]
(25,35]
(35,45]
(45,55]
(55,65]
Age Group
HealthstateCurrent
1
Mild IV
Mild No IV
Moderate IV
Moderate No IV
Severe IV
Severe No IV

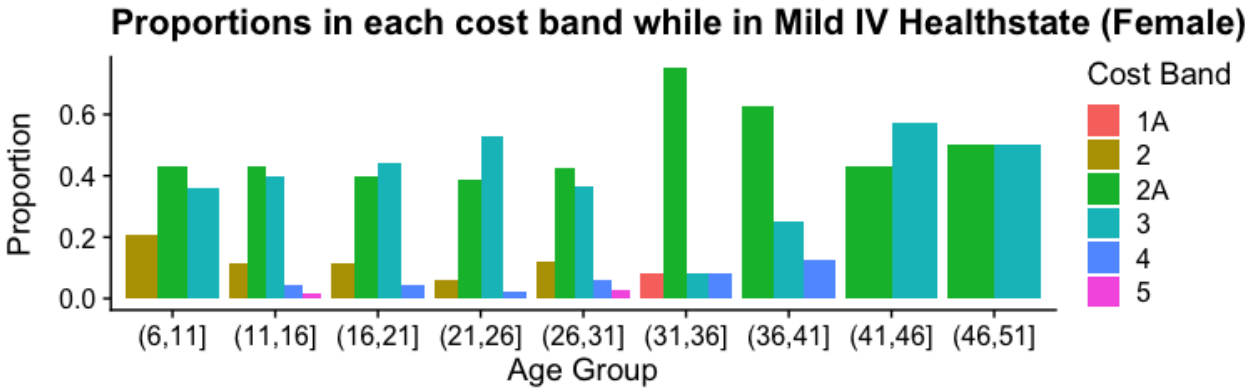


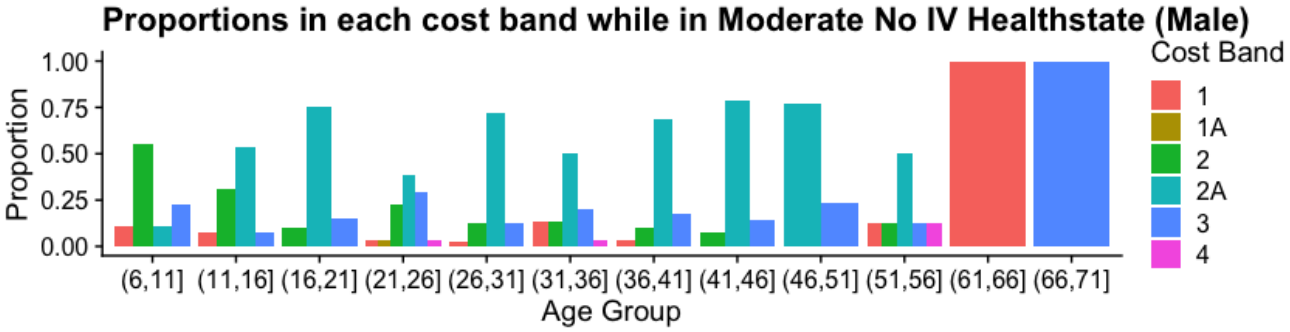
8.1.2 Cost band proportions

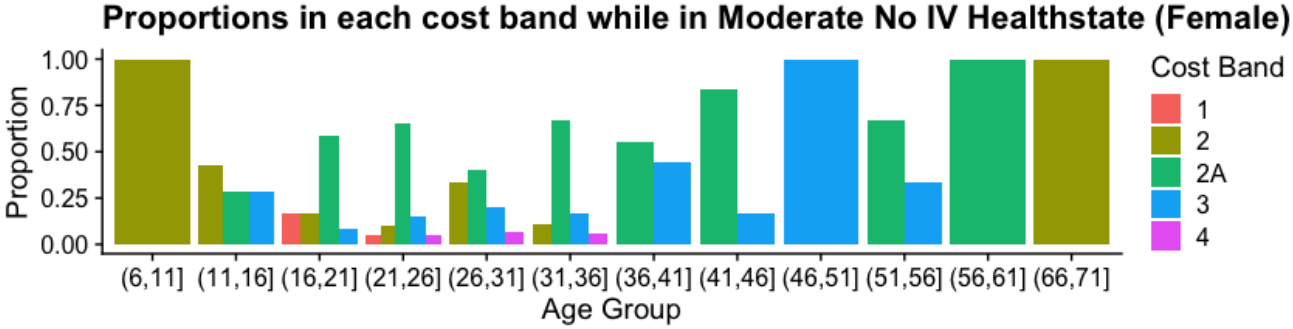


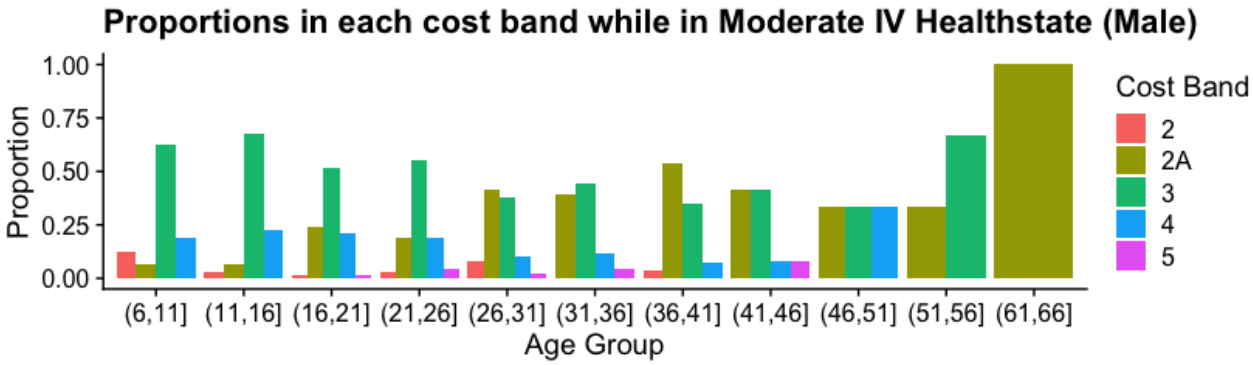


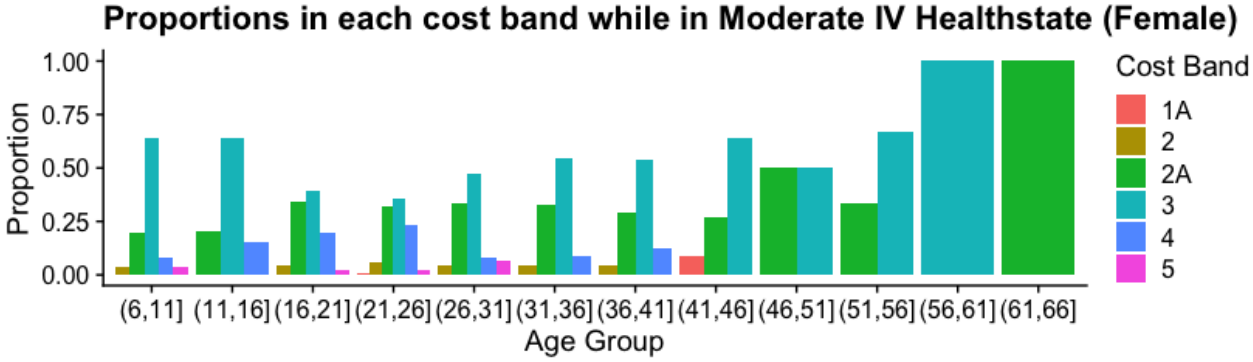

Proportions in each cost band while in Mild IV Healthstate (Male)
Proportion
1.00
0.75
0.50
0.25
0.00
(6,11] (11,16] (16,21] (21,26] (26,31] (31,36] (36,41] (41,46] (46,51] (51,56] (56,61]
Age Group
Cost Band
1A
2
2A
3
4
5


Proportions in each cost band while in Mild IV Healthstate (Female)
Proportion
0.6
0.4
0.2
0.0
(6,11] (11,16] (16,21] (21,26] (26,31] (31,36] (36,41] (41,46] (46,51]
Age Group
Cost Band
1A
2
2A
3
4
5


Proportions in each cost band while in Moderate No IV Healthstate (Male)
Proportion
1.00
0.75
0.50
0.25
0.00
(6,11] (11,16] (16,21] (21,26] (26,31] (31,36] (36,41] (41,46] (46,51] (51,56] (61,66] (66,71]
Age Group
Cost Band
1
1A
2
2A
3
4


Proportions in each cost band while in Moderate No IV Healthstate (Female)
Proportion
1.00
0.75
0.50
0.25
0.00
(6,11] (11,16] (16,21] (21,26] (26,31] (31,36] (36,41] (41,46] (46,51] (51,56] (56,61] (66,71]
Age Group
Cost Band
1
2
2A
3
4


Proportions in each cost band while in Moderate IV Healthstate (Male)
Proportion
1.00
0.75
0.50
0.25
0.00
(6,11]
(11,16]
(16,21]
(21,26]
(26,31]
(31,36]
(36,41]
(41,46]
(46,51]
(51,56]
(61,66]
Age Group
Cost Band
2
2A
3
4
5


Proportions in each cost band while in Moderate IV Healthstate (Female)
Proportion
1.00
0.75
0.50
0.25
0.00
(6,11]
(11,16]
(16,21]
(21,26]
(26,31]
(31,36]
(36,41]
(41,46]
(46,51]
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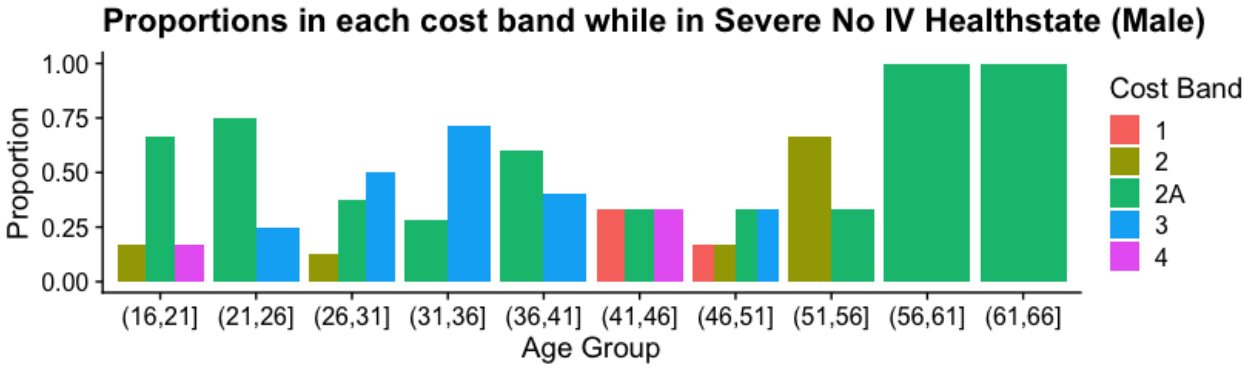
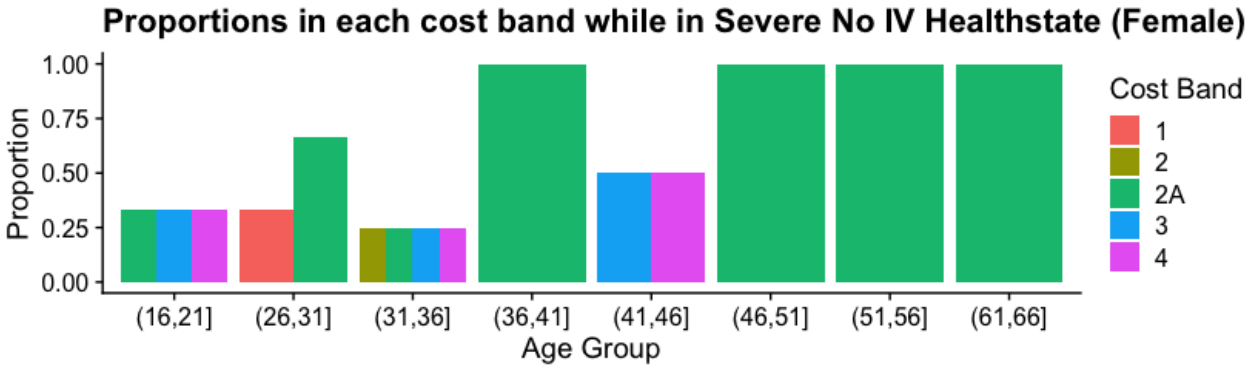
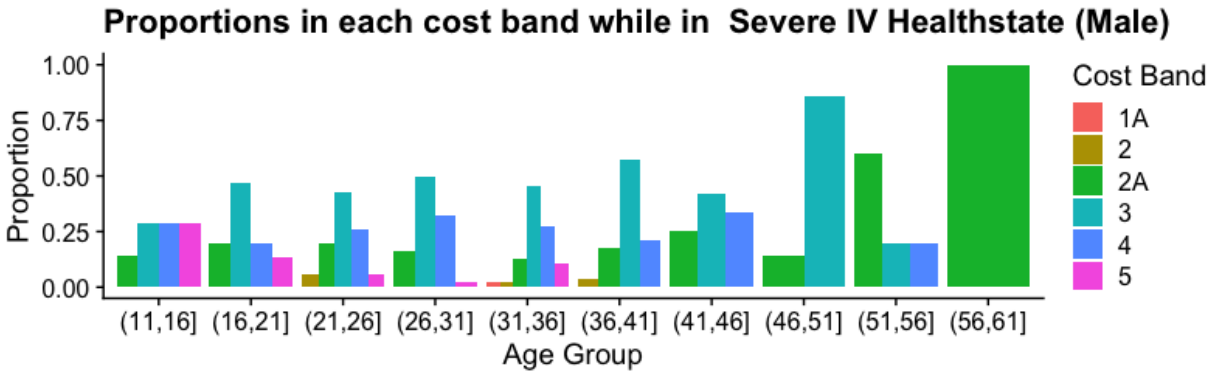
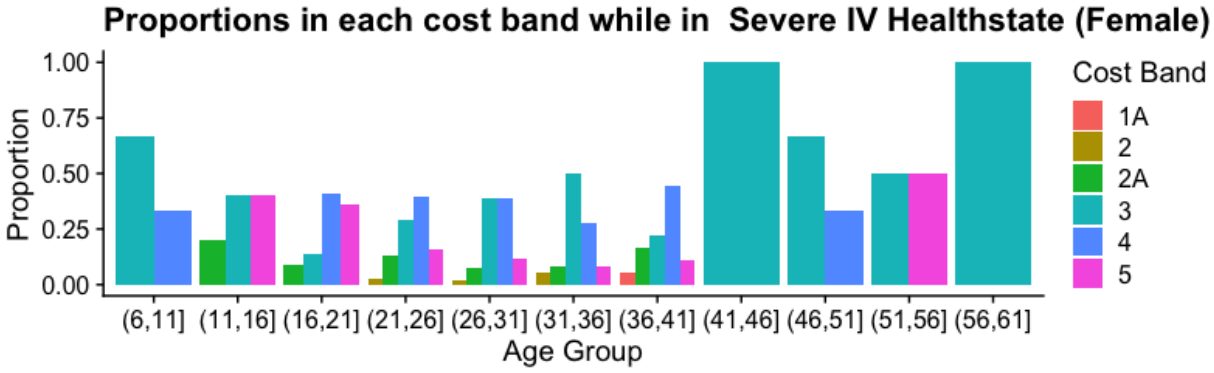
(61,66]
Age Group
Cost Band
1A
2
2A
3
4
5


Proportions in each cost band while in Severe No IV Healthstate (Male)
Proportion
1.00
0.75
0.50
0.25
0.00
(16,21]
(21,26]
(26,31]
(31,36]
(36,41]
(41,46]
(46,51]
(51,56]
(56,61]
(61,66]
Age Group
Cost Band
1
2
2A
3
4


Proportions in each cost band while in Severe No IV Healthstate (Female)
Proportion
1.00
0.75
0.50
0.25
0.00
(16,21]
(26,31]
(31,36]
(36,41]
(41,46]
(46,51]
(51,56]
(61,66]
Age Group
Cost Band
1
2
2A
3
4

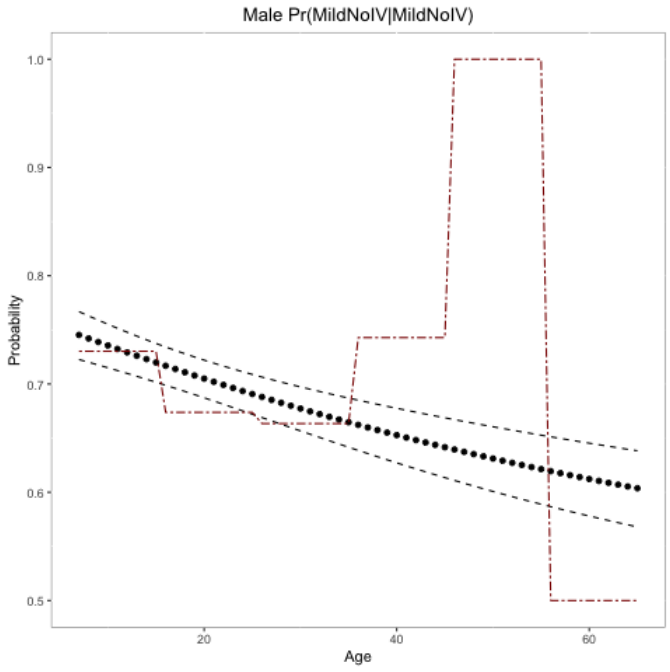

Proportions in each cost band while in Severe IV Healthstate (Male)
Proportion
1.00
0.75
0.50
0.25
0.00
(11,16]
(16,21]
(21,26]
(26,31]
(31,36]
(36,41]
(41,46]
(46,51]
(51,56]
(56,61]
Age Group
Cost Band
1A
2
2A
3
4
5

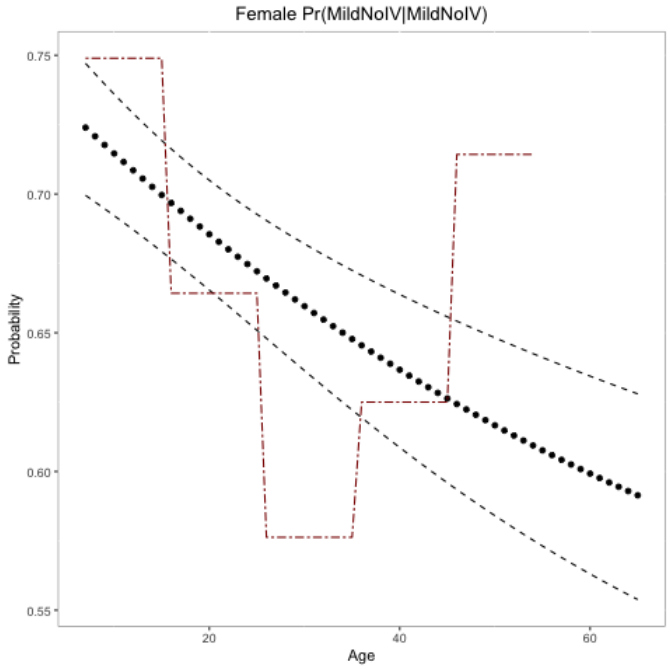

Proportions in each cost band while in Severe IV Healthstate (Female)
Proportion
1.00
0.75
0.50
0.25
0.00
(6,11]
(11,16]
(16,21]
(21,26]
(26,31]
(31,36]
(36,41]
(41,46]
(46,51]
(51,56]
(56,61]
Age Group
Cost Band
1A
2
2A
3
4
5

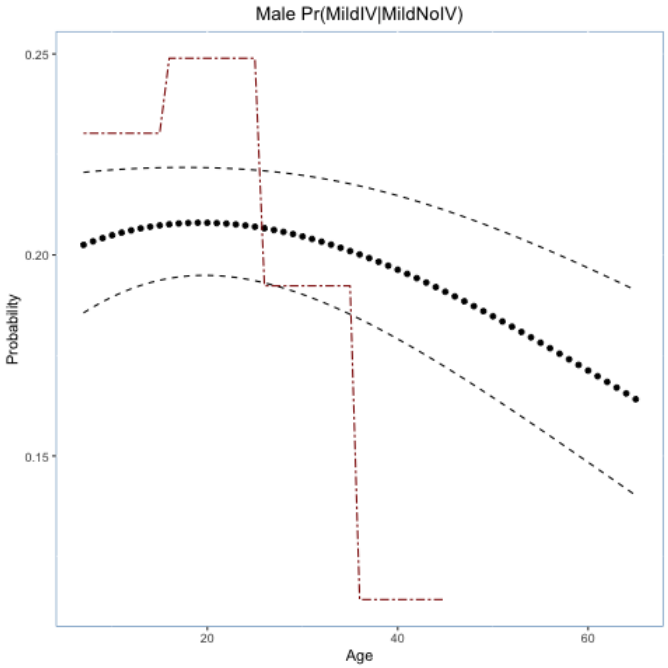
8.2 Appendix 2: Plot of observed and derived health state transitions probabilities from the U.K. CF Data Registry (2016)

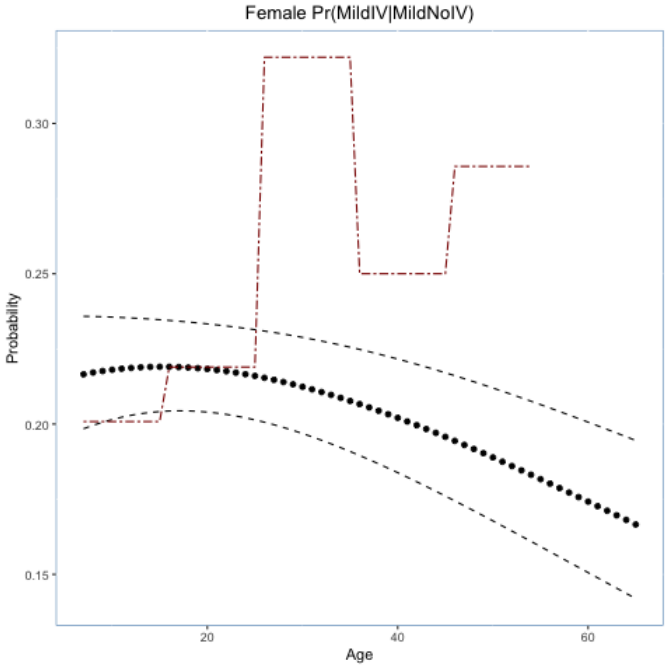
8.2.1 Previous health state

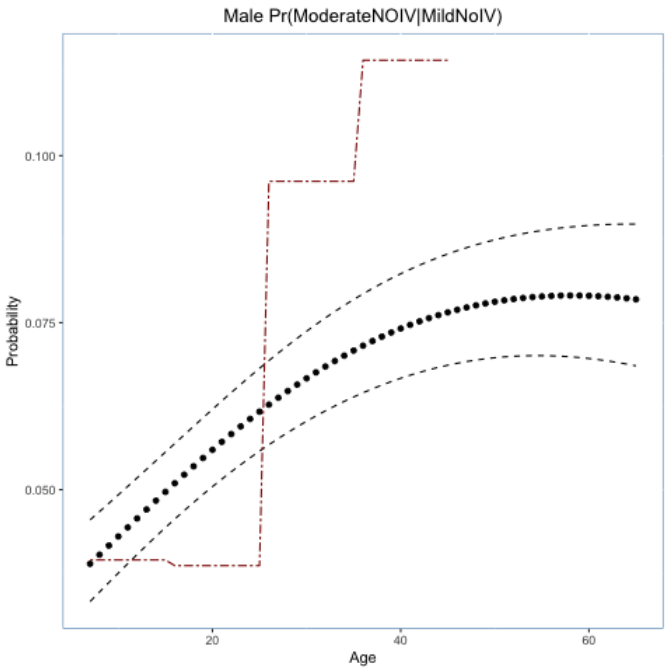
8.2.1.1 Mild No IV

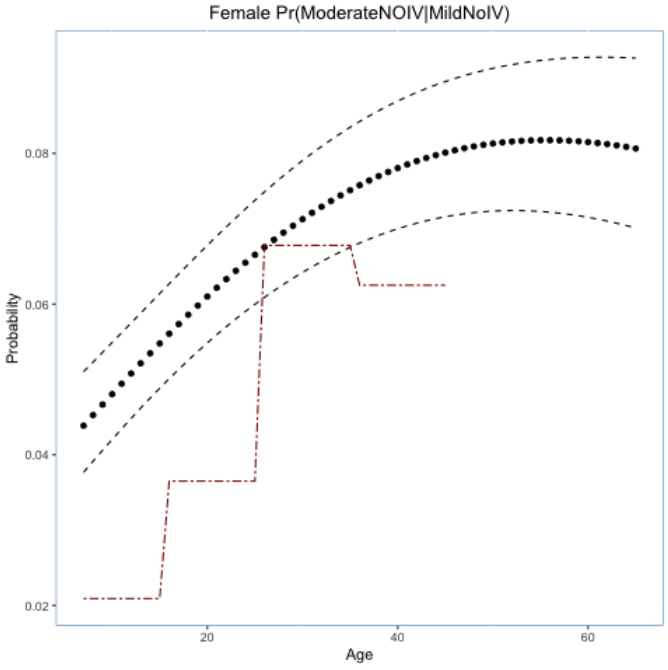


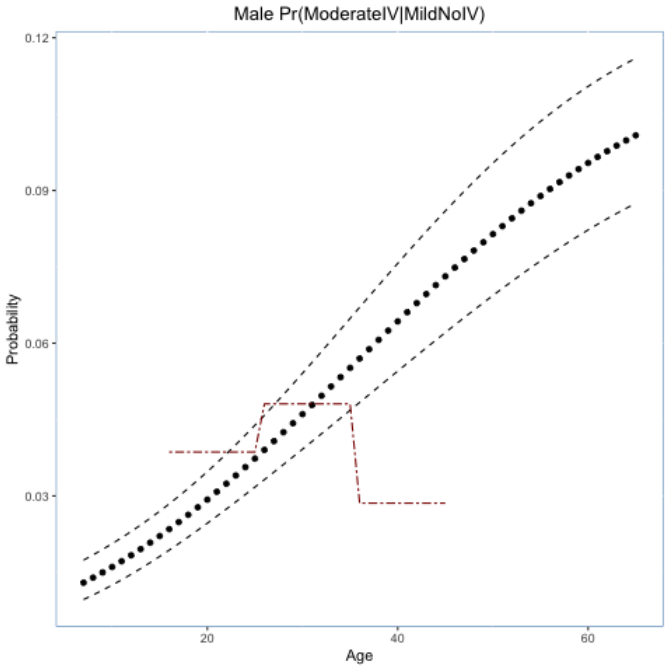


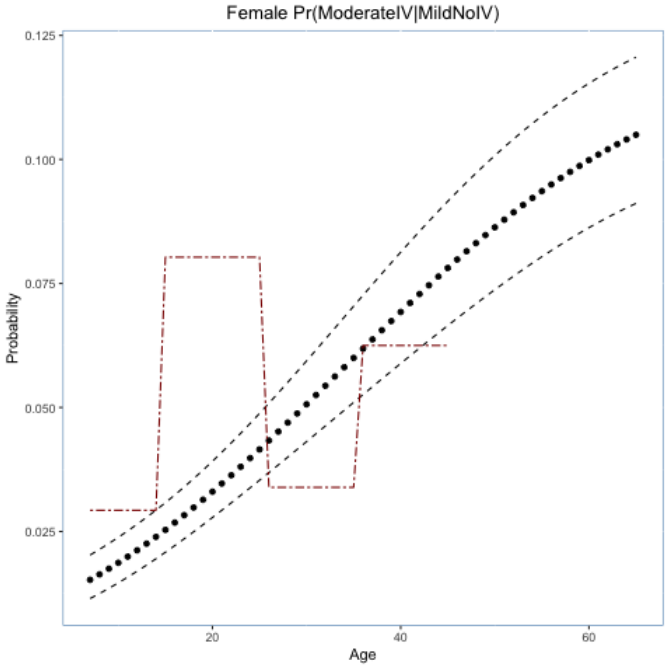

Male Pr(MildIV|MildNoIV)
Probability
0.25
0.20
0.15
20
40
60
Age

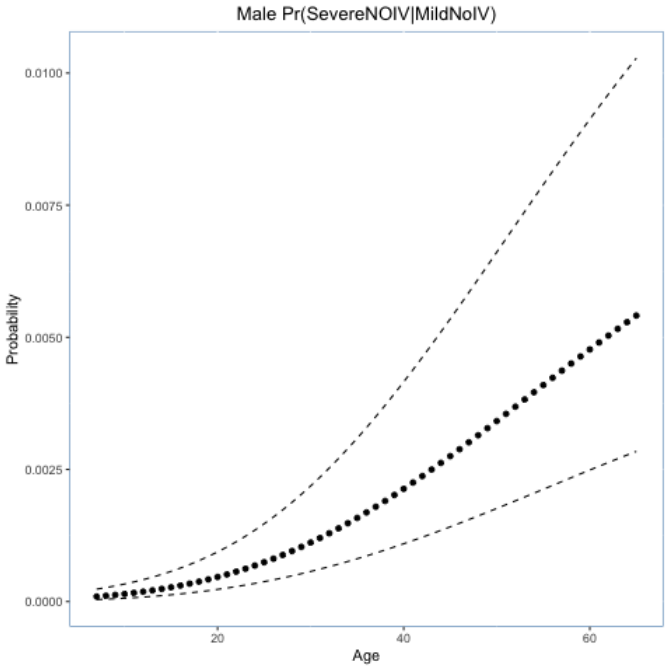

Female Pr(MildIV|MildNoIV)
Probability
0.30
0.25
0.20
0.15
20
40
60
Age

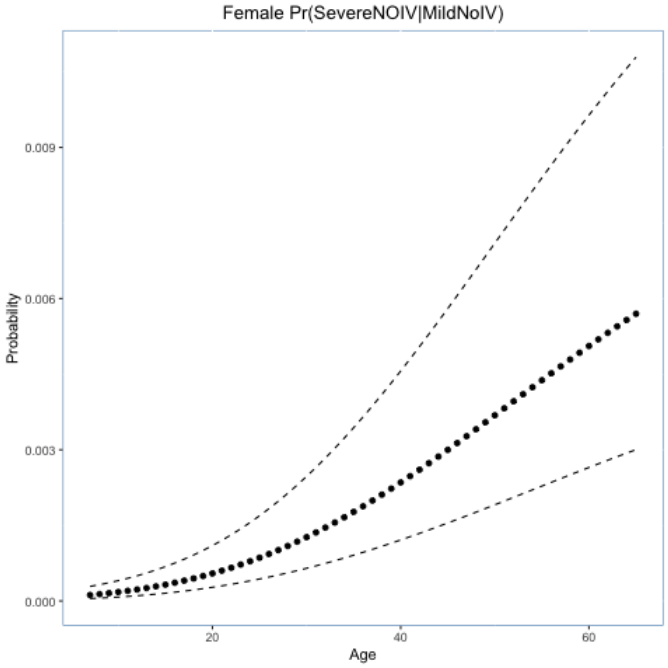

Male Pr(ModerateNOIV|MildNoIV)
Probability
0.100
0.075
0.050
20
40
60
Age

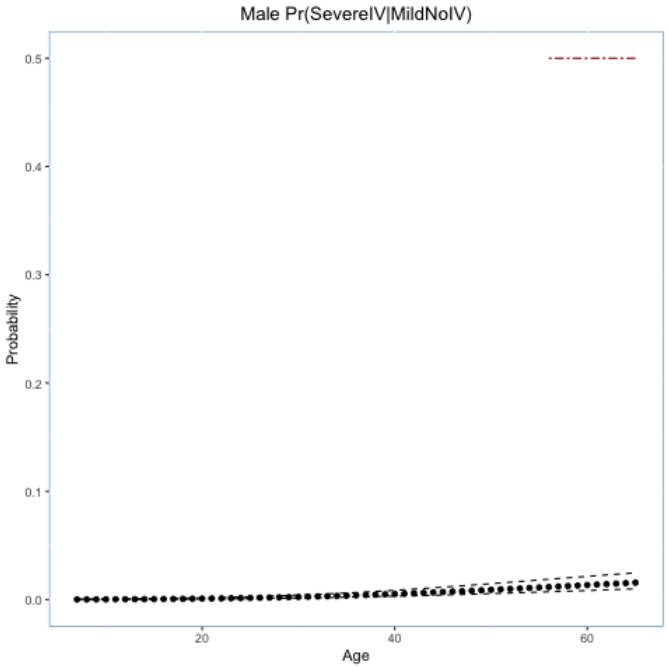

Female Pr(ModerateNOIV|MildNoIV)
Probability
0.08
0.06
0.04
0.02
20
40
60
Age

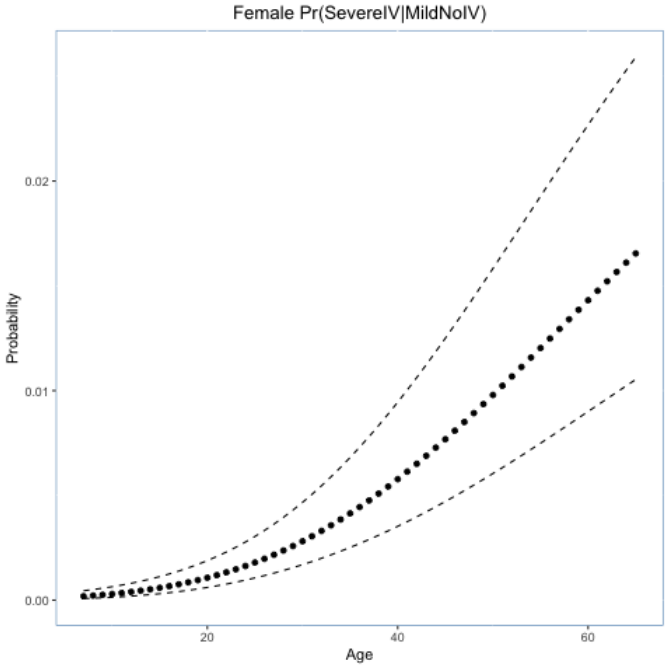

Male Pr(ModerateIV|MildNoIV)
0.12
0.09
0.06
0.03
Probability
20
40
60
Age

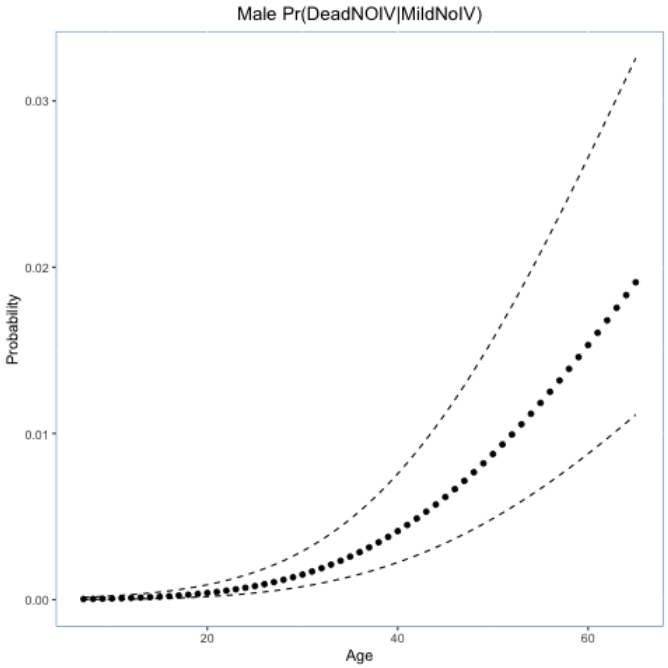

Female Pr(ModerateIV|MildNoIV)
0.125
0.100
0.075
0.050
0.025
Probability
20
40
60
Age

