Economics of asthma: estimating quality of life in people with asthma attacks

By

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Abstract

Asthma effects 5.4 million people in the United Kingdom. It is a chronic respiratory condition defined as frequent episodes of breathlessness, chest tightness and wheezing. An asthma attack is the progressive worsening of these symptoms, and can lead to increased healthcare resource use and reduced quality of life. It can be a costly disease, with over £1 billion of direct costs in England and Wales and over £130 million spent in Scotland.

Patient reported outcome measures (PROMs) can be used to measure quality of life, but it is currently not clear which preference-based measures are more appropriate for asthma. In most studies, quality of life is measured by PROMs at particular time points, such as baseline and 12 months, however an asthmatic episode may occur in between these time points due to the unpredictable nature of these events. Therefore, the loss in quality of life associated with an episode may not be fully captured. Alternatively, an event could occur at 12 months. This may result in an underestimation of quality of life, measured by the area under the curve technique.

Consequently, this thesis explored quality of life in acute asthmatics. Firstly, a systematic review explored the cost effectiveness of non-pharmacological asthma management interventions and the methodologies used to estimate costs and outcomes in the included studies. Secondly, a prospective cohort study estimated the loss in quality of life associated with an asthma-related crisis event (A&E attendance or hospital admission) using PROMs. Thirdly, the preference-based measures from the cohort study data set were compared using psychometric techniques.

This thesis has indicated that largest decreases in quality of life occurred during the first four weeks from the crisis event for all PROMs considered. The EQ-5D-5L and the AQL-5D had better psychometric performance compared to the other preference-based measures.

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Abbreviations

15D	15 Dimensions
ACQ	Asthma Control Questionnaire
AESM	Asthma Episode Self-Management Simulation
A&E	Accident & Emergency
AOMS	Asthma Outcome Monitoring System Questionnaire
AQLQ	Asthma Quality of Life Questionnaire
AQoL	Assessment of Quality of Life
AUC	Area Under the Curve
BMI	Body Mass Index
CBA	Cost Benefit Analysis
CCA	Cost Consequences Analysis
CEA	Cost Effectiveness Analysis
CHEERS	Consolidated Health Economic Evaluation Reporting Standards
COMET	Core Outcome Measures in Effectiveness Trials
CONSORT	Consolidated Standards of Reporting Trials
COPD	Chronic Obstructive Pulmonary Disease
CUA	Cost Utility Analysis
DALY	Disability Adjusted Life Year
EQ-5D-3L	EuroQol 5 Dimensions 3 Level
EQ-5D-5L	EuroQol 5 Dimensions 5 Level
EORTC QLQ	European Organization for Research and Treatment of Cancer Quality of Life Questionnaire
FSAS	Functional Severity of Asthma Scale
GERD	Gastroesophageal Reflux Disease
GP	General Practitioner
HAQ	Health Assessment Questionnaire
HRQL	Health Related Quality of Life
HUI	Health Utilities Index
HYEs	Healthy Years Equivalents
ICER	Incremental Cost Effectiveness Ratio

ID	Identification
IT	Information technology
KASE-AQ	Knowledge, Attitude & Self-Efficacy Asthma Questionnaire
MAQLQ-M	Modified Marks Asthma Quality of Life
MSIS-29	Multiple Sclerosis Impact Scale
NHS	National Health Service
NHS EED	National Health Service Economic Evaluation Database
NICE	National Institute for Health and Care Excellence
NMB	Net Monetary Benefit
NNUH	Norfolk and Norwich University Hospital
OHS	Oxford Hip Score
PAAPS	Personalised asthma action plans
PAQLQ	Paediatric Asthma Quality of Life Questionnaire
PedsQL	Paediatric Quality of Life Inventory
PEF	Peak Expiratory Flow
PIRC	Paediatric Illness-Related Competence Scale
PIS	Participant Information Sheet
PPI	Patient and Public Involvement
PQLQ	Paediatric Asthma Quality of Life Questionnaire
PROMS	Patient Reported Outcome Measures
QALY(s)	Quality Adjusted Life Year(s)
QHES	Quality of Health Economic Studies
RCP	Royal College of Physicians
SES	Self Efficacy Scale
SF-36	Short Form 36
SF-6D	Short Form 6 Dimensions
SGRQ	St. Georges Respiratory Questionnaire
TTO	Time Trade Off
UK	United Kingdom
VAS	Visual Analogue Scale
WHS	World Health Survey

WPAI	Work Productivity and Activity Impairment
WTP	Willingness to Pay

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Many people deserve a moment of thanks for their continued support and guidance throughout my PhD journey, and I would like to take this opportunity to express my gratitude.

Firstly, this PhD would not have been possible without the initial belief and encouragement from my three supervisors who granted me the opportunity to undertake this project, and my funders (National Institute for Health Research, Collaboration for Leadership in Applied Health Research and Care, East of England). I will be forever grateful! My primary supervisor (Professor Garry Barton), secondary supervisor (Professor Andrew Wilson), and tertiary supervisor (Professor Tracey Sach) provided continued support throughout the duration of my PhD from initial thoughts to thesis drafts and papers, of which my appreciation does not wear thin. I particularly give thanks to Professors Barton and Sach for their health economic insight and Professor Wilson for his clinical expertise. I also thank Ms Angela Robinson and Dr Chris Skedgel for their time and constructive feedback during my upgrade from MPhil to PhD.

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I also thank all those who have taught me over the three years and enhanced my learning and training skills in different stages of my PhD; from Good Clinical Practice training through to more technical aspects such as psychometric training. I also thank those who gave me the opportunity to present at various different conferences (asthma and health economic conferences) as it allowed me to get the exposure and expertise from different disciplines, which helped to strengthen my PhD project.

Special thanks goes to my partner, family and friends for their continued support, encouragement and love throughout this journey. This was very necessary and so deeply valued – I am so grateful that they are in my life.

Publications from thesis

I, Christina-Jane Crossman-Barnes, wrote and structured this thesis. However, there was a collaborative work, which contributed to the overall thesis, where a publication was the end result. The publication achieved from this thesis is listed as follows:

Chapter 2:

Crossman-Barnes C-J, Peel A, Fong-Soe-Khioe R, Sach T, Wilson A, Barton G. Economic evidence for nonpharmacological asthma management interventions: A systematic review. *Allergy*. 2017;00:1–14

CJCB, TS, AW and GB were involved in the design of this study from conception. CJCB, AP and RFSK participated in the systematic process of screening the titles, abstracts and full texts of articles based on the eligibility criteria. CJCB, AP and RFSK also contributed to the data extraction and quality assessment stages. CJCB drafted the manuscript, with all authors providing critical revisions and final approvals.

Submitted manuscripts

I have submitted two additional manuscripts from **Chapters 3, 4 and 5** of my thesis. The titles and authors of these manuscripts are detailed below:

Chapters 3 & 4:

Crossman-Barnes C-J, Sach T, Wilson A, Barton G.

Estimating loss in quality of life associated with asthma-related crisis events (ESQUARE): a cohort, observational study.

Chapter 5:

Crossman-Barnes C-J, Sach T, Wilson A, Barton G.

The construct validity and responsiveness of the EQ-5D-5L, AQL-5D and a bespoke TTO in acute asthmatics.

CJCB, TS, AW and GB were involved in the design of the study from conception. CJCB was involved in recruitment, consent, follow up, data collection and analysis of the participants in the study. CJCB drafted the manuscript, with all authors providing critical revisions and final approvals.

Conference attendance

Throughout my PhD, I have attended several conferences and presented either poster or oral presentations. From each conference, I have had the opportunity to network and present to a varied audience from different professional backgrounds, whilst gaining some feedback on my work. Below is a list of the conferences that I have attended over my PhD years and the type of presentation that was given.

Conferences & Locations	Months and Years	Presentations
EuHEA PhD student-supervisor conference, Paris (France) and Lausanne (Switzerland)	September 2015 and 2017	Oral (2017)
Asthma UK Centre for Applied Research, Manchester and Edinburgh (UK)	September 2015 and 2016	Posters (2015 and 2016)
The Faculty of Medicine and Health Sciences Conference, Norwich (UK)	May 2016 and 2017	Poster (2016) and Oral (2017)
Connecting for research, CLAHRC, Cambridge (UK)	June 2016	Poster
International Health Economic Association conference, Boston (USA)	July 2017	Oral
Joint Asthma UK Centre for Applied Research and Mechanisms Research Centre, London (UK)	September 2017	Oral
Primary Care Respiratory Society Conference, Telford, (UK)	September 2017	Poster

CHAPTER 1

ASTHMA, A COMMON LUNG CONDITION: BACKGROUND TO THE DISEASE AND ECONOMICS

"What people need to know is that asthma isn't a minor 'wheeze-disease'. It kills over five thousand people in America every year, and I could've been one of them."

(Jackie Joyner-Kersee, retired American athlete)

Preface

Asthma is more serious than people tend to think. Some people may not fully understand the condition, and how it can impact someone's life. It can be unpleasant to live with this condition day in and day out, especially if the sufferer has a severe case that is not well controlled. A wheeze is just one of the symptoms that may be experienced with asthma; three more common symptoms frequently associated with this disease are shortness of breath, coughing and chest tightness. These symptoms often appear sporadically and can be time varying.

Economics in health care is crucial for society. We are dependent on our health care services and with an increasing population; the demand for health care services will inevitably increase. However, the budget for such services can only stretch so far, and efficiency, efficacy, and effectiveness are often the terms health care policy makers take into consideration. They make frequent decisions about the health care services and resources to see if they should be increased, reduced or even cut completely from the sector. These decisions are important because resources are scarce, and so policy makers have to decide and prioritise services, where if they seek to maximise the benefits from a given budget then they provide those services that have the greatest benefit for a given cost. To guide them into making these tough decisions, health economists use a process of economic evaluation in order to evaluate and analyse costs and benefits in health care.

This chapter provides an opening introduction into asthma. It will highlight how this lung condition has affected different socio-economic groups across the world, and explore the prevalence of this condition in different countries. Definitions and diagrams will aid the explanation of the lung condition further. Following this, I will provide information about what triggers contribute to asthma flare-ups and severe asthma attacks. Each individual will have different severities of asthma, but all individuals have the chance of suffering from an asthma attack. The chapter will also discuss what happens during an asthma attack and how to manage and treat asthma. To round off this chapter, I will discuss, the core economic concepts involved in economic evaluation and consider how these can be used to explore asthma further. The chapter will conclude with the aims and structure of this thesis.

1.1 The Prevalence and Cost of Asthma

Statistics show that asthma is a common condition with increasing global prevalence (Braman, 2006), with 5.4 million people suffering from asthma in the United Kingdom (UK) (Royal College of Physicians, 2014). For the UK, this equates to 1 person in every 12 adults suffering with this condition, with deaths of 3 times a day (Asthma UK, 2014). The true global prevalence of asthma can be difficult to obtain due to gaps in asthma statistics. From the latest Global Burden of Disease Study, it has been reported that as many as 334 million people in the world suffer from asthma (Global asthma network, 2014), however since the analysis took place between 2008 and 2010, the global asthma prevalence could have changed since then.

An earlier analysis conducted between 2000 and 2002 stated that there were 235 million people who suffered from asthma (WHO, 2015a). The difference between these different year periods (2008 to 2010, and 2000 to 2002) in the number of asthma sufferers is just short of 100 million people. This difference cannot fully confirm that the burden of asthma has increased by this amount because of the shortfalls in the literature (Global asthma network, 2014). Despite this, asthma continues to grow across all demographic groups, affecting people of different ages, ethnic groups and races, across developing and developed countries and within urban and rural areas (Ferkol and Schraufnagel, 2014).

A previous study helped to identify the prevalence of asthma in different countries by asking individuals asthma related questions using a World Health Survey (WHS) (To et

al., 2012). These individuals were based across 70 different countries where the sample was stratified by age, gender, and urban or rural living environments. **Figure 1** shows the worldwide prevalence of *clinical asthma* with five countries showing areas of the highest prevalence. The term *clinical asthma*, means doctor diagnosed asthma and/or been previously treated for asthma or having recently taken asthma medications over the last 2 weeks (To et al., 2012). Brazil, the Netherlands, UK, Sweden, and Australia are the countries showing the highest prevalence of clinical asthma. They had prevalence's of 13.0%, 15.3%, 18.2%, 20.2% and 21.5% respectively, with a range of asthma prevalence between 1.0% (Vietnam) to 21.5% (Australia) in all included countries.

Figure 1: Worldwide prevalence of clinical asthma

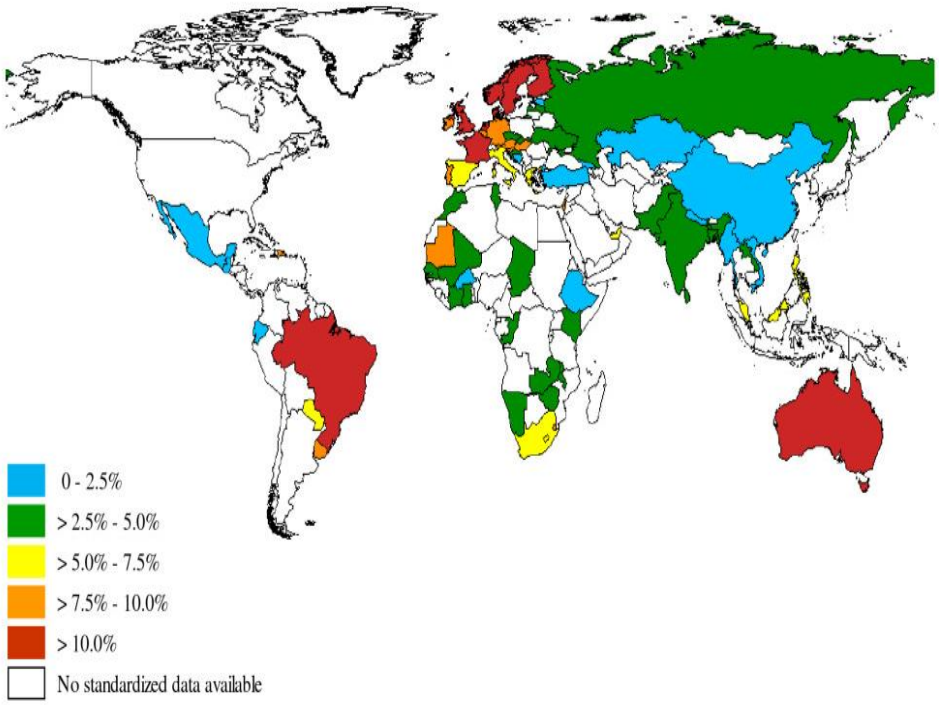


Figure taken from: (To et al., 2012)

The range of prevalence for *doctor diagnosed* asthma - which simply means being diagnosed with asthma – was very similar to the prevalence of *clinical asthma* being between 0.2% (China) and 21.0% (Australia) of the included countries (To et al., 2012). A further question asked in the WHS referred to experience of wheezing in the last year. This was termed *symptoms of asthma*, meaning, whistling or wheezing attacks occurred

over the last year (To et al., 2012). The highest prevalent countries for the *symptoms of asthma* **(Figure 2)** were the same as the highest prevalent countries for *clinical asthma* but with the increasing rates observed in order of Sweden (21.6%), Brazil (22.6%), the UK (22.6%), the Netherlands (22.7%) and Australia (27.4%).

Figure 2: Worldwide prevalence of wheezing asthma

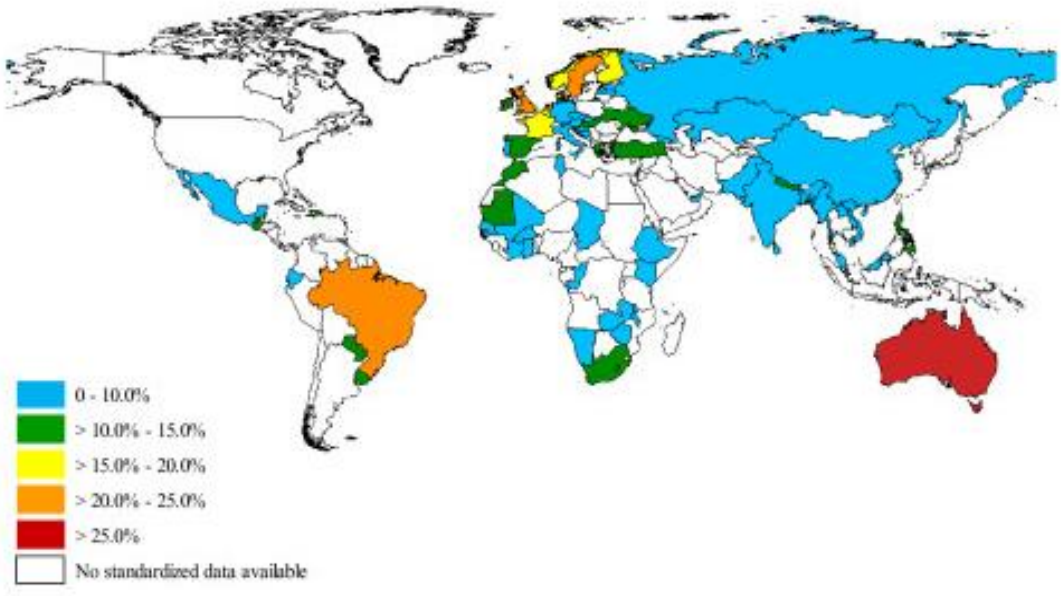


Figure taken from: (To et al., 2012)

There were very minimal differences in *clinical asthma* between urban (4.91%) and rural (4.86%) locations, in most regions, except the Western Pacific (To et al., 2012). Interestingly, another study highlighted that people from Latino and African-American backgrounds showed higher rates of asthma diagnoses and severity, particularly in inner-city urban areas (Gold et al., 2013) and most asthma deaths occur in low and lower middle income countries (WHO, 2015a). However, despite this global representation of asthma prevalence in **Figure 1** and **Figure 2**, only ages between 18 and 45 years were captured through the WHS, which omits populations outside of this range. Asthma sufferers older than 45 years were excluded, perhaps due to the overlap between asthma and Chronic Obstructive Pulmonary Disease (COPD), where the latter has higher prevalence in those over 40 years. (WHO., 2016). Nevertheless, it has been reported that 10-14 year olds and 75-79 year olds bear the greatest asthma burden categorised as a disability and early death (Global asthma network, 2014).

There are a number of other conditions that are associated with asthma (Boulet and Boulay, 2011). The more commonly reported ones known to have this association are chronic rhinitis, chronic sinusitis, gastroesophageal reflux disease (GERD), obstructive sleep apnoea, physiological disturbances, (such as; depression and anxiety), chronic respiratory infections, COPD, hyperventilation syndrome, vocal cord dysfunction, hormonal disturbances, obesity and smoking (Boulet and Boulay, 2011). Asthma can contribute to the development or worsening of these comorbidities through various factors such as reduced activities, poor quality of sleep and taking oral corticosteroids as part of medication (Boulet and Boulay, 2011). It is presently unclear which age groups present with higher prevalence of comorbidities associated with asthma. Further research is needed to ascertain this, particularly in children (de Groot et al., 2010).

The economic costs associated with asthma are high, because of the morbidity and mortality from asthma and other associated comorbidities (Mukherjee et al., 2014). Costs are further attributed to poor asthma management, smoking, asthma severity, age, gender and disability status (Bahadori et al., 2009). Poor asthma management – often associated with low socioeconomic status - or sub-optimal use of asthma medications and services, results in significantly larger expenses on healthcare and society compared to those patients who have relatively well-controlled asthma (Gold et al., 2013).

Both *direct* and *indirect costs* are considered in the costing of asthma care. *Direct costs* are associated with inpatient care, physician and nursing care, bloods, drugs, diagnostic tests and devices, accident and emergency (A&E) care, ambulances, research and education (Bahadori et al., 2009). *Indirect costs* are associated with lost days at work or school, caring time for children, travel and waiting time (Bahadori et al., 2009). It is known for direct costs to be much higher than indirect costs (Bahadori et al., 2009). There are discrepancies amongst studies on the definitions of direct and indirect costs, and so these terms should be used with caution.(Drummond et al., 2015)

The direct health care costs for patient care and management of asthma in England & Wales, and Scotland, are estimated at over £1 billion and over £130 million per year. (Mukherjee et al., 2014). For England and Wales, 20% of this cost is spent on asthma patients who are hospitalised, where around 1400 patients are admitted to hospital each

week (Asthma UK, 2015). It has also been reported that indirect costs (time off work and productivity losses) amount to £6 billion in the UK (Scott, 2015). With such increasing prevalence, the burden of asthma will continue to cause a major cost impact on healthcare services and on society, unless costs can be reduced and asthma management improved. The National Health Service (NHS) cannot withstand this level of high cost, as resources are scarce and funds are limited. Therefore, it is important to continually find ways that can improve the health care system and society. In order to relate to the extent of this burden, it is important to understand how asthma is defined and how debilitating it can be. To help identify with this, the next section will define asthma and highlight the typical symptoms associated with this condition.

1.2 Definition and Symptoms of Asthma

Asthma is a common, chronic respiratory condition that affects the lung function (Cartier, 1994). It is defined as frequent episodes of breathlessness and wheezing (whistling sounds), which varies amongst individuals (WHO, 2015a). Symptoms can include tightness of the chest, shortness of breath, wheezing or coughing (Royal College of Physicians, 2014). The coughing is usually presented in the form of a dry, hoarse cough that often makes the throat sore and irritated. These symptoms can be worse at night or in the morning, and can even disrupt sleep, hence affecting sleeping patterns (National Heart Lung and Blood Institute, 2007).

A person with asthma presents with irreversible inflamed and narrower airways compared to an individual who does not have asthma or a respiratory condition (WHO, 2015a). The airways transport oxygen to the lungs, and so those who have asthma have reduced airflow. Various triggers, which exacerbate the condition and lead to an asthma attack, can expedite the decrease of airflow to the lungs. Examples of such triggers will be explained in more detail, later on in this chapter.

Asthma severity can range from mild to severe. This is often identified from the frequency of symptoms, which can occur as often as several times a day or multiple times a week. Individuals who do physical activity can also experience worsening of their symptoms (WHO, 2015a). More severe asthmatics have difficulties most of the time and this can hinder their usual activities and performances in the workplace or school environment (Cartier, 1994).

Providing a comprehensive definition for asthma, and its severity or frequency of symptoms has proven challenging (Stirling and Chung, 2001, Royal College of Physicians, 2014). It is recognised that the frequency of asthma symptoms, the lung function impairment and the control of asthma symptoms through treatment management all have a factor in determining the definition (Stirling and Chung, 2001). Severe asthma indicates more frequent occurrences of asthma attacks, stronger medications, and possible admissions to hospital or A&E attendances (Royal College of Physicians, 2014).

Asthma symptoms can occur at any age (National Heart Lung and Blood Institute, 2007). They can appear dormant and resurface some years later. It is not truly known what causes the onset of these asthma symptoms, but we are aware of who is more likely to get asthma and the certain triggers which activate this condition (WHO, 2015a). The next section will discuss these typical triggers

1.3 What Causes Asthma and how is it diagnosed?

A person with asthma usually has this condition because of genetic factors combined with an allergic reaction to environmental stimuli (WHO, 2015a). In the absence of a gold standard definition, it is difficult to diagnose newly presenting cases, although it is clinically appropriate to identify any presence of more than one of the typical symptoms, (shortness of breath, tight chest, wheezing and coughing), as a starting point for a diagnosis (British Thoracic Society. Scottish Intercollegiate Guidelines Network, 2014). Asthma can develop early in life as a child, or later in life as an adult (late-onset asthma), whilst at work (occupational asthma) or even seasonal (Royal College of Physicians, 2014). People with asthma can have allergic or non-allergic asthma.

The National Institute for Health and Care Excellence (NICE) recommend that lung function tests are performed to help confirm the diagnosis of asthma in individuals (National Institue for Health and Care Excellence, 2015). In particular, NICE prefers the use of spirometry compared to the peak expiratory flow (PEF) to examine the breathing capacity of an individual. However, once diagnosed, the PEF is a good indicator that is used for asthma monitoring (British Thoracic Society. Scottish Intercollegiate Guidelines Network, 2016). It is an instrument that measures airflow in the airways. This enables

clinicians and people with asthma to see what their best/normal PEF reading is, and if the readings fall, then both parties know that the person with asthma requires further medical assistance. Furthermore, trials of different treatment strategies are being undertaken to identify which medications work best for the patient (British Thoracic Society. Scottish Intercollegiate Guidelines Network, 2014).

Factors such as age, sex, and atopic (hyper allergic) history in both patient and family, and abnormal lung function also play a role in the diagnosis (British Thoracic Society. Scottish Intercollegiate Guidelines Network, 2014). For children, it is likely that males grow out of their asthma during puberty, whereas females are more likely to remain with their asthma during adolescence. For those who have coexisting atopy, such as eczema or allergic rhinitis (hay fever), or have a family history of atopy, in particular maternal atopy, then they have an increased risk of being diagnosed with asthma. However, this risk is not only limited to these individuals. Smokers or exposure to smoke, being premature at birth, or having bronchiolitis when a young child, also increases the risk of asthma diagnosis further.

Environmental factors also cause asthma symptoms to be noticeable – the range is extensive (Royal College of Physicians, 2014, British Thoracic Society. Scottish Intercollegiate Guidelines Network, 2014). Exposure to irritants; such as pollen, dust mites, animal fur, cigarette smoke, pollution and chemical fumes, are some of the common allergens and airborne irritants that might stimulate symptoms in people who have asthma. Other triggers include, a sudden change in temperature or weather conditions, whether that be rain, extreme heat, sudden icy conditions, or thunderstorms can be further triggers, which worsen asthma symptoms. Food allergies and particular medicines, (e.g. aspirin, ibuprofen, beta-blockers), might play a role too, and it may be surprising to some, but emotional changes can also cause an effect, including laughter and stress. Exposure to these triggers can result in a person suffering from an asthma attack. The onset of an asthma attack can happen very quickly without any noticeable developments and can get progressively worse over time, which could be fatal and cause death. To understand what happens to an asthma sufferer during an asthma attack, the next section will detail the scientific process.

1.4 What does an Asthma Attack mean?

An asthma attack is an acute response to triggers, which causes a person's asthma symptoms to worsen. The chest tightness, wheezing, breathlessness and/or coughing can suddenly escalate and lead to increased difficulties in speaking, walking, eating, sleeping and undertaking usual activities (Asthma UK, 2015). When asthma attacks occur, structural changes in the airways take place, (in both cases of mild or severe asthma), and the airways narrow causing airway obstruction. The structural changes in the airways are called airway remodelling, and the smooth muscle usually becomes scarred and enlarged due to hypertrophy (increase in cell size) and hyperplasia (increase in the number of muscle cells) spreading through the airways (Jarjour and Kelly, 2002, Holgate, 2008).

Asthma attacks can vary in terms of severity, and physicians often categorize them as mild, moderate, severe and life threatening (British Thoracic Society. Scottish Intercollegiate Guidelines Network, 2016). Sometimes asthma symptoms can be eased by taking the prescribed medications, usually a Ventolin inhaler (Asthma UK, 2015). However, if the patient does not get any relief from the Ventolin inhaler, then depending on the severity of their symptoms, a GP visit or A&E attendance usually follows. Patients may call the ambulance service immediately, or at the GP visit, the GP may refer the patients to hospital. Upon attendance to hospital, initial assessment of clinical features (e.g. ability to talk in sentences), PEF, oxygen levels and blood gases are taken routinely, in order to categorize the acute asthma into mild, moderate, severe or life threatening asthma (British Thoracic Society. Scottish Intercollegiate Guidelines Network, 2016). Once the test results categorize the asthma, decisions are made to admit patients and decide on their treatment pathway. The median length of stay is reported as 7 days (Gibbison et al., 2013), where physicians and nurses aim to get the patient's PEF to between 70% and 75% of their normal PEF before discharge (British Thoracic Society. Scottish Intercollegiate Guidelines Network, 2016, Camargo et al., 2009). In addition, patients are likely to have been experiencing their asthma symptoms for a few days prior to admission, with symptoms rapidly increasing two or three days before an asthma attack (Asthma UK, 2016).

Having an asthma attack is unpleasant and can leave someone distressed and out of control. To prevent regular occurrences of these asthma attacks, it remains important to

have a good asthma management plan and strategy that allows the person with asthma to be able to control their symptoms and minimize the likelihood of a severe asthma attack. People who don't have well-controlled asthma often have low asthma control test scores, concurrent with low health-related quality of life (HRQL) scores (Guilbert et al., 2011). These individuals are at higher risk of having extra GP visits, A&E attendances and hospital admissions (Guilbert et al., 2011). Controlling the occurrence of asthmatic events and managing symptoms properly has benefits for both asthma sufferers and the healthcare services in general. Therefore, the next section will discuss what common steps are taken to manage asthma.