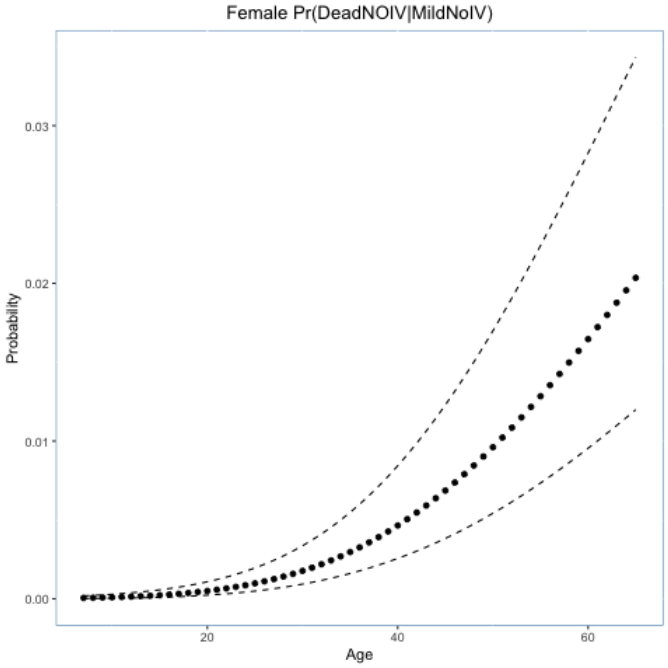

Male Pr(SevereNOIV|MildNoIV)
Probability
0.0100
0.0075
0.0050
0.0025
0.0000
20
40
60
Age

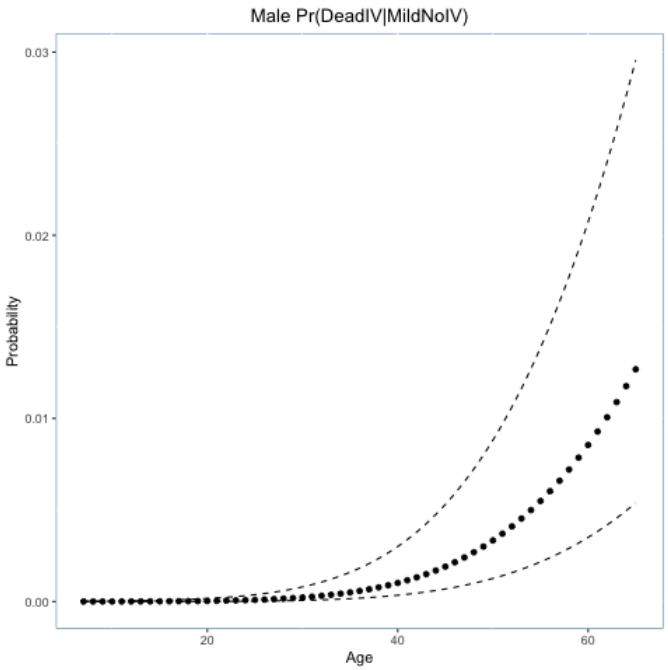

Female Pr(SevereNOIV|MildNoIV)
Probability
0.009
0.006
0.003
0.000
20
40
60
Age

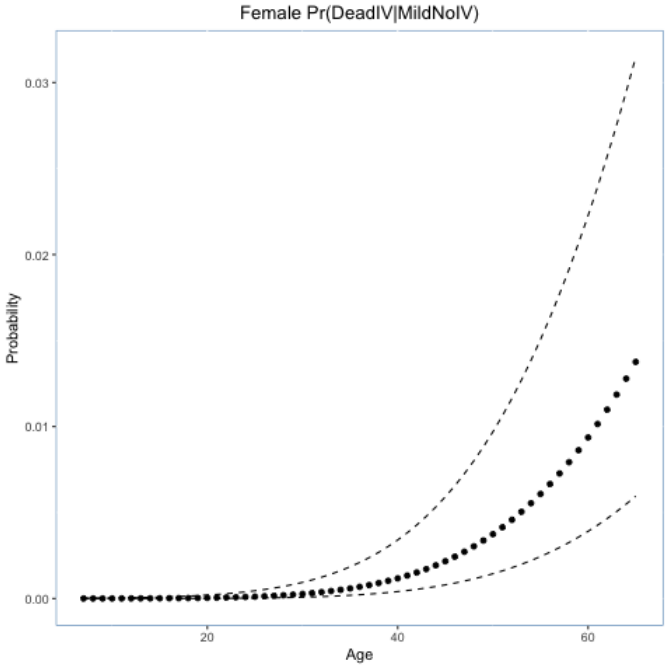

Male Pr(SevereIV|MildNoIV)
Probability
0.5
0.4
0.3
0.2
0.1
0.0
20
40
60
Age


Female Pr(SevereIV|MildNoIV)
Probability
0.02
0.01
0.00
20
40
60
Age

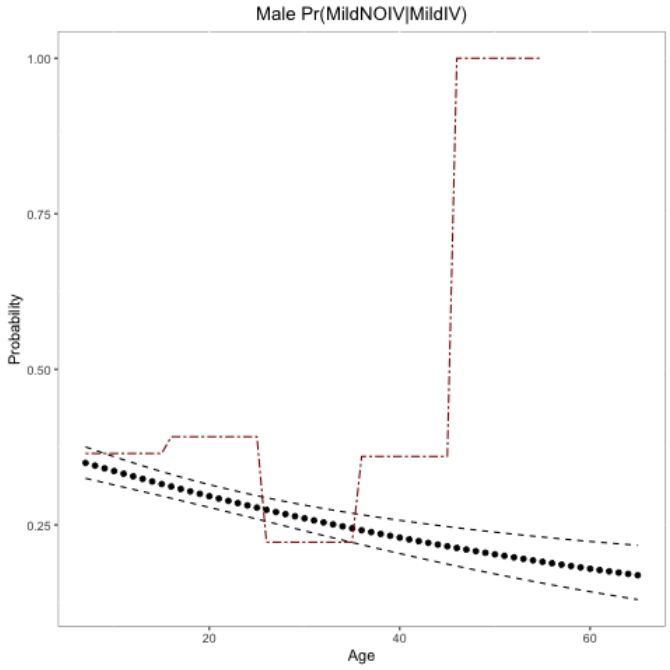

Male Pr(DeadNOIV|MildNoIV)
Probability
0.03
0.02
0.01
0.00
20
40
60
Age

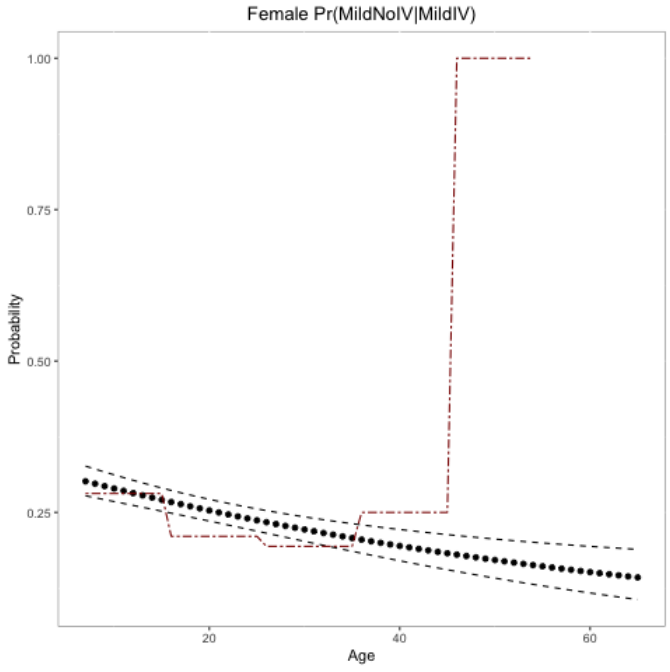

Female Pr(DeadNOIV|MildNoIV)
Probability
0.03
0.02
0.01
0.00
20
40
60
Age

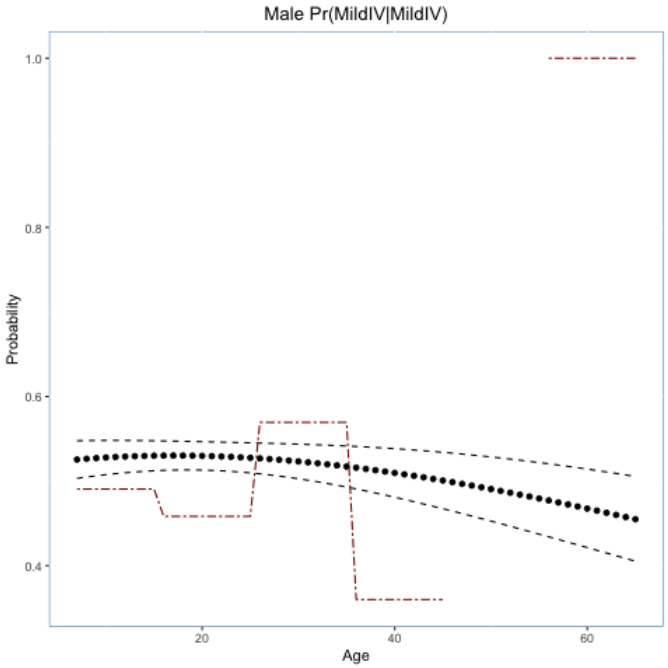

Male Pr(DeadIV|MildNoIV)
Probability
0.03
0.02
0.01
0.00
20
40
60
Age

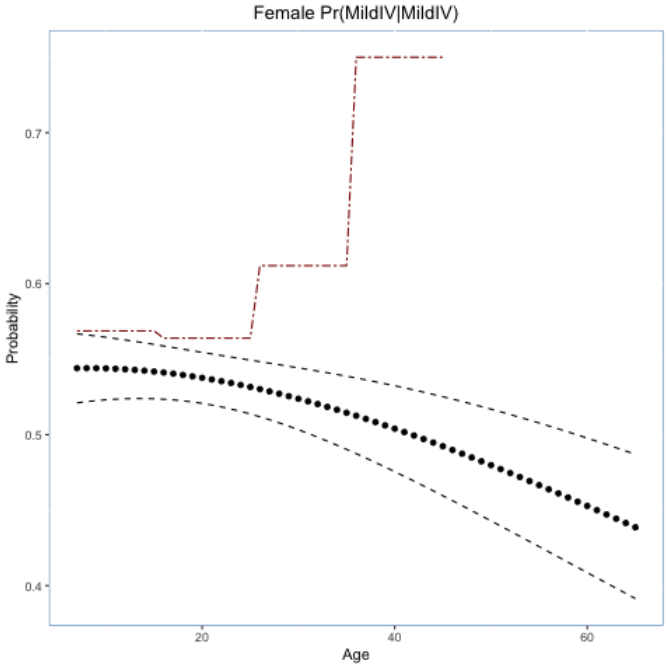

Female Pr(DeadIV|MildNoIV)
Probability
0.03
0.02
0.01
0.00
20
40
60
Age

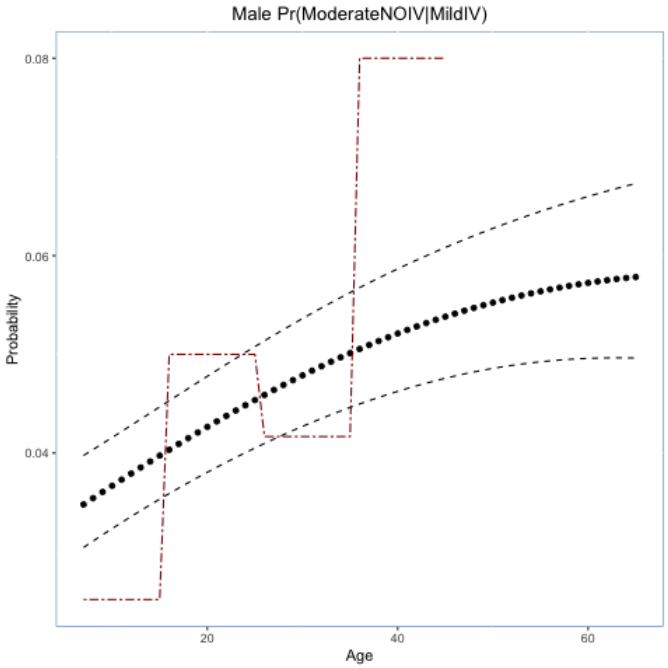
8.2.1.2 Mild IV

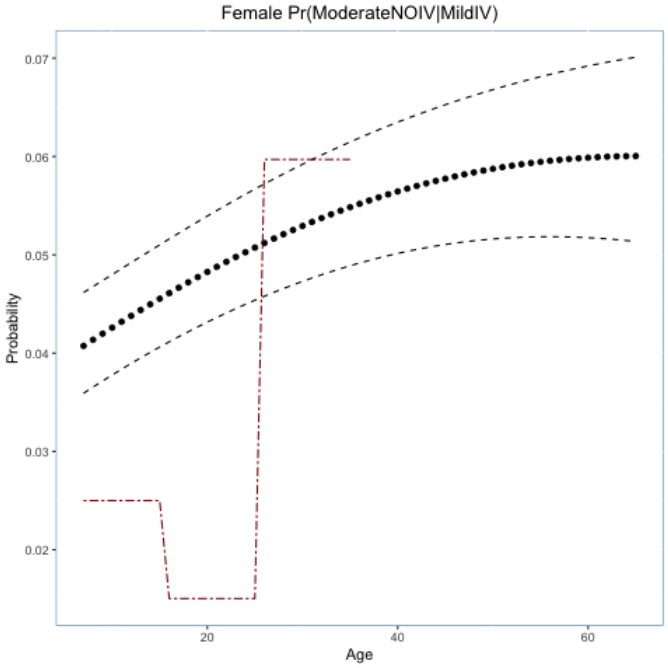

Male Pr(MildNOIV|MildIV)
1.00
0.75
0.50
0.25
Probability
20
40
60
Age

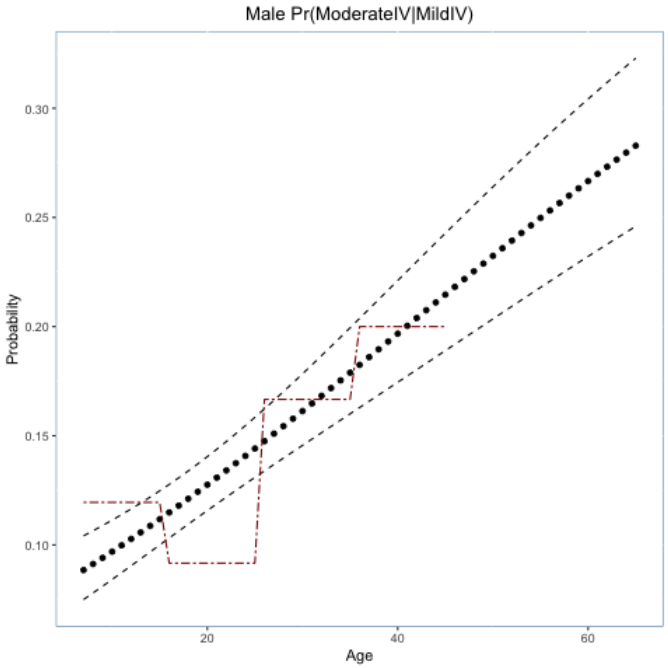

Female Pr(MildNoIV|MildIV)
1.00
0.75
0.50
0.25
Probability
20
40
60
Age

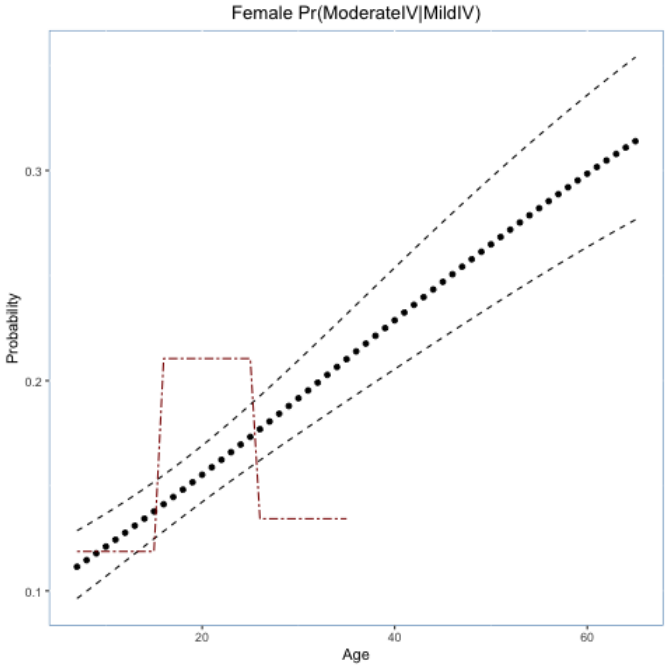

Male Pr(MildIV|MildIV)
Probability
1.0
0.8
0.6
0.4
20
40
60
Age

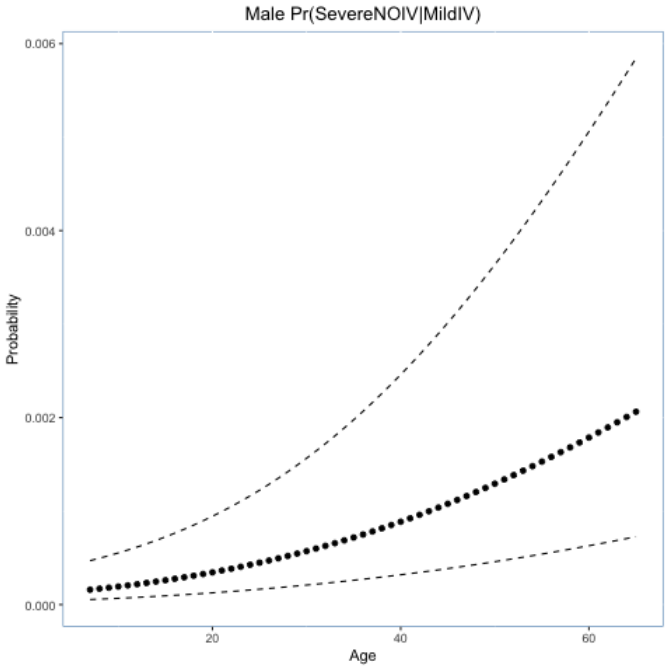

Female Pr(MildIV|MildIV)
Probability
0.7
0.6
0.5
0.4
20
40
60
Age

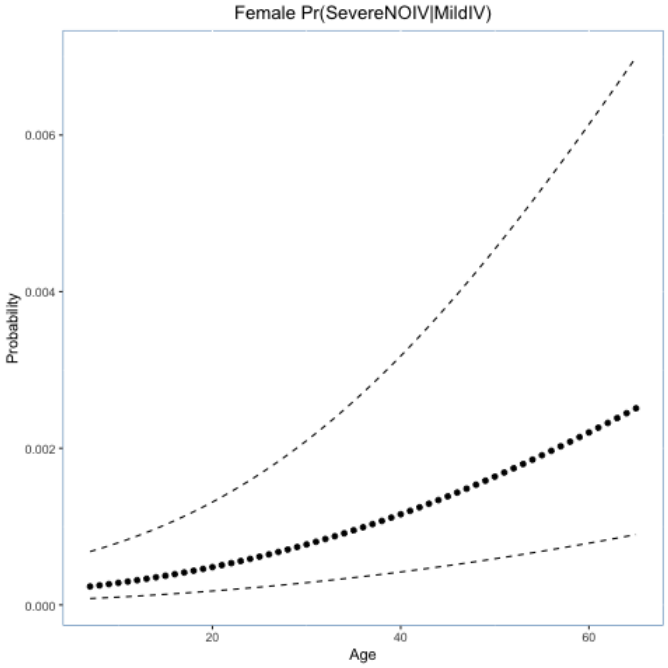

Male Pr(ModerateNOIV|MildIV)
Probability
0.08
0.06
0.04
20
40
60
Age

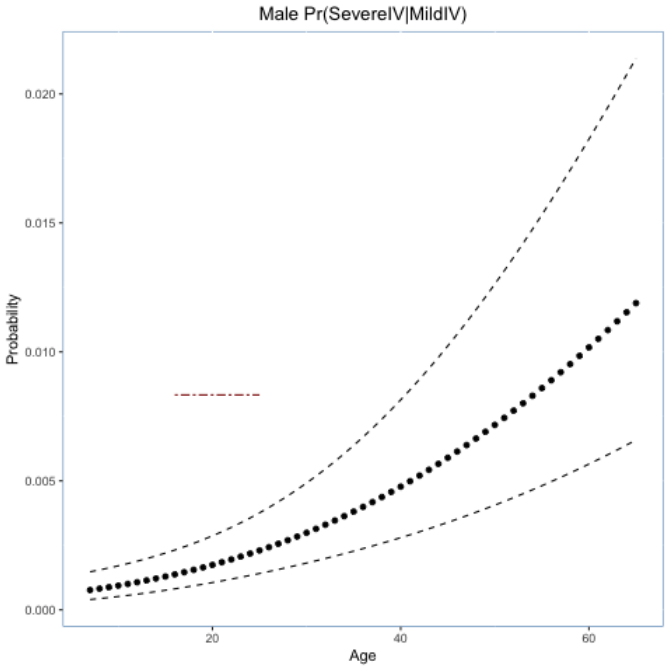

Female Pr(ModerateNOIV|MildIV)
Probability
0.07
0.06
0.05
0.04
0.03
0.02
20
40
60
Age

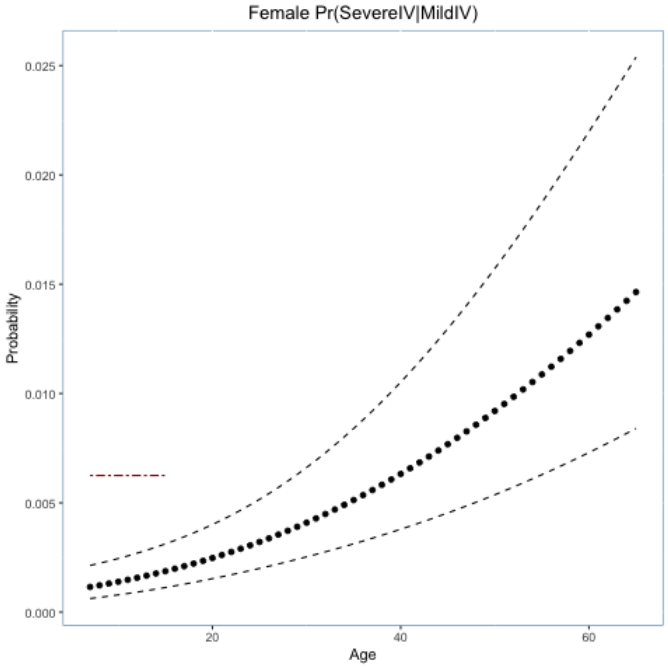

Male Pr(ModerateIV|MildIV)
Probability
0.30
0.25
0.20
0.15
0.10
20
40
60
Age

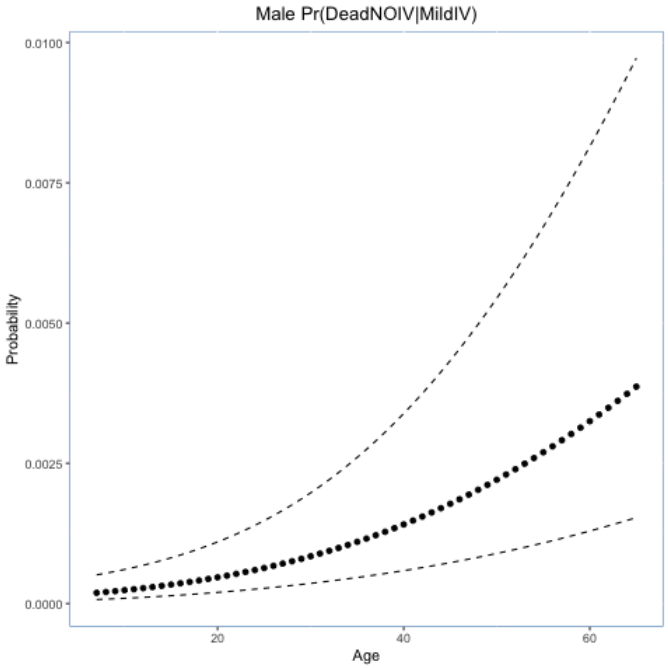

Female Pr(ModerateIV|MildIV)
Probability
0.3
0.2
0.1
20
40
60
Age

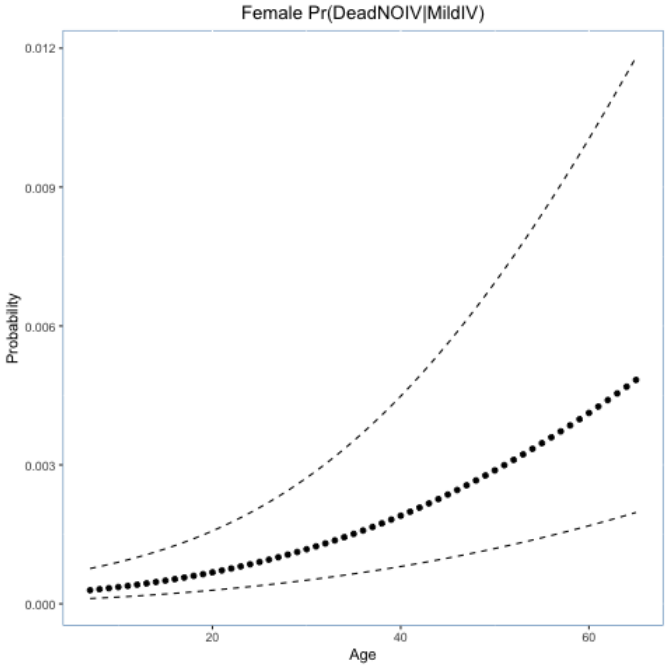

Male Pr(SevereNOIV|MildIV)
Probability
0.006
0.004
0.002
0.000
20
40
60
Age

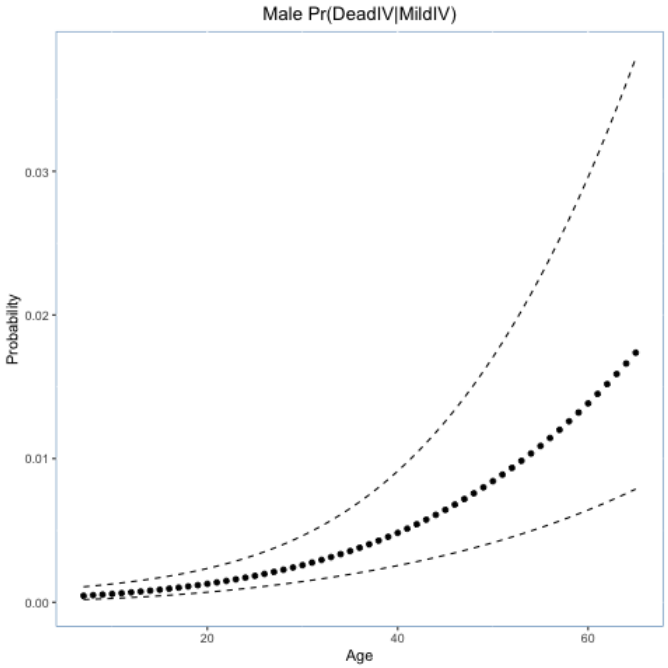

Female Pr(SevereNOIV|MildIV)
Probability
0.006
0.004
0.002
0.000
20
40
60
Age

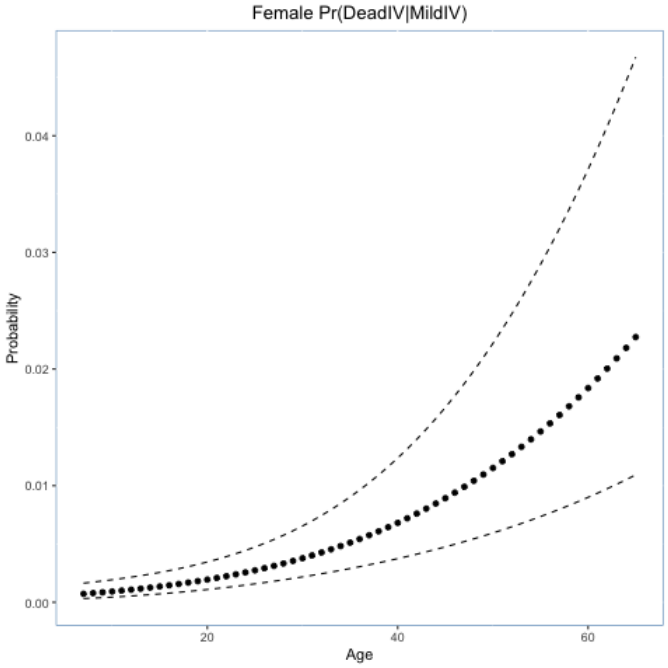

Male Pr(SevereIV|MildIV)
Probability
0.020
0.015
0.010
0.005
0.000
20
40
60
Age


Female Pr(SevereIV|MildIV)
Probability
0.025
0.020
0.015
0.010
0.005
0.000
20
40
60
Age

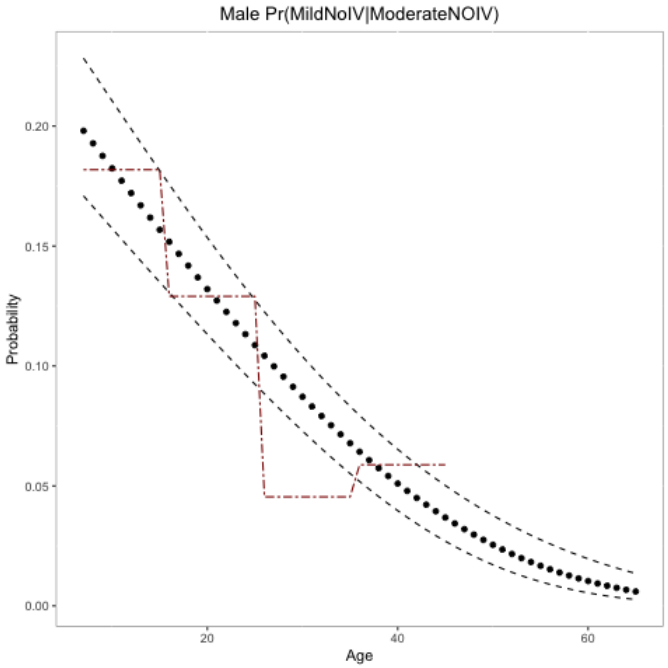

Male Pr(DeadNOIV|MildIV)
0.0100
0.0075
0.0050
0.0025
0.0000
Probability
20
40
60
Age

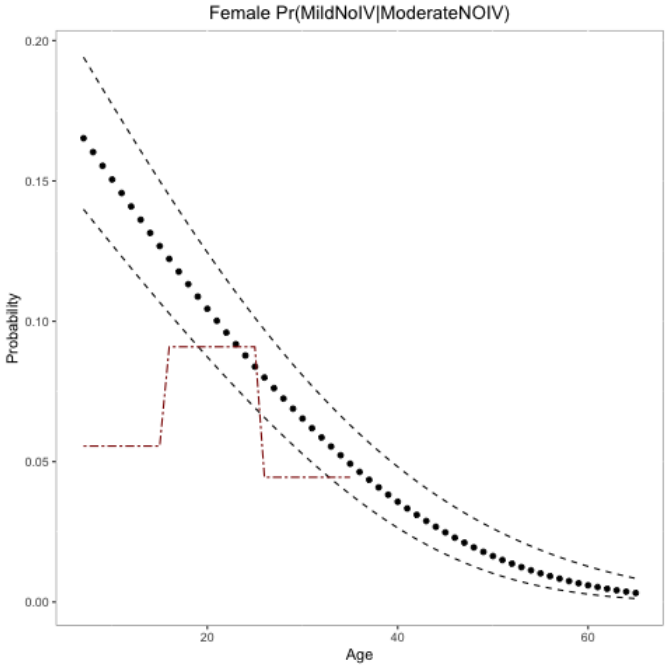

Female Pr(DeadNOIV|MildIV)
0.012
0.009
0.006
0.003
0.000
Probability
20
40
60
Age