1.5 Asthma management and Treatment

Monitoring treatment, after diagnosis has been made, usually occurs in an asthma review which takes place once every year (British Thoracic Society. Scottish Intercollegiate Guidelines Network, 2014). This is subject to the individual being "well" in between each period of review, as otherwise additional appointments may have to be made to extend the asthma management further. Additional appointments occur because of unscheduled GP appointments, A&E attendances or hospital admissions due to asthma during the year.

The management of asthma can be categorised into self-management, pharmacological and non-pharmacological management (British Thoracic Society. Scottish Intercollegiate Guidelines Network, 2014). *Self-management* is defined as individual tasks to manage the condition (medically and emotionally), with support on how to recognise and act on deterioration (Pinnock, 2015). Potential methods for effective self-management are education based management with information technology (IT), and personalised asthma action plans (PAAPs) (British Thoracic Society. Scottish Intercollegiate Guidelines Network, 2014). The PAAPs enable the recording of loss of asthma control and include specific advice about how to recognise this. They also cover action points that should be taken when asthma deteriorates. However, this style of PAAP will not suit all patients, as some patients will be illiterate, or blind. To cater for the illiterate population, a study conducted in Turkey designed a pictorial asthma action plan and tested its effectiveness combined with a standardised educational program (Pur Ozyigit et al., 2014). They discovered that for their female population aged between 18 and 55 years old, their asthma control and HRQL improved over a 6 month period. It was also shown that the pictorial asthma action plan and the education program worked effectively together as there were

no hospital admissions over this 6 month period and fewer A&E attendances were seen. Even though, this study showed comprehensive findings, the male population were excluded from this study design, and therefore not generalizable to the male population.

During the approach of an asthma plan, it is important to have a good relationship with the clinician or healthcare professional that is involved. This professional partnership will gain patient confidence, knowledge and skills, and hopefully the patient will become more willing to discuss their treatment and come to a joint decision on how to move forward to better improve health (Bateman et al., 2008). Some studies which include trials in self-management of asthma have used both primary care and secondary care population groups (British Thoracic Society. Scottish Intercollegiate Guidelines Network, 2014). Even though this can be a difficult task to get the patients involved and compliant to the trial investigation, it has been shown to reduce A&E attendances, hospital admissions and use of health care resources.

Pharmacological management follows a cycle in a step-wise motion, which is seen in **Figure 3** (Bateman et al., 2008). Firstly, there is assessment of the asthma control, if the asthma is not controlled then increasing the treatment is considered, otherwise if controlled for ≥ 3 months then reducing the treatment is considered, and then finally control is to be maintained (van Weel et al., 2008). A preventer medication (helps to prevent an asthma attack) and reliever medication (helps to improve symptoms when having an asthma attack) are usually administered to patients with asthma.

Figure 3: The step-wise process displayed as part of asthma pharmacological management with different treatment options available.

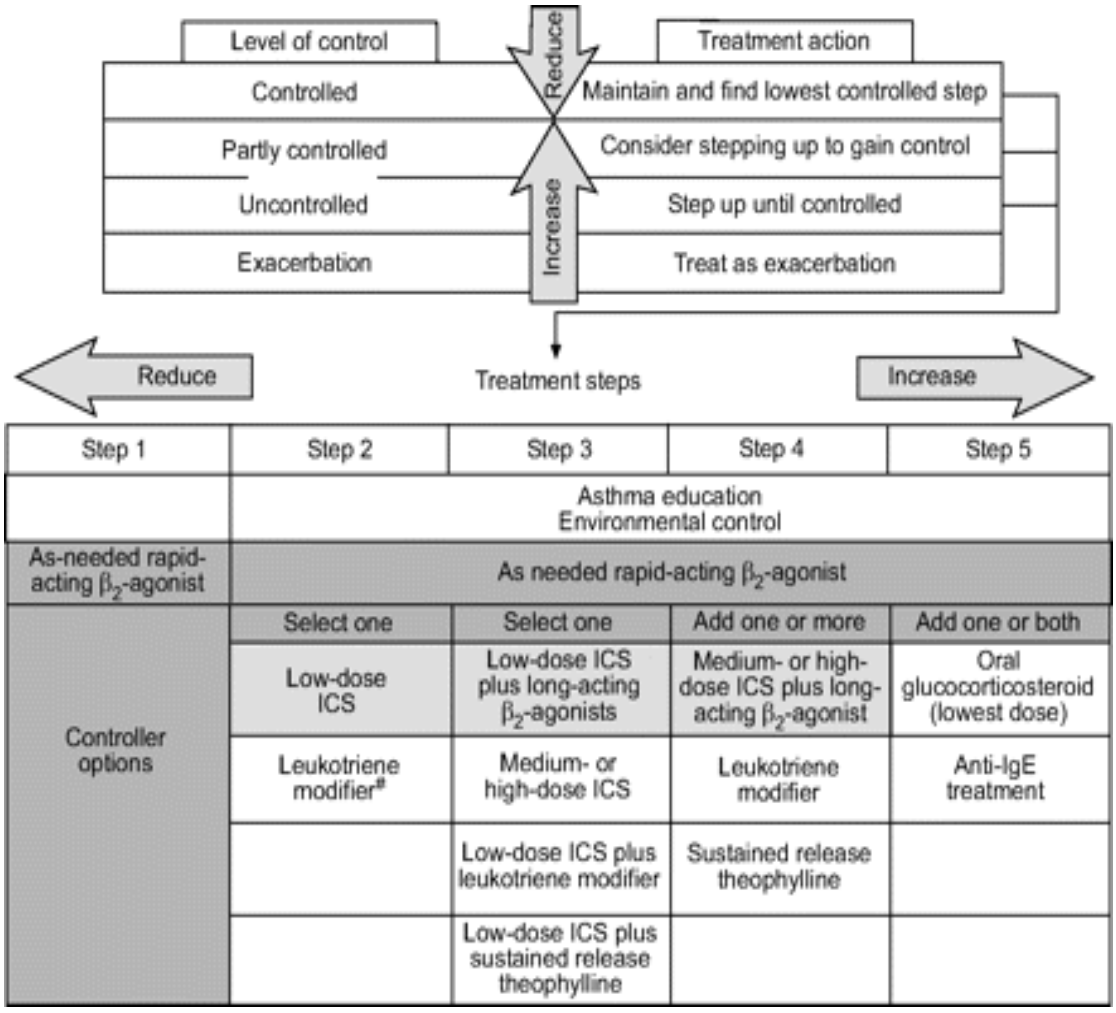


Figure taken from: (Bateman et al., 2008)

For the non-pharmacological asthma management, it is important to minimise risk to the patients by reducing exposure to their known triggers, which cause their asthma to flare-up (Funston and Higgins, 2014). This will play a huge part in keeping their asthma controlled, and reduce any sudden asthma attacks, which may require a hospital admission and more intensive forms of treatment. Further education programmes are encouraged, through health professionals and also school staff (Lawlor, 2015). For

children, it is vital that school staff members are aware of asthma and its difficulties so that they are fully equipped if a child's asthma condition deteriorates whilst on their school premises (Lawlor, 2015).

It is also important to realise that it is not just down to the healthcare practitioners and the educational programs to help manage asthma, but it also lies in the hands of the person who has asthma. People with asthma have to want to improve their asthma control and management. An effective way of doing this, in addition to what has already been outlined above, is by doing physical activity. A group of mild to moderate asthma patients have been shown to improve their asthma control and quality of life over a four month period after starting a physical activity program (Mancuso et al., 2013). After being monitored for a further six months, their asthma control and quality of life had resided to a steady controlled state. However, the HRQL questionnaire (Asthma Quality of Life Questionnaire) that was used to capture this data was only asked at baseline, 4, 8, and 12 months, and so we are unaware of any potential drops in asthma control and quality of life in between these time points. This study also leaves a thought, as to whether the same results would occur for those with more severe asthma. The importance of quality of life, what it is, and how it relates to asthma sufferers will be discussed in the next section.

1.6 Quality of life in asthmatics

The term 'quality of life', can be used in different contexts such as housing, relationships, work and social life. HRQL specifically relates to an individual's health and any clinical interventions associated with this. Quality of life in asthma patients can deteriorate differently from person to person, depending on the severity of their condition (Royal College of Physicians, 2014), with some factors being more detrimental than others. It is important to be able to maintain or improve someone's quality of life especially if they are bearing the burden of distress from it on a daily basis.

Typically, the areas of concern for measuring HRQL are the individual's physical, mental and social attributes (Andresen and Meyers, 2000). Other areas may also be assessed, but this is often related to whether a *generic* or *disease-specific* approach is taken (Guyatt et al., 1999). The term *generic* means how the particular HRQL aspects relate to people in general, (i.e. it can be used across a range of different conditions), and the *disease-specific* term means how particular HRQL aspects relate to people with a specific disease or

condition. HRQL can be measured on a utility scale (a scale for valuing health), with 0 representing the dead state and 1 representing the perfect health state (Kopec and Willison, 2003).

To determine what factors really reduced HRQL in asthmatics, a study was conducted where they interviewed 150 patients who were 18-70 years old and presented them with a list of 152 items (Juniper et al., 1992). This list of 152 items was generated in the item selection phase where people with asthma were interviewed and it included what was important to patients with asthma. The 150 patients included in this phase of the study then identified the most important items from this list, and amongst the obvious physical and environmental items, tiredness, irritability and mood changes also seemed to reduce HRQL. The aim from this study was to create a questionnaire that can be used to assess HRQL in asthmatics; the Asthma Quality of Life Questionnaire (AQLQ). The AQLQ is a disease-specific questionnaire and is composed of 32 questions with 4 domains, which are symptoms, activity limitation, emotional function and environmental stimuli. Each question can be responded to on a 7 point scale ranging from severely impaired (score 0) to not impaired at all (score 7) (Young et al., 2011).

A study assessing the quality of life in bronchial asthma patients showed that out of the 4 domains, the symptom domain showed the maximum number of limitations of this questionnaire (Nalina et al., 2015). In addition, females had more of a limitation in their quality of life compared to males, accompanied with patients being obese. Age and BMI were also associated with lower HRQL according to Nalina et al. (2015). Another study used a generic quality of life questionnaire, the 15D, to assess what factors influenced quality of life with asthma patients (Al-kalemji et al., 2013). The 15D is composed of 15 different dimensions with 5 different levels for each dimension. The levels range from no problems for level 1 to severe problems for level 5, and it is a self-completed questionnaire with utility values ranging between 0 and 1. The results of this study showed that anxiety, depression, smoking, female gender and obesity were all associated with lower levels of quality of life in asthmatics. However, there was a significant number of participants who were obese and had psychiatric comorbidities, and so these individuals may have had an effect on the outcome of the results. It is interesting to see here that a generic quality of life questionnaire was used for this study (Al-kalemji et al., 2013), but for the earlier study a disease-specific quality of life questionnaire was used

(Nalina et al., 2015). Despite this difference, the results show correlations between both studies for gender and BMI as being factors that have an effect on the quality of life of asthmatics.

HRQL are useful measures in studies. Types of economic evaluations, e.g. a cost-utility analysis (CUA), are often undertaken (see **section 1.8.1** for the outline of different types of economic evaluations) with the value of different interventions compared, *Quality Adjusted Life Years (QALYs),* (which incorporates quality of life and life expectancy) (Whitehead and Ali, 2010). QALYs are important for the patients and healthcare system to ensure effective decisions are made by policy and decision makers to maximise the value that can be obtained from the budget for health care interventions (Kind et al., 2009). NICE recommends the use of QALYs when conducting health technology assessments, to enable comparability between different interventions for different diseases, for fair judgement and to measure their clinical effectiveness (Ara and Wailoo, 2011, NICE, 2013). There are several ways in which we can obtain a QALY for health economic analysis, and in the next section, I will explain how we can obtain QALYs for asthma by using different quality of life measures.

1.7 Measuring & valuing quality of life

There are different ways in which quality of life can be measured, and as mentioned above, there are several ways in which we can obtain QALYs for our analyses. Generic and disease-specific questionnaires can be used to capture HRQL, and other methods involving groups of people can be used to gather information by way of direct elicitation techniques (Drummond et al., 2015).

In the previous section, I gave examples of two different questionnaires that have been used in other studies to capture the HRQL in asthmatics; the AQLQ (disease-specific questionnaire) and the 15D (generic questionnaire). There are many other questionnaires, which can be used to capture quality of life in general, and this will form part of the discussion in the section below. Converting the scores from completed questionnaires into values, which can be used for QALYs, enables a CUA to be undertaken. However, the conversion may not be that simple, and other options may need to be considered, such as mapping.

This section will discuss the different direct elicitation methods that can be used as an alternative or in conjunction with questionnaires. There will also be discussions on the use of generic and disease-specific questionnaires, and how they can assist in the process of valuation.

1.7.1 Direct Elicitation methods

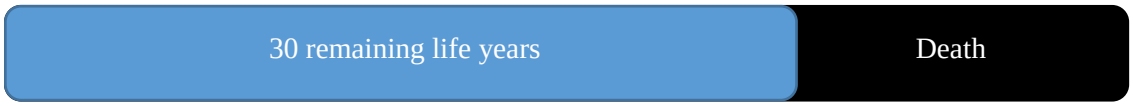
There are three widely used direct elicitation methods. They are the time trade-off, the standard gamble and the visual analogue scale. Both the time trade-off (TTO) and the standard gamble have been used in the development of well-known questionnaires, (the EQ-5D, the SF-6D and the HUI).

The idea behind the TTO is to consider two different health states **(Figure 4** and **Figure 5)**. Typically, one of the states will match a particular health description (e.g. Stage III breast cancer, or severe cystic fibrosis), and the other state will often represent full health (e.g. Healthy individual with no health impediments). The respondent will be faced with a question about these two health states and asked whether they would be willing to give up any life years from the diseased health state, in order to live for a shorter number of years in full health, followed by death (Attema et al., 2013). The typical approach is to ask this question over and over again at different intervals in order to reach the point of indifference. For example, one will start at the half-way point in healthy life years remaining and move up or down in intervals depending on a yes or no response to living in the diseased health state. If the respondent responds with yes (in that they would prefer half the stated period in full health, compared to a specific period in current health), then the question would be asked again decreasing the years of full health in intervals, otherwise the years would increase in intervals. When the point of indifference has been reached, dividing this by the total number of life years questioned, will be the utility score which is then used in economic analyses.

Figure 4: Time trade-off example

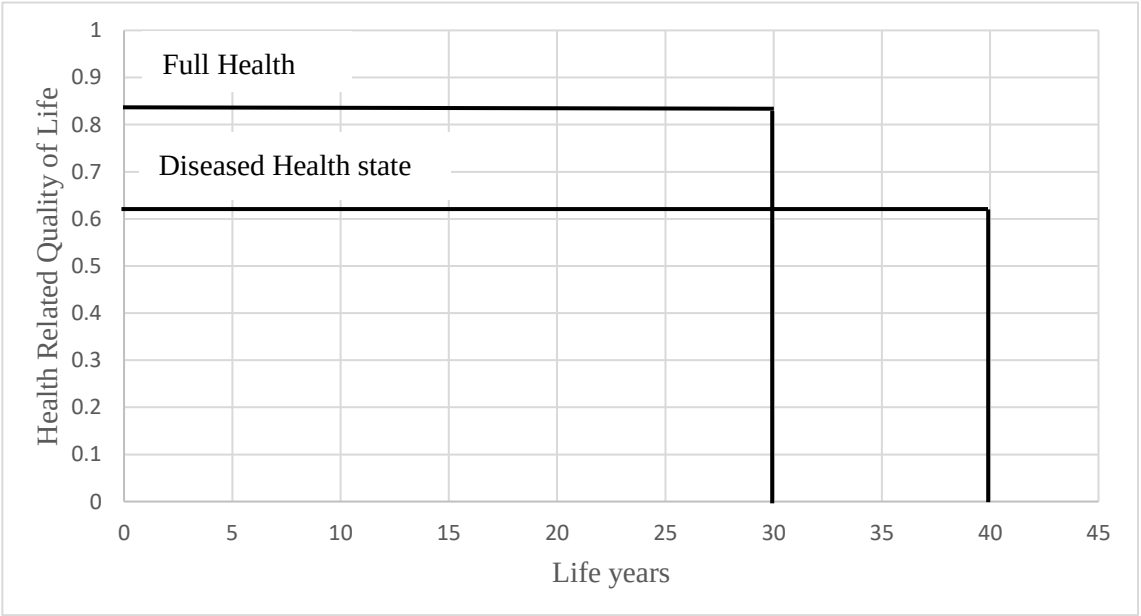
A: Diseased health state (e.g. Stage III breast cancer or cystic fibrosis)

B: Full Health (e.g. healthy individual with no health impediments)



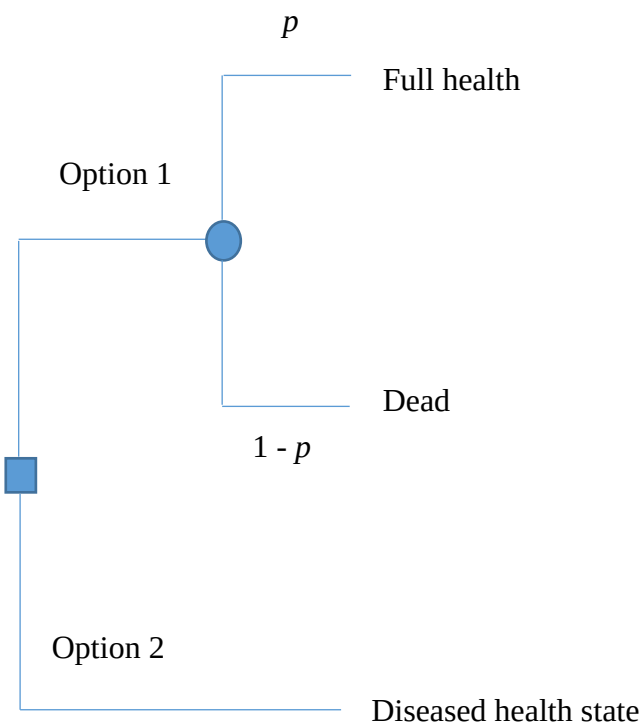
Utility score: $30 \div 40 = 0.75$

Figure 5: Graphical representation of time trade-off



On the other hand, the *standard gamble* takes more of a direct approach and also considers the respondents risk attitude (Gafni, 1994). The standard gamble tends to start with a 50:50 choice between two alternatives **(Figure 6)**. On one alternative, the gamble lies with a certain probability of being in 'full health' or $1 - probability$ being 'dead'. The other alternative is remaining in the diseased health state. In this case, the probability (p) is varied until a point of indifference is met, where the point of indifference (p) becomes the utility score.

Figure 6: Standard gamble example



The third most widely used direct elicitation method is the EQ *visual analogue scale* (VAS), and this can be thought of as a thermometer scale that has fixed, equal intervals (Drummond et al., 2015). It is one of the simplest methods of measuring quality of life. As long as the EQ VAS has fixed, equal intervals, it can be scaled differently (e.g. from 0 to 1, or 0 to 10 or 0 to 100).

The respondents who answer these questions can differ from study to study depending on whose preferences the study wishes to take. Some studies believe that the preferences of the public should be the preference chosen in direct elicitation techniques and others believe the patients should be chosen instead. It is thought that the public are more representable of the population. The public are also the taxpayers in the UK, and because the NHS has a public funded system where the population's tax contributes to this, it is also considered that the general population should have a right in valuing health states (Drummond et al., 2015). Despite this argument, the general population may not fully understand the constraints of living in a particular chronic health state if they have not experienced it before. Even though there are health state descriptions to support and consolidate the general population's thought process, areas of certain conditions can still be misinterpreted (Stamuli, 2011). Therefore, it is argued that the individuals who actually suffer from chronic health conditions should be the ones to value them, because they are the most knowledgeable about their condition and know the true merits of it. However, when comparing these two perspectives from the general population and the patients themselves, it can be noticed that the utility values concluded from participating in the direct elicitation methods can be lower or higher by the general population or patients respectively (Suarez-Almazor et al., 2001, Suarez-Almazor and Conner-Spady, 2001).

Research has shown that patients adapt to their health state as they get used to their condition over time, which may lead to higher valuations (Whitehead and Ali, 2010). This could be a disadvantage to patients because using their 'higher' preferences could lead to a lower QALY gain estimate when comparing interventions and deciding on which treatments should be implemented (Drummond et al., 2015). Some studies highlight this difference found between public and patient preferences (Ubel et al., 2003), and particularly noticed this when valuing severe health states (De Wit et al., 2000). However

other studies do not acknowledge a strong difference between patient and public valuation (Stamuli, 2011).

Measuring utilities using the direct elicitation techniques mentioned above can be a time-consuming process and there are other methods, which can be used to estimate utilities. A simpler approach is to use questionnaires that are multi-attribute and have scores; often termed generic questionnaires. The most commonly used generic questionnaires will be highlighted in the next section.

1.7.2 Preference-based measure: Questionnaires

Generic questionnaires are regularly used in studies and aim to cover a broad range of health dimensions that could be applicable to a variety of diseases. Examples of commonly used generic questionnaires are the EuroQol 5 Dimensions (EQ-5D), the Short Form 6 Dimensions (SF-6D) and the Health Utilities Index (HUI) (Conner-Spady and Suarez-Almazor, 2003, Whitehead and Ali, 2010). Examples of other less commonly used questionnaires, at least in the UK/Europe, are the 15 Dimensions (15D), developed in Finland, and the Assessment of Quality of Life (AQoL), developed in Australia.

Amongst the three aforementioned most commonly used generic questionnaires, there have been many comparison studies which have found that each questionnaire produces different estimations of utility values for the same health-related condition. For example, it has been shown that the mean utility values have been estimated to be 0.79 (95% CI 0.78 – 0.81) for the EQ-5D, 0.77 (95% CI 0.76 – 0.77) for the SF-6D and 0.56 (95% CI 0.55 – 0.57) for the HUI3 for people with hearing impairments (Barton et al., 2005). The differences in utility values are related to how each preference-based measure has been measured (e.g. the description of health states; the elicitation techniques and the population group involved) and valued (e.g. algorithms). Therefore, it is important to be aware of these differences in generic questionnaires, especially when comparing preference-based outcome results with other studies.

There are now two versions of the EQ-5D, the original renamed to be the EQ-5D-3L and the newest formed version called the EQ-5D-5L (Devlin and Krabbe, 2013). The EQ-5D-3L was originally created by using the TTO technique on approximately 3000 members

of the UK adult general population (Rabin and de Charro, 2001). The adult members had to give preferences for the scoring function of six previously developed attributes by the EuroQol Group (members are from multiple countries), and econometric modelling was used to develop the scoring function. The six attributes that were initially created by the EuroQol Group were mobility, self-care, main activity, social relationships, pain and mood. However, these six attributes were soon revisited and reduced to five attributes; mobility, self-care, usual activity, pain/discomfort and anxiety/depression. From these attributes, each one was subjected to 3 levels (no problems, some problems, and severe problems), and this meant that there could be a combination of 243 different health states. When the questionnaire is completed, each attribute and its associated level is recorded as a 5 digit number, where no problems, some problems and severe problems are noted as 1, 2, and 3 respectively. The 5 digit number (e.g. 12321 for no problems in mobility, some problems in self-care, severe problems doing usual activities, some problems with pain/discomfort and no problems with anxiety/depression), is then converted into a utility value using an algorithm, where the range of utility values could be from -0.594 (33333) to 1.000 (11111) (Kind et al., 1999). The EQ-5D-3L was based on preferences from the UK population, however, other countries also wanted to translate this questionnaire and re-estimate utility scores based on valuations for their own population. Therefore developments of this translation took place, where over 170 are available for self-completion in different languages.

The EQ-5D-5L is based on the same five attributes that were created by the EuroQol Group for the EQ-5D-3L, but with 5 levels attached to each attribute instead (Herdman et al., 2011). The 5 levels are no problems, slight problems, moderate problems, severe problems, and extreme problems. The idea behind the creation of the new 5 level version, was to help detect the smaller health changes that are sometimes seen in patients who have milder conditions, with the hope that this would reduce ceiling effects. The creation of the 5 levels involved face-to-face interviews with members of the general public. There were two occurrences of this, with the first interview pooling potential names for the levels, and the second interview choosing two alternative 5 level options testing out its face validity and content validity amongst a mixed group of healthy and chronically ill individuals. With the 5 level option and the same five attributes, this allows 3125 different possible combination of health states. For the new EQ-5D-5L questionnaire, there have been developments of a mapping process from the EQ-5D-3L to the EQ-5D-5L to enable

values to be used (van Hout et al., 2012, NICE, 2017) (**Section 1.7.3** will discuss the process of mapping).

One of the other most commonly used preference-based measures is the SF-6D. This was developed from another questionnaire, called the Short Form 36 (SF-36) a generic questionnaire that is widely used in health studies. A disadvantage that the SF-36 has, is that although it is detailed and is well used to judge the effectiveness of interventions, it doesn't have the ability to estimate QALYs for cost utility analyses in economic evaluations. Therefore, Brazier et al. (2002) created an instrument from the SF-36 that would enable analysts to calculate QALYs (SF-6D), by providing an estimation of preference-based values from the general population. The SF-6D was formed by taking the 11 items from the SF-36 and reducing them to form 8 dimensions, where 2 of the dimensions were later combined. The 6 dimensions were named as physical functioning, role limitations, social functioning, pain, mental health and vitality. The six dimensions each had a level (ranging from 1 to 4 or 1 to 6) with decreasing limitation in activities, with 4 or 6 being the most limited. There are 18,000 unique combinations of health states that can be derived from this multi-attribute system.

Unlike the EQ-5D, the SF-6D used a different elicitation technique which was the standard gamble. This approach was done using 836 members of the UK general population, where each individual provided a valuation for 6 health states. The population was varied by age group, education and social class. It wasn't possible to provide estimations for all the 18,000 health states, and so 249 estimations were valued instead, which was enough to generate a model.

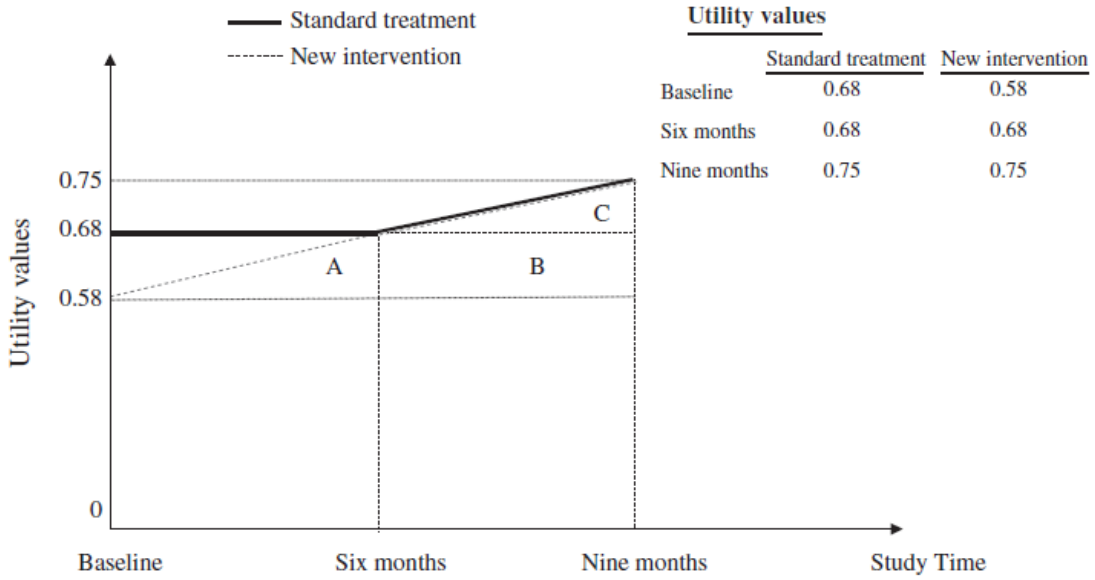
The third most commonly used preference-based measure is the Health Utilities Index (HUI) (Horsman et al., 2003). There are two types (HUI2 and HUI3) which are known to be used more often because of their multi-attributes which are considered to be of higher importance compared to HUI1 (Feeny et al., 2002). It is recommended that HUI3 should be used in primary analysis as it is the more descriptive measure (this was developed after HUI2 to adapt the measure to be more applicable to clinical studies). The HUI2 has some dimensions in the questionnaire that the HUI3 doesn't have, and so it is still seen as a secondary option and may be more suited to particular studies. The general public were also involved in developing this questionnaire, and both the standard gamble

and the EQ VAS techniques were used. However, this time, the population were from Canada and were the schoolchildren's parents. There are slight variations in the different dimensions, with HUI2 having sensation, mobility, emotion, cognition, self-care, pain and fertility as dimensions, and HUI3 having vision, hearing, speech, ambulation, dexterity, emotion, cognition and pain as dimensions. The levels within the dimensions varied as well with HUI2 ranging from 1 to 5, and HUI3 ranging from 1 to 6 with the higher numbers representing the most limitations.