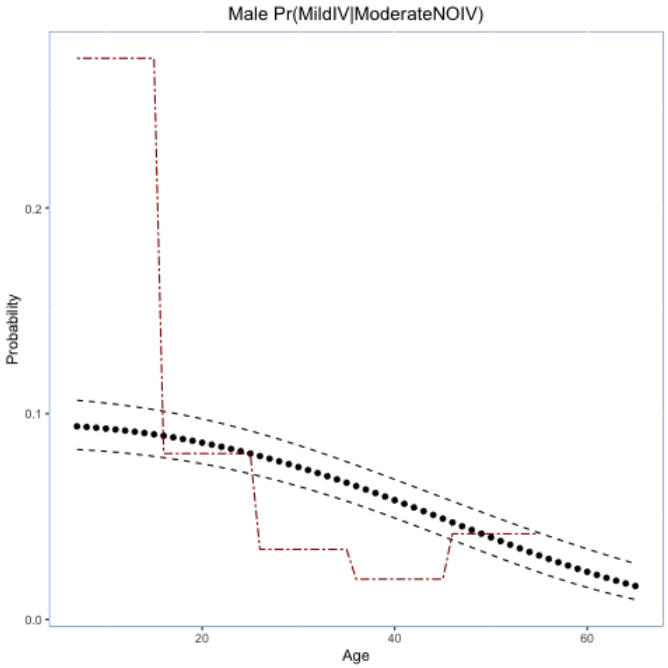

Male Pr(DeadIV|MildIV)
Probability
0.00
0.01
0.02
0.03
20
40
60
Age

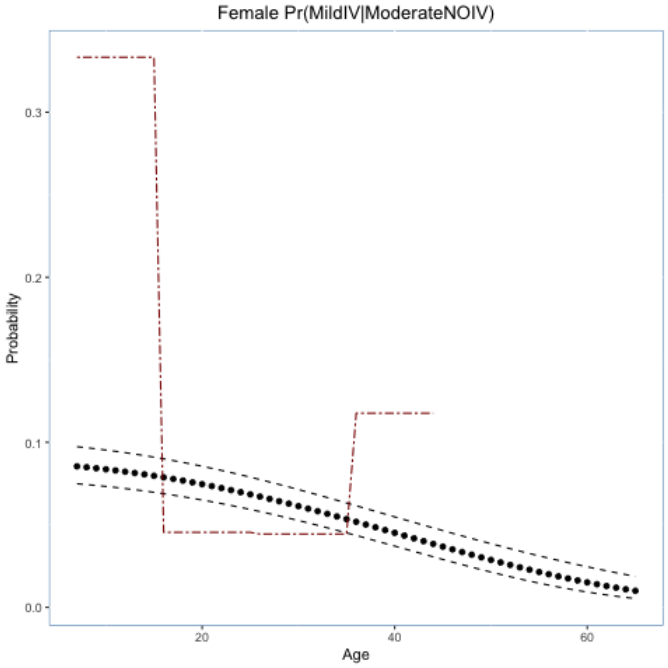

Female Pr(DeadIV|MildIV)
Probability
0.00
0.01
0.02
0.03
0.04
20
40
60
Age

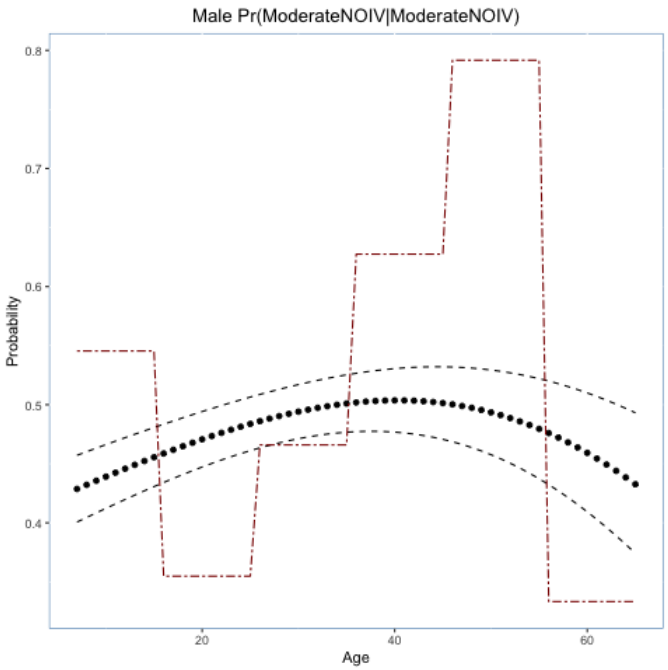
8.2.1.3 Moderate No IV

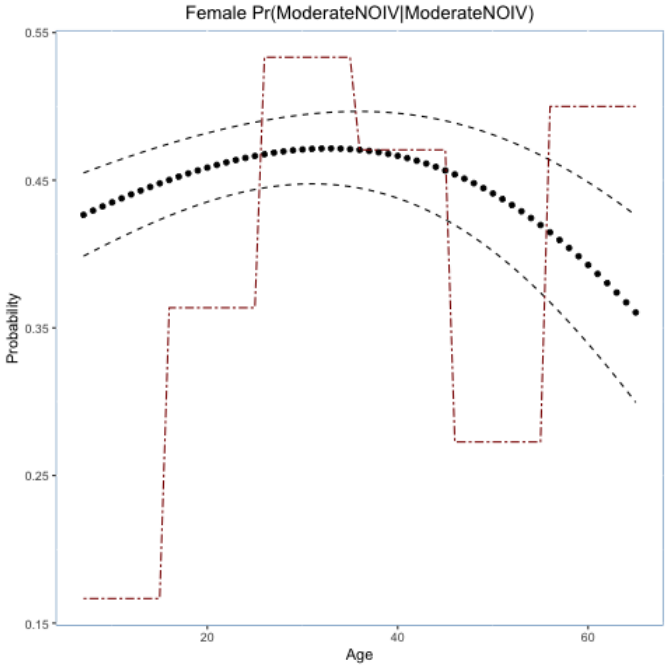


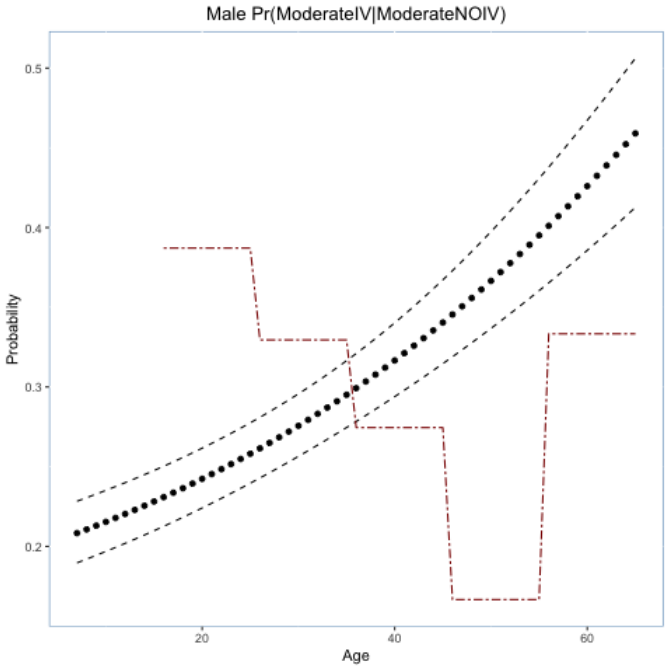


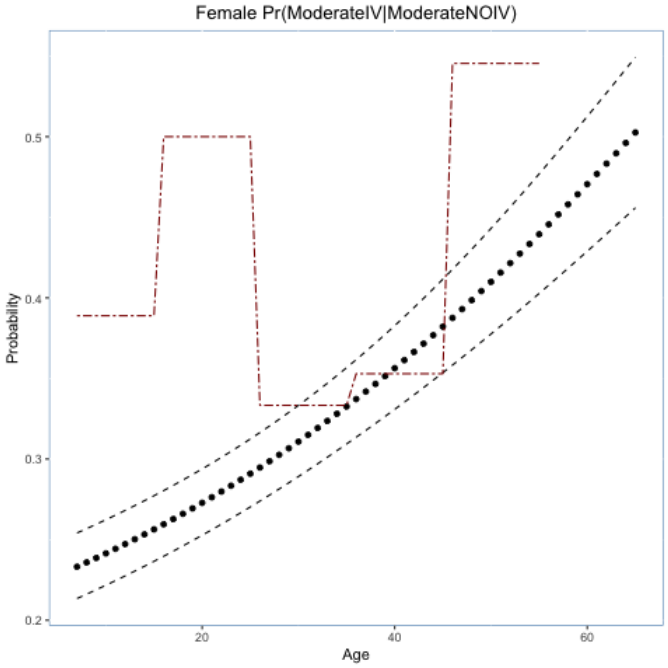

Male Pr(MildIV|ModerateNOIV)
Probability
0.0
0.1
0.2
20
40
60
Age

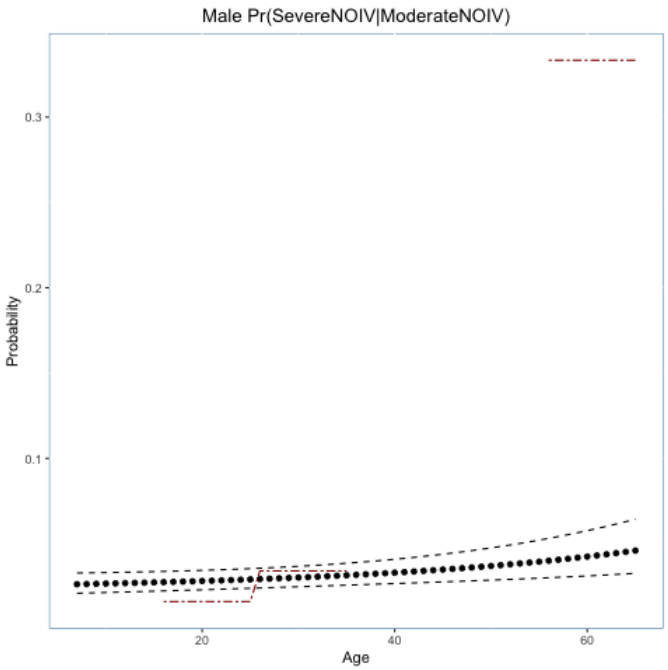

Female Pr(MildIV|ModerateNOIV)
Probability
0.0
0.1
0.2
0.3
20
40
60
Age

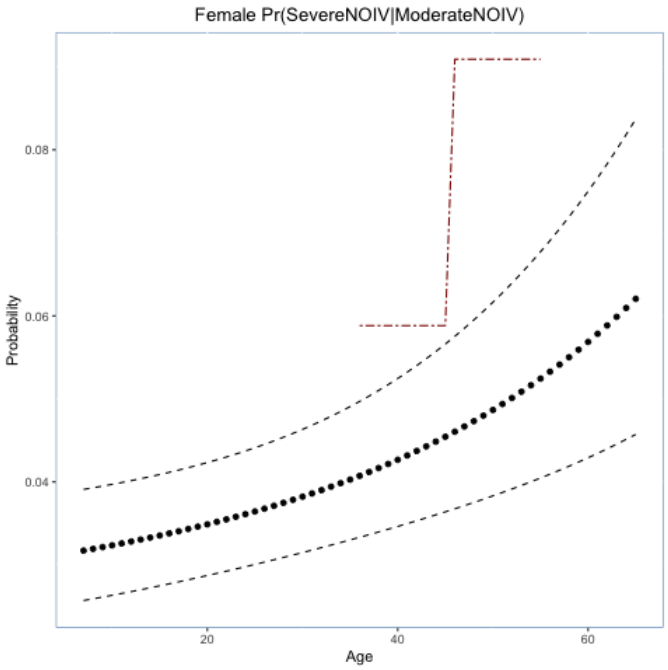

Male Pr(ModerateNOIV|ModerateNOIV)
Probability
0.8
0.7
0.6
0.5
0.4
20
40
60
Age

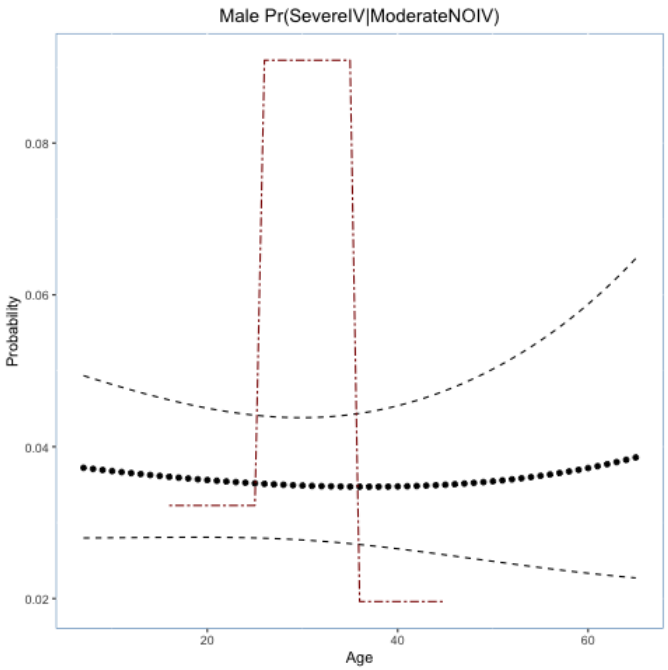

Female Pr(ModerateNOIV|ModerateNOIV)
Probability
0.55
0.45
0.35
0.25
0.15
20
40
60
Age

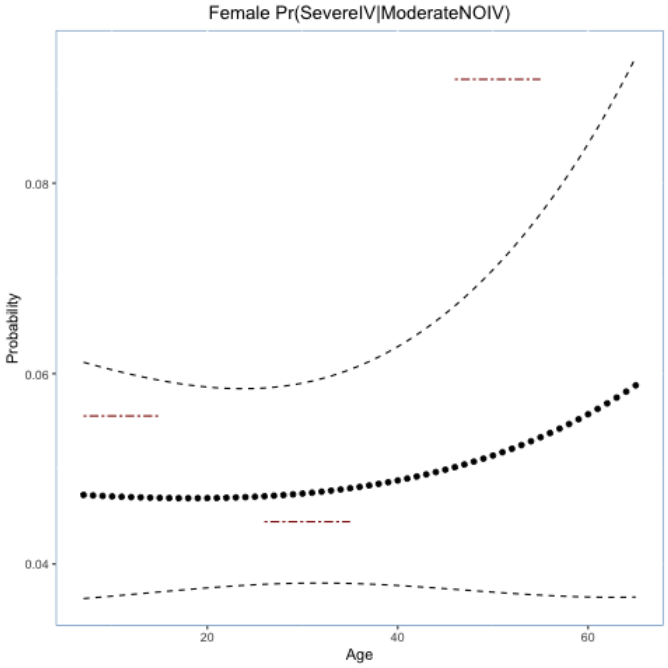

Male Pr(ModerateIV|ModerateNOIV)
Probability
0.5
0.4
0.3
0.2
20
40
60
Age

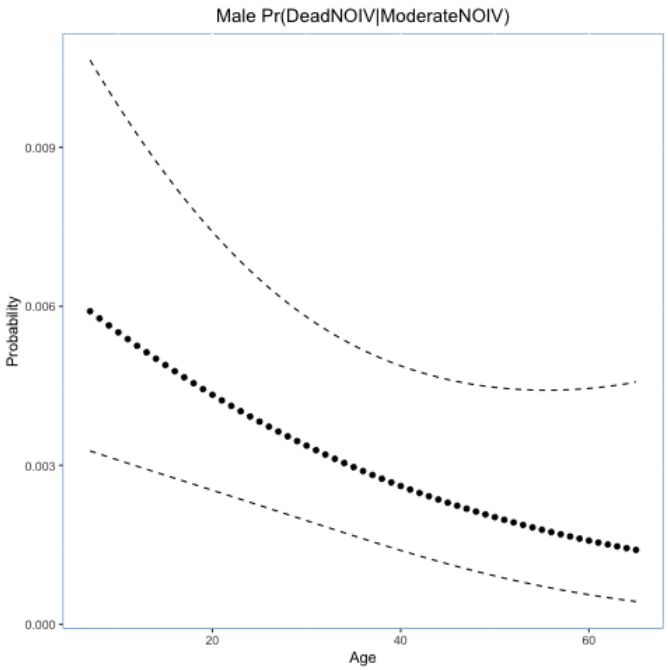

Female Pr(ModerateIV|ModerateNOIV)
Probability
0.5
0.4
0.3
0.2
20
40
60
Age

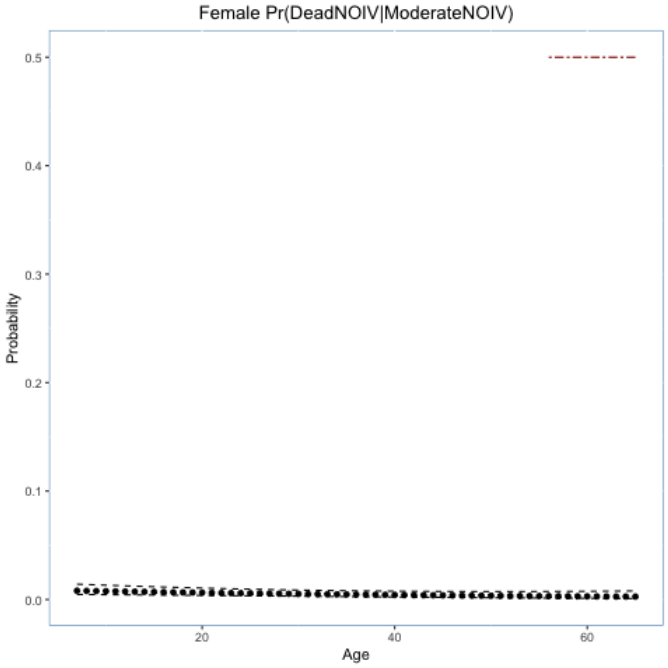

Male Pr(SevereNOIV|ModerateNOIV)
Probability
0.3
0.2
0.1
20
40
60
Age

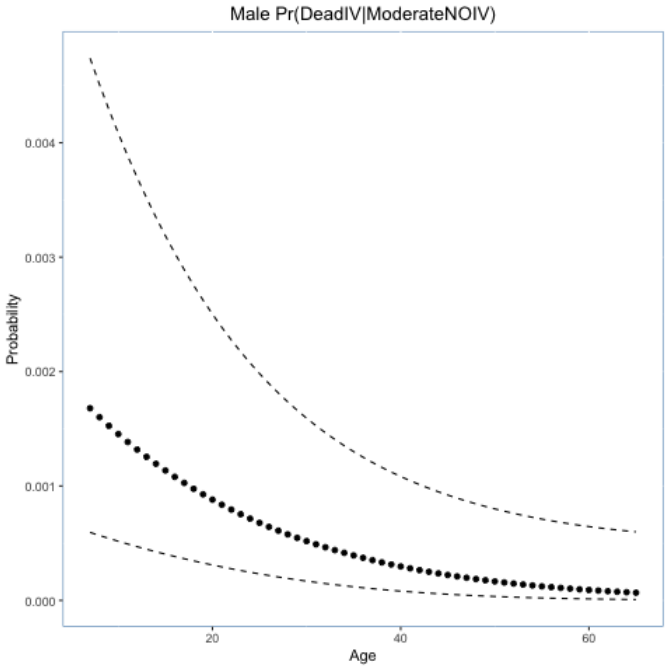

Female Pr(SevereNOIV|ModerateNOIV)
Probability
0.08
0.06
0.04
20
40
60
Age

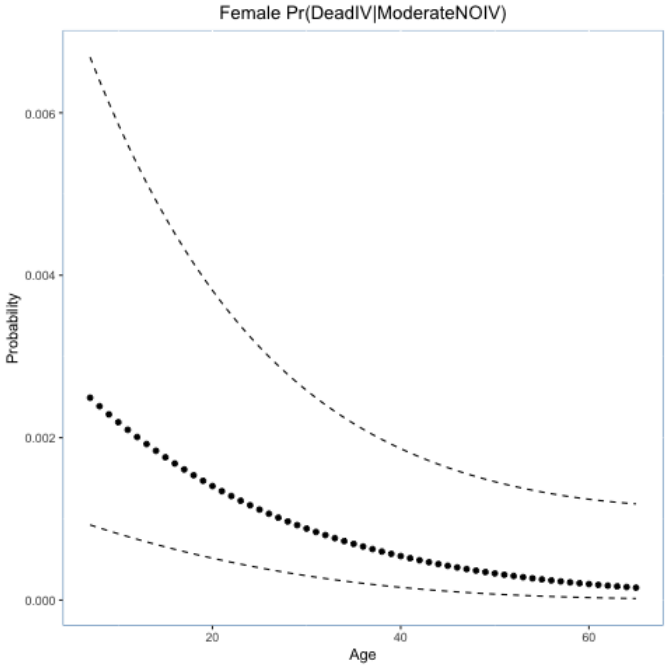

Male Pr(SevereIV|ModerateNOIV)
Probability
0.08
0.06
0.04
0.02
20
40
60
Age


Female Pr(SevereIV|ModerateNOIV)
Probability
0.08
0.06
0.04
20
40
60
Age

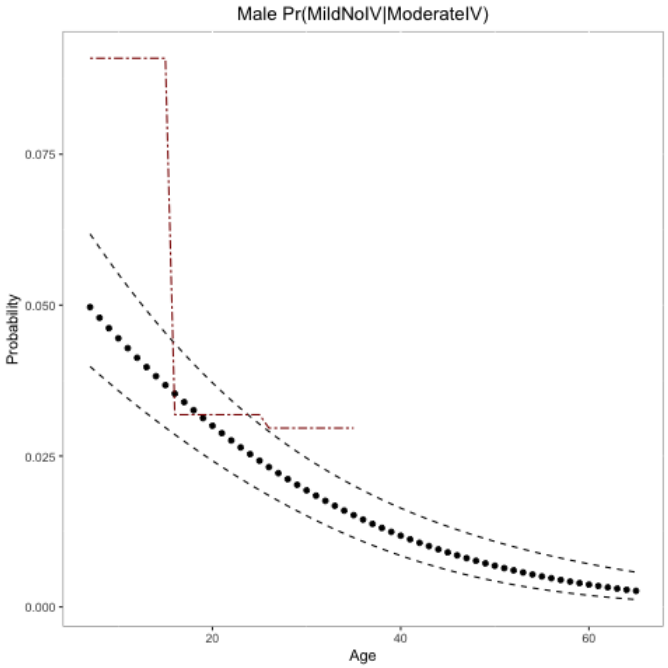

Male Pr(DeadNOIV|ModerateNOIV)
Probability
0.009
0.006
0.003
0.000
20
40
60
Age

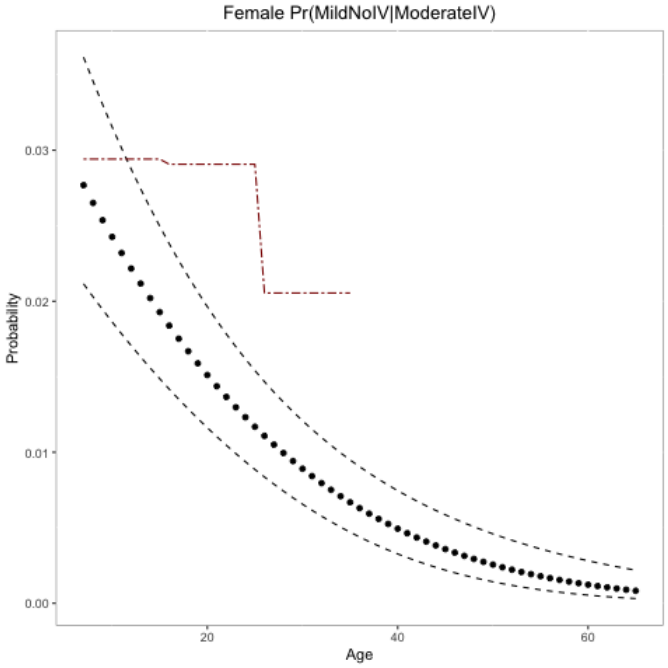

Female Pr(DeadNOIV|ModerateNOIV)
Probability
0.5
0.4
0.3
0.2
0.1
0.0
20
40
60
Age

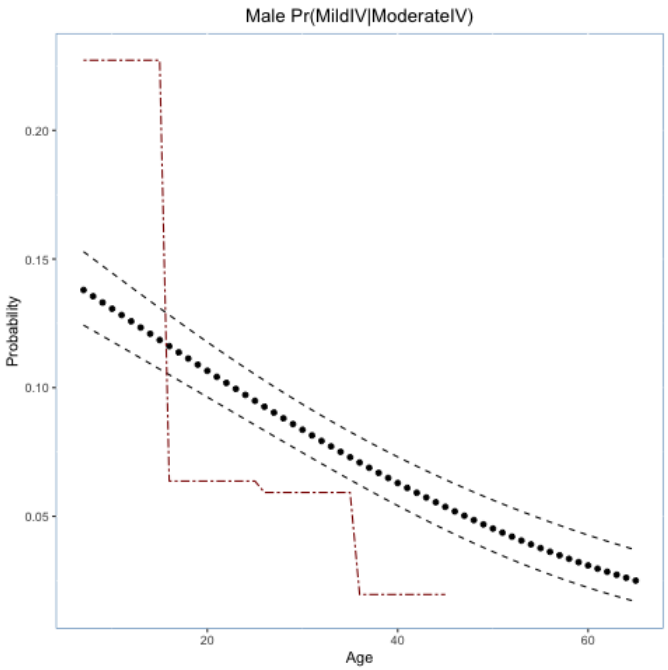

Male Pr(DeadIV|ModerateNOIV)
Probability
0.004
0.003
0.002
0.001
0.000
20
40
60
Age

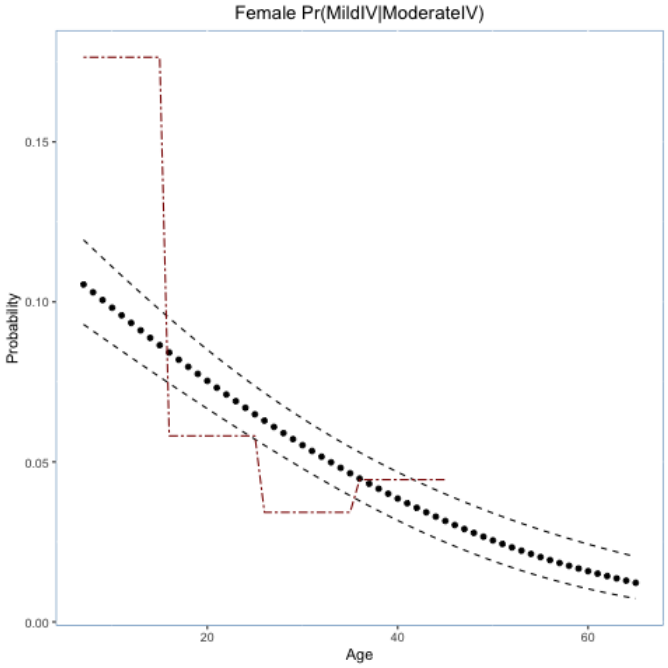

Female Pr(DeadIV|ModerateNOIV)
Probability
0.006
0.004
0.002
0.000
20
40
60
Age

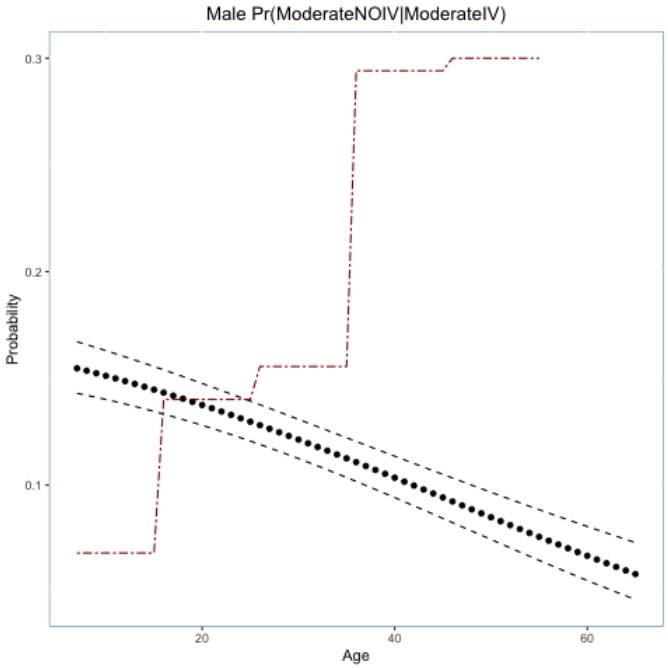
8.2.1.4 Moderate IV

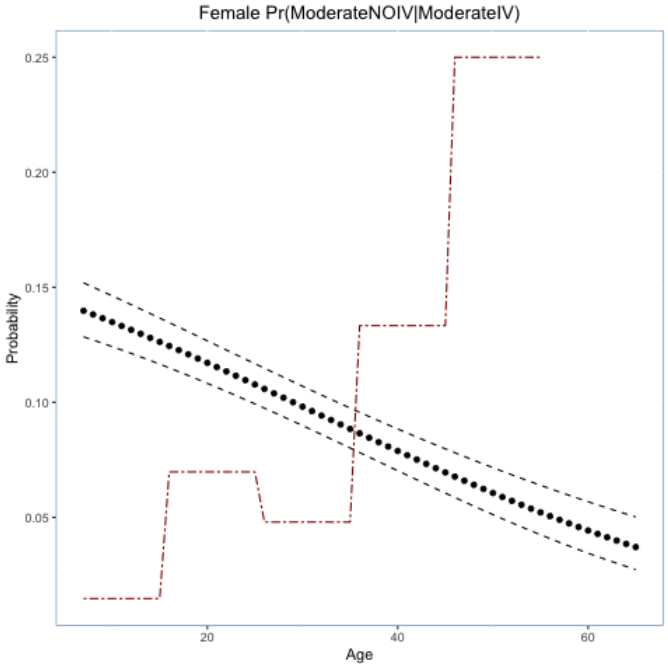


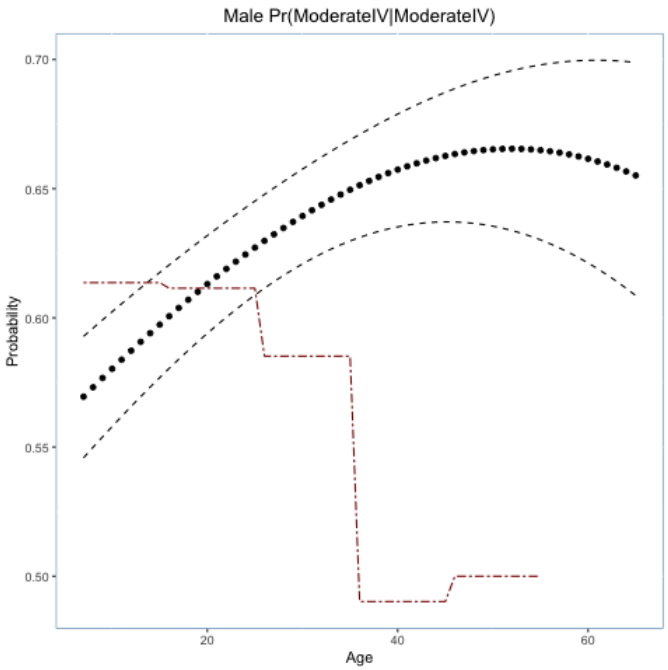


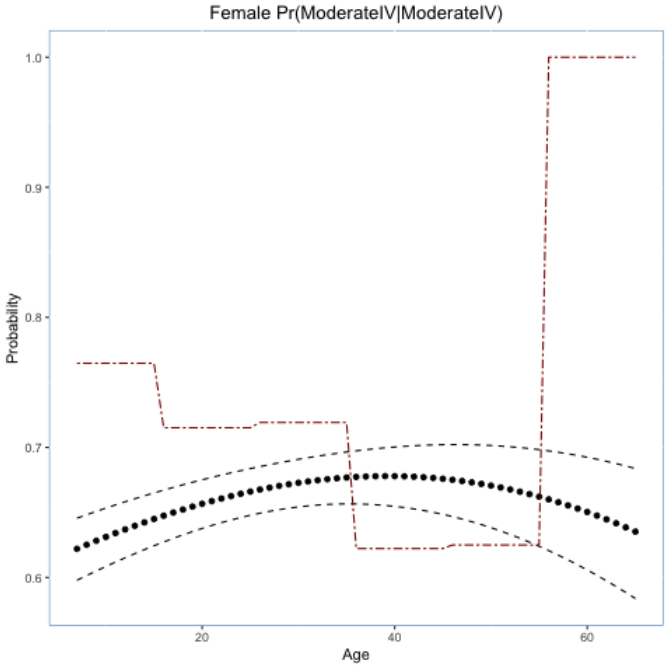

Male Pr(MildIV|ModerateIV)
Probability
0.20
0.15
0.10
0.05
20
40
60
Age

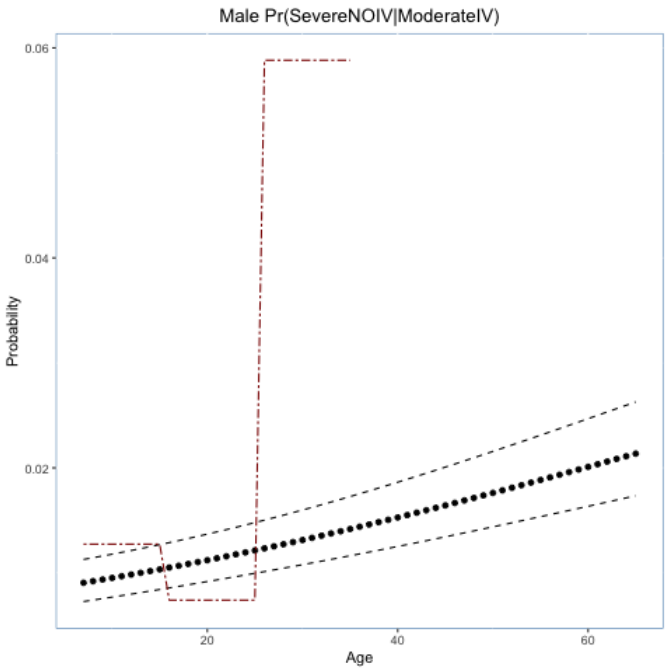

Female Pr(MildIV|ModerateIV)
Probability
0.15
0.10
0.05
0.00
20
40
60
Age

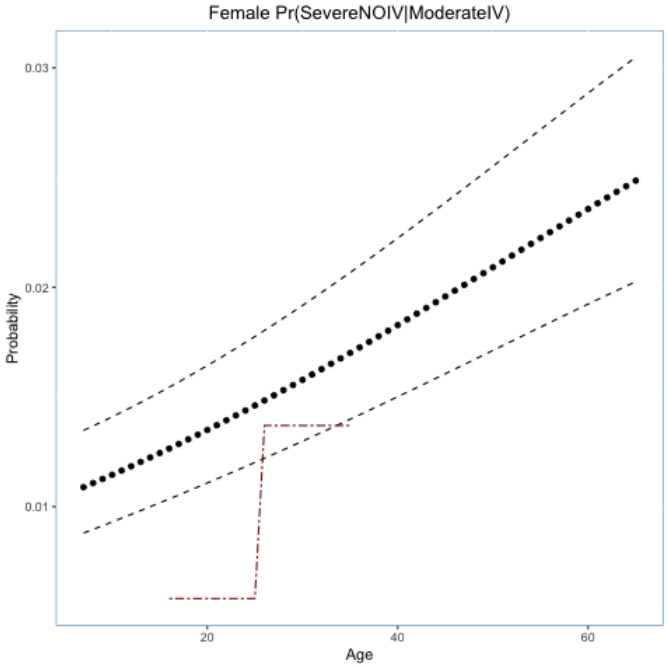

Male Pr(ModerateNOIV|ModerateIV)
Probability
0.3
0.2
0.1
20
40
60
Age

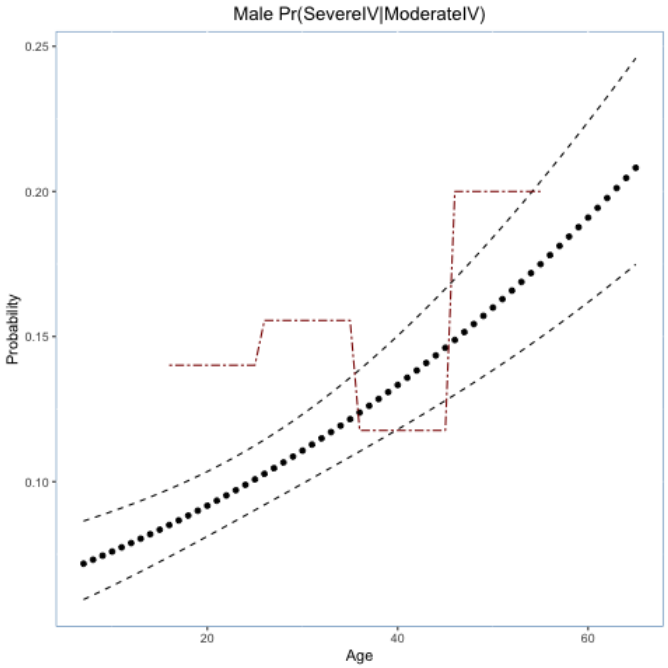

Female Pr(ModerateNOIV|ModerateIV)
Probability
0.25
0.20
0.15
0.10
0.05
20
40
60
Age

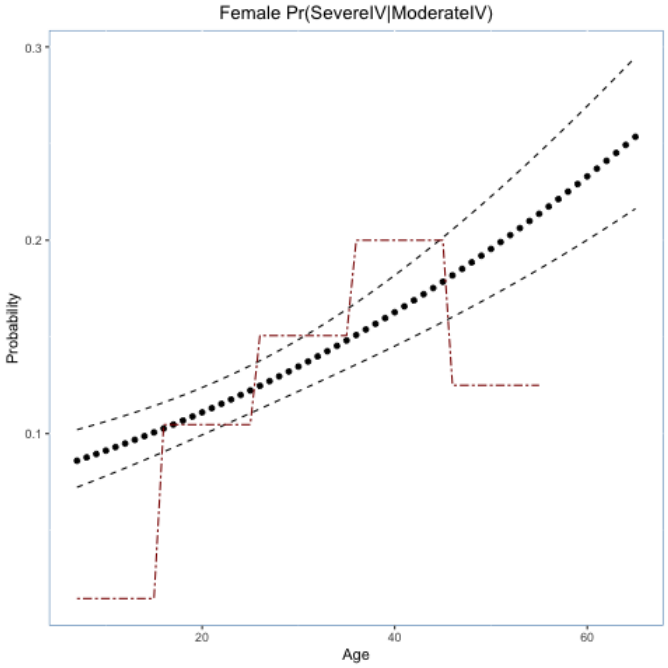

Male Pr(ModerateIV|ModerateIV)
Probability
0.70
0.65
0.60
0.55
0.50
20
40
60
Age

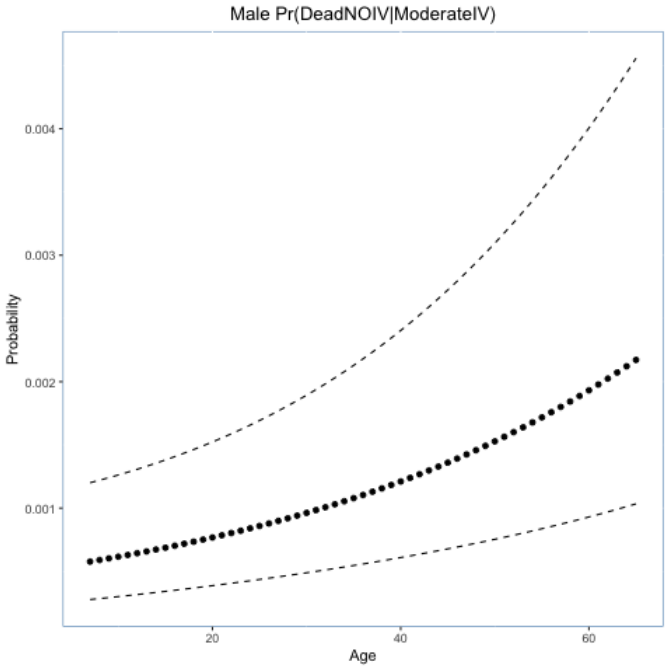

Female Pr(ModerateIV|ModerateIV)
Probability
1.0
0.9
0.8
0.7
0.6
20
40
60
Age

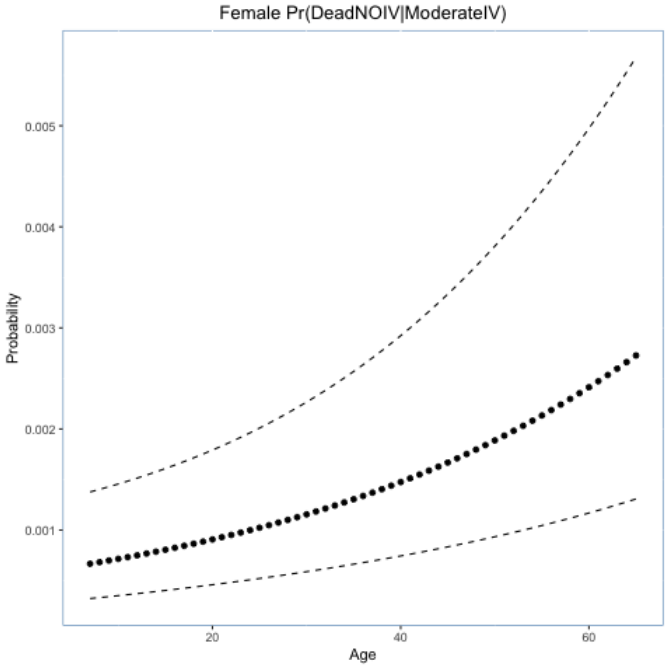

Male Pr(SevereNOIV|ModerateIV)
0.06
0.04
0.02
Probability
20
40
60
Age

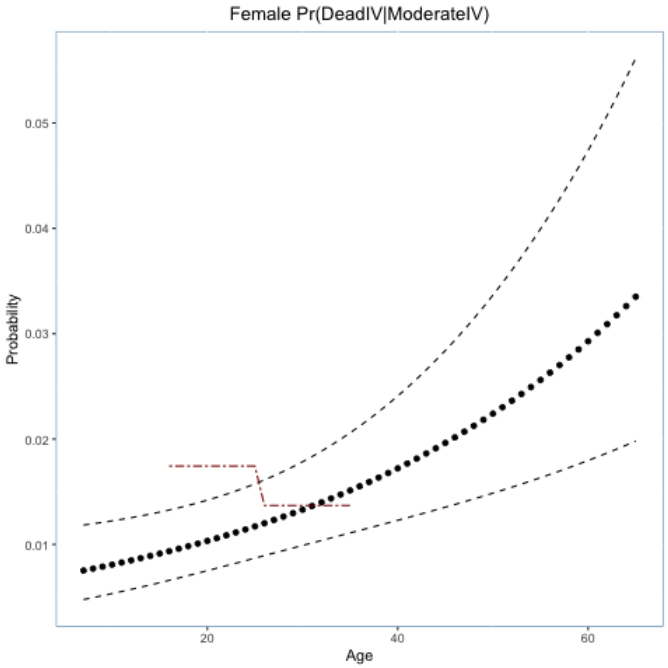

Female Pr(SevereNOIV|ModerateIV)
0.03
0.02
0.01
Probability
20
40
60
Age

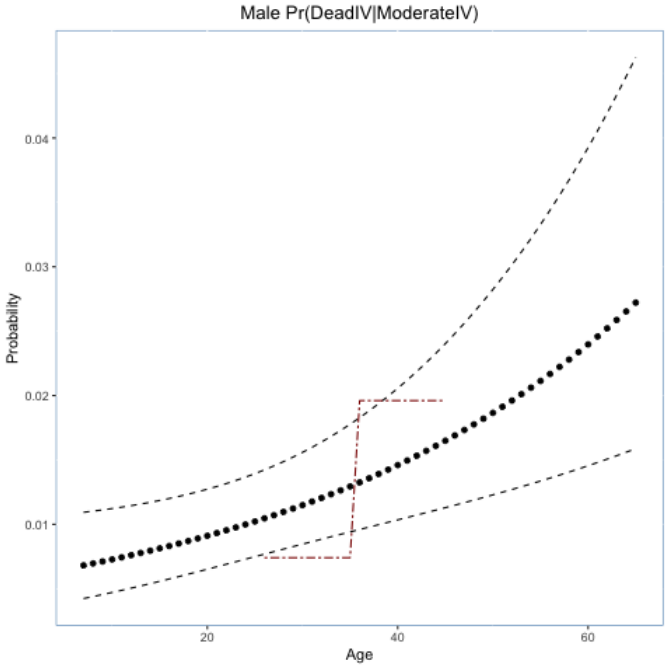

Male Pr(SevereIV|ModerateIV)
Probability
0.25
0.20
0.15
0.10
20
40
60
Age


Female Pr(SevereIV|ModerateIV)
Probability
0.3
0.2
0.1
20
40
60
Age

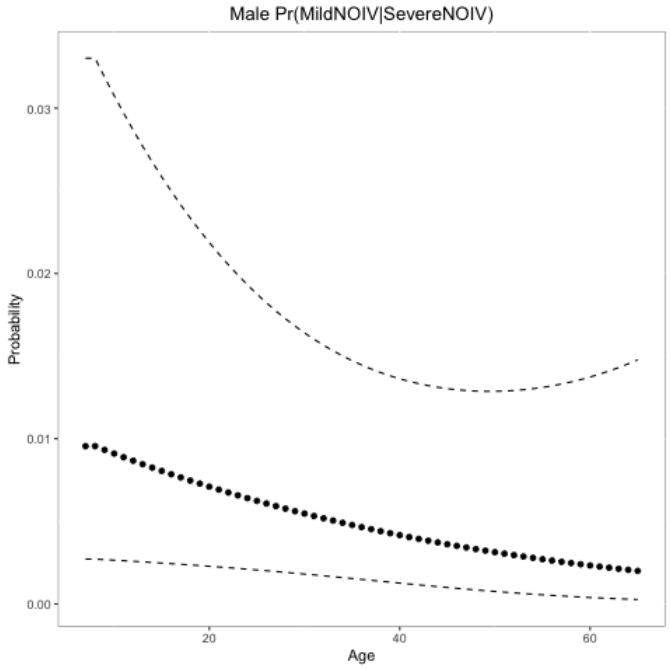

Male Pr(DeadNOIV|ModerateIV)
Probability
0.004
0.003
0.002
0.001
20
40
60
Age

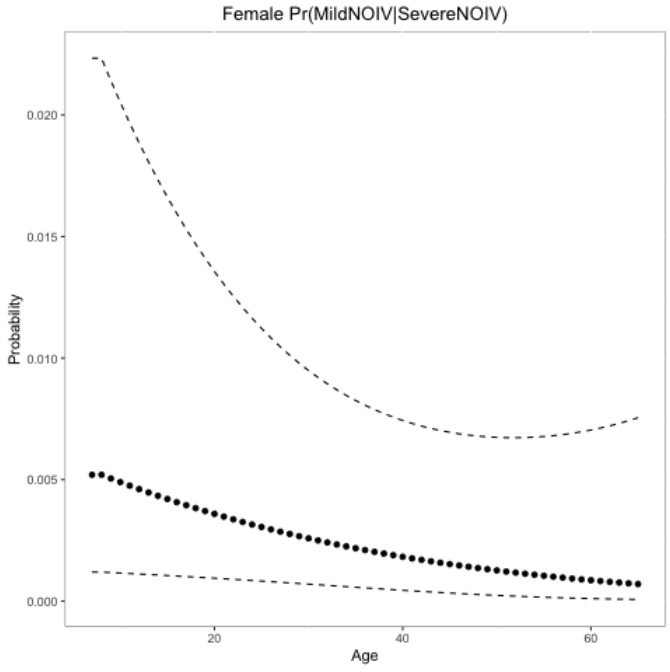

Female Pr(DeadNOIV|ModerateIV)
Probability
0.005
0.004
0.003
0.002
0.001
20
40
60
Age

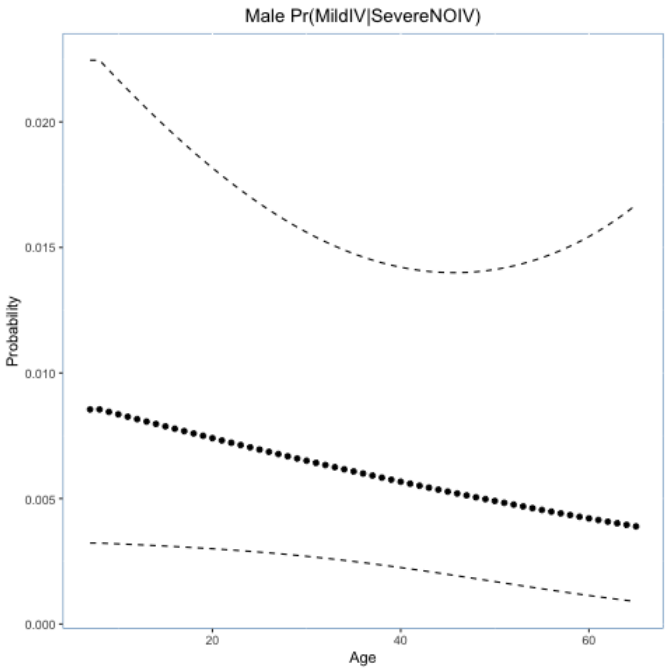

Female Pr(DeadIV|ModerateIV)
Probability
0.05
0.04
0.03
0.02
0.01
20
40
60
Age

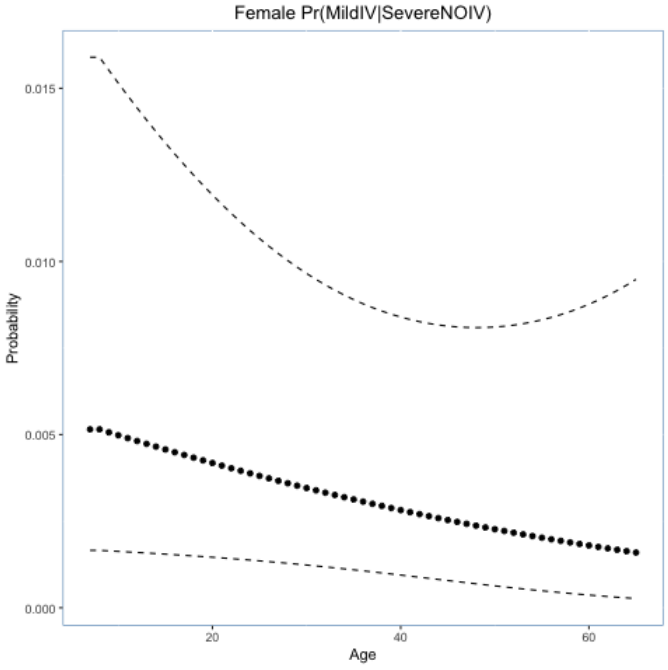

Male Pr(DeadIV|ModerateIV)
Probability
0.04
0.03
0.02
0.01
20
40
60
Age

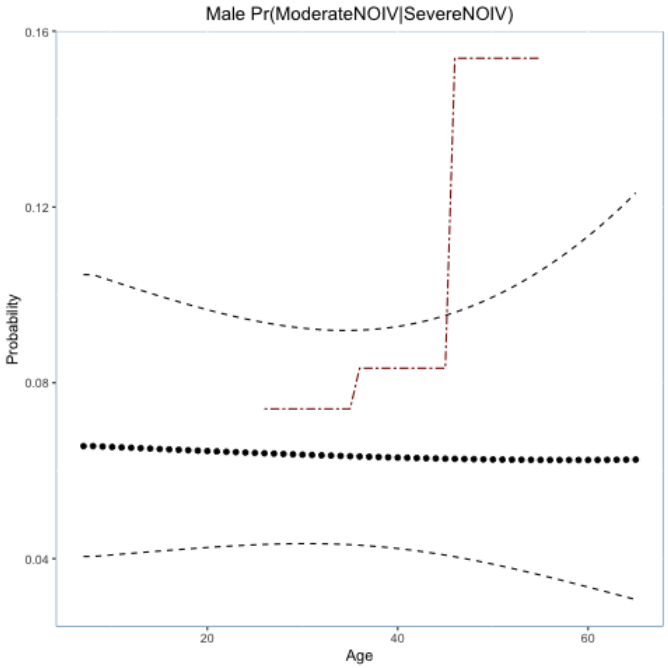
8.2.1.5 Severe No IV

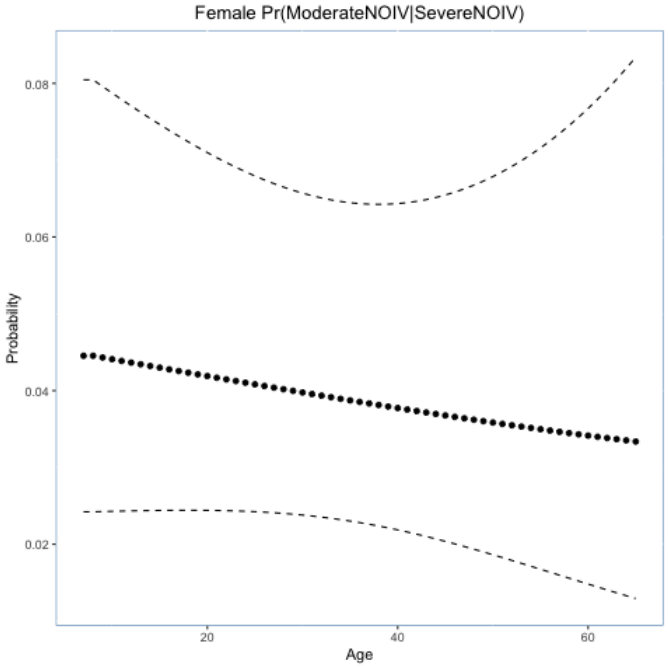


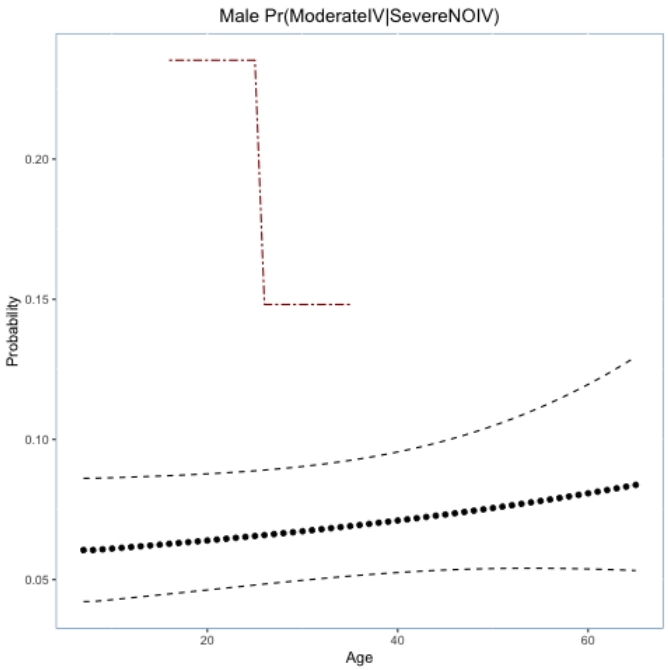


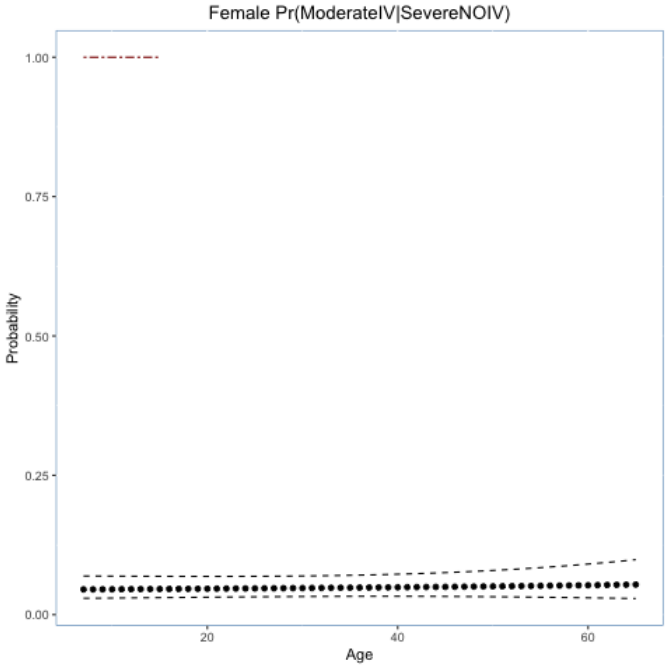

Male Pr(MildIV|SevereNOIV)
Probability
0.020
0.015
0.010
0.005
0.000
20
40
60
Age

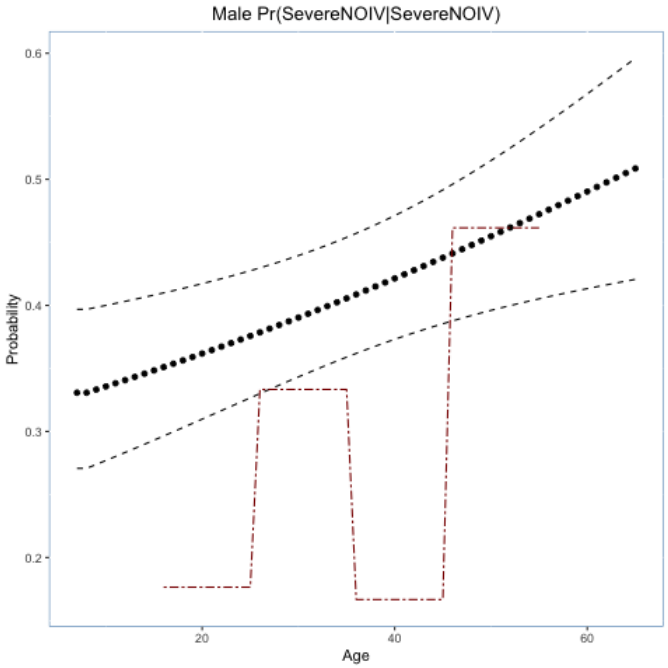

Female Pr(MildIV|SevereNOIV)
Probability
0.015
0.010
0.005
0.000
20
40
60
Age

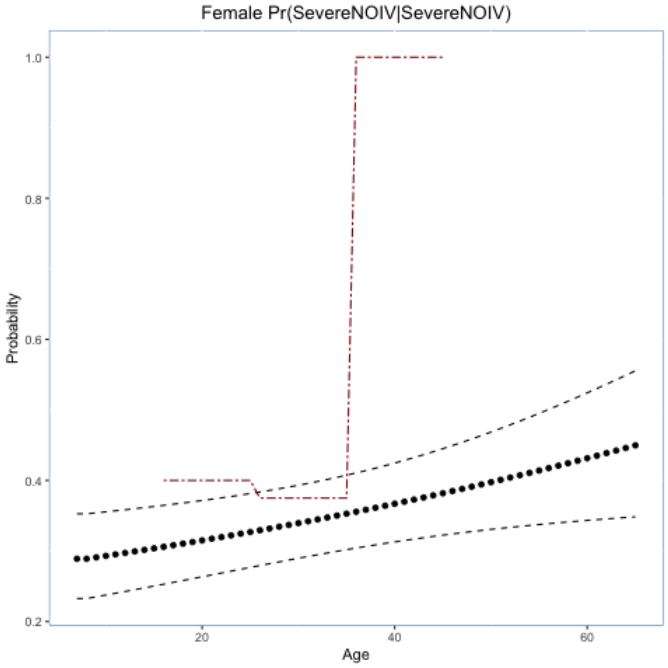

Male Pr(ModerateNOIV|SevereNOIV)
0.16
0.12
0.08
0.04
Probability
20
40
60
Age

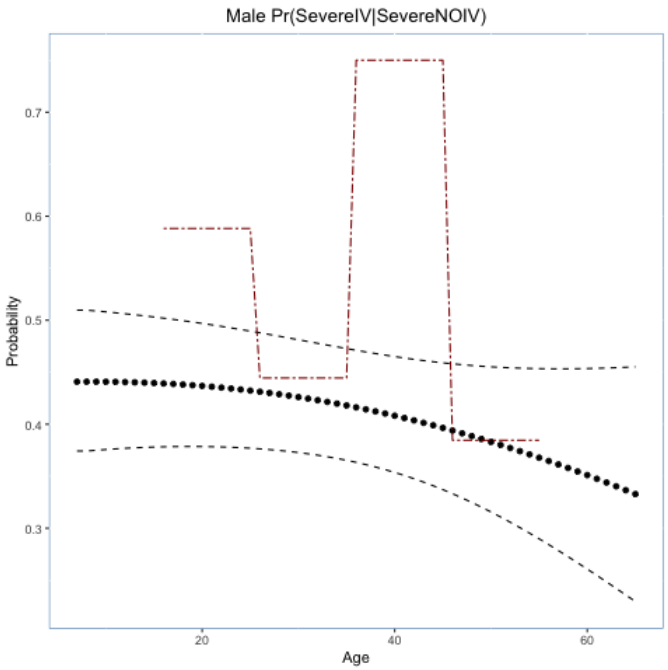

Female Pr(ModerateNOIV|SevereNOIV)
0.08
0.06
0.04
0.02
Probability
20
40
60
Age

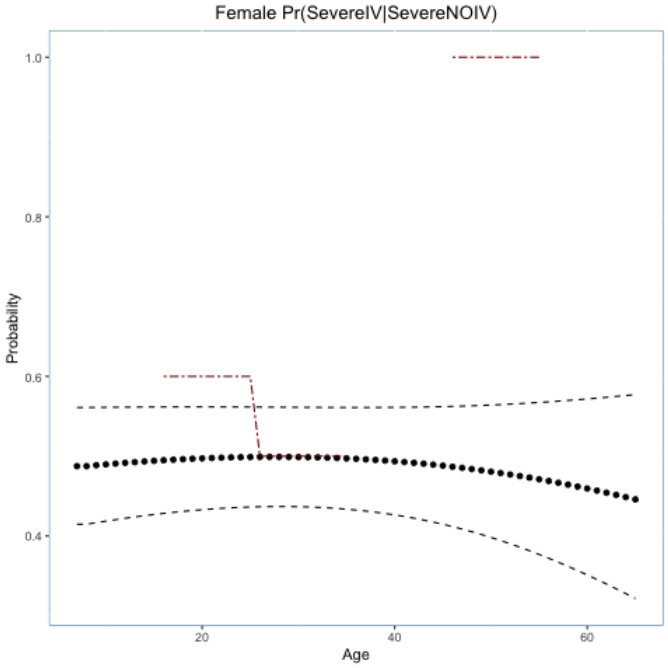

Male Pr(ModerateIV|SevereNOIV)
Probability
0.20
0.15
0.10
0.05
20
40
60
Age

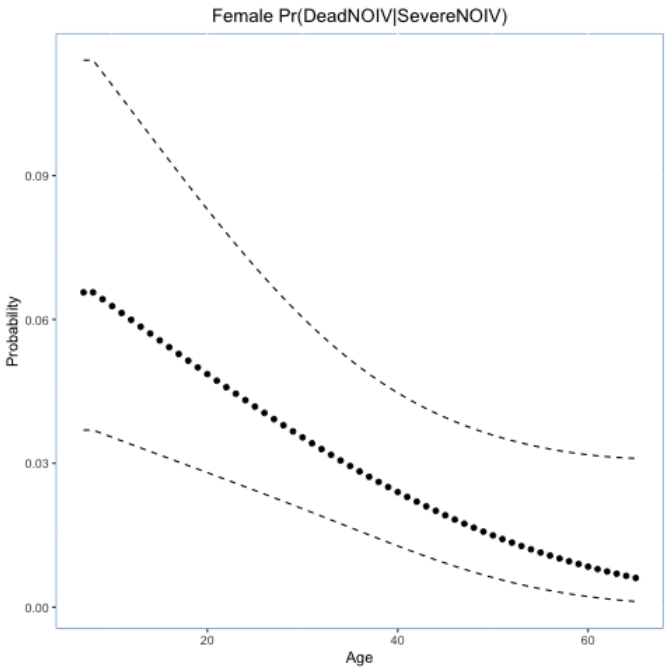

Female Pr(ModerateIV|SevereNOIV)
Probability
1.00
0.75
0.50
0.25
0.00
20
40
60
Age