Aside from these generic preference-based questionnaires, there are also other condition specific measures (preference-based and non-preference-based measures) which can be used to do the former. It has been argued that they are more suited for specific conditions, because the condition-specific questionnaires, ask questions which are more sensitive to the condition of interest (Chen et al., 2005). However, it is also recognised that preference-based condition specific measures might lead to exaggerated health problems, leading the utility values to be incomparable (Brazier and Tsuchiya, 2010). Nevertheless, there is limited evidence for this, and so preference-based condition-specific measures continue to be developed and compared. Examples of such preference-based condition-specific measures include three which were derived from the Health Assessment Questionnaire for arthritis, Quality of life Questionnaire for Cancer 30 for cancer, and the Multiple Sclerosis Impact Scale 29 for multiple sclerosis (Versteegh et al., 2012b). Other examples include a preference-based condition specific measure for asthma using the AQLQ (Yang et al., 2011), and for urinary incontinence using the King's Health Questionnaire (Brazier et al., 2008). Further examples of non-preference-based condition-specific questionnaires are the Chronic Respiratory Questionnaire (Guyatt et al., 1999) and the Western Ontario and McMaster University Osteoarthritis Index (WOMAC) (Bellamy et al., 1988).

From the above two techniques, (direct elicitation methods and preference-based measures), the HRQL can be estimated to derive a QALY. As the QALY quantifies quality of life and quantity, the approach used to estimate the QALY is the area under the curve method (Manca et al., 2005). Data can be collected at particular time points, in order to capture any change, and the HRQL can be multiplied by the time point (see **Figure 7** for an example). In a trial, the QALYs gained are often summarised across participants to form, for example, mean estimates (Smith et al., 2009).

Figure 7: Estimating QALYs using the area under the curve method



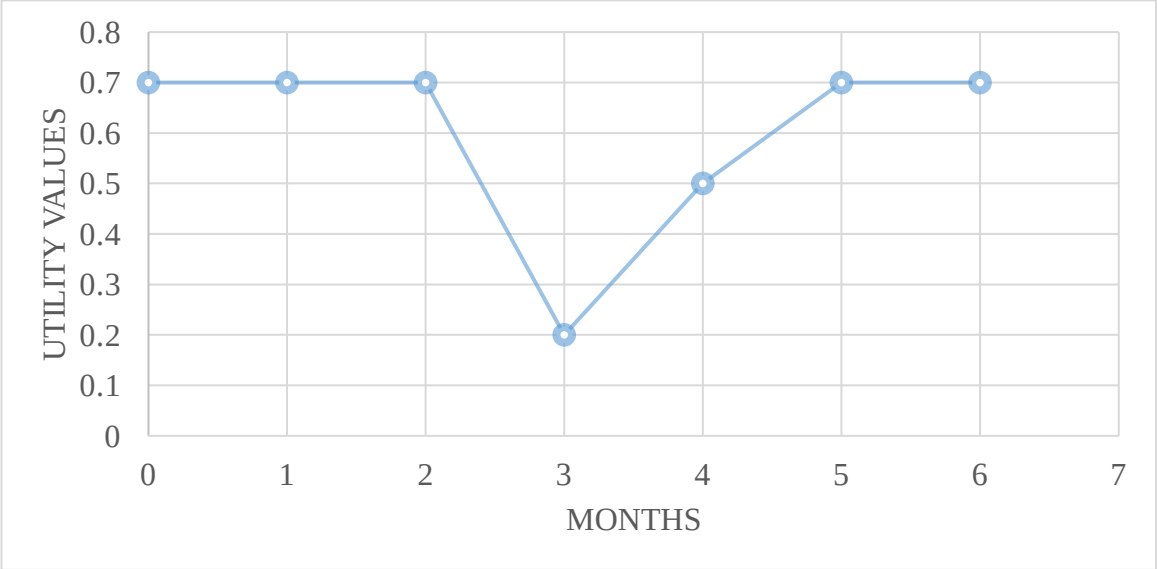
$$QALY_{\text{standard treatment}} = \left[\frac{(0.68+0.68)}{2}\frac{6}{12} + \frac{(0.68+0.75)}{2}\frac{3}{12}\right]$$

$$QALY_{\text{new intervention}} = \left[\frac{(0.58+0.68)}{2}\frac{6}{12} + \frac{(0.68+0.75)}{2}\frac{3}{12}\right]$$

Figure taken from Manca et al. (2005)

The approach of capturing quality of life at set time points, such as the above at baseline, six months and nine months (**Figure 7**), is often undertaken in many studies (perhaps at different time points). With quality of life measured at set time points over a period of time, it is common to use the assumption of linear interpolation in between the time points, as illustrated above for the total area under the curve approach. However, quality of life could be different in different people, (i.e. lower or higher in between these points), and if this is the case, then this would not be captured at these measurement points. Situations when this might occur, are when estimating the quality of life in someone who has a chronic condition, such as asthma, as asthma attacks can be sporadic and cause immediate and reduced quality of life when they occur (**Figure 8**).

Figure 8: An example of estimated utility values at different time points for someone who has an asthma attack at 3 months



For example, using the graph above, (**Figure 8**), if only two quality of life time points were observed at 0 months and 6 months then the AUC linear estimate would be as follows:

$$\frac{6}{12} \times 0.7 = 0.35\ QALYs$$

However, if including the time point captured at 3 months in the estimation in addition to the 0 and 6 month time points, then the calculation would be as follows:

$$\left(\frac{2}{12} \times 0.7\right) + \left(\frac{1}{2} \times (0.2 + 0.7) \times \frac{1}{12}\right) + \left(\frac{1}{2} \times (0.2 + 0.5) \times \frac{1}{12}\right) + \left(\frac{1}{2} \times (0.5 + 0.7) \times \frac{1}{12}\right) + \left(\frac{1}{12} \times 0.7\right)$$
$$= 0.117 + 0.0375 + 0.0292 + 0.005 + 0.0583 = 0.247\ QALYs$$

From the two examples above, it is evident, that by just having 2 time points at 0 and 6 months, the first QALY estimation (0.35), is higher than the second QALY estimation (0.25), which has considered the additional time points at 3 and 4 months. Therefore, the

first QALY estimation is an overestimation compared to the second. This example shows that it takes 2 months to recover from the crisis event, and revert back to a utility value of 0.7. This indicates that the decision to choose when to collect utility data and how often utility is measured is important. If the time between one time point and another is too wide apart, then the QALY loss may be underestimated, and if the time points are too close together then this may cause a participant burden to arise and be impracticable for the participant to complete. A judgement on what is necessary to capture such information should be made, with careful consideration of the participant population.

In some cases, studies may wish to use the condition-specific measures in economic evaluations **(see section 1.8**), but in order to estimate QALYs they will need to convert the values from the condition-specific measure into utility data, so that they can be used in analyses such as CUA. This allows the prediction of preference-based values (Drummond et al., 2015). This process is called mapping or cross-walking and is recognised by NICE in populating economic models (NICE, 2013).

1.7.3 Mapping

The process of mapping involves three important stages, and involves two datasets, with one of them termed the *'estimation' data set* and the other one termed the *'study' data set* (Chuang and Whitehead, 2012). The *estimation data set* will hold information from the same population group regarding a preference-based measure and a non-preference-based measure that was used. The *study data set* will only hold one of these measures; the non-preference-based measure. It is important that the characteristics of the population from the two data sets are alike to enhance the generalizability of the estimation, and it is also important to ensure that there is overlapping content of the two measures used to capture the relationship for estimation on the HRQL (Longworth and Rowen, 2013). Once these data sets have been identified, the first step is to establish the statistical relationship between the two measures (preference-based and non-preference-based) in the estimation data set by typically using regression method techniques (Brazier et al., 2010) as this will help to inform which model type should be used (Longworth and Rowen, 2013). The next step will be to use the result from the regression to enable a prediction of the preference-based measure in the study data set, (i.e. the condition specific score and other scores used in the mapping function). Lastly, the predicted results can then be used in economic evaluations such as the cost utility analysis (NICE, 2013).

If using mapping methods to predict EQ-5D values, condition-specific measures are not the only measures that can be used. Other options are generic-based measures, clinical indicators of disease therapy and sociodemographic variables (Longworth and Rowen, 2013). Nevertheless, it should be acknowledged that different model types have been used amongst mapping studies. The tobit regression model has been used in a mapping study from an oral health related quality of life measure (Oral Health Impact Profile) to a generic measure (Euroqol) (Brennan and Spencer, 2006). This is different to the ordinary least squares regression model which has been used in several studies. The latter has mapped from a cancer specific questionnaire (EORTC QLQ-C30), a health assessment questionnaire (HAQ), a multiple sclerosis specific questionnaire (MSIS-29), and oxford hip score questionnaire (OHS) to the EQ-5D or other preference-based measures (Versteegh et al., 2012a, Kontodimopoulos et al., 2009, Pinedo-Villanueva et al., 2013). An alternative method to mapping is the Rasch analysis which has been recently used in the development of a preference-based asthma measure, the AQL-5D (Young et al., 2011).

Quality of life can be used in analyses to complement healthcare decisions. There is a particular technique called the CUA that uses QALYs to aid decisions, and other techniques are used to address other health outcomes. These techniques will be discussed in more detail in the next section and they all come under one umbrella term; economic evaluation.

1.8 Economic evaluation

Economic evaluation is an important method, which is used to help make informed decisions about the healthcare system. Often policy makers question whether a particular service or treatment option is running efficiently and consider how to improve it. Alternatively, they may wish to decide which treatment to provide. When considering these decisions, then forgoing the benefit of a particular service or treatment option might be necessary, if such services or treatment options were to change. This is known as the *'opportunity cost',* and how large or small this cost is, can depend on how the health care system is run (Palmer and Raftery, 1999). Taking the example of the UK's publicly funded health care system, the allocation of funding for different services is dependent on a fixed budget that is set each year by the government. With resources (such as;

facilities, equipment, staff and time) being scarce, choices have to be made which leaves the opportunity costs to fall against the health outcomes. The reason for this is because the increase in costs for one service means that the health benefits gained in patients from another service cannot be continued due to the resources being unavailable. In order to make these informed decisions, health economists analyse and compare the costs and consequences of alternative courses of action (Drummond et al., 2015). The costs and the consequences can be considered in different ways (Byford and Raftery, 1998). These perspectives are typically divided into the health provider, the patient, the third party payer or a broader societal perspective. The focus could be only on health care resources used (e.g. costs associated with the time allocated for GP visit or the length of stay in hospital), or it could be inclusive of patient costs too (e.g. transportation costs to and from hospital, medication costs, loss of productivity). How broad or narrow a perspective taken, is the decision of the researcher before a study commences and this should be stated explicitly (Byford and Raftery, 1998). There are different techniques that can be used in the approach of economic evaluation and some are considered full or partial economic evaluations. The different types of economic evaluations will be discussed below in the next section.

1.8.1 Analysis techniques

A full *economic evaluation* is 'the comparative analysis of alternative courses of action in terms of both their costs and consequences' (Drummond et al., 2015). There are three techniques which are considered to take the defined approach. These are cost benefit analysis (CBA), cost effectiveness analysis (CEA), and CUA. There are other approaches which are partial economic evaluations, and examples of these are cost consequences analysis (CCA) and cost minimization analysis (CMA) (Drummond et al., 2015). A CCA provides a list of disaggregated costs and outcomes with no analytical decision made by the author, but instead allows the reader or decision-maker to decide on which treatment option is worth being carried out. On the other hand, a CMA, is an analysis where both treatment options are assumed to be providing the same therapeutic effect, leaving just the costs of both treatments left to be compared against each other to identify the cheaper treatment.

CBA was the first type of a full economic evaluation technique to be recognised, and is an analysis of costs and benefits measured in monetary units. The costs are thought of as

the value of the resources used, and the benefits are thought of as the value placed upon the outcome. However, there have been difficulties in converting the health benefits into a monetary value, for example in increased survival, so it is not commonly used in health technology assessments, (Pinto-Prades et al., 2009).

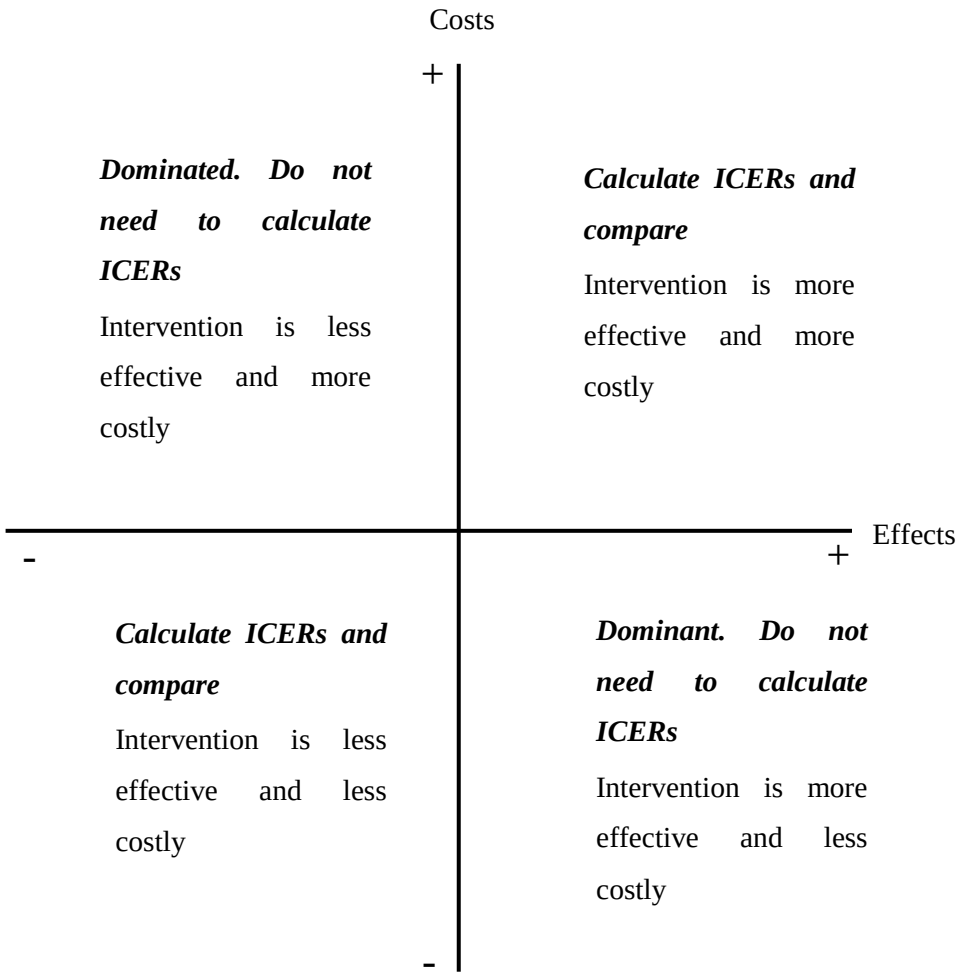
CEA is another type of a full economic evaluation which looks at costs in monetary terms but compares this to a non-monetary objective, such as the number of life years saved or alternative intervention programmes. Once the alternatives have been compared, then decisions can start to be made about whether the alternatives are cost effective or not. This is typically done by calculating the incremental cost effectiveness ratio (ICER) which is calculated by the incremental change in costs divided by the incremental change in effectiveness.

$$ICER = \frac{(C_2 - C_1)}{(E_2 - E_1)}$$

C are the costs of the interventions; E are the effects of the interventions

The idea behind the ICER is to choose interventions which have the lowest ICER in order to get value for money. However, there is often uncertainty around the value of the ICER on a patient or parameter level and so statistical analysis surrounding the ICER is often performed (O'Brien and Briggs, 2002). The ICER can be graphically represented on a cost effectiveness plane (**Figure 9**), which has four quadrants (O'Brien and Briggs, 2002, Black, 1990).