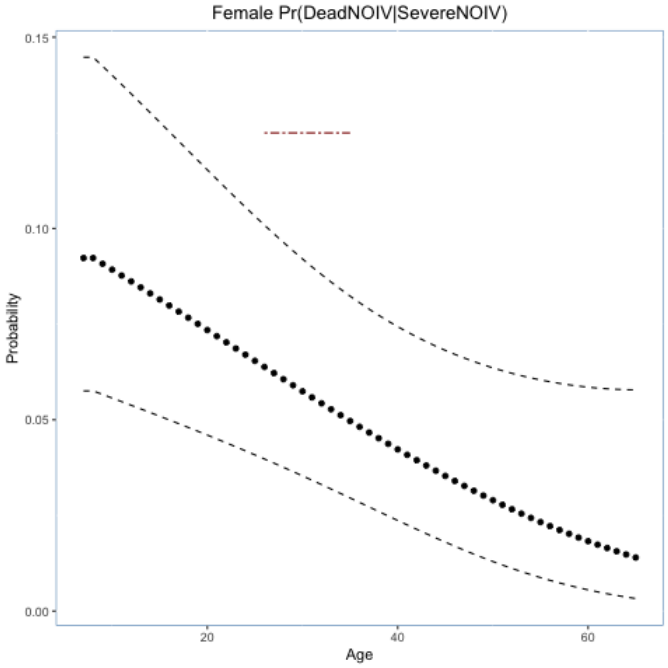

Male Pr(SevereNOIV|SevereNOIV)
Probability
0.6
0.5
0.4
0.3
0.2
20
40
60
Age

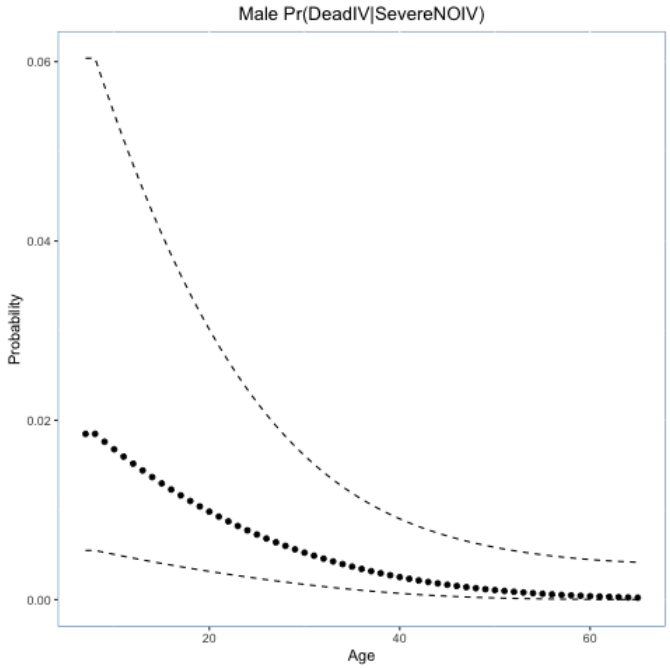

Female Pr(SevereNOIV|SevereNOIV)
Probability
1.0
0.8
0.6
0.4
0.2
20
40
60
Age

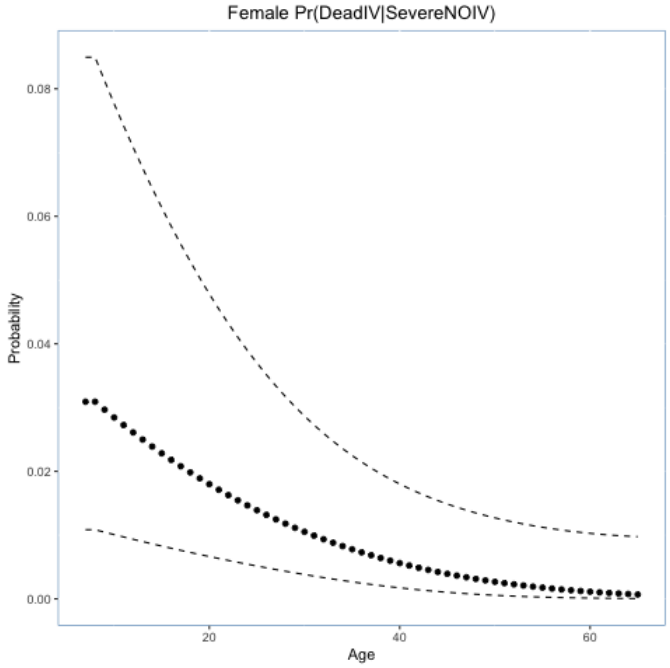

Male Pr(SevereIV|SevereNOIV)
Probability
0.7
0.6
0.5
0.4
0.3
20
40
60
Age


Female Pr(SevereIV|SevereNOIV)
Probability
1.0
0.8
0.6
0.4
20
40
60
Age

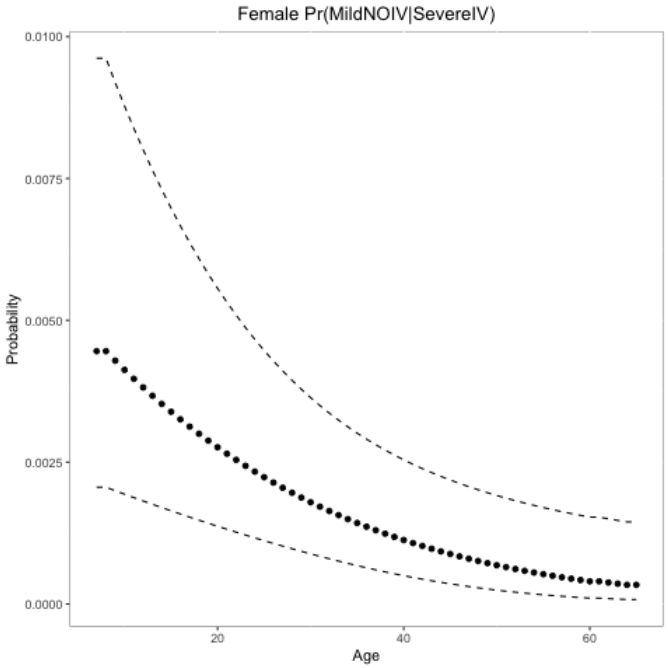

Female Pr(DeadNOIV|SevereNOIV)
Probability
0.09
0.06
0.03
0.00
20
40
60
Age

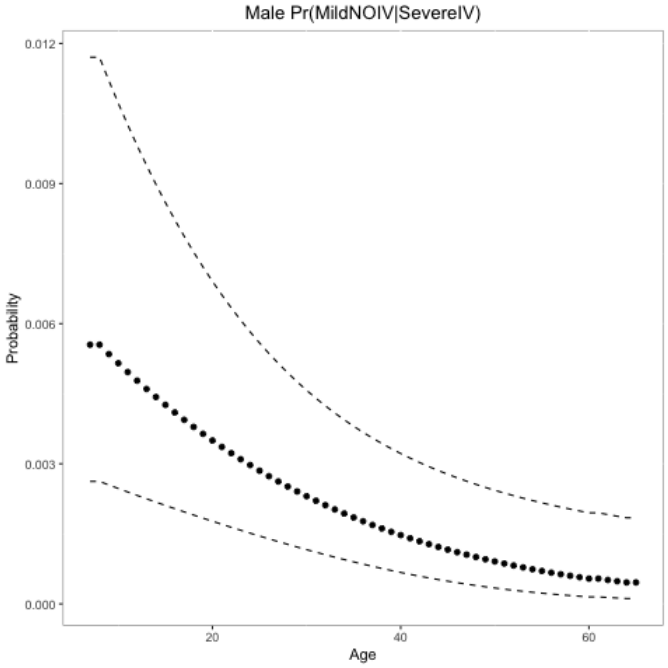

Female Pr(DeadNOIV|SevereNOIV)
Probability
0.15
0.10
0.05
0.00
20
40
60
Age

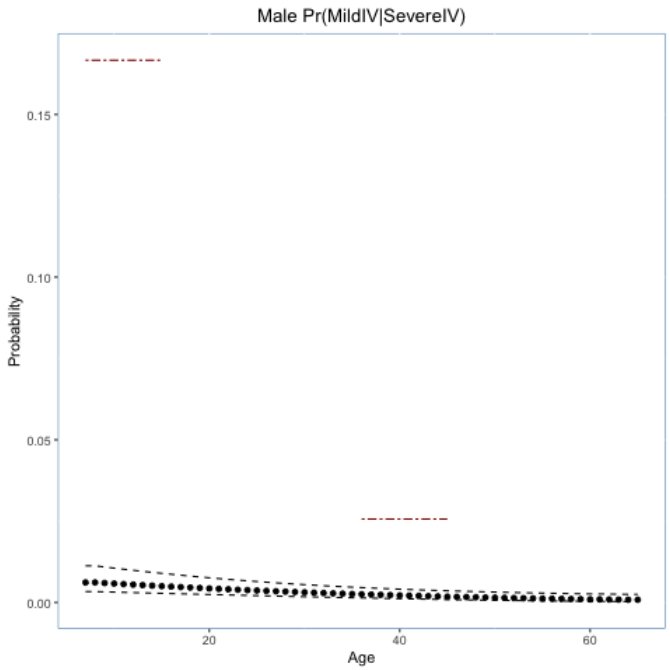

Male Pr(DeadIV|SevereNOIV)
Probability
0.06
0.04
0.02
0.00
20
40
60
Age

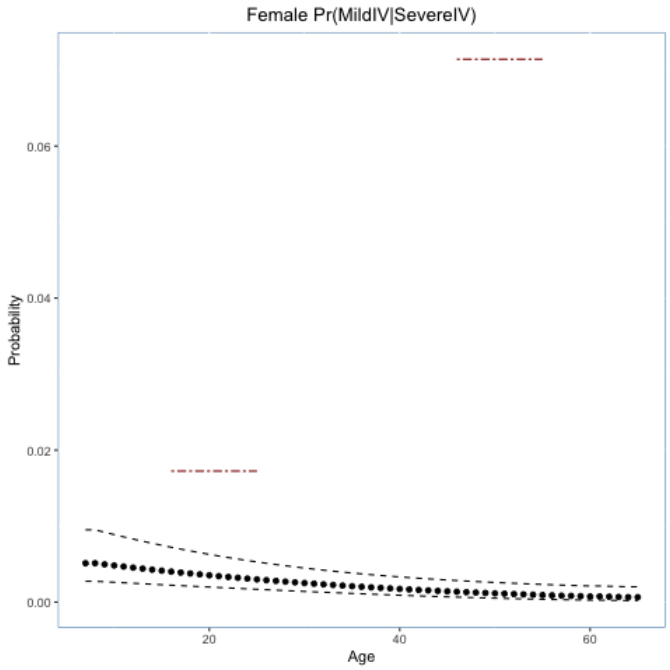

Female Pr(DeadIV|SevereNOIV)
Probability
0.08
0.06
0.04
0.02
0.00
20
40
60
Age

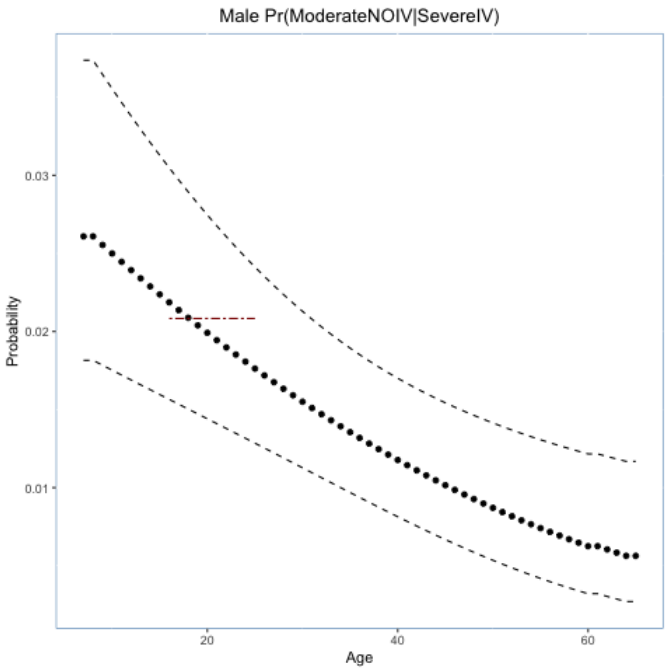
8.2.1.6 Severe IV

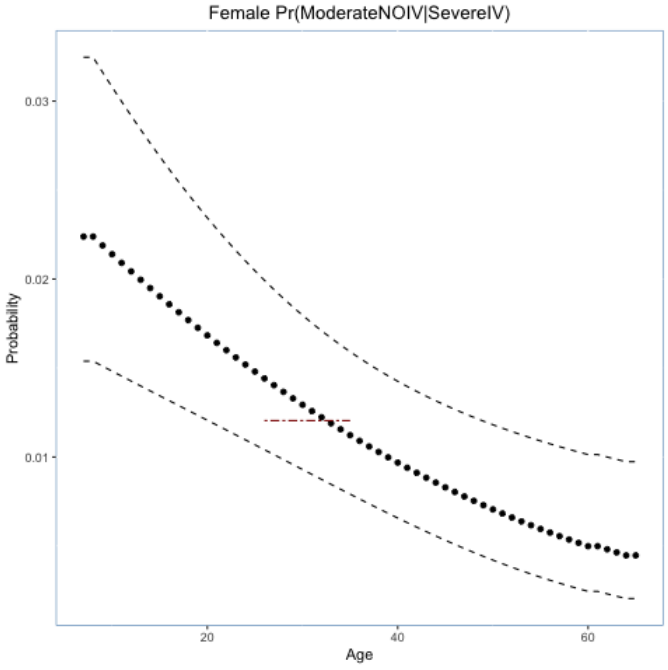


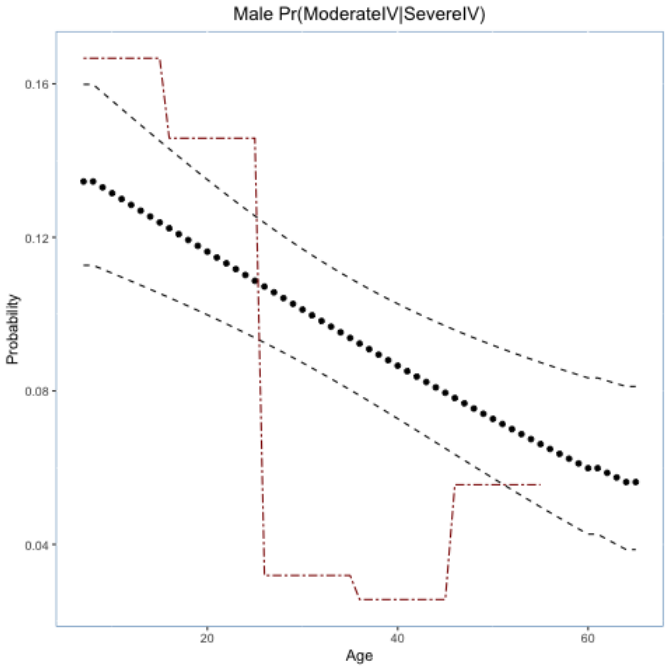


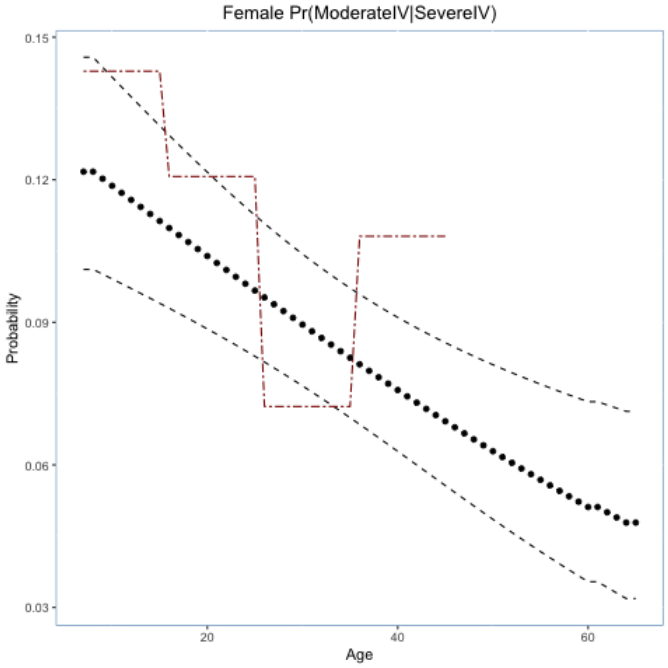

Male Pr(MildIV|SevereIV)
Probability
0.15
0.10
0.05
0.00
20
40
60
Age

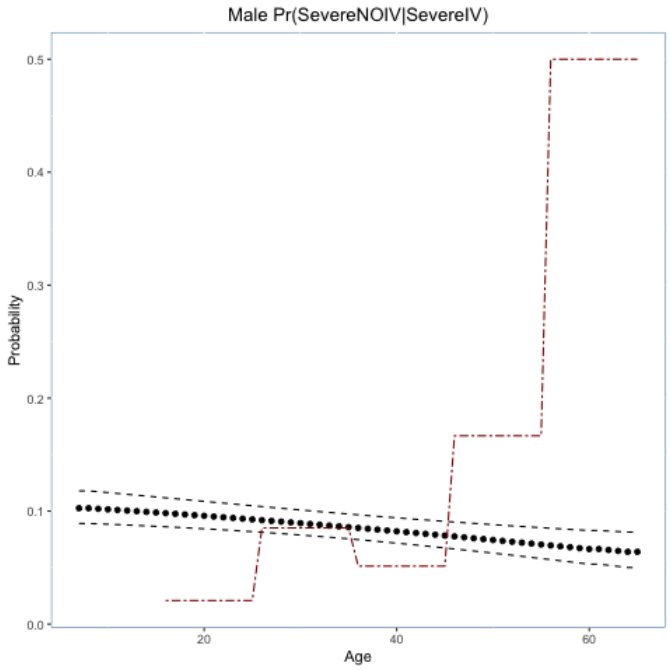

Female Pr(MildIV|SevereIV)
Probability
0.06
0.04
0.02
0.00
20
40
60
Age

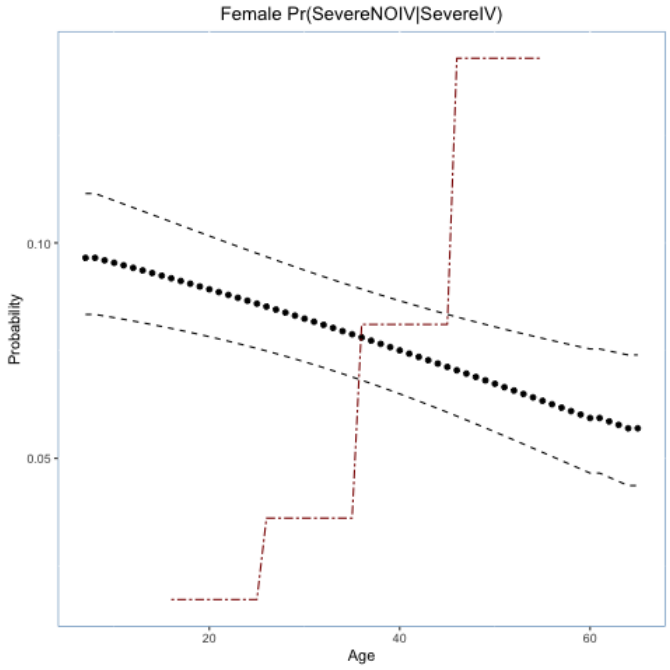

Male Pr(ModerateNOIV|SevereIV)
Probability
0.03
0.02
0.01
20
40
60
Age

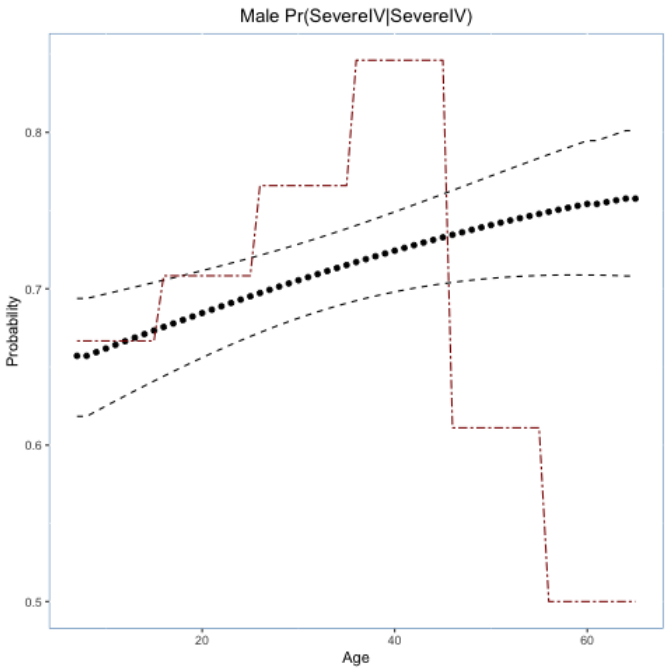

Female Pr(ModerateNOIV|SevereIV)
Probability
0.03
0.02
0.01
20
40
60
Age

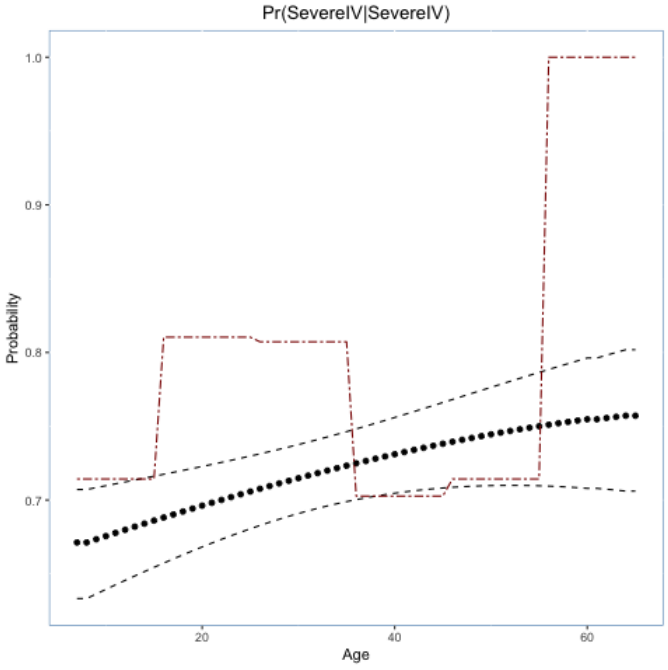

Male Pr(ModerateIV|SevereIV)
Probability
0.16
0.12
0.08
0.04
20
40
60
Age

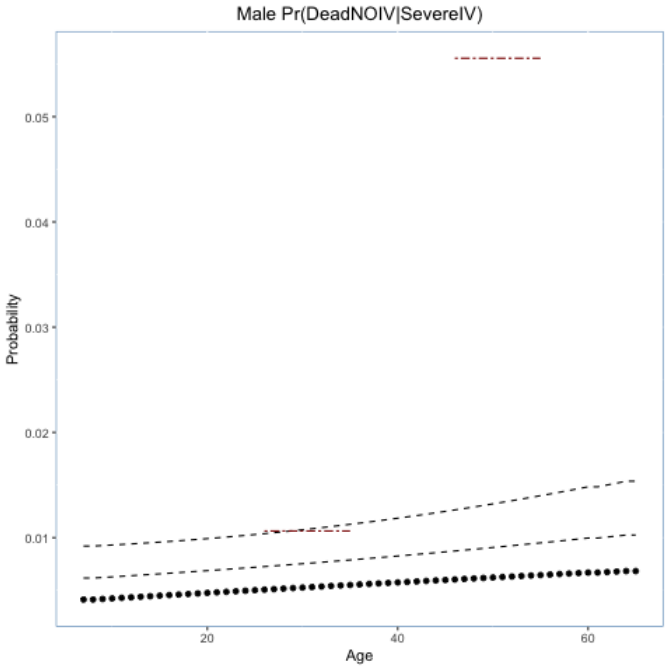

Female Pr(ModerateIV|SevereIV)
Probability
0.15
0.12
0.09
0.06
0.03
20
40
60
Age

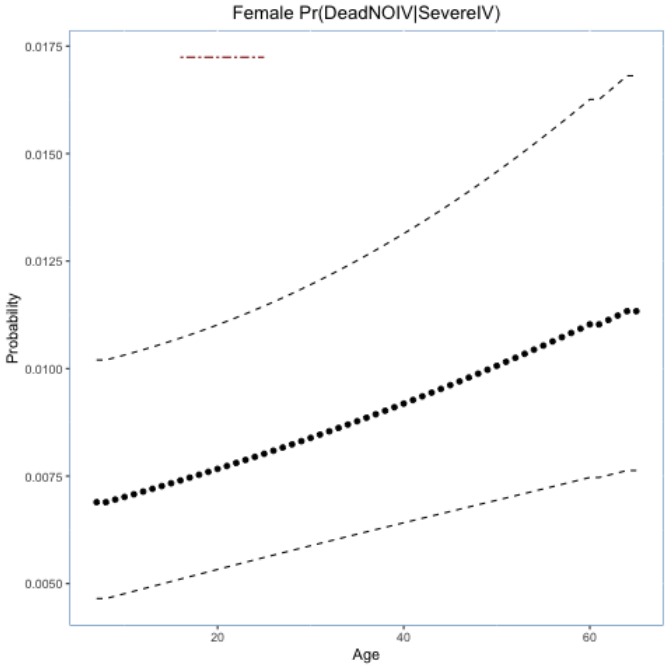

Male Pr(SevereNOIV|SevereIV)
Probability
0.0
0.1
0.2
0.3
0.4
0.5
20
40
60
Age

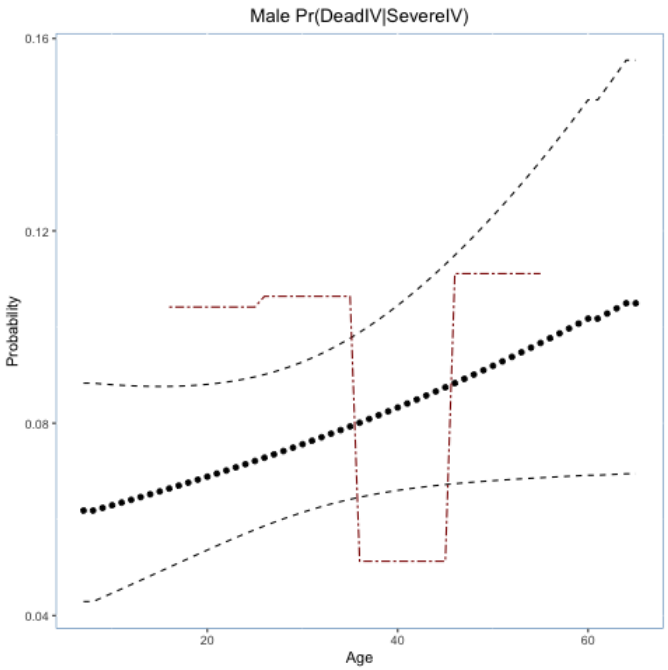

Female Pr(SevereNOIV|SevereIV)
Probability
0.05
0.10
20
40
60
Age

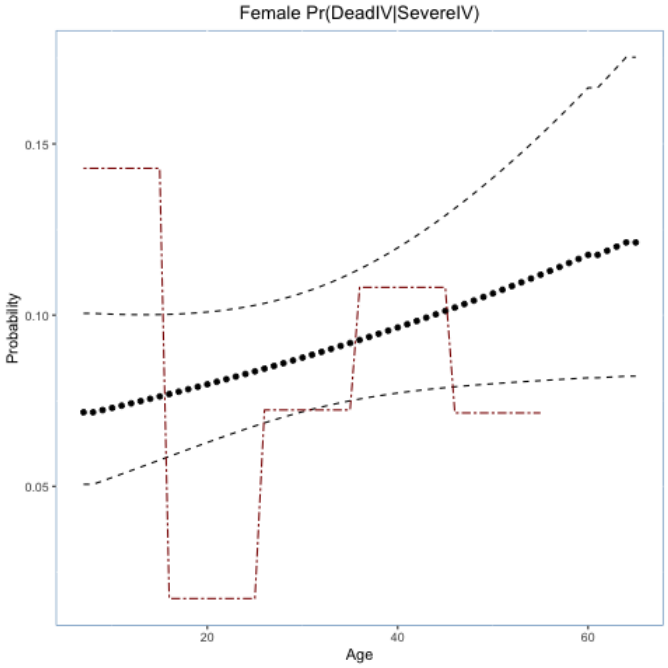

Male Pr(SevereIV|SevereIV)
Probability
0.8
0.7
0.6
0.5
20
40
60
Age


Pr(SevereIV|SevereIV)
Probability
1.0
0.9
0.8
0.7
20
40
60
Age


Male Pr(DeadNOIV|SevereIV)
Probability
0.05
0.04
0.03
0.02
0.01
20
40
60
Age


Female Pr(DeadNOIV|SevereIV)
Probability
0.0175
0.0150
0.0125
0.0100
0.0075
0.0050
20
40
60
Age

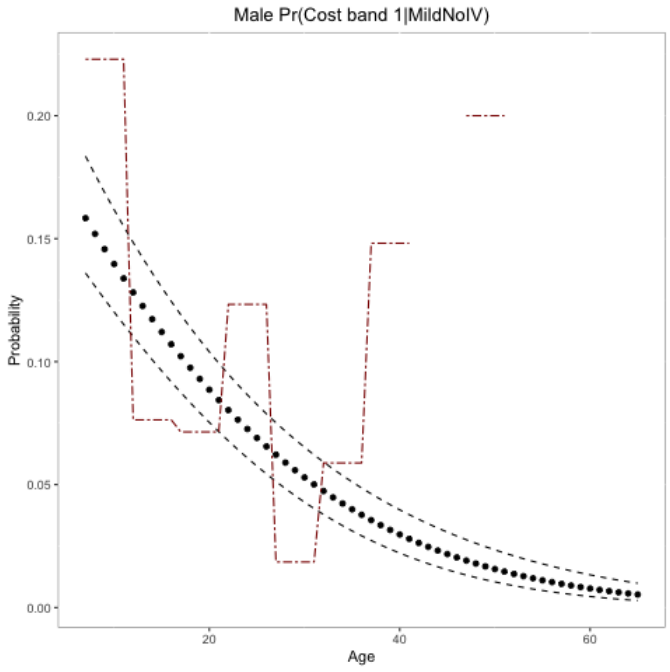

Male Pr(DeadIV|SevereIV)
0.16
0.12
0.08
0.04
Probability
20
40
60
Age

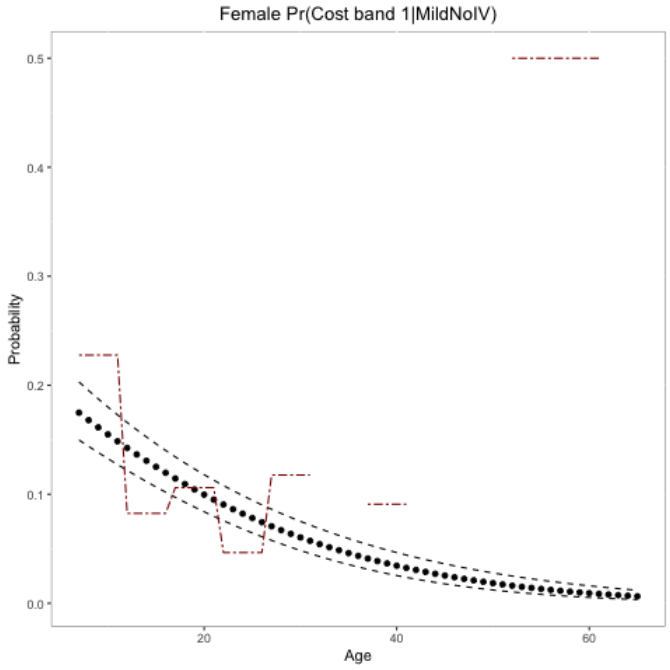

Female Pr(DeadIV|SevereIV)
0.15
0.10
0.05
Probability
20
40
60
Age

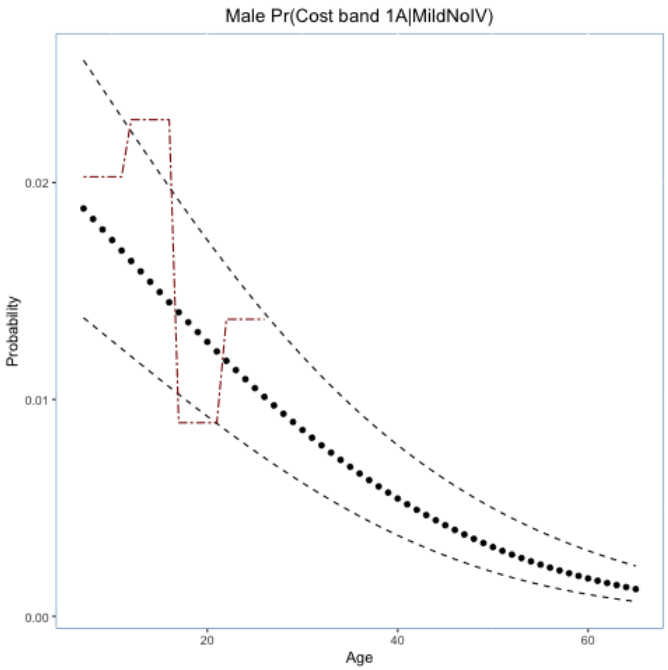
8.3 Appendix 3: Plot of observed and derived cost band probabilities from the U.K. CF Data Registry (2016) by current health state

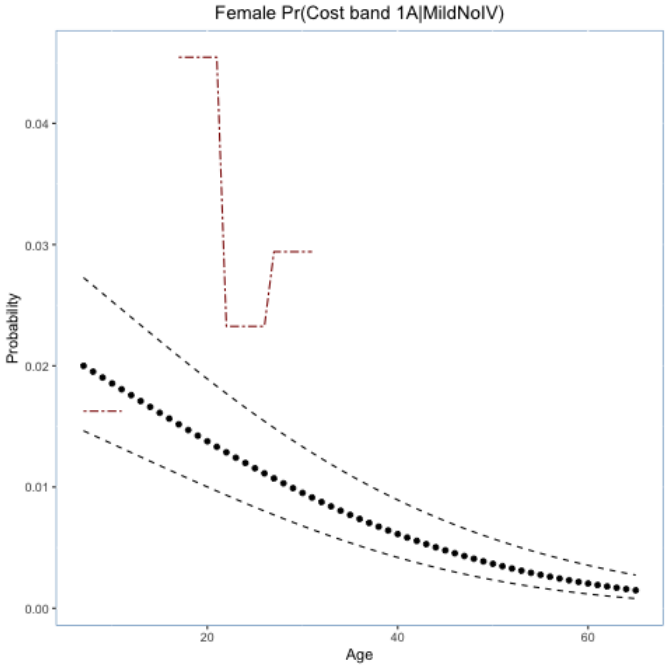
8.3.1 Cost Band probabilities

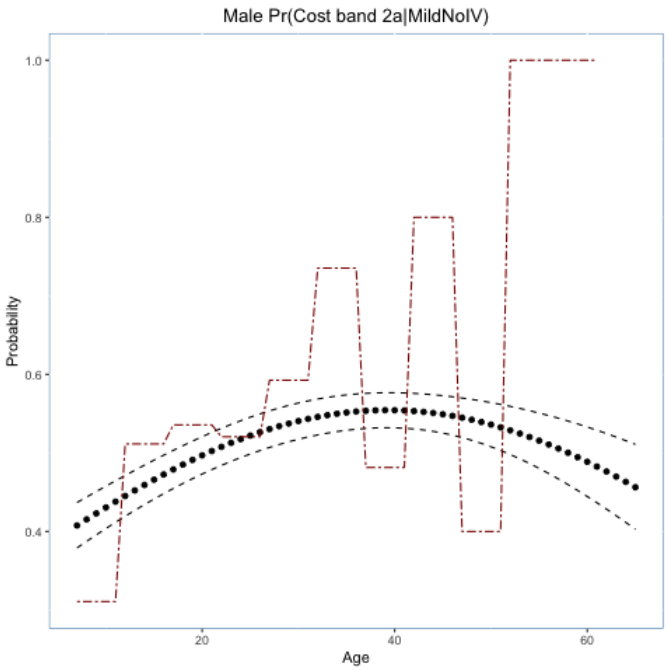
8.3.1.1 Mild No IV

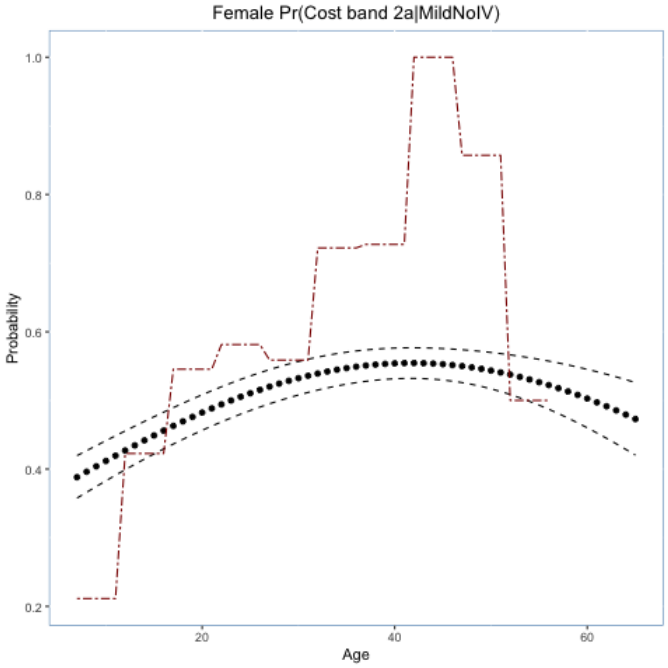


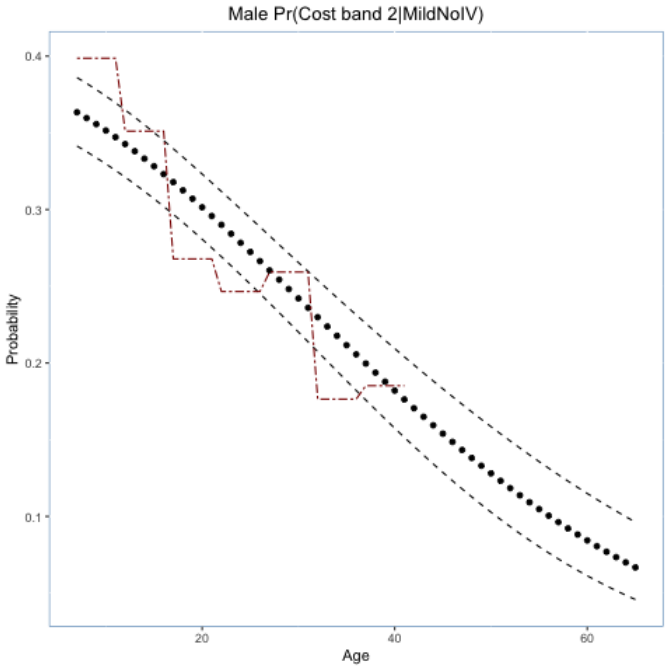


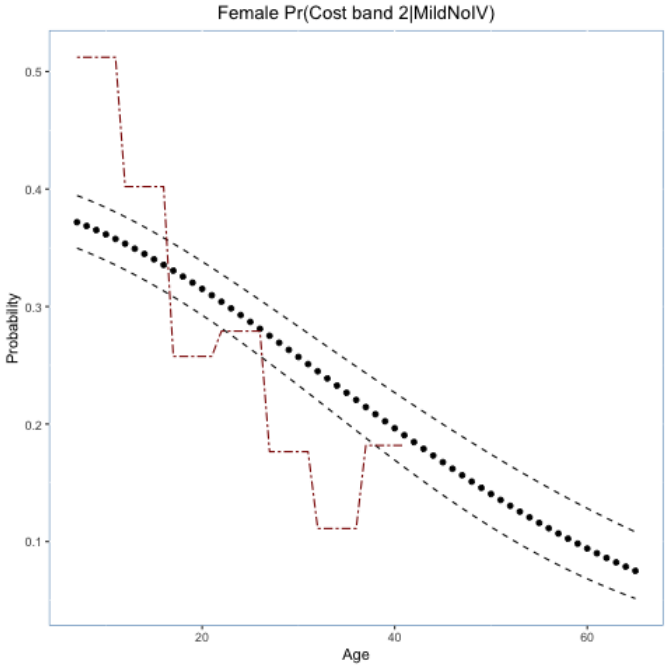

Male Pr(Cost band 1A|MildNoIV)
Probability
0.00
0.01
0.02
20
40
60
Age

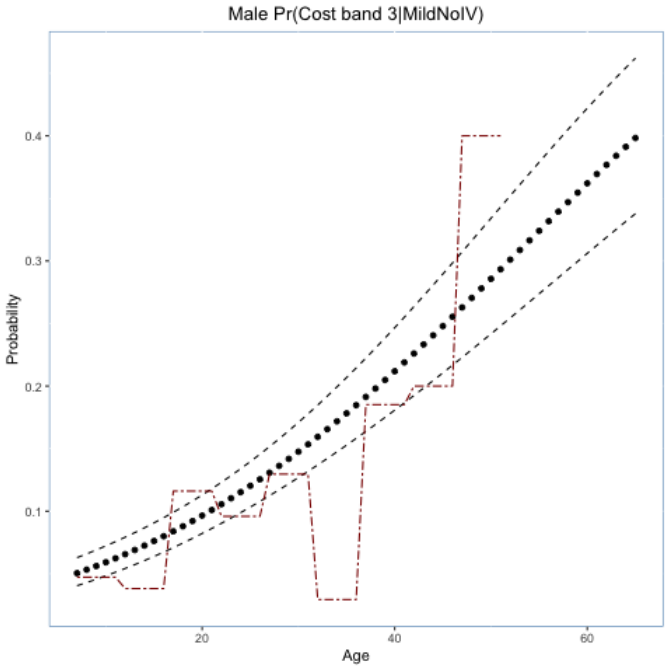

Female Pr(Cost band 1A|MildNoIV)
Probability
0.00
0.01
0.02
0.03
0.04
20
40
60
Age

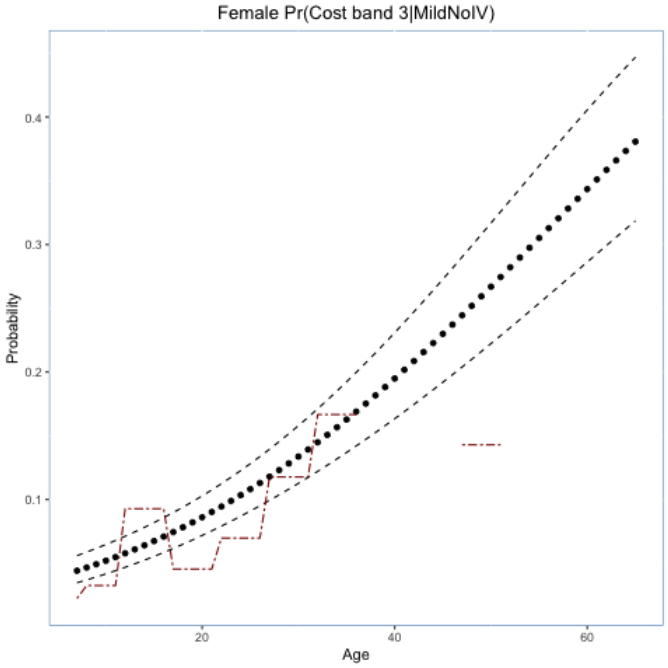

Male Pr(Cost band 2a|MildNoIV)
Probability
1.0
0.8
0.6
0.4
20
40
60
Age

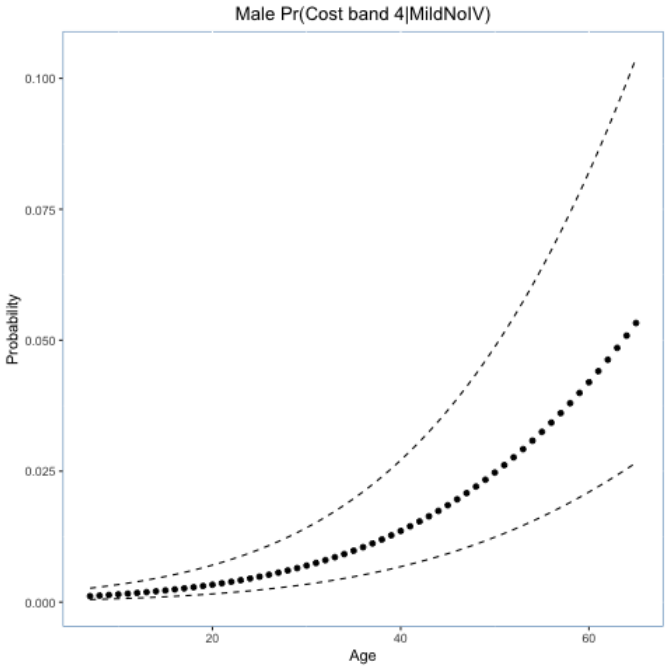

Female Pr(Cost band 2a|MildNoIV)
Probability
1.0
0.8
0.6
0.4
0.2
20
40
60
Age

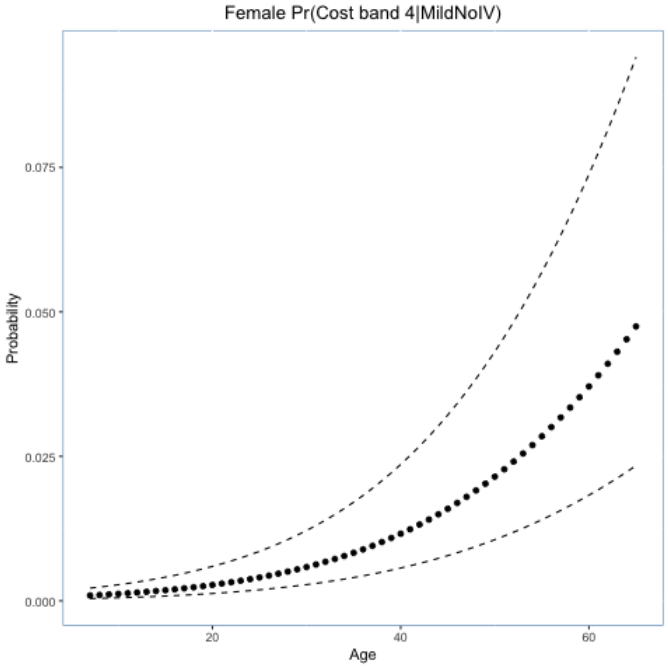

Male Pr(Cost band 2|MildNoIV)
Probability
0.4
0.3
0.2
0.1
20
40
60
Age

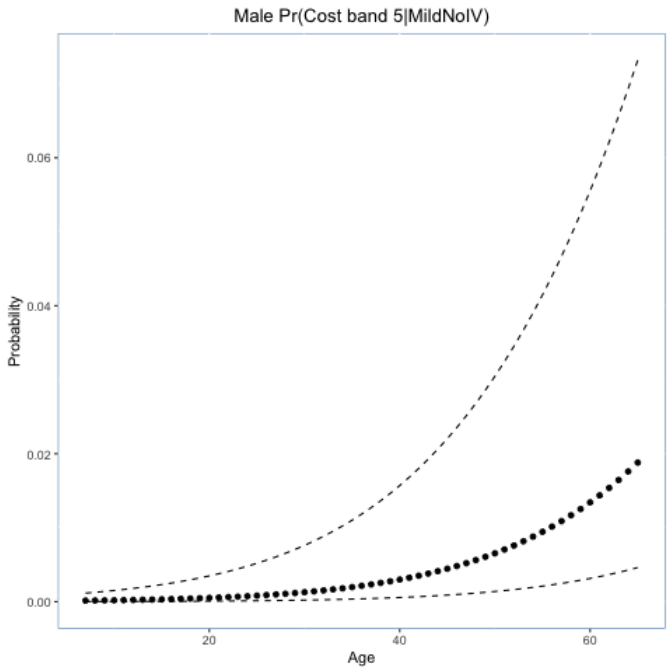

Female Pr(Cost band 2|MildNoIV)
Probability
0.5
0.4
0.3
0.2
0.1
20
40
60
Age

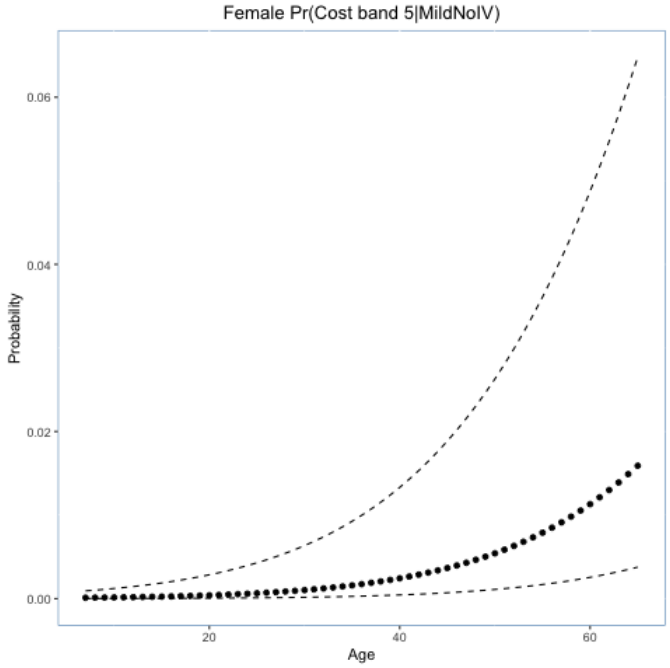

Male Pr(Cost band 3|MildNoIV)
Probability
0.1
0.2
0.3
0.4
20
40
60
Age


Female Pr(Cost band 3|MildNoIV)
Probability
0.1
0.2
0.3
0.4
20
40
60
Age

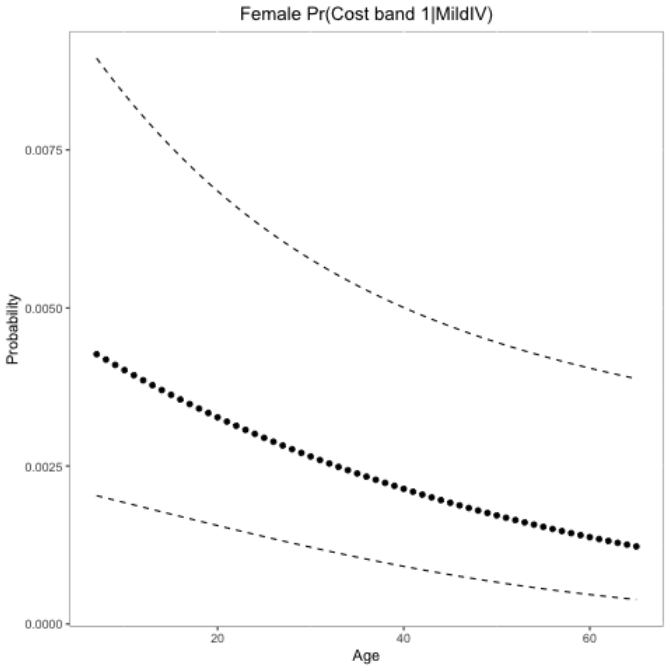

Male Pr(Cost band 4|MildNoIV)
0.100
0.075
0.050
0.025
0.000
Probability
20
40
60
Age

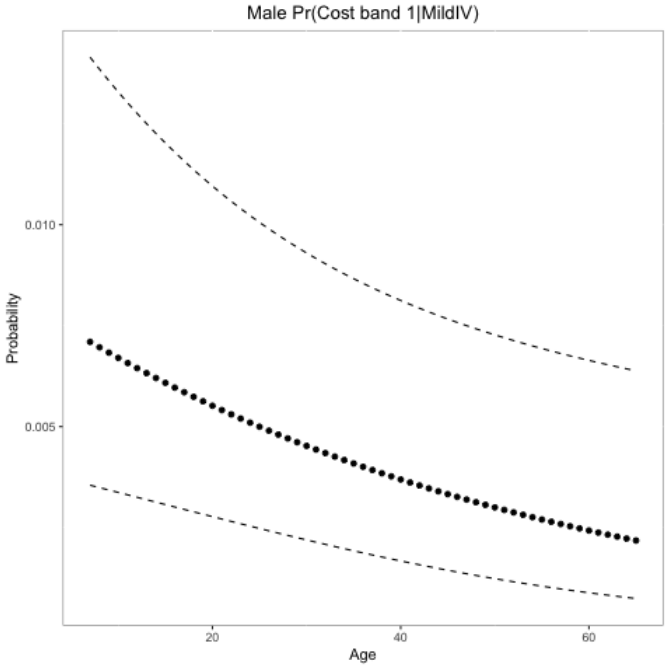

Female Pr(Cost band 4|MildNoIV)
0.075
0.050
0.025
0.000
Probability
20
40
60
Age

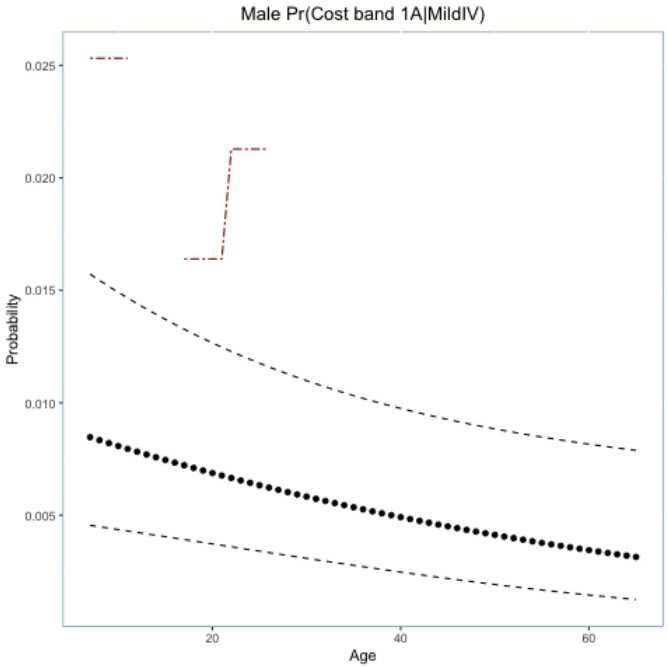

Male Pr(Cost band 5|MildNoIV)
Probability
0.06
0.04
0.02
0.00
20
40
60
Age

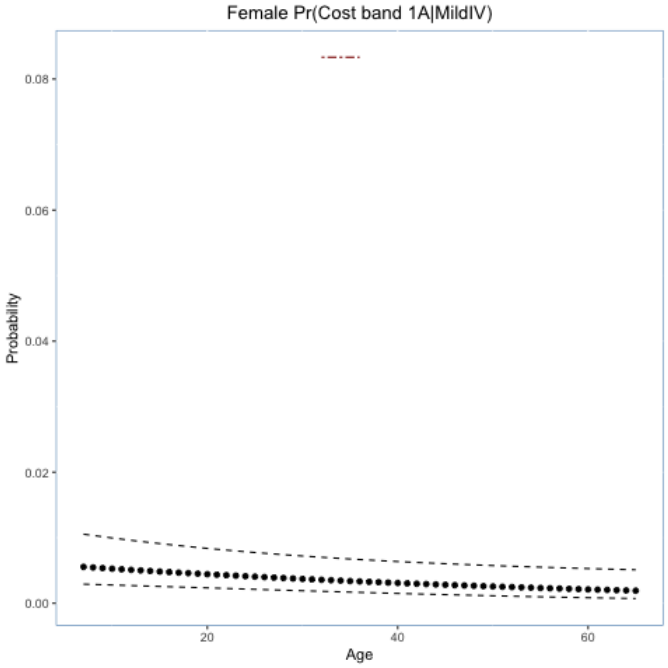

Female Pr(Cost band 5|MildNoIV)
Probability
0.06
0.04
0.02
0.00
20
40
60
Age

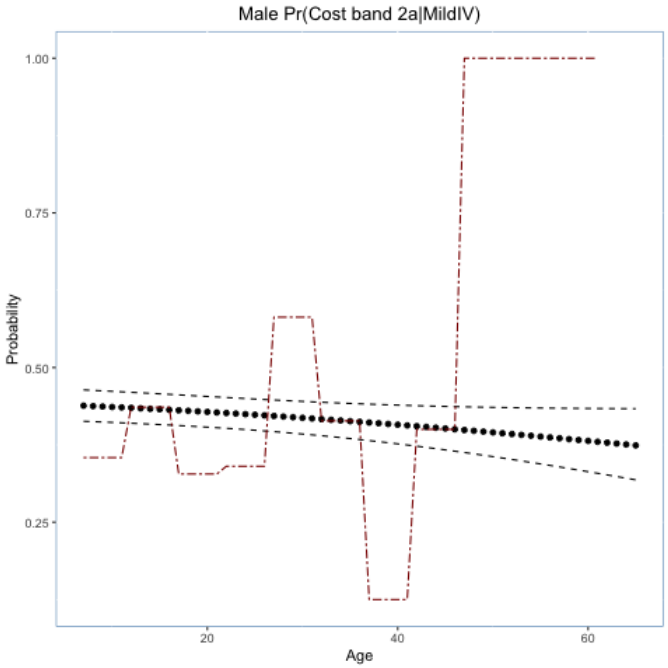
8.3.1.2 Mild IV

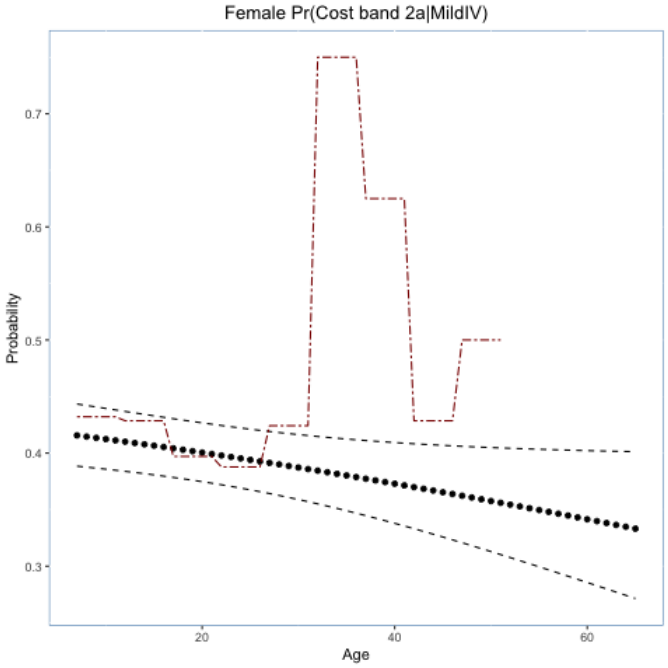

Female Pr(Cost band 1|MildIV)
Probability
0.0075
0.0050
0.0025
0.0000
20
40
60
Age

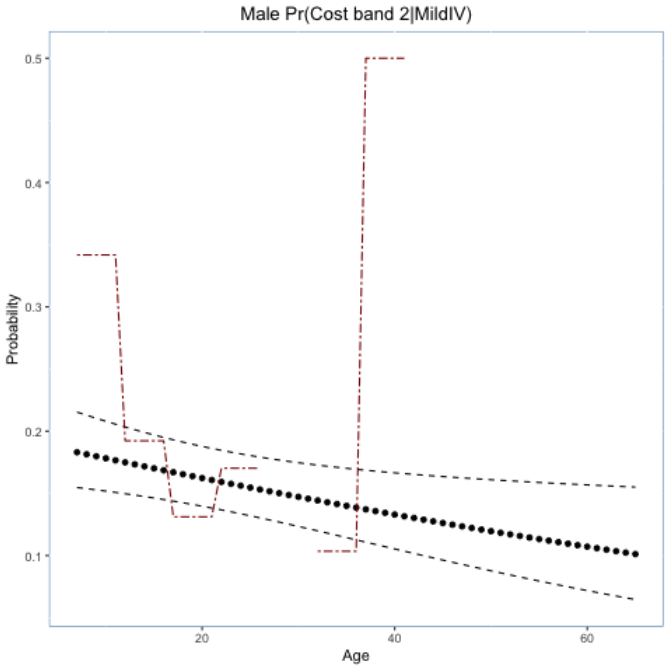

Male Pr(Cost band 1|MildIV)
Probability
0.010
0.005
20
40
60
Age

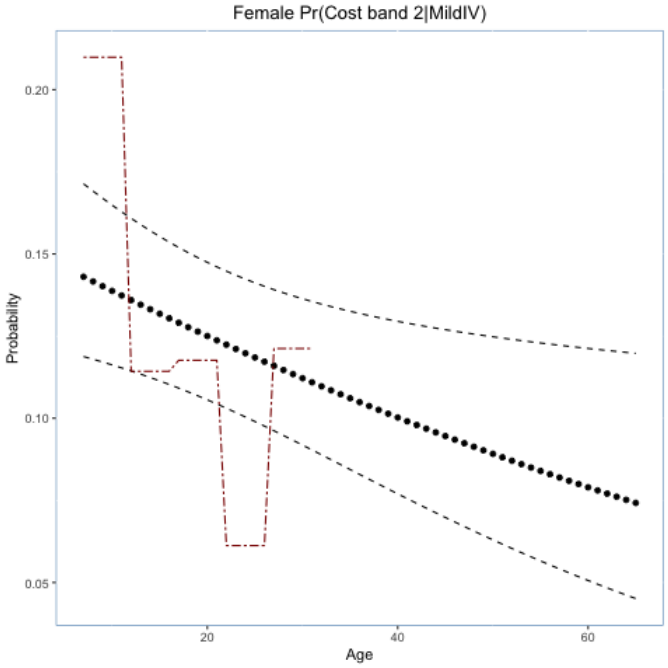

Male Pr(Cost band 1A|MildIV)
Probability
0.025
0.020
0.015
0.010
0.005
20
40
60
Age

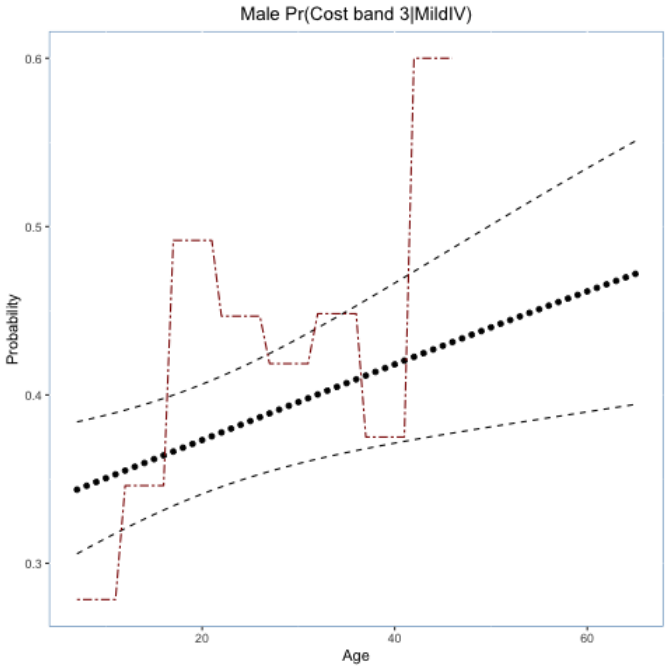

Female Pr(Cost band 1A|MildIV)
Probability
0.08
0.06
0.04
0.02
0.00
20
40
60
Age

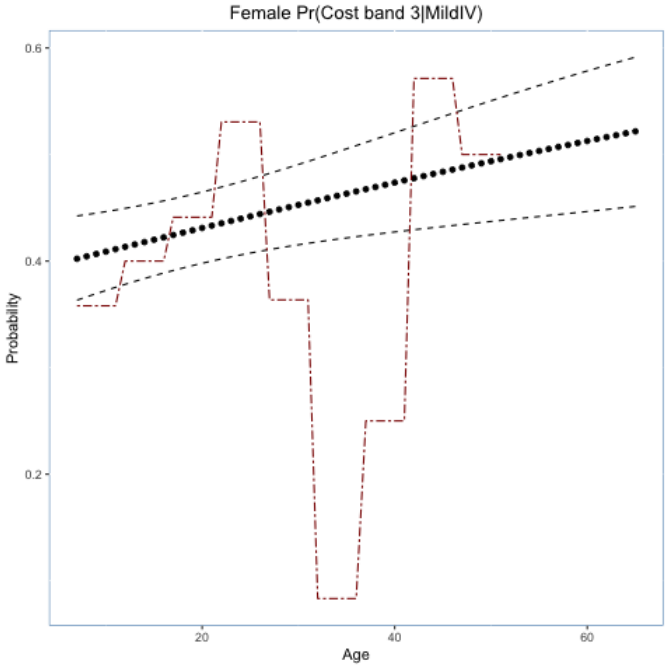

Male Pr(Cost band 2a|MildIV)
1.00
0.75
0.50
0.25
Probability
20
40
60
Age

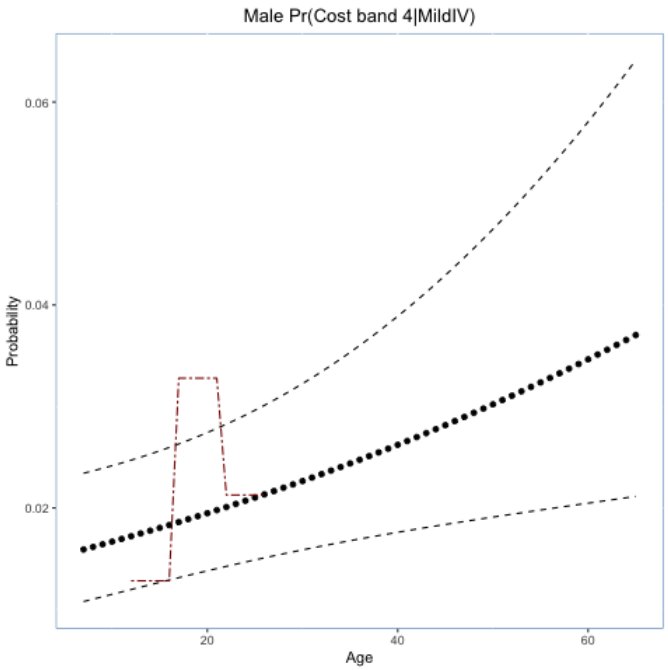

Female Pr(Cost band 2a|MildIV)
0.7
0.6
0.5
0.4
0.3
Probability
20
40
60
Age

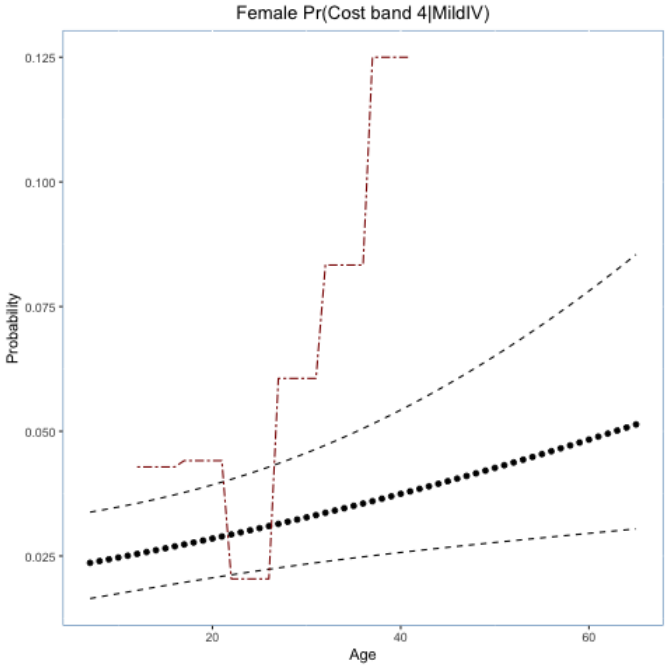

Male Pr(Cost band 2|MildIV)
Probability
0.5
0.4
0.3
0.2
0.1
20
40
60
Age

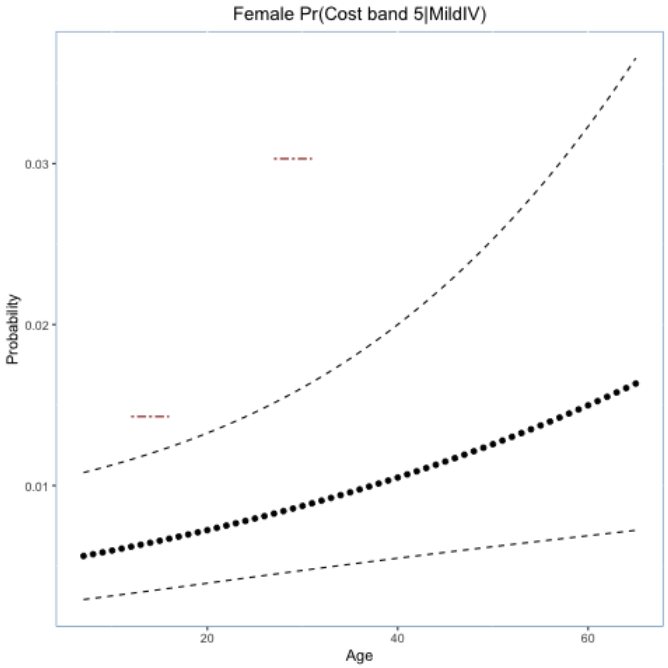

Female Pr(Cost band 2|MildIV)
Probability
0.20
0.15
0.10
0.05
20
40
60
Age

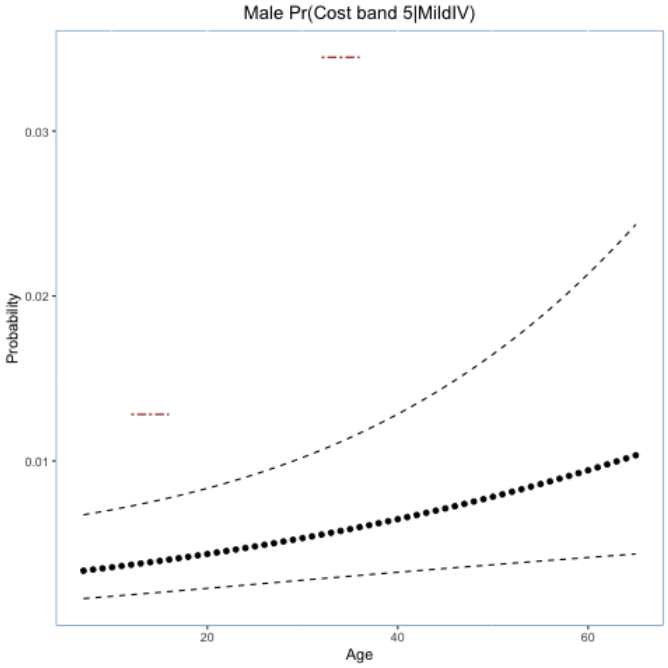

Male Pr(Cost band 3|MildIV)
Probability
0.6
0.5
0.4
0.3
20
40
60
Age


Female Pr(Cost band 3|MildIV)
Probability
0.6
0.4
0.2
20
40
60
Age

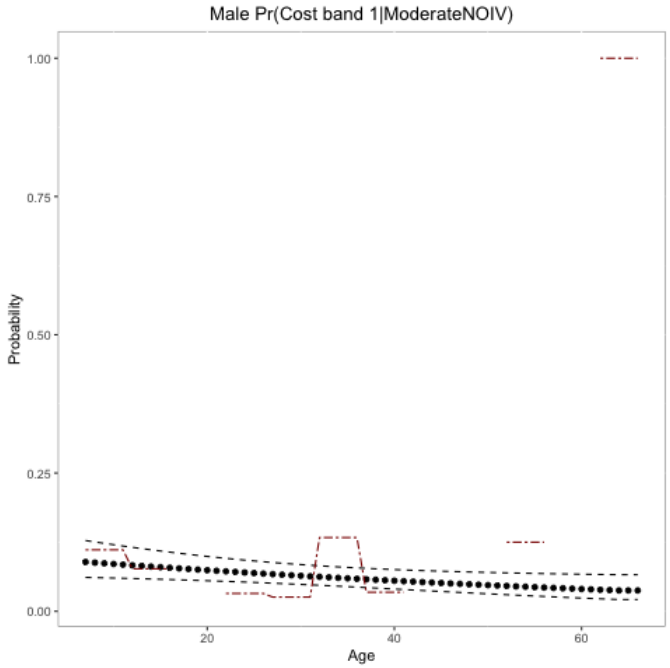

Male Pr(Cost band 4|MildIV)
Probability
0.06
0.04
0.02
20
40
60
Age

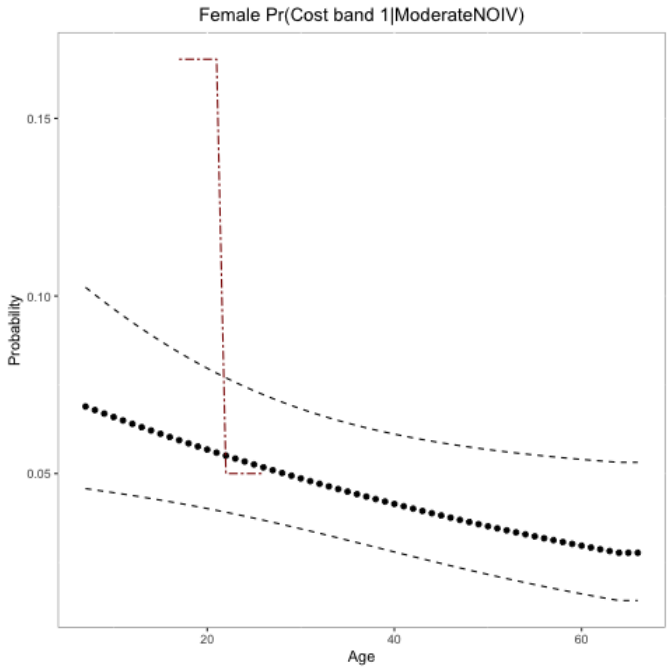

Female Pr(Cost band 4|MildIV)
Probability
0.125
0.100
0.075
0.050
0.025
20
40
60
Age

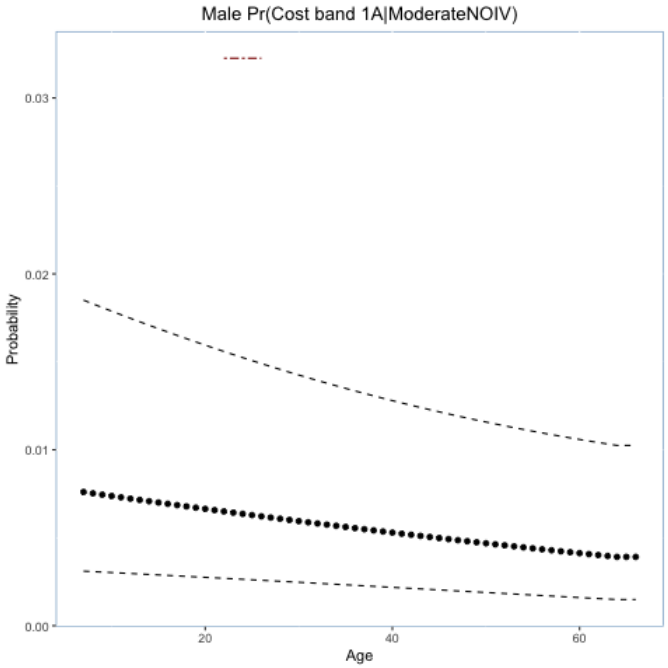

Female Pr(Cost band 5|MildIV)
Probability
0.03
0.02
0.01
20
40
60
Age

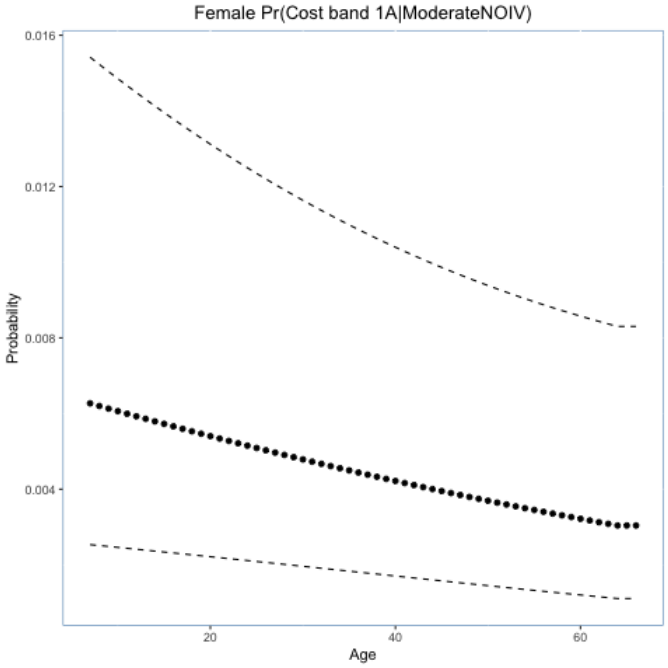

Male Pr(Cost band 5|MildIV)
Probability
0.03
0.02
0.01
20
40
60
Age

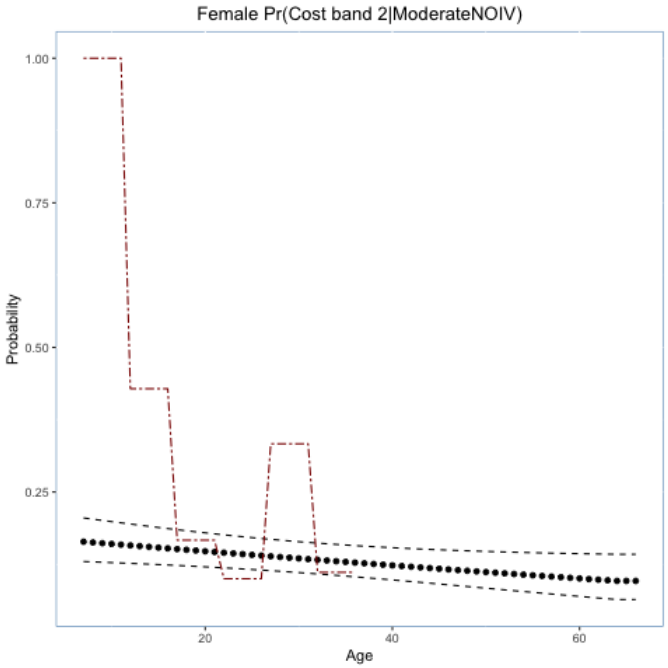
8.3.1.3 Moderate No IV

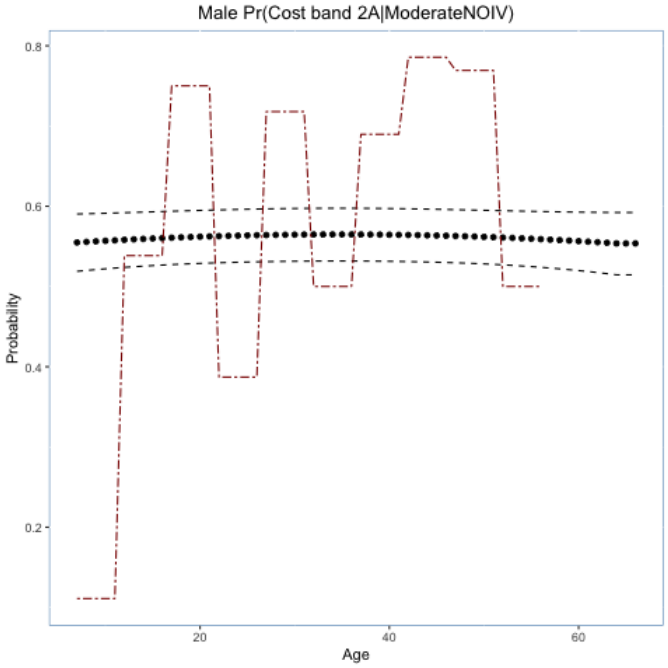


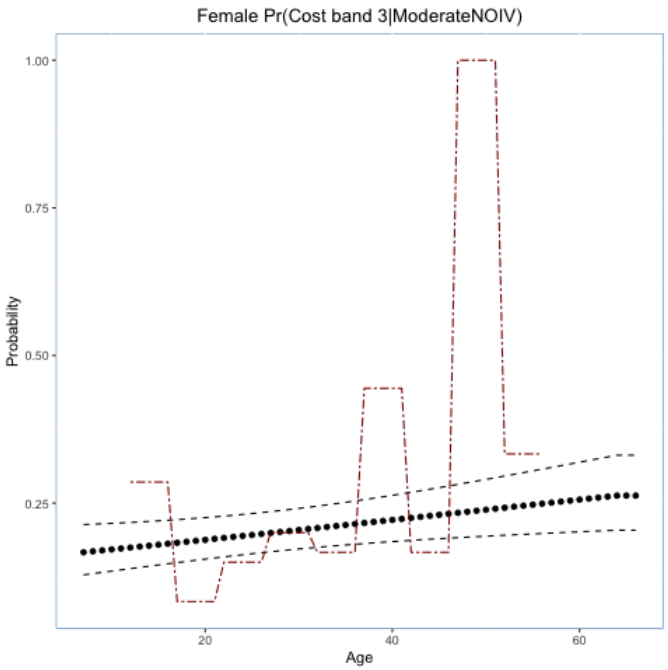


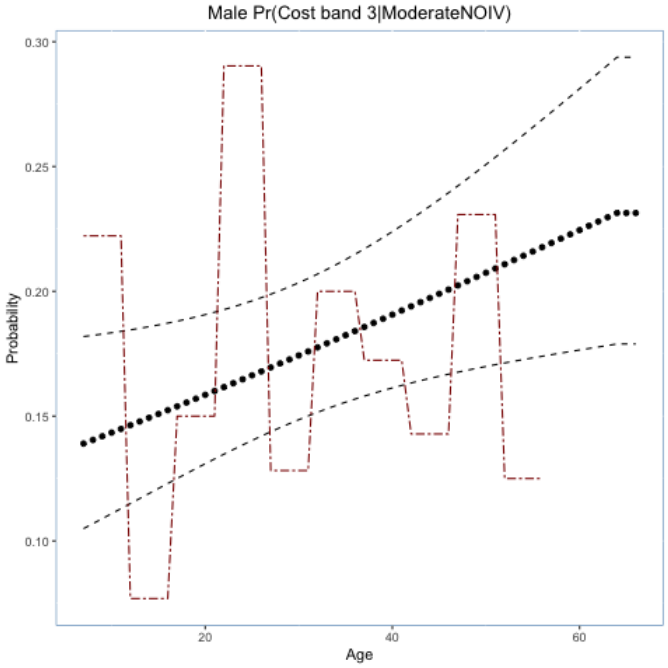

Male Pr(Cost band 1A|ModerateNOIV)
0.03
0.02
0.01
0.00
Probability
20
40
60
Age

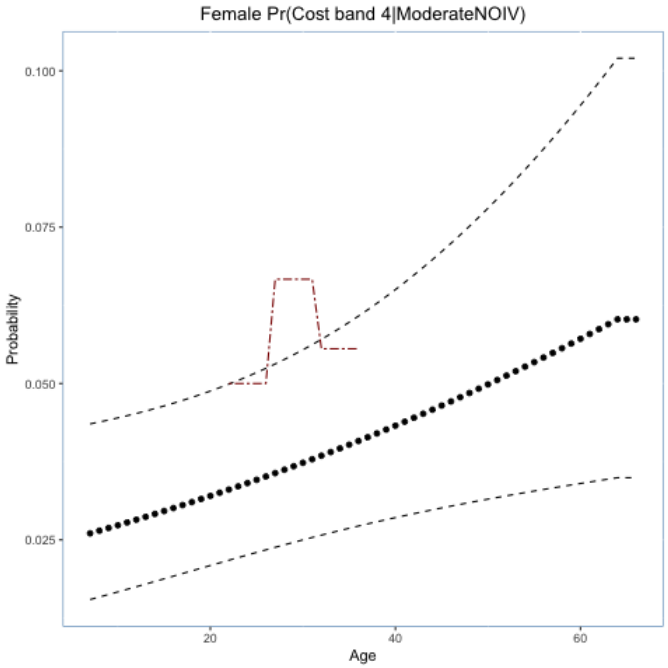

Female Pr(Cost band 1A|ModerateNOIV)
0.016
0.012
0.008
0.004
Probability
20
40
60
Age