Figure 9: The Cost-Effectiveness Plane showing four quadrants where an ICER could be located.



In addition to calculating the ICER, some studies also calculate the Net Monetary Benefit (NMB), which is a re-arrangement of the ICER formula providing a simplified ranking process from most cost effective to least cost effective at a given threshold.

$$NMB = (\lambda \times \Delta E) - \Delta C$$

λ is the WTP threshold; ΔE is the incremental effectiveness; ΔC is the incremental costs

The NMB has an advantage over the ICER, as it is able to quantify the sampling uncertainty that arises from the ICER and bootstrapping, and display this as a function of the threshold (Drummond et al., 2015).

Finally, CUA is a type of CEA that takes into account the health benefits of the patients by analysing their utility, which can be understood as a person's preference in relation to their health outcomes. The utilities are scored between 0 (death state) and 1 (full health state) and can be obtained in various ways as discussed earlier in **section 1.7**. For this analysis the costs are often compared with QALYs, although other comparisons could be the disability adjusted life year (DALY) or the healthy years equivalents (HYEs). The willingness to pay (WTP) threshold of acceptability of an intervention ranges between £20,000 and £30,000 per QALY in the UK according to NICE (McCabe et al., 2008). If the ICER falls between this range, then the intervention is deemed to be cost-effective, however sensitivity analyses are also usually taken into account to address the uncertainty issues before a decision is made.

1.9 The importance of my study

The extensive review of the literature shows how significant the condition of asthma is, and indicates that this is a condition that requires addressing in research for both medical and economic reasons. Having an asthma attack can be triggered by many factors, and even with knowledge of these triggers, individuals can become subject to asthma attacks beyond their control causing A&E attendance or hospital admission. With asthma being costly to society, it is important to focus on ways by which this can be reduced, as healthcare resources are scarce and consideration needs to be given to the efficiency, effectiveness and efficacy of interventions (e.g. new treatments and therapies).

One of the main drivers of this PhD research, stemmed from an earlier study called ARRISA (Smith et al., 2012). The current literature lacks high quality primary care research in non-pharmacological asthma interventions, and shows that people with severe and poorly controlled asthma were often omitted from studies due to their complexity in other clinical and psychosocial characteristics (Yoon et al., 1991, Smith et al., 2007). This lead to the development of the ARRISA study, which involved the design of an asthma risk register intervention, which was used on computer systems in primary care practices, to flag up patients who were categorised as at-risk (Smith et al., 2012). This cluster trial, only collected routine data, (e.g. primary care based clinical data, medications, and secondary care), and so permission was not granted from the patients to ask them to complete quality of life questionnaires, such as the EQ-5D. They also defined moderate to severe exacerbations as those resulting in out of hours contact, a course of oral

prednisolone, accident and emergency (A& E) attendance, hospitalization and death. A later study, which is currently in process of recruitment, is an expansion of the ARRISA study using more study sites in the UK, (ARRISA-UK) (NETSCC, 2015). The latter study uses a term 'crisis events', which is defined as people who have A&E attendances, hospitalizations and deaths. Therefore, due to the emphasis on poor non-pharmacological research and the focus on at-risk asthma patients from these studies above, it was clear that further work was required to strengthen these areas.

As discussed earlier in the previous sections, CUA is a type of economic evaluation that analyses costs and health benefits measured in QALYs. From the incorporation of QALYs in their analysis, this gives the advantage of being able to compare interventions with others in unrelated disease areas. That said, the difficulty lies within the methods used previously, as they may not capture the true quality of life associated with asthma.

For example, quality of life are captured at specific time points (e.g. baseline, 3 months, 6 months), and when estimating the QALYs, linear interpolation is assumed (see **Figure 7**). Howbeit, with an asthma attack being such a critical event, the recovery process can be quite erratic over the course of the event. Therefore, the assumption of a steady improvement from baseline to 3 months for example, would be suggesting inaccuracy in the estimation, such that an asthma attack could be missed, and the recovery of the attack in between. Getting the timing right when estimating quality of life in people with asthma is imperative (Schilling et al., 2016, Luyten et al., 2011), and it is important to measure this at the earliest opportunity, so as to minimize bias in the estimation (Dritsaki et al., 2017). Consequently, within this study an alternative approach was taken to provide an estimation in capturing the loss in quality of life associated with an asthma-related crisis event (A&E attendance or hospital admission). Participants were monitored over an 8 week period.

By estimating this loss in quality of life more accurately over 8 weeks, this will enable future studies to count the number of A&E attendances and hospital admissions, and in turn estimate the total loss in quality of life. For example, the ARRISA study (Smith et al., 2012) only used routine data, and so this will be useful to capture the loss in quality of life associated with a crisis event. Outside of this study, it will then be possible to estimate the benefits of interventions that seek to reduce asthma-related A&E attendances

or hospital admissions, and compare them to the benefits of other health care interventions. Thereby, this will enable interventions that are able to achieve the greatest benefit for a given cost (i.e. constitute best value for money) to be identified.

1.10 Conclusion

It is clear that asthma is a concerning lung condition that needs to be clinically and economically improved across the world. The prevalence of asthma appears to be continually increasing, with parts of Europe, Australia and Brazil having the highest impacts of the asthma burden. Having frequent asthma symptoms that can progressively worsen, when exposed to a certain trigger can cause constriction of the airways, a build-up of sticky mucus and reduced air flow leading to an asthma attack which could be a life-threatening emergency. Different treatments, time and patience is required to attempt to control and even eradicate these symptoms completely in order to prevent the occurrence of asthma attacks.

Finding a way to control and manage these asthma symptoms in patients is important. If management of asthma is improved, this will hopefully lead to fewer asthma symptoms being presented, fewer or no asthma attacks, and increased quality of life. However, resources are scarce and there are different ways to measure and value quality of life, with consideration of whose preferences to take into account and which perspective to address in economic evaluations. To date, there is not a definite direction of which approach to take, but there are valid reasons for both preferences and perspectives.

Economic evaluations, in particular CUA, are a useful method when comparing interventions against the same or different disease populations, by taking into account the costs and quality of life. These analyses help to infer how resources should be distributed in the healthcare service and help policy makers decide what the best value is for money.

In line with this, the next chapter will systematically and critically review economic evaluation studies, which are investigating non-pharmacological asthma interventions. Systematic reviews are fundamental in understanding information across a large number of studies, where they help to build research questions and provide evidence for

rationales. Currently, a lot of work has been done on pharmacological interventions, however, less work has explored non-pharmacological interventions, as the ARRISA study stated (Smith et al., 2012). Therefore, the next chapter **(Chapter 2)** will explore non-pharmacological intervention studies in more detail, and also discuss the methodologies used to estimate costs and benefits in their studies.

In **Chapter 3**, the methodology of a cohort study design will be detailed which investigates estimating the loss in quality of life associated with an asthma-related crisis event (A&E attendance and hospital admission). The two chapters that follow this, **(Chapter 4 and Chapter 5),** will provide the results of this cohort study using various statistical analyses, of which include descriptive statistics, multi-level modelling and psychometric techniques. The final chapter, **(Chapter 6)**, will bring the whole thesis together in a discussion, which will provide a summary of findings and reflection of the works by highlighting the contribution to the literature, strengths and limitations and suggestions for future research.

CHAPTER 2

ECONOMIC EVALUATION EVIDENCE FOR NON-PHARMACOLOGICAL ASTHMA MANAGEMENT INTERVENTIONS: SYSTEMATIC REVIEW

"Since the effects of choosing one course of action over another will not only have effects on health, but also on health care resources as well as other effects outside of health care, informing health care decisions requires consideration of costs and benefits." (Drummond et al., 2015)

Preface

As highlighted in the previous chapter, the prevalence of asthma is continuingly increasing. Everyday activities can be challenging for some people who have asthma, and in extreme circumstances, their asthma symptoms can worsen and lead to an attack, potentially leading to either an A&E attendance or hospital admission. Managing asthma is important to help reduce these adverse events and improve quality of life. A method of analysing asthma and investigating ways to improve outcomes is through economic evaluation, particularly the CUA for incorporation of QALYs in the analysis. Different interventions and conditions can be compared by analysing the costs and health outcomes. This can help to identify which service constitutes the best value for money. Indicating what is best value for money, is important given our scarce resources in healthcare. One of the ways to inform this comparison is through systematic reviews, as they provide an in depth, structured review which systematically addresses a research question by reviewing current evidence. This chapter will review non-pharmacological asthma studies systematically, (as these have been less explored compared to pharmacological interventions, and are also more relevant in the context of the ARRISA studies (Smith et al., 2012, NETSCC, 2015)), and will provide:

1. An update of an earlier systematic review by exploring which additional studies are cost effective.
2. An extension by critically exploring in detail the methodologies used to estimate the costs and benefits in all studies.

2.1 Background

Initially, before the systematic review was conducted, a targeted scoping search of reviews was done to gather evidence of what was previously found in this area of asthma and economics. The rationale for doing this search was to use the conclusions found from reviewing the reviews, to help develop the aims and objectives of the more structured systematic literature review which will be discussed further in this chapter.

To highlight some of the evidence found in the literature, an initial search was conducted using Medline (Ovid), Embase (Ovid), and National Health Services Economic Evaluation Database (NHS EED). These databases are recommended by NICE, and previous studies have also highlighted that these databases will identify the majority of economic evaluation published literature (Sassi et al., 2002, Alton et al., 2006, Royle and Waugh, 2003). The key search terms were informed by Yong and Shafie (2014) and WHO (2015b), with restrictions of these appearing only in the titles and abstracts. The terms were (Asthma OR "Asthma-related" OR Exacerbation OR wheezing OR "shortness of breath") AND (Pharmacoeconomics OR Econ* OR "Economic evaluation" OR Cost* OR "Cost benefit" OR "Cost utility" OR "Cost effectiveness"). There were no restrictions placed on the period of years for inclusion, therefore all articles were searched from 1946 to Present for Medline, and from 1974 to 15 January 2015 for Embase. After conducting this search and screening the articles, 8 were identified as reviews and categorized into four different sub-groups; analytical standard and guideline advice reviews, all intervention reviews, pharmacological reviews and management reviews. These are now discussed below.

2.1.1 Analytical standard & Guideline Advice Reviews

Two studies were identified within this group (Persson and Ghatnekar, 2003, Feenstra et al., 2002). Many cost effectiveness studies have been carried out within the area of asthma, and guidelines are already in place for cost effectiveness studies (Drummond and Jefferson, 1996). However, Persson and Ghatnekar (2003) noticed that limited studies have focused on analysing and evaluating the analytical standards and adherence to such standards in cost effectiveness asthma treatment studies.

Therefore, their aim was to focus on evaluating the analytical standards, (as referred to in guidelines and textbooks) in cost effectiveness asthma studies, which focused on inhaled corticosteroids (ICS) up until the year 2000. They conducted a search using Medline and Embase databases and assessed their included studies for adherence to standards based on study design, perspective and costs, outcome measures, marginal cost analysis (additional cost for one extra unit gained) and sensitivity analysis coupled with validity and discussion. From their included 18 studies, they found analytical standards had continued to improve over time. However, Persson and Ghatnekar (2003) noted room for improvement in the studies in relation to the costs and perspectives in individual studies, and also the study design and methodologies. They concluded that further research needs to comply with these principles in order to improve the generalizability of health economic studies.

On the other hand, Feenstra et al. (2002) conducted a systematic search for economic literature that was compared against four guidelines (The Netherlands: Guidelines for general practitioners & Paediatric pulmonologists, the American guidelines: from the National Institutes of Health, and the British Thoracic Society) used to analyse long-term care. Long-term care was considered to be one of the three important aspects of interventions for asthma patients, and the comparison was done to possibly add additional advice in the guidelines and enhance cost effectiveness research. The cost effectiveness evidence provided well matched advice for the inhaled steroids, despite no mention of this in the guidelines. However, there was limited evidence for comparing inhaled steroids to cromolyn, and also comparing different short-acting bronchodilators. Nevertheless, self-management programs and inpatient rehabilitation was seen to be cost effective in severe asthmatic children, but the result for mild to moderate asthmatics remained inconclusive.

Even though Feenstra et al. (2002) provided more of a broader search compared to Persson and Ghatnekar (2003) in terms of the number of databases used, Feenstra et al. (2002) still limited the studies to those mostly from high income countries, (including studies from the USA, UK, and the Netherlands). This may have limited the demographic and socioeconomic generalizability of the study.

2.1.2 All Interventions

The quality of health economic asthma intervention studies (of all types) were explored between the years 2002 and 2007 (Campbell et al., 2008). From inputting search terms into Medline and NHSEED, there were 40 papers that were included in this analysis. The Quality of Health Economic Studies (QHES) tool was used to quality assess the studies with the majority of the studies (65%) scoring between 50 and 74 out of 100, where a score of 100 would be the best quality score. It was concluded that the studies provided strong economic evaluation evidence but some lacked an appropriate time horizon that was deemed long enough for the chronic state of the condition. In comparison, another study addressing the clinical, economic and humanistic characteristics of asthma reported that clinical studies showed high quality scores for study design, setting, participants, and statistical methods (Ismaila et al., 2013). However, there was insufficient evidence documented for any sources of bias, handling of missing data, loss to follow up and the way sensitivity analyses were performed.

The issue of time horizon was also considered by Feenstra et al. (2002), who believed that a follow up time of less than 3 months was unacceptable, and studies were excluded if they fell into this category. Persson and Ghatnekar (2003), Campbell et al. (2008) and Yong and Shafie (2014) also noted the importance of the follow up time and mentioned that this should be long enough to assess effectiveness, but no numerical length was provided. Additionally, three studies (Persson and Ghatnekar, 2003, Feenstra et al., 2002, Ismaila et al., 2013) discussed the reporting of costs in their reviewed studies. Indeed it was highlighted that the costs estimated in the studies and their perspectives chosen, were not completely related to each other (Ismaila et al., 2013). This lead to inconclusive findings amongst the rates of resource utilization, asthma-related costs and the difference in quality of life for asthma individuals (Ismaila et al., 2013). In order for cost effectiveness to be addressed, it is essential for direct costs to be estimated (Feenstra et al., 2002). More importantly, Persson and Ghatnekar (2003) and Willems et al. (2006), state that a societal perspective is more comprehensive as all costs and health effects are taken into account regardless of who is the payer of costs or receiver of effects.

2.1.3 Pharmacological Review

There was only one review study identified which had a pharmacological focus only (Norman et al., 2013). The focus was on Omalizumab and its clinical and cost effectiveness in asthma patients aged between 6 and 11 years old. From comparison of papers within this area, it was concluded that the drug did improve patients' health outcomes, however it caused a significant implication on cost and was above the threshold deemed acceptable by NICE.

2.1.4 Non-Pharmacological Reviews

In the last category, the three studies related to management, with Willems et al. (2006) addressing the issue of self-management interventions in asthma individuals. The second, investigating the different inhaler devices in children aged between 5 and 15 year olds (Peters et al., 2002), and the third aiming to investigate enhanced management in asthmatics (Yong and Shafie, 2014).

From the 21 included studies in the review of Willems et al. (2006), the self-management intervention was a peak flow monitoring intervention which seemed to be cost effective. However, this conclusion was taken with caution due to the low methodological quality of the papers, and the included studies being limiting in their perspectives chosen. This therefore, didn't provide a comprehensive cost analysis. In conjunction, Yong and Shafie (2014) also concluded that enhanced asthma management interventions were overall cost-reducing, but there were some reservations about this due to studies not providing a total cost of the interventions. Like Campbell et al. (2008) the QHES checklist was used to quality assess the included studies, but Yong and Shafie (2014) used a modified version of the QHES checklist to account for the double barrelled questions within the checklist. It was reported that the QHES scores of the same studies included in the reviews of Campbell et al. (2008) and Yong and Shafie (2014) were mostly lower for Yong and Shafie (2014). Moreover, in line with Campbell et al. (2008), it was noticed that longer time horizons were required from the studies to capture the chronic condition of asthma more effectively.

2.1.5 Importance of this systematic review

The above reviews have provided an overview in relation to different asthma interventions. Much work has focused on pharmacological interventions on asthma, and fewer works have considered non-pharmacological interventions, as highlighted in an earlier review (Yong and Shafie, 2014). It has been recognised that there needs to be clearer reporting of methods, outcome measures and all appropriate costs to improve generalizability and validity (Yong and Shafie, 2014, Feenstra et al., 2002). In recognition of these weaknesses, it seems appropriate to expand knowledge further in non-pharmacological asthma studies and draw upon more of the methodologies used in such studies, as the above reviews discussed have been heavily focussed on clinical interventions and their level of cost effectiveness. Even though the areas covered are relevant aspects that are important when making healthcare decisions, the methodologies of the papers have been poorly discussed. In order to ensure healthcare decisions are made appropriately, it is essential to critically appraise the evidence upon which they are based.

Due to the paucity of non-pharmacological research in asthma patients, an earlier ongoing cluster randomised control trial, the ARISSA-UK study (NETSCC, 2015), is exploring a non-pharmacological intervention in primary care (at-risk registers to stop asthma crisis). However, this study only plans to use routine data, and patient data reporting their quality of life is not planned. Therefore, there is an inability to conduct a CUA using QALYs from this study, (which is a method favoured by NICE to compare the costs and benefits of health interventions and enhance comparability amongst other studies). In light of this study and others, it is important to know what methods are used to estimate costs and benefits, in order to provide replicability in reporting and comparability across studies. Therefore, there is reason to explore these objectives further in a systematic review focused on non-pharmacological interventions, as it will further inform the methods used in the ARISSA-UK study (NETSCC, 2015), and provide knowledge on what PROMs have been used to measure quality of life in people with asthma. Gaining knowledge from this systematic review about the different PROMs used to measure quality of life in asthma, will also assist in the development of a prospective cohort study which will aim to estimate the utility loss associated with an asthma-related crisis event. The results from this prospective cohort study, will inform the ARISSA-UK study (NETSCC, 2015) by enabling the assignment of a QALY loss to each asthma-related A&E attendance or hospital admission (crisis event).

Due to an earlier comprehensive review discussing enhanced asthma management interventions (Yong and Shafie, 2014), it seemed appropriate to update and extend this work to include a more critical review about the methodologies used to estimate costs and outcomes. The update will involve a continuation of their outcome measure of comparing the cost effectiveness of interventions from post 2012 until January 2016, and the extension will cover all relevant papers that meet the inclusion criteria from 1990 to January 2016 to explore the methods used. The protocol for this review was registered with PROSPERO International Prospective Register of Systematic Reviews with registration number: CRD42016032963. This study will also help to address the methods chosen for the ongoing cluster randomised control trial, termed ARRISA-UK (NETSCC, 2015).

2.2 Objectives

The objectives for this study involved an update and expansion of a previous review by Yong and Shafie (2014).

The update investigated the cost effectiveness of enhanced asthma management interventions from 2012 to January 2016, to investigate which interventions were deemed to be cost effective.

The expansion sought to detect the array of methods used in estimating and evaluating both costs and outcomes for economic analyses. This study is particularly interested in identifying the methods used in costing all of the NHS costs, including the study intervention costs. This is because the cost of developing and executing an intervention is part of the total costs of the intervention, and so the methods behind this are just as important.

2.3 Methods

2.3.1 Search strategy

As the secondary objective for this review, was to update Yong and Shafie (2014), and the fact that this paper was comprehensive with good reasoning, it seemed appropriate to

use the search terms presented. The databases that Yong and Shafie (2014) used were ScienceDirect, Wiley Online Library, EbscoHost, Embase (via OvidSP), Medline (via OvidSP) and Scopus. Even though there were a number of databases used here, there were still some relevant databases which appeared worthy of being searched. Therefore, to add to this list of databases, CINAHL (via EbscoHost), Cochrane (CENTRAL), NHS Economic Evaluation Database (NHS EED), ClinicalTrials.gov, ProQuest and Open Grey were also included in the search strategy. The latter three databases were included to identify any unpublished material. The search terms for the additional databases were adapted slightly from Yong and Shafie (2014).

All of the search terms consisted of short words used to capture studies, which focused on asthma, non-pharmacological interventions, and economic evaluations.

Table 1 shows the combinations of words used to identify relevant papers for this review. Asterisks and quotations were used for an inclusive search and to retrieve papers, which included the specific quoted phrases. The databases were searched from 1990 until January 2016 to ensure the papers found were replicable and also widen the search using the additional databases. The start date of this search was the same start date used in the Yong and Shafie 2012 study, to ensure that any relevant papers meeting the research question were detected for this review.

Table 1: List of databases searched systematically with their corresponding search terms.

Databases	Search terms
Sciencedirect	(asthma* OR (inflammatory OR airway) disease) AND ((asthma W/5 (pharmacy OR pharmacist)) AND (intervention OR manage*)) AND ("economic evaluation" OR "pharmacoeconomic" OR "cost effectiveness" OR "cost benefit" OR "cost utility" OR cost analysis OR (asthma W/5 cost))

Databases	Search terms
Wiley Online Library	(asthma* OR “asthma* manage”) AND (intervene* OR manage) AND (“economic evaluation” OR cost analysis OR “cost effectiveness” OR “cost benefit” OR “cost utility” OR asthma cost)
EbscoHost (includes CINAHL)	asthma* AND (asthma* N15 ((pharmacy OR pharmacist) OR (intervent* OR manage*))) AND (econom* OR cost analysis OR “cost effectiveness” OR “cost benefit” OR “cost utility” OR pharmacoeconom* OR “healthcare cost” OR asthma N10 cost)
Embase & Medline (via Ovid SP)	asthma*.ti OR “asthma* manage”.ti) AND (intervene* OR manage)) AND (“economic evaluation” OR cost analysis OR “cost effectiveness” OR “cost benefit” OR “cost utility” OR asthma cost)
Scopus	TITLE-ABS-KEY (asthma* OR respiratory) AND TITLE-ABS-KEY (asthma* pharmacy* manage* OR “pharmac* intervention” OR “asthma* manage*”) AND TITLE-ABS-KEY ((asthma OR pharmac*) W/15 economics OR pharmacoeconomics OR “cost effectiveness” OR “cost benefit” OR “cost utility” OR cost analysis OR (economic evaluation) OR healthcare cost)
Cochrane (CENTRAL)	asthma* AND (interven* OR manage*) AND (pharmacoeconom* OR "economic evaluation" OR "cost effectiveness" OR "cost benefit" OR "cost utility")
NHS EED	asthma* AND (interven* OR manage*) AND (pharmacoeconom* OR "economic

Databases	Search terms
	evaluation" OR "cost effectiveness" OR "cost benefit" OR "cost utility")
ClinicalTrials.gov	(asthma* OR “asthma* manage”) AND (intervene* OR manage) AND (“economic evaluation” OR cost analysis OR “cost effectiveness” OR “cost benefit” OR “cost utility” OR asthma cost)
ProQuest	asthma* AND (asthma* N/15 ((pharmacy OR pharmacist) OR (interven* OR manage*))) AND ("economic evaluation" OR "cost effectiveness" OR "cost utility" OR "cost benefit" OR pharmacoeconom*)
Open Grey	asthma* AND (interven* OR manage*) AND (pharmacoeconom* OR "cost effectiveness" OR "cost benefit" OR "cost utility" OR "economic evaluation")

2.3.2 Eligibility criteria

The articles that were considered for inclusion in this review were those defined as an economic evaluation. For the purpose of this review, this could be a CEA, CUA, CBA or a cost consequences analysis (CCA). These types of economic evaluations were chosen, because the primary objective of this study was to identify the methods used to estimate both the costs and outcomes analysed. Therefore, the types of economic evaluations didn’t have to satisfy the definition of a full economic evaluation defined by Drummond et al. (2015) as ‘the comparative analysis of alternative courses of actions in terms of both their costs and consequences’. Other types of economic studies were excluded, as well as letters, editorials, magazines, conference abstracts and reviews.

The population criteria for this review were people who had asthma of all severity types and all ages. There were no other restrictions on the population group; both genders, different socio-economic environments and different countries were included in the criteria. The intervention of focus for the papers reviewed were non-pharmacological asthma interventions. This included interventions which didn’t have a medication

intervention; such as an asthma educational intervention, an environmental intervention or a self-management intervention. However, comparators could be pharmacological, non-pharmacological or usual care alternatives. Only studies written in English of full original research papers were included in this review. **Table 2** shows the inclusion criteria for this systematic review.

Table 2: Inclusion criteria for the included studies in the systematic review

Category	Inclusion	Exclusion
Study design	Economic Evaluation: Cost-effectiveness analysis (CEA), Cost-utility analysis (CUA), Cost-benefit analysis (CBA), Cost-consequences analysis (CCA). Full original research papers	Other types of economic studies. Letters, editorials, magazines, conference abstracts, and reviews.
Language	English only studies	Non-English studies
Population	Asthma of all severity types Male and Female Any age All socio-economic groups All countries	Not asthma
Intervention	Non-pharmacological interventions (e.g. educational, environmental, management)	Pharmacological interventions (e.g. medication)
Comparator	Non-pharmacological	N/A

Category	Inclusion	Exclusion
	Pharmacological Usual care alternative	

2.3.3 Data extraction process

Once the said databases were searched, all of the studies which appeared were transferred into EndNote Software manager to store as one collective. Any duplicates found within the EndNote programme were removed electronically. After this stage was completed, the titles and abstracts were ready to screen for inclusion. The title and abstract screening process was done independently by two reviewers (CJCB & AP or CJCB & RFSK). If from reading the title, it wasn't obvious to include the study, then the abstract was read for further consideration. At this stage, three decisions were made; definitely include, definitely don't include, or read the full text. One reviewer, (CJCB), then compared the two screening outcomes from each reviewer and discussed with the other reviewer if there were any discrepancies. Once discrepancies were discussed, a final decision was made on whether the article should be considered for inclusion at this stage. After this stage had been completed, the full texts were read and a final decision was made on the included studies.

The included studies were then organised in the data extraction table ready for the data to be extracted under the headings of first author, year, country of population, study design, patient population, intervention and control characteristics, study perspective, time horizon, discount rate, price year, resource use, methods of estimating & valuing resources and intervention cost component, cost results, outcome measures, method of estimating outcomes, outcome results, response rates, ICER, statistical analysis, sensitivity analysis (see **Table 3**). The data was extracted by two independent reviewers, and then compared against each other to see if there were any areas of discrepancies. The discrepancies were discussed and a final decision was made on the data extracted.

Table 3: Pre-designed data extraction table

Study details	First author; Publication year; Country of population
	Study design
	Patient population
	Study perspective; time horizon; discount rate
	Currency & price year
Intervention & Comparator details	Description of Intervention & Comparator
Resources & outcomes	Range of resource use measured
	Types of outcomes measured
Methods	Method of estimating & valuing resource use
	Method of estimating intervention cost component
	Methods of estimating & valuing outcomes
Results	No.; mean age; gender (%); ethnicity (%) of intervention and comparator groups
	Response rates
	Cost results
	Outcome results
	ICER or Net benefit/Net present value
	Statistical analysis; sensitivity analysis

2.3.4 Quality assessment process

The quality assessment process was the same as the data extraction process i.e. each paper was individually quality assessed by two independent reviewers and checked by one reviewer for any discrepancies. Again, discrepancies were resolved through discussion to arrive at a final decision. There were two quality of life checklists that were used in this review. The main one was the QHES checklist that was adapted by Yong and Shafie (2014), but originally designed by Chiou et al. (2003). Due to part of this review featuring as an update, it seemed reasonable to include the adapted QHES checklist for consistency. This adapted version was easy to use and assign quality values to the individual papers due to Yong and Shafie (2014) including separate weighted values to multiple criteria **(see Appendix 1)**. By assigning scores to individual components of the QHES checklist, an overall score ranging from 0 to 100 was estimated for each study, with less than 25

indicating extremely poor quality, 25-49 indicating poor quality, 50-74 indicating fair quality and greater than 74 indicating high quality.