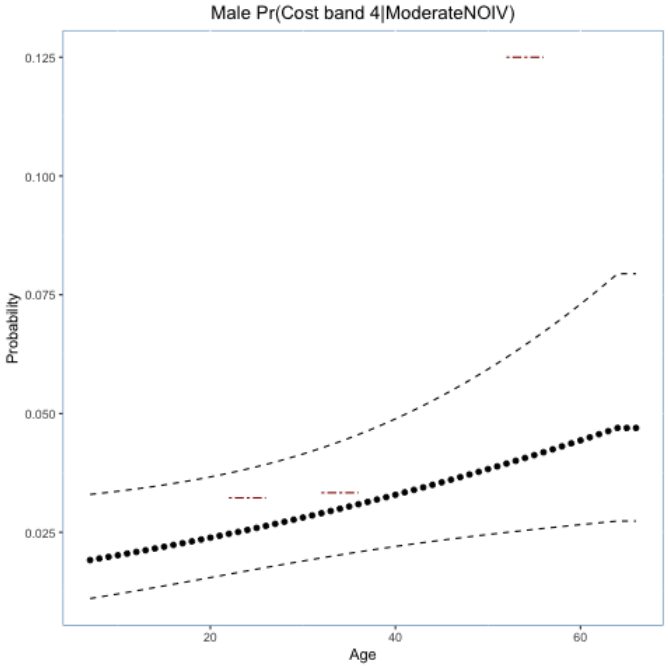

Female Pr(Cost band 2|ModerateNOIV)
Probability
1.00
0.75
0.50
0.25
20
40
60
Age

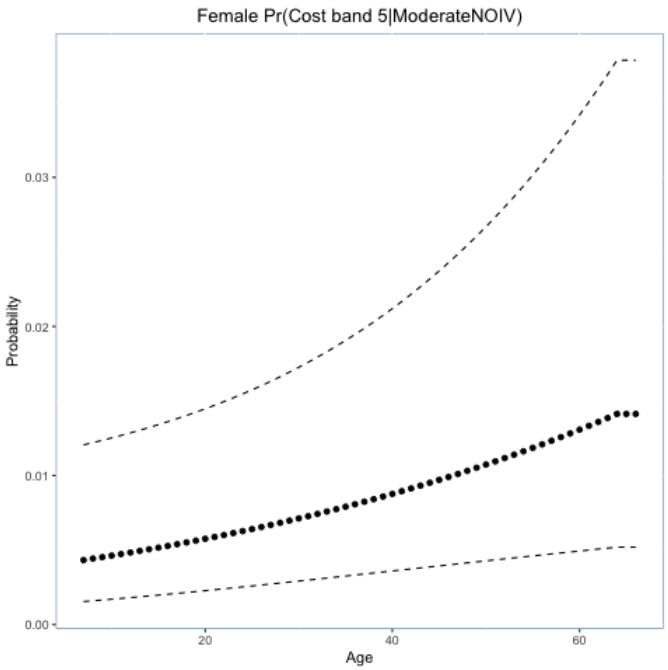

Male Pr(Cost band 2A|ModerateNOIV)
Probability
0.8
0.6
0.4
0.2
20
40
60
Age

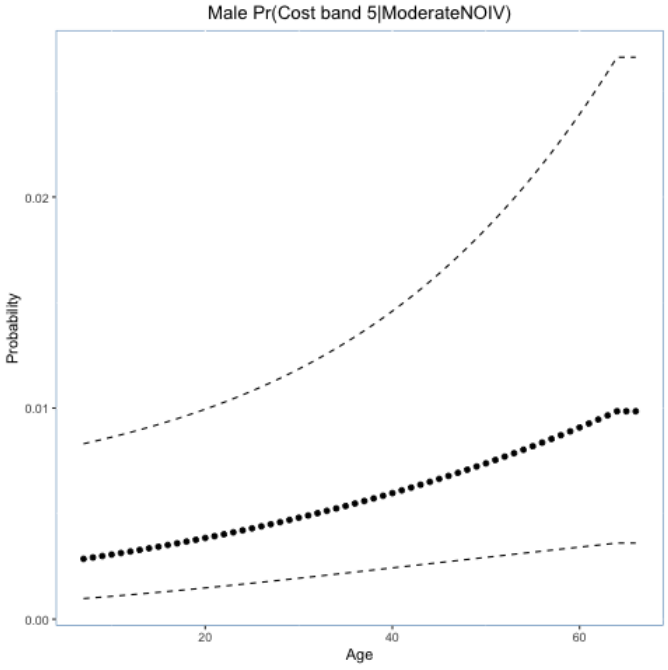

Female Pr(Cost band 3|ModerateNOIV)
Probability
1.00
0.75
0.50
0.25
20
40
60
Age


Male Pr(Cost band 3|ModerateNOIV)
Probability
0.30
0.25
0.20
0.15
0.10
20
40
60
Age

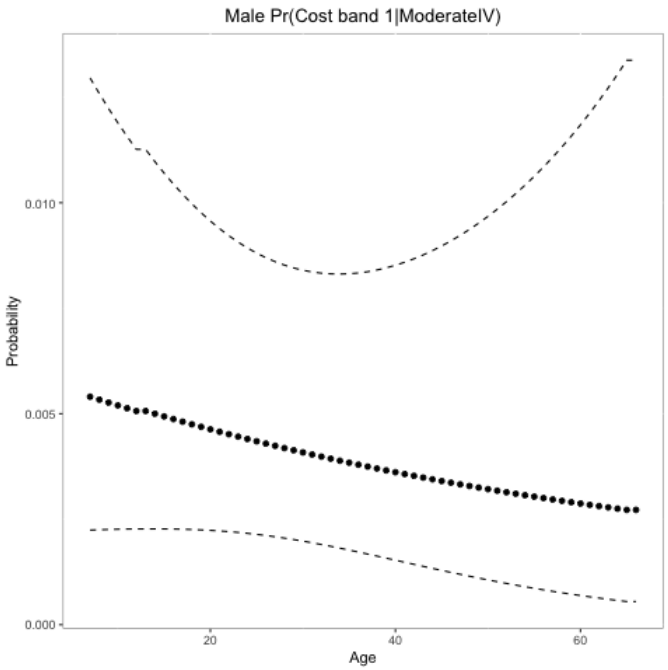

Female Pr(Cost band 4|ModerateNOIV)
Probability
0.100
0.075
0.050
0.025
20
40
60
Age

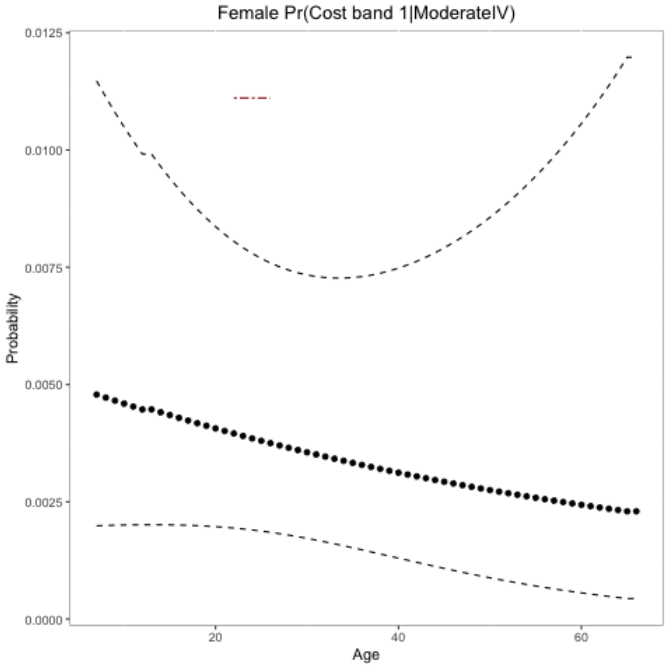

Male Pr(Cost band 4|ModerateNOIV)
Probability
0.125
0.100
0.075
0.050
0.025
20
40
60
Age

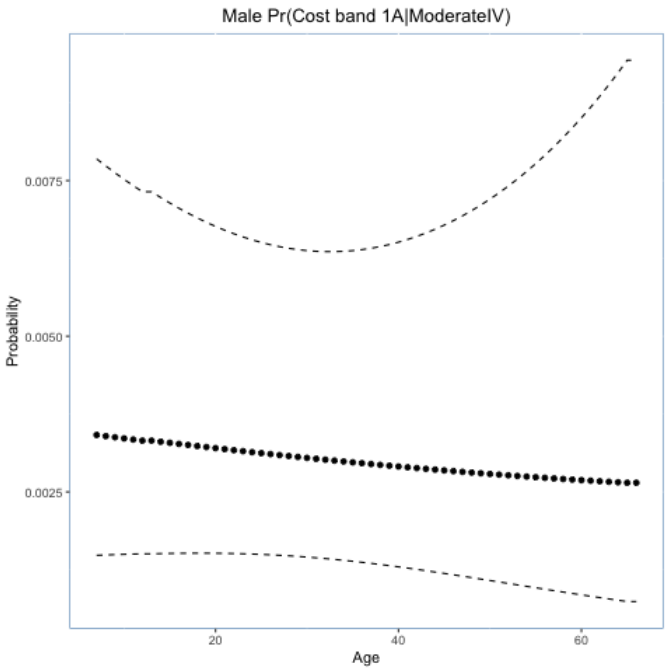

Female Pr(Cost band 5|ModerateNOIV)
Probability
0.03
0.02
0.01
0.00
20
40
60
Age

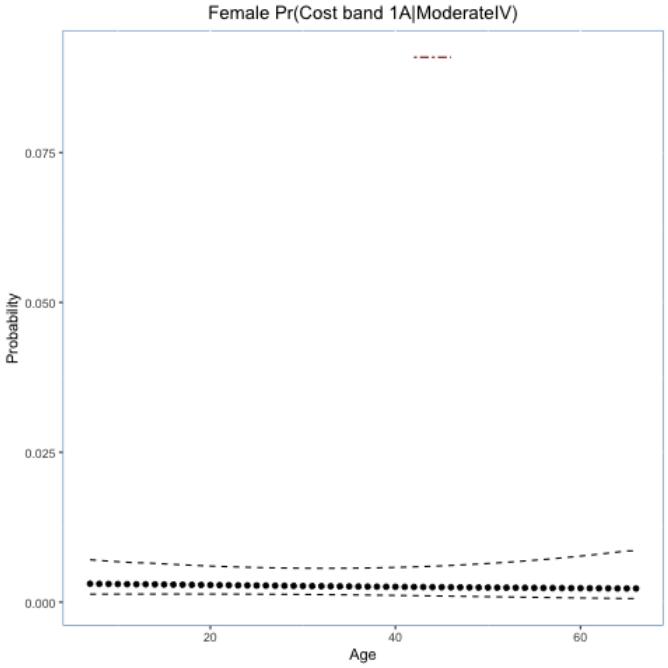

Male Pr(Cost band 5|ModerateNOIV)
Probability
0.02
0.01
0.00
20
40
60
Age

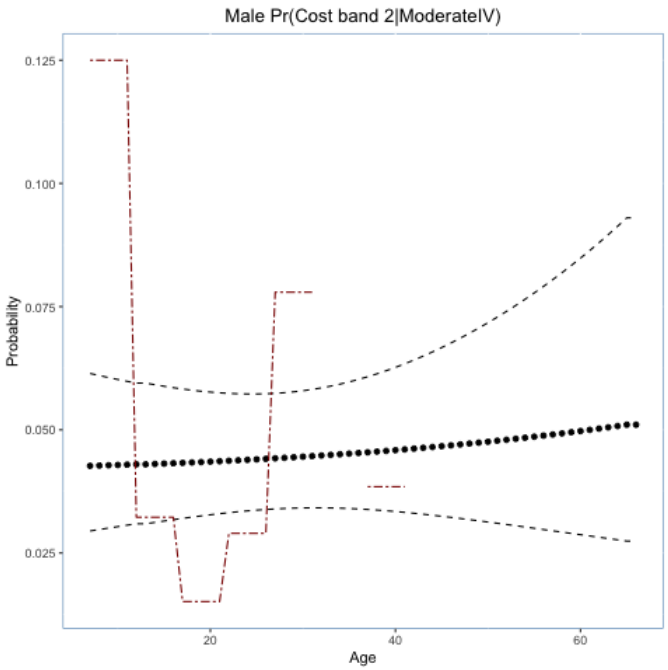
8.3.1.4 Moderate IV

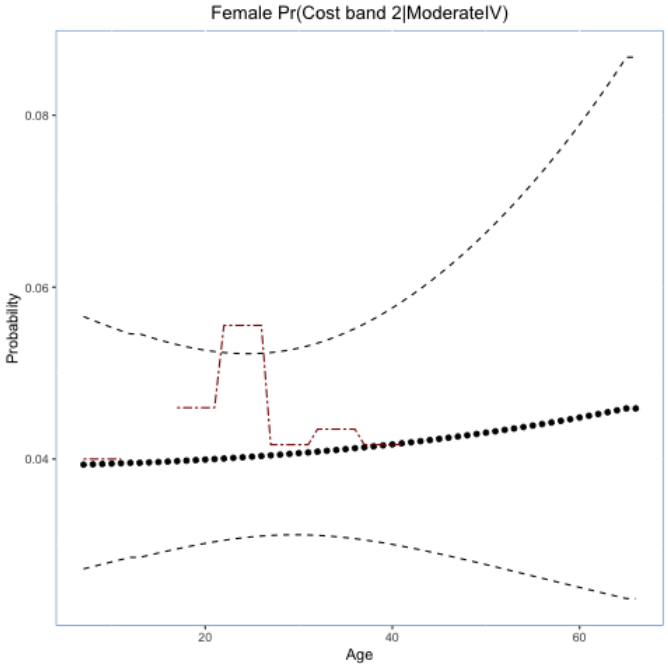


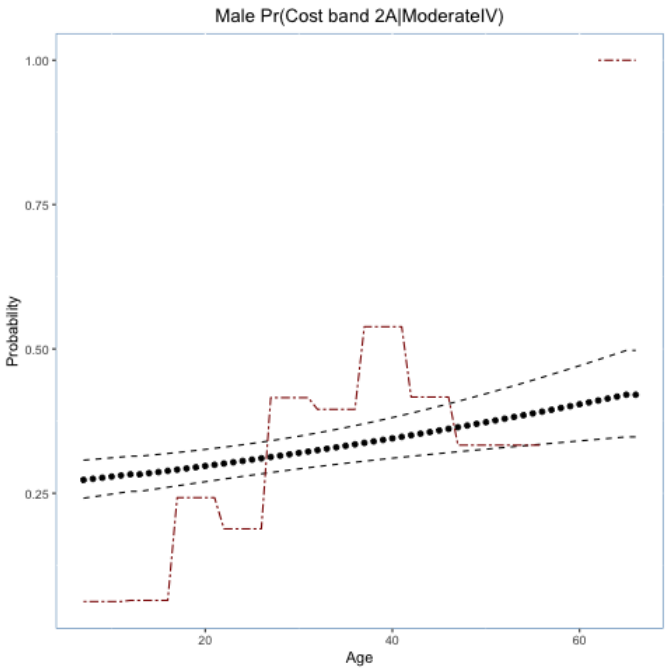


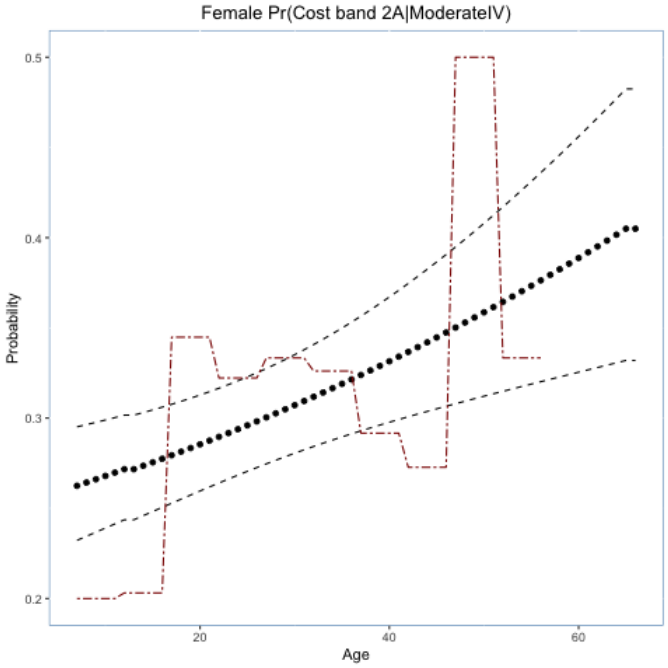

Male Pr(Cost band 1A|ModerateIV)
Probability
0.0075
0.0050
0.0025
20
40
60
Age

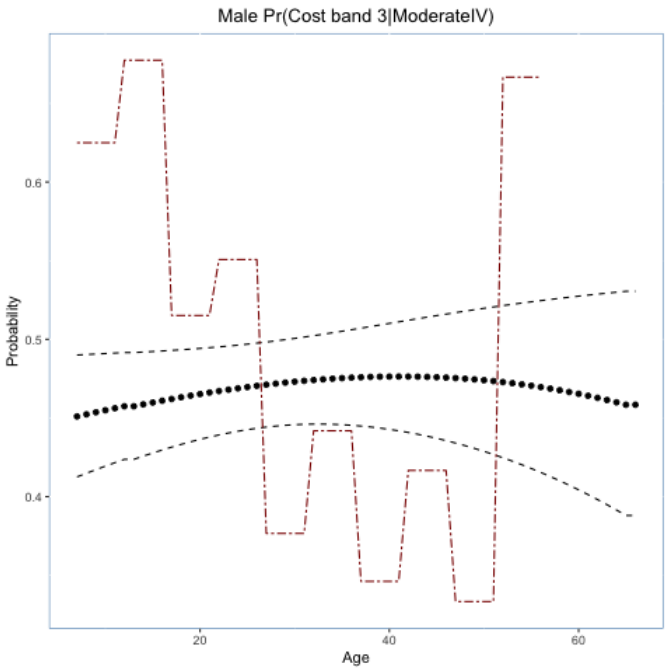

Female Pr(Cost band 1A|ModerateIV)
Probability
0.075
0.050
0.025
0.000
20
40
60
Age

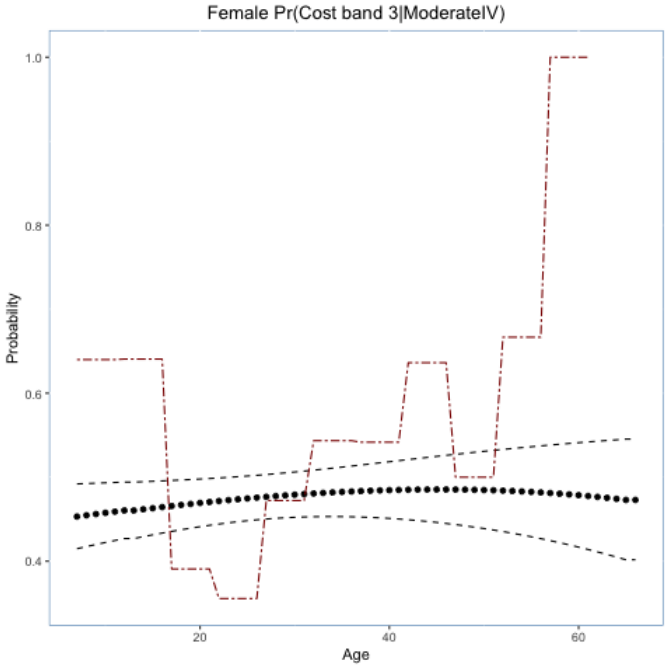

Male Pr(Cost band 2|ModerateIV)
Probability
0.125
0.100
0.075
0.050
0.025
20
40
60
Age

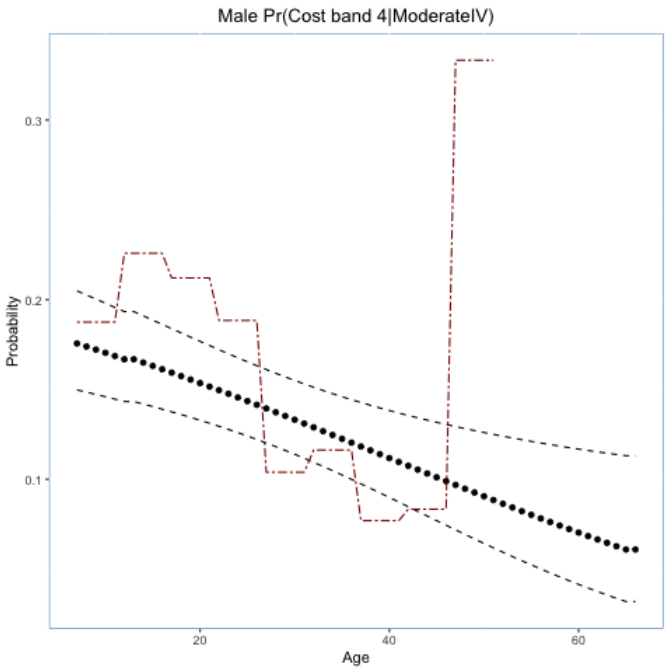

Female Pr(Cost band 2|ModerateIV)
Probability
0.08
0.06
0.04
20
40
60
Age

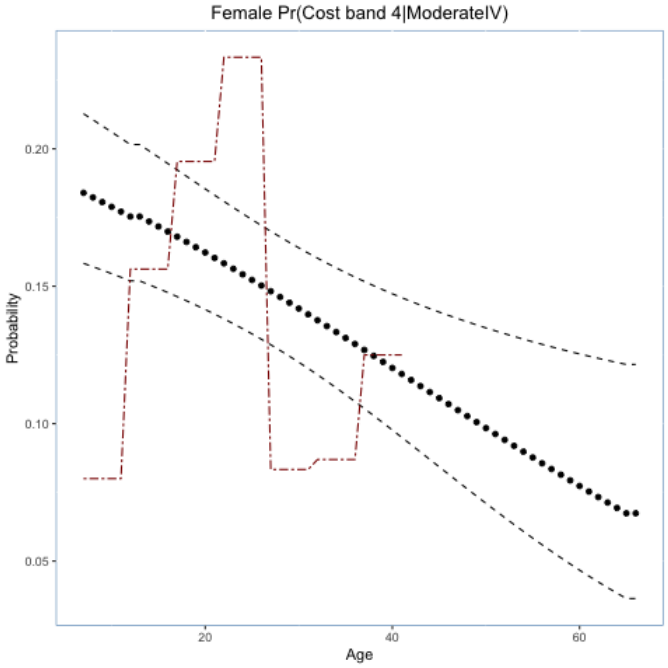

Male Pr(Cost band 2A|ModerateIV)
1.00
0.75
0.50
0.25
Probability
20
40
60
Age

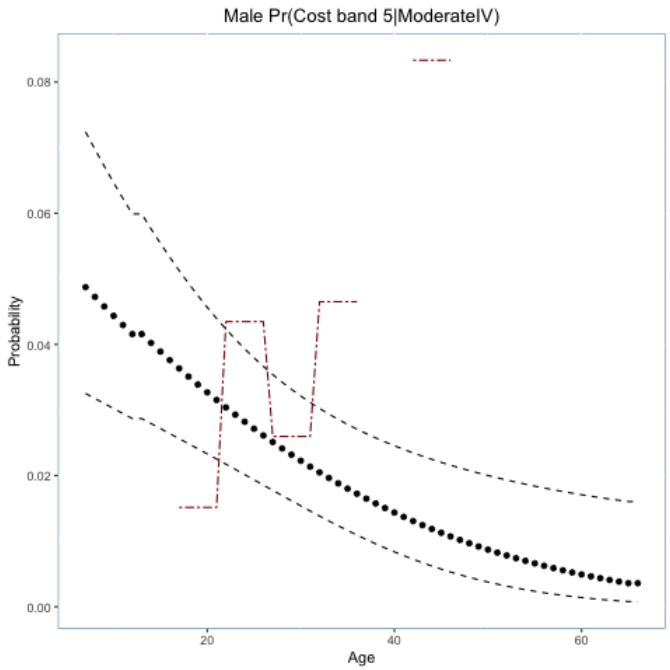

Female Pr(Cost band 2A|ModerateIV)
0.5
0.4
0.3
0.2
Probability
20
40
60
Age

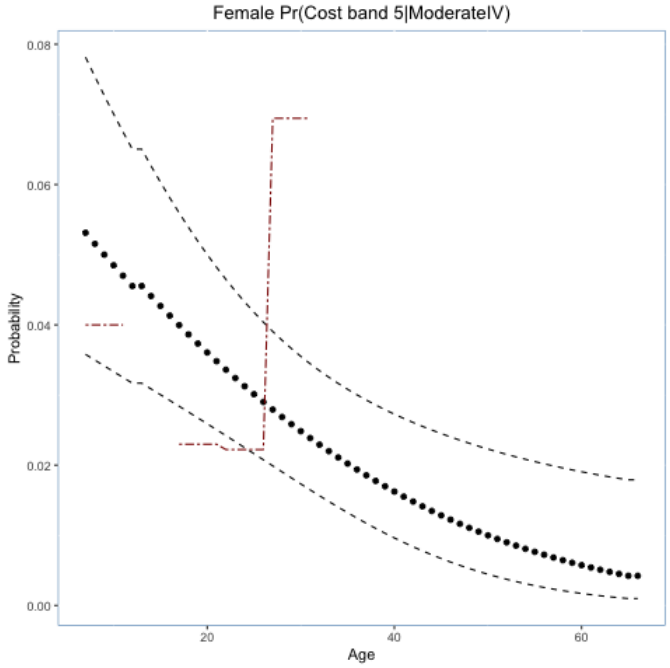

Male Pr(Cost band 3|ModerateIV)
Probability
0.6
0.5
0.4
20
40
60
Age


Female Pr(Cost band 3|ModerateIV)
Probability
1.0
0.8
0.6
0.4
20
40
60
Age

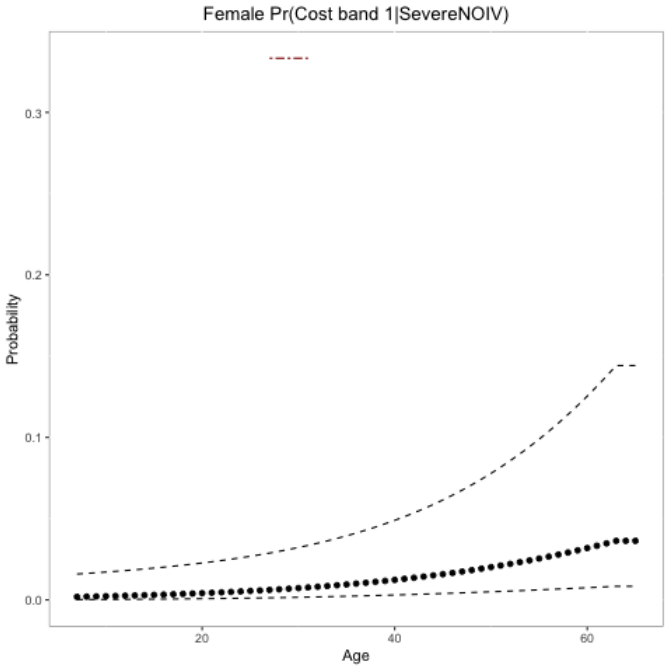

Male Pr(Cost band 4|ModerateIV)
Probability
0.3
0.2
0.1
20
40
60
Age

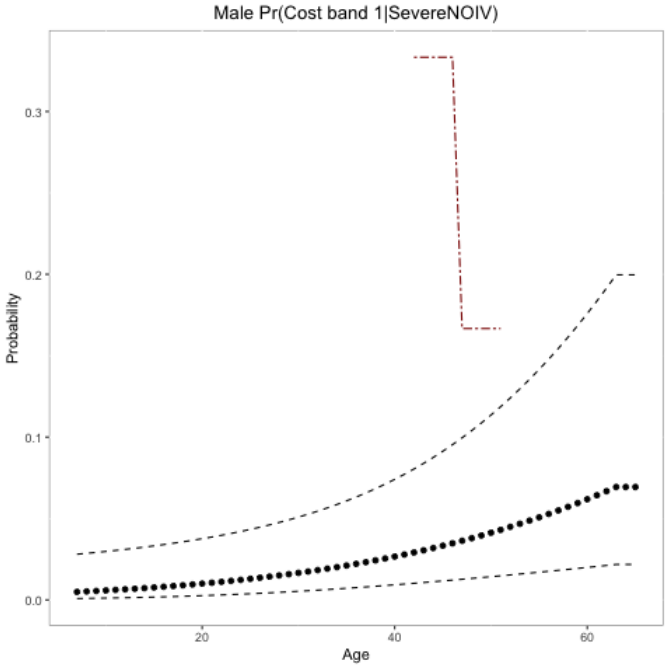

Female Pr(Cost band 4|ModerateIV)
Probability
0.20
0.15
0.10
0.05
20
40
60
Age

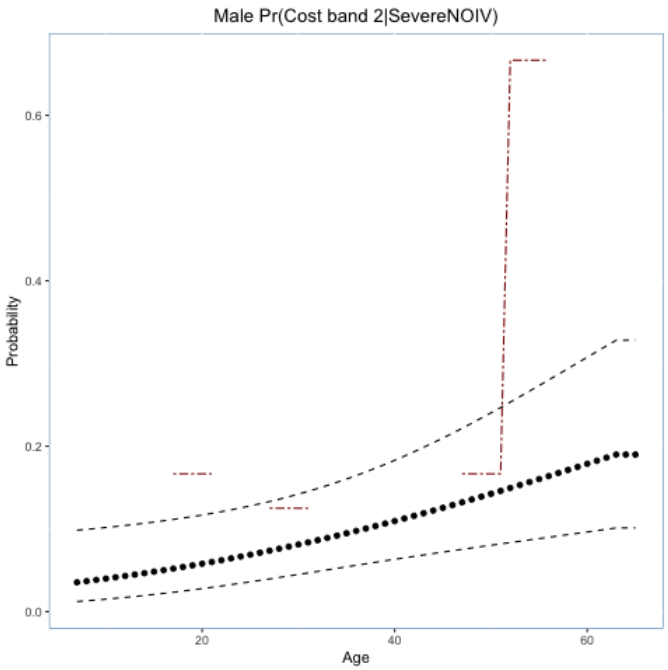


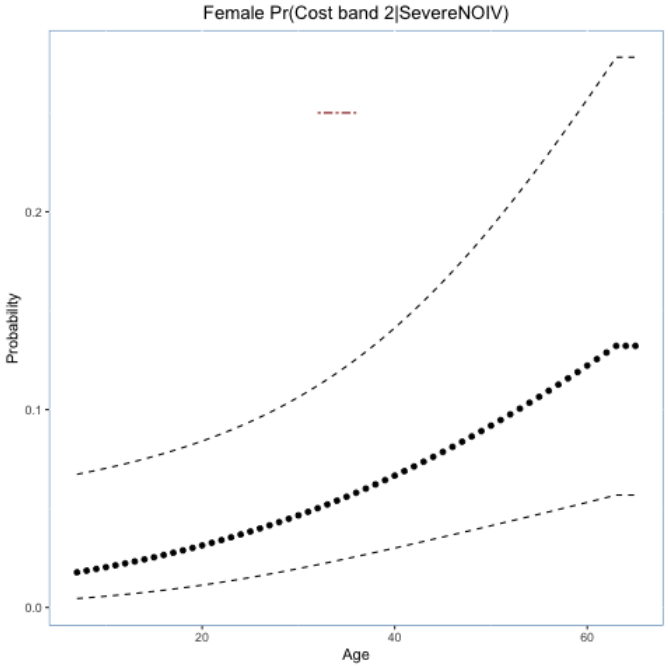


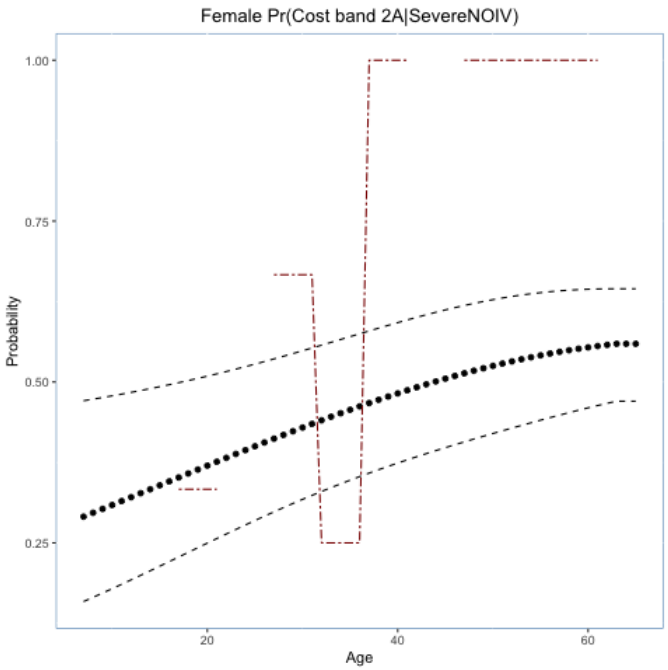
8.3.1.5 Severe No IV

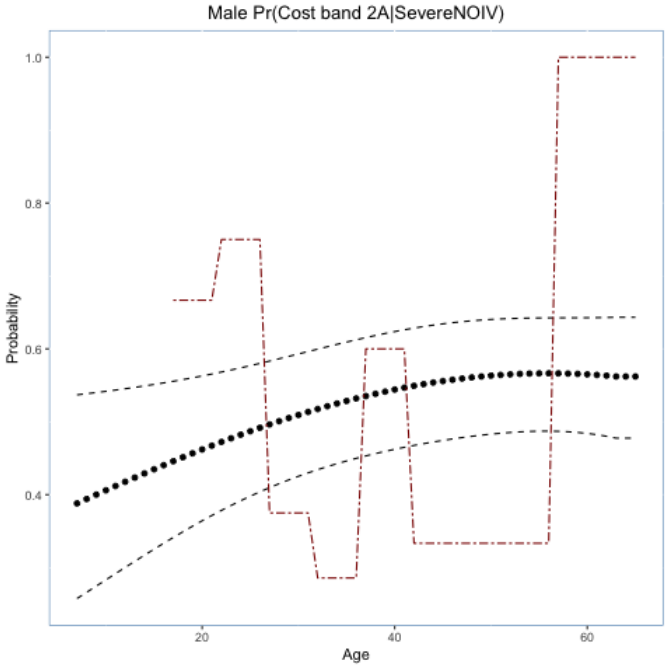

Female Pr(Cost band 1|SevereNOIV)
Probability
0.0
0.1
0.2
0.3
20
40
60
Age

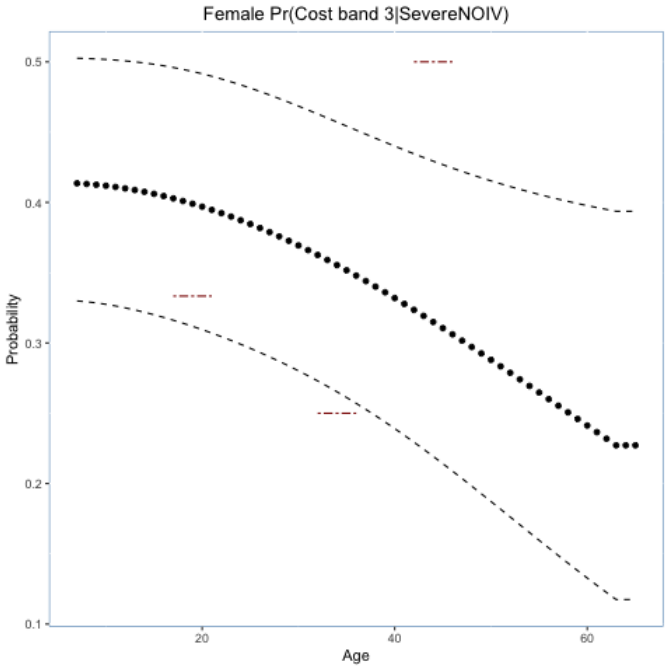

Male Pr(Cost band 1|SevereNOIV)
Probability
0.0
0.1
0.2
0.3
20
40
60
Age

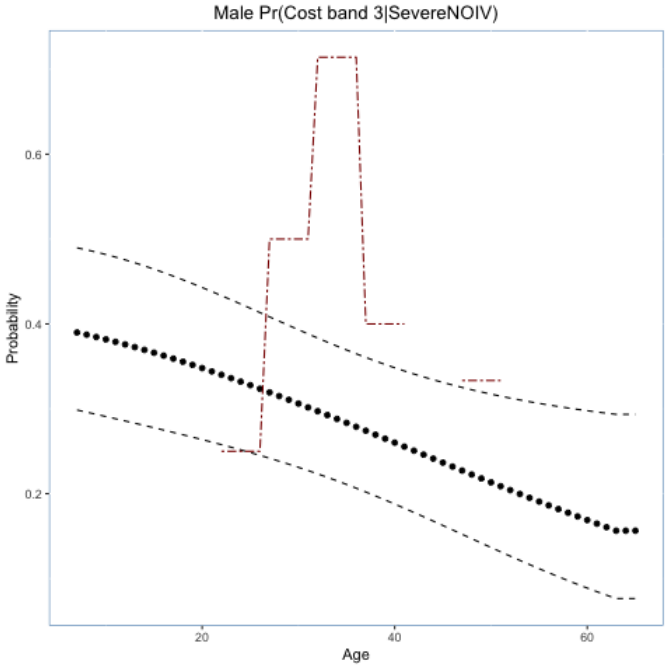

Male Pr(Cost band 2|SevereNOIV)
Probability
0.0
0.2
0.4
0.6
20
40
60
Age

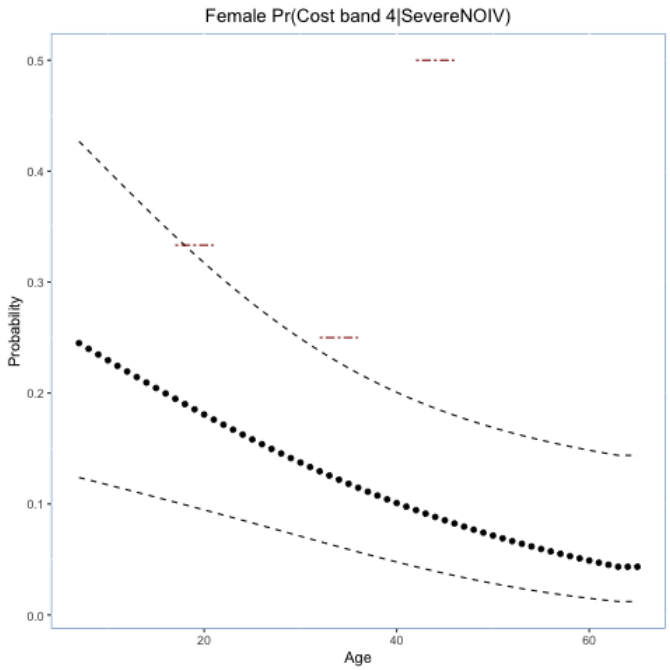

Female Pr(Cost band 2|SevereNOIV)
Probability
0.0
0.1
0.2
20
40
60
Age

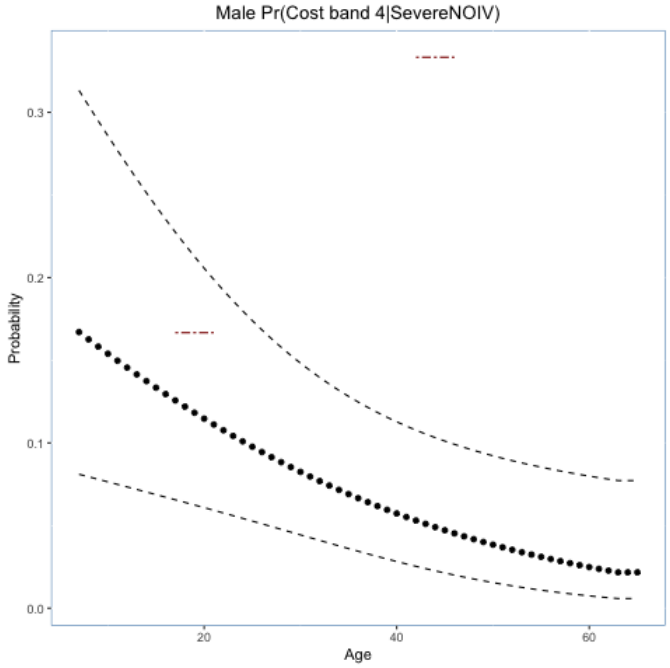

Female Pr(Cost band 2A|SevereNOIV)
1.00
0.75
0.50
0.25
Probability
20
40
60
Age

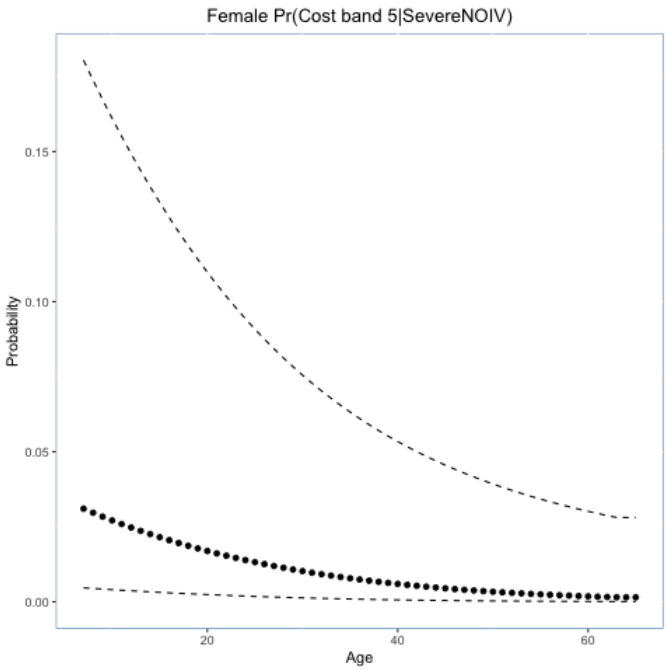

Male Pr(Cost band 2A|SevereNOIV)
1.0
0.8
0.6
0.4
Probability
20
40
60
Age

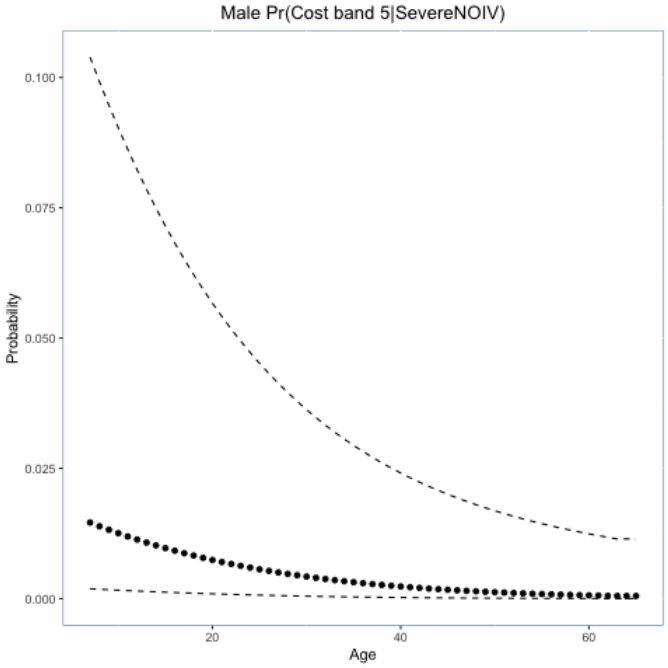

Female Pr(Cost band 3|SevereNOIV)
Probability
0.5
0.4
0.3
0.2
0.1
20
40
60
Age


Male Pr(Cost band 3|SevereNOIV)
Probability
0.6
0.4
0.2
20
40
60
Age

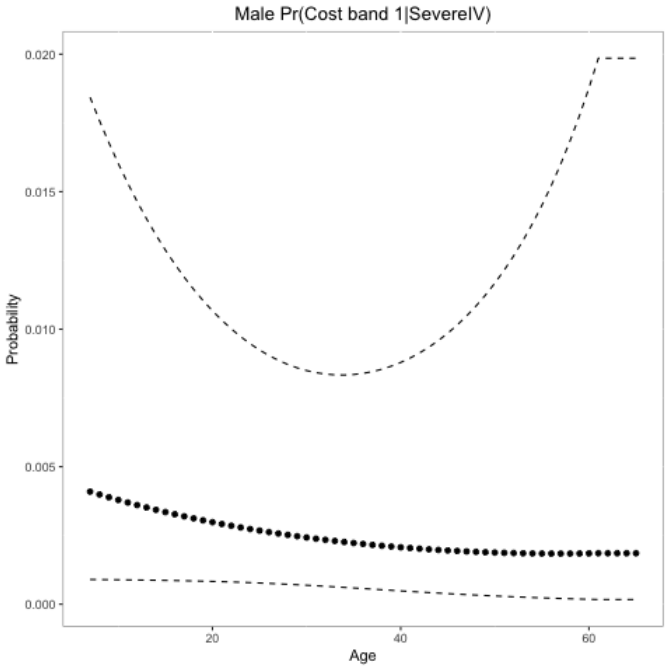

Female Pr(Cost band 4|SevereNOIV)
Probability
0.0
0.1
0.2
0.3
0.4
0.5
20
40
60
Age

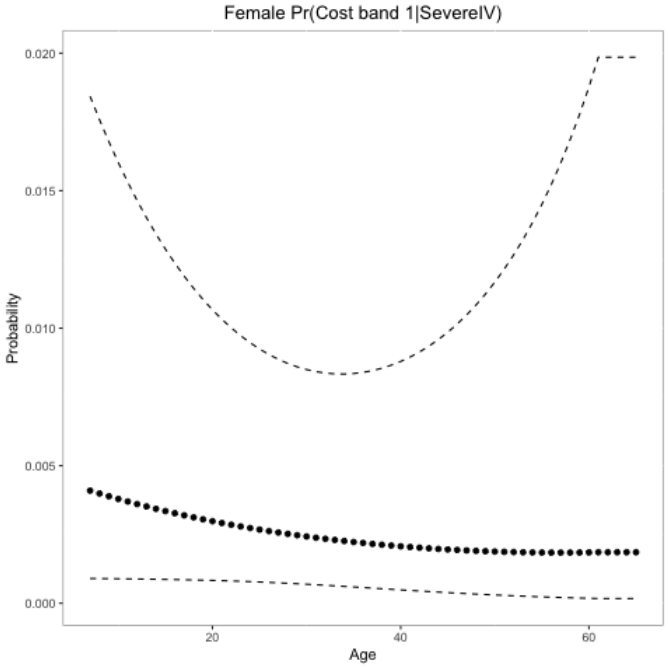

Male Pr(Cost band 4|SevereNOIV)
Probability
0.0
0.1
0.2
0.3
20
40
60
Age

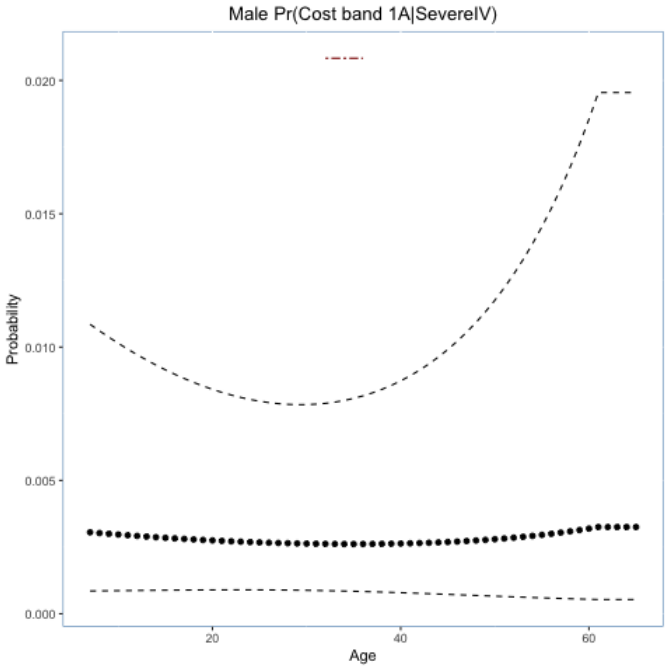


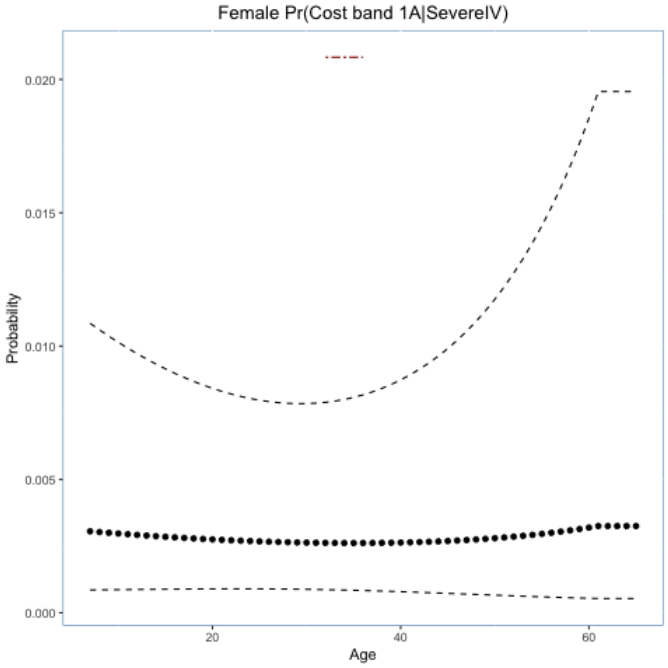


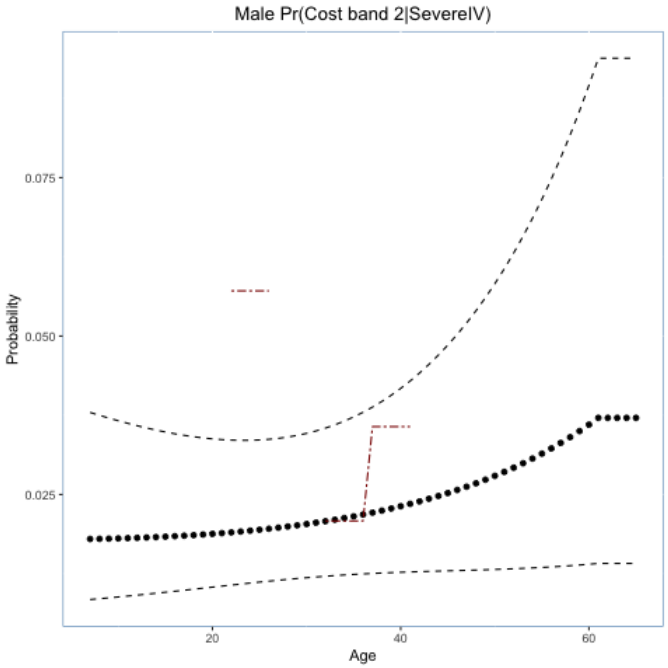
8.3.1.6 Severe IV

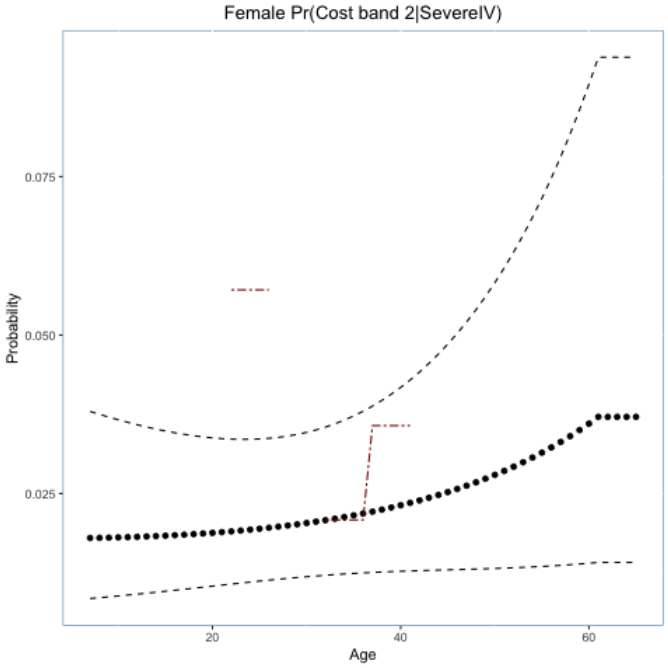

Male Pr(Cost band 1|SevereIV)
Probability
0.020
0.015
0.010
0.005
0.000
20
40
60
Age

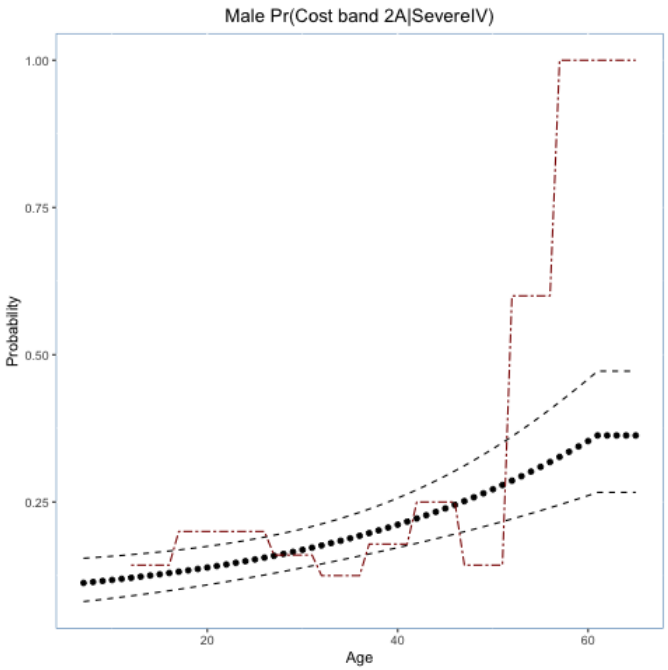

Female Pr(Cost band 1|SevereIV)
Probability
0.020
0.015
0.010
0.005
0.000
20
40
60
Age

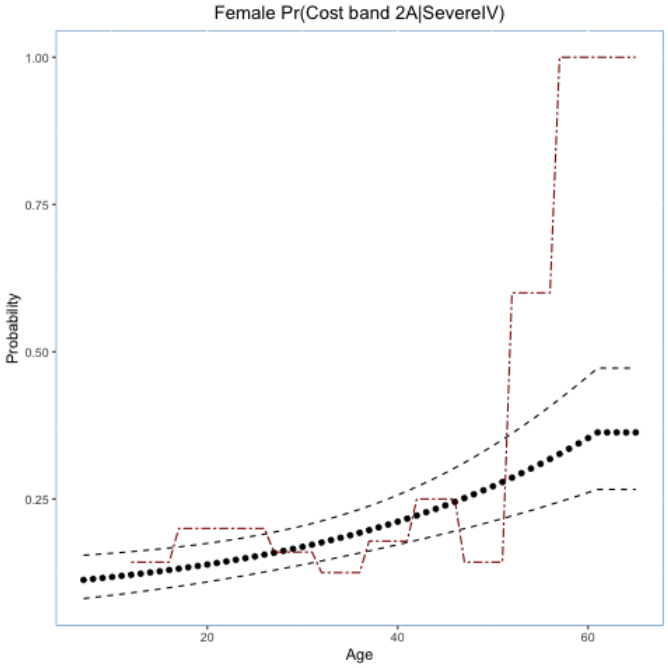

Male Pr(Cost band 1A|SevereIV)
Probability
0.020
0.015
0.010
0.005
0.000
20
40
60
Age

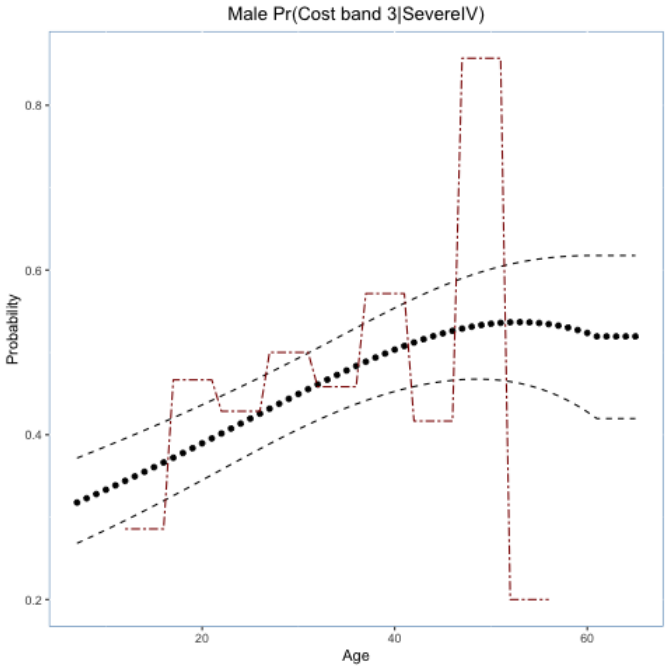

Female Pr(Cost band 1A|SevereIV)
Probability
0.020
0.015
0.010
0.005
0.000
20
40
60
Age

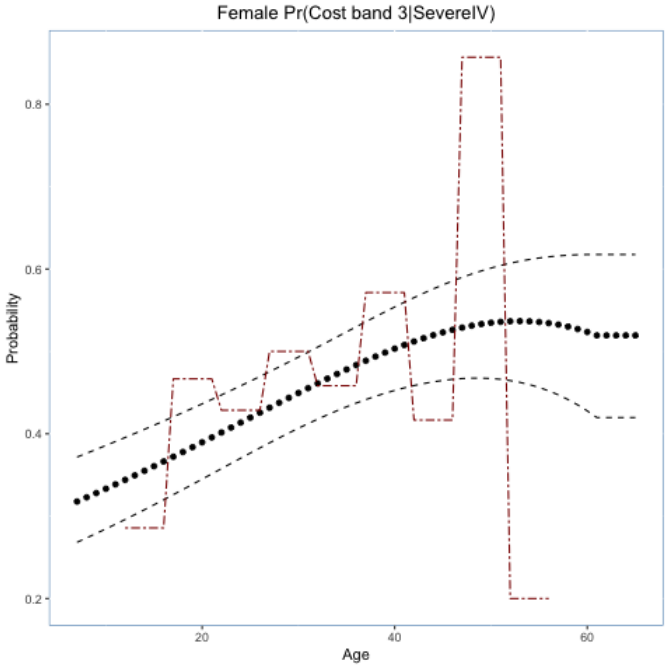

Male Pr(Cost band 2|SevereIV)
Probability
0.075
0.050
0.025
20
40
60
Age

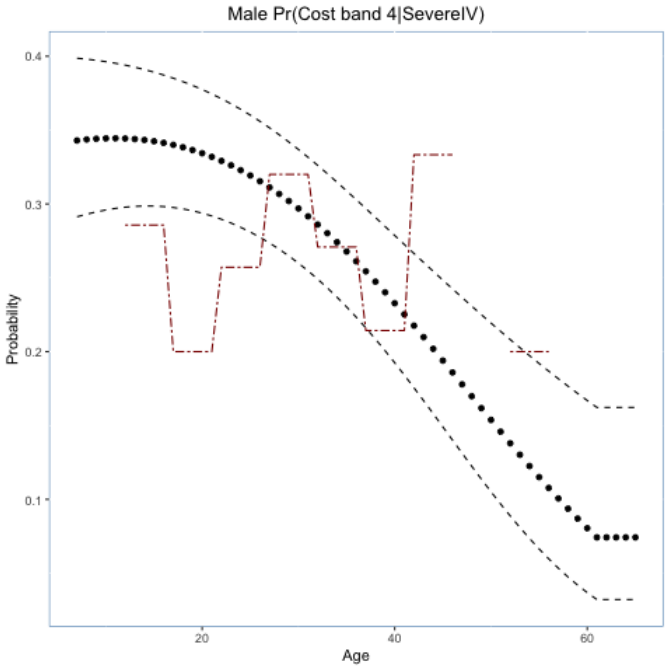

Female Pr(Cost band 2|SevereIV)
Probability
0.075
0.050
0.025
20
40
60
Age

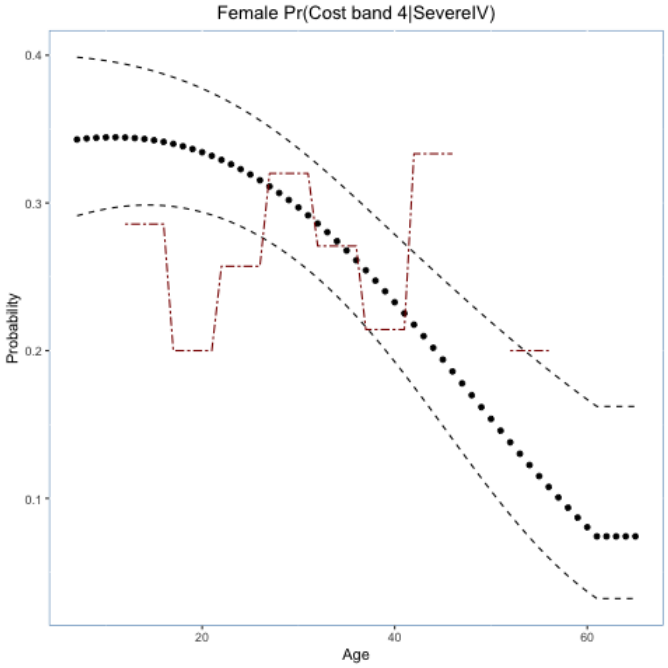

Male Pr(Cost band 2A|SevereIV)
1.00
0.75
0.50
0.25
Probability
20
40
60
Age

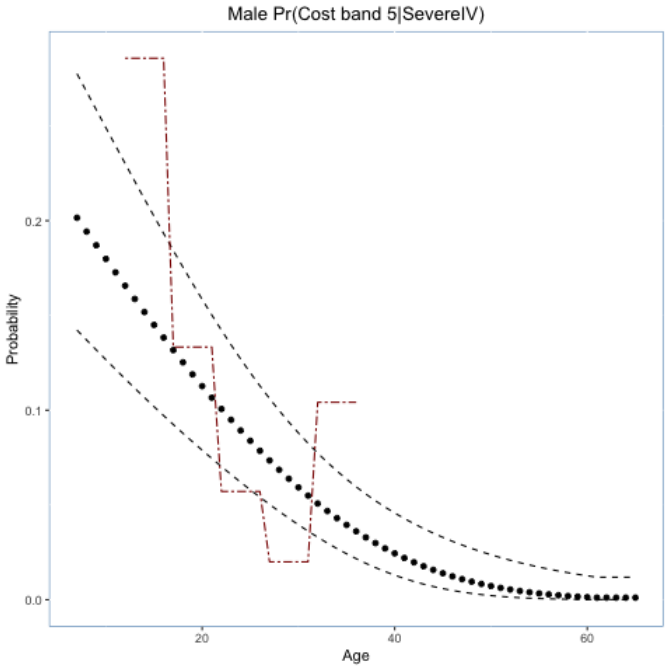

Female Pr(Cost band 2A|SevereIV)
1.00
0.75
0.50
0.25
Probability
20
40
60
Age

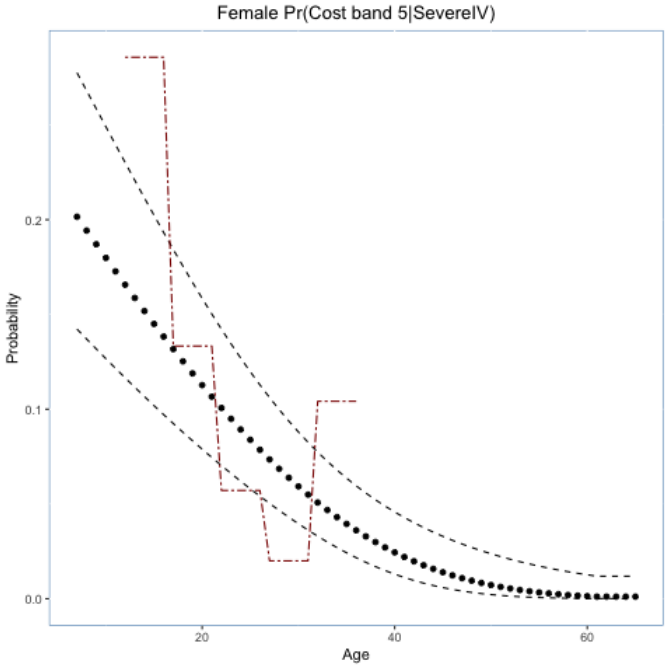

Male Pr(Cost band 3|SevereIV)
Probability
0.2
0.4
0.6
0.8
20
40
60
Age


Female Pr(Cost band 3|SevereIV)
Probability
0.2
0.4
0.6
0.8
20
40
60
Age


Male Pr(Cost band 4|SevereIV)
Probability
0.4
0.3
0.2
0.1
20
40
60
Age

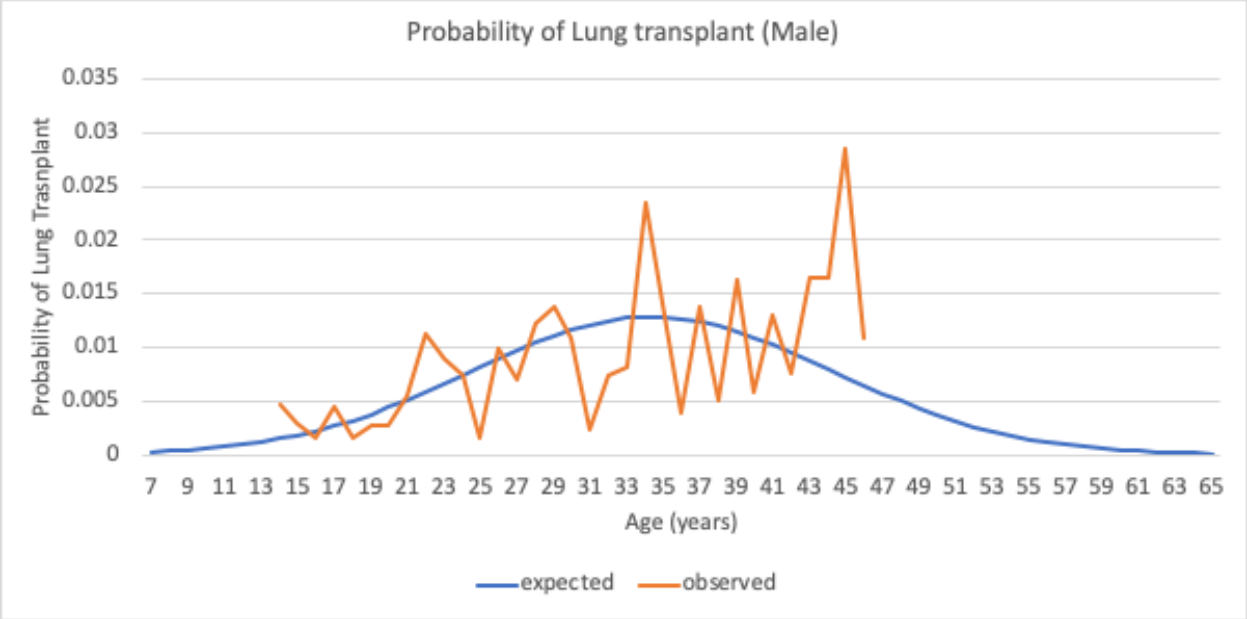

Female Pr(Cost band 4|SevereIV)
Probability
0.4
0.3
0.2
0.1
20
40
60
Age

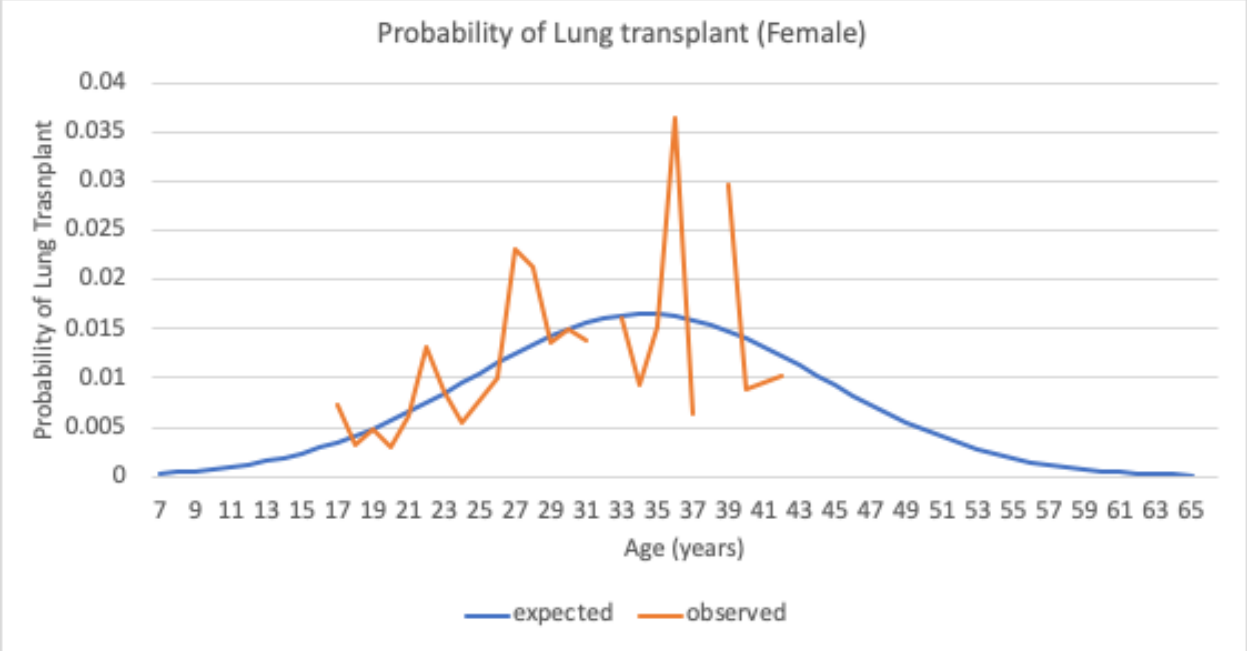

Male Pr(Cost band 5|SevereIV)
Probability
0.0
0.1
0.2
20
40
60
Age


Female Pr(Cost band 5|SevereIV)
Probability
0.0
0.1
0.2
20
40
60
Age

8.4 Appendix 4 : Plot of observed and derived lung transplant probabilities from the U.K. CF Data Registry (2016) by age and gender

8.4.1 Probability of lung transplant





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