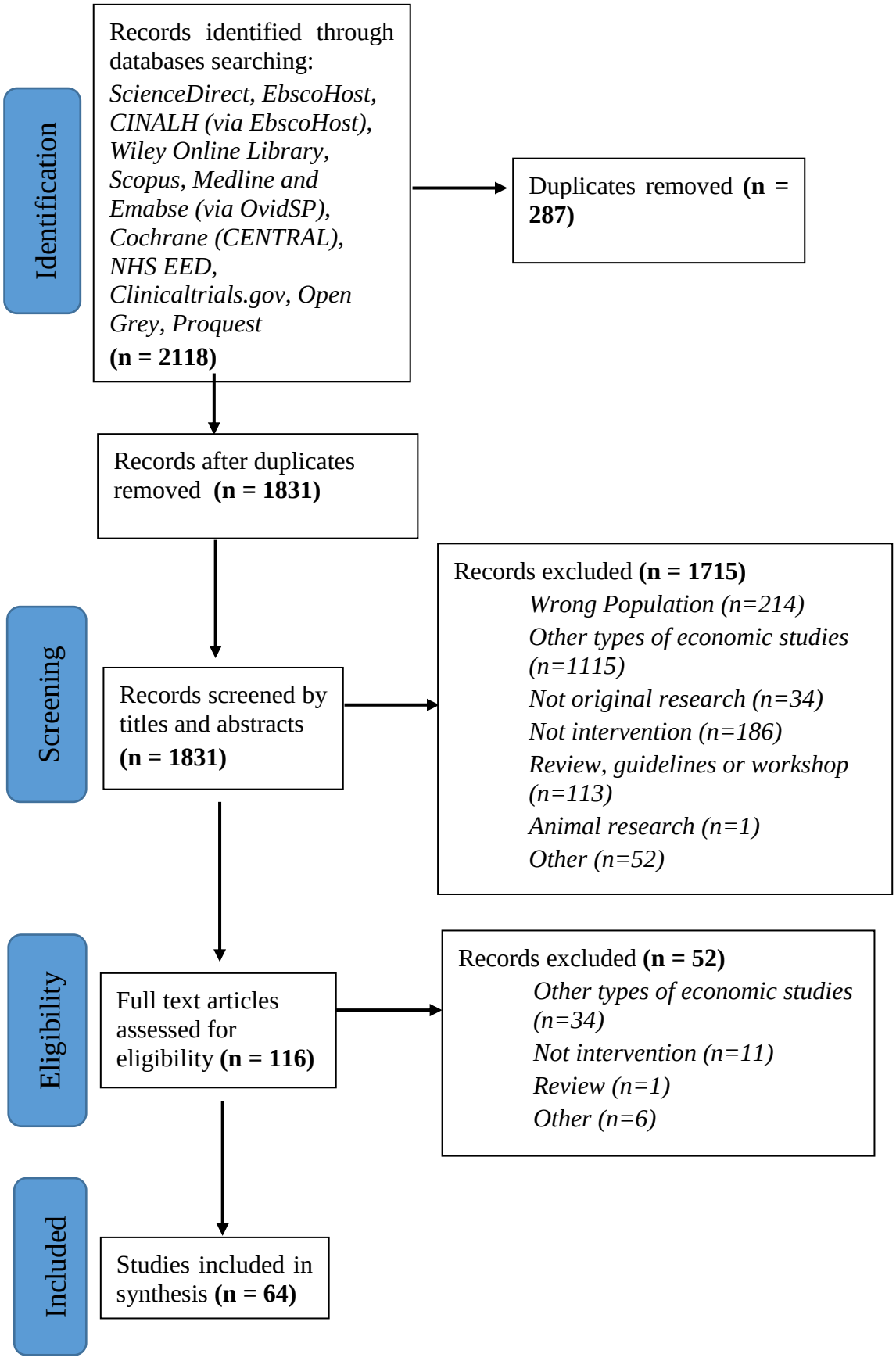
In addition to this tool, and for model based studies that were included in this review, the Philips et al. (2004) criteria was also used to provide a more in-depth quality assessment for this category of study designs.

2.4 Results

From the extensive search strategy, 2118 studies were found from the databases used. After electronically and manually removing 287 duplicates from this total, we were left with 1831 studies, of which the titles and abstracts were screened. At this stage, the excluded records from this figure were due to the wrong population (12.5%), other types of economic studies (65.0%), not being original research (2.0%), pharmacological interventions (10.8%), reviews, guidelines or workshops (6.6%), animal research (0.06%) and other (3.0%). Exclusion of these studies, allowed 116 studies to be assessed by full text which lead to a further 52 studies being excluded. These were excluded due to other types of economic studies (65.4%), not the intervention (21.2%), review (1.9%), and other (11.5%). This left 64 studies included in the analysis **(Figure 10).**

The 64 included studies, included all of the 49 papers that Yong and Shafie (2014) identified between the years 1990 and 2012, and 15 additional papers. However, out of the 15 additional papers that were identified from searching the database from 1990 until January 2016, 5 papers (Castro et al., 2003, Flores et al., 2009, Higgins et al., 1998, Karnick et al., 2007, Atherly et al., 2009) were found that could have been identified from the period of 1990 to 2012 that Yong and Shafie (2014) screened. These papers could have been additionally found due to using a wider search strategy.

Figure 10: PRISMA Flow Diagram



2.4.1 Characteristics of the 15 additional papers

Table 4 describes the characteristics of the included studies found in addition to Yong and Shafie (2014).

Overall, from the fifteen additional papers found, there were five CEA studies (Atherly et al., 2009, Flores et al., 2009, Lara et al., 2013, Mogasale and Vos, 2013, Ryan et al., 2012), one CUA (Willems et al., 2007), four CBA studies (Bhaumik et al., 2013, Fabian et al., 2014, Karnick et al., 2007, Tai and Bame, 2011) and five CCA studies (Higgins et al., 1998, Castro et al., 2003, McCowan et al., 1997, Turcotte et al., 2014, Smith et al., 2012). Of these studies, there were seven randomised control trials (Castro et al., 2003, Flores et al., 2009, Karnick et al., 2007, McCowan et al., 1997, Ryan et al., 2012, Smith et al., 2012, Willems et al., 2007), three before and after studies (Higgins et al., 1998, Lara et al., 2013, Turcotte et al., 2014), two model-based studies (Fabian et al., 2014, Mogasale and Vos, 2013), two cohort studies (Bhaumik et al., 2013, Tai and Bame, 2011) and one quasi experimental study (Atherly et al., 2009).

The majority of these studies were based in the United States (Atherly et al., 2009, Bhaumik et al., 2013, Castro et al., 2003, Fabian et al., 2014, Flores et al., 2009, Higgins et al., 1998, Karnick et al., 2007, Tai and Bame, 2011, Turcotte et al., 2014), second to that European (McCowan et al., 1997, Ryan et al., 2012, Smith et al., 2012, Willems et al., 2007), one Caribbean (Lara et al., 2013) and one Australian (Mogasale and Vos, 2013).

The population groups chosen were mostly children focused (Atherly et al., 2009, Bhaumik et al., 2013, Fabian et al., 2014, Flores et al., 2009, Higgins et al., 1998, Karnick et al., 2007, Lara et al., 2013, McCowan et al., 1997, Tai and Bame, 2011, Turcotte et al., 2014) with one adult only study (Castro et al., 2003), and combination of the two (Mogasale and Vos, 2013, Ryan et al., 2012, Smith et al., 2012, Willems et al., 2007). Only seven studies (Bhaumik et al., 2013, Castro et al., 2003, Higgins et al., 1998, Karnick et al., 2007, Lara et al., 2013, Ryan et al., 2012, Turcotte et al., 2014) stated the ethnic background of the populations chosen, with five of those representing a mixed ethnic population (Bhaumik et al., 2013, Castro et al., 2003, Higgins et al., 1998, Karnick et al., 2007, Turcotte et al., 2014).

The interventions compared in these papers were mainly educational based provided by school, health professionals, or environmental assessors (Atherly et al., 2009, Bhaumik et al., 2013, Castro et al., 2003, Flores et al., 2009, Higgins et al., 1998, Karnick et al., 2007, Lara et al., 2013, Turcotte et al., 2014, Willems et al., 2007); asthma management based using applications and/ or at-risk registers (McCowan et al., 1997, Mogasale and Vos, 2013, Ryan et al., 2012, Smith et al., 2012, Tai and Bame, 2011) and appliances based (Fabian et al., 2014).

The study perspectives chosen were varied, including societal (Atherly et al., 2009, Bhaumik et al., 2013, Tai and Bame, 2011, Willems et al., 2007), governmental (Fabian et al., 2014), payer (Karnick et al., 2007), and healthcare (Mogasale and Vos, 2013, Ryan et al., 2012, Smith et al., 2012, Willems et al., 2007), though almost half did not state which perspective was taken (Castro et al., 2003, Flores et al., 2009, Higgins et al., 1998, Lara et al., 2013, McCowan et al., 1997, Turcotte et al., 2014). The time horizon of these studies ranged from 3 months (Atherly et al., 2009) to 10 years, with the longer horizon being a model-based study (Fabian et al., 2014). Two studies had a time horizon of 6 months (Castro et al., 2003, Ryan et al., 2012), about half of the studies had a time horizon of 1 year (Flores et al., 2009, Higgins et al., 1998, Lara et al., 2013, Mogasale and Vos, 2013, Smith et al., 2012, Turcotte et al., 2014, Willems et al., 2007), and the other few ranged between just under 2 years to 4 years (Karnick et al., 2007, Bhaumik et al., 2013, McCowan et al., 1997).

Table 4: Characteristics of the 15 additional studies

First author, Year, Country of Population	*Study Design (Type of economic evaluation)*	*Patient population group*	*Description of Intervention & Comparator(s)*	*Intervention participants (No., mean age, gender (%), ethnicity (%))*	*Comparator participants (No., mean age, gender (%), ethnicity (%))*	*Study perspective, time horizon, discount rate*	*Currency & price year*	*Statistical analysis, sensitivity analysis*	*ICER or Net benefit / Net present value*
Atherly et al, 2009, United States	Prospective Quasi experimental (CEA)	524 asthma adolescents from middle and high schools, grades 6-12	**Int:** Power breathing educational program including three 90 minutes sessions focusing on asthma education, asthma control strategies and psychosocial concerns. **Com:** No education program	No. 225 Mean age: 13.90 Male: 54.4% Female: 46.6% Ethnicity: Not stated	No. 233 Mean age: 13.40 Male: 49.3% Female: 50.7% Ethnicity: Not stated	Societal 3 months Not Applicable	US ($) 2003-2004	Mean comparison pre and post intervention, Ordinary Least Squares regression analysis including t-test. Not stated	$3.90 per symptom-free day gained
Bhaumik et al, 2013, United States	Prospective Cohort (CBA)	661 people hospitalized or had asthma-related Emergency Department visits from 4 low income	**Int:** Received services provided by the Community Asthma Initiative (CAI).	No. 102 Mean age: 7.90 Male: 53.9% Female: 46.1% White: 6.9%	No. 559 Mean age: 7.1 Male: 59.8% Female: 40.2% White: 4.1%	Societal 3 years 10%	US ($) 2006	Chi-squared test for categorical variables. Unpaired t-test for continuous variables. Paired t test for comparison of costs, no. of	Net present value: Adjusted cost savings for year 1 = $111,588,

First author, Year, Country of Population	*Study Design (Type of economic evaluation)*	*Patient population group*	*Description of Intervention & Comparator(s)*	*Intervention participants (No., mean age, gender (%), ethnicity (%))*	*Comparator participants (No., mean age, gender (%), ethnicity (%))*	*Study perspective, time horizon, discount rate*	*Currency & price year*	*Statistical analysis, sensitivity analysis*	*ICER or Net benefit / Net present value*
		urban zip codes in Boston	**Com:** Did not receive services provided by CAI	African-American: 41.2% Hispanic/Latino: 46.1% Asian/Pacific Islander/Native American: 5.9%	African-American: 59.2% Hispanic/Latino: 34.6% Asian/Pacific Islander/Native American: 2%			Emergency Department visits & hospital stays. Multivariate regression analysis to control for gender, age and race/ethnicity. Not stated	year 2 = $16,365, year 3 = $83,863
Castro et al, 2003, United States	Prospective RCT (CCA)	96 asthma patients admitted to the Barnes-Jewish Hospital from September 1996 to July 1999	**Int:** Three consecutive nurses provided intervention including completion of daily "Asthma Care" flow sheet, asthma education, self-management plan and consultations. **Com:** normal care provided by patients' private primary physician	No. 50 Mean age: 35.00 Male: 20% Female: 80% African American: 86% Non-African American: 24%	No. 46 Mean age: 38 Male: 15% Female: 85% African American: 78%, None African American: 22%	Not stated 6 months Not Applicable	US ($) 1999	T-tests and chi-squared tests to compare variables between groups. Wilcoxon's test used for skewed variables. Logistic regression used to identify variables that had an independent association with readmission to hospital twice or more in the year from initial hospitalization. Log rank test used	Not Applicable Mean cost: Int = $5,726; Con = $12, 188 Mean change in AQLQ: Int = 1.4, Con = 1.2

First author, Year, Country of Population	*Study Design (Type of economic evaluation)*	*Patient population group*	*Description of Intervention & Comparator(s)*	*Intervention participants (No., mean age, gender (%), ethnicity (%))*	*Comparator participants (No., mean age, gender (%), ethnicity (%))*	*Study perspective, time horizon, discount rate*	*Currency & price year*	*Statistical analysis, sensitivity analysis*	*ICER or Net benefit / Net present value*
								to perform survival curves. Not stated	
Fabian et al, 2014, United States	Prospective Model (CBA)	1 million children living in low income multi-family housing consistent with public housing residents	7 interventions included: Fix and/or operate kitchen and bathroom exhaust fans. Replace gas stoves with electric ovens. Eliminate use of stove for heating by fixing the heating system. Smoke-free housing policy. Use of HEPA filters. Integrated pest management. Weatherization.	Not stated	Not stated	Governmental 10 years Not stated	US ($) 2009	Probabilistic model.	Not stated
Flores et al, 2009, United States	Prospective RCT (CEA)	220 African American and Latino asthmatic children enrolled	**Int:** Parent mentors (had training) met with children and families 3 days after child had	No. 112 Mean age: 7.10 Male: 59.8% Female: 40.2%	No. 108 Mean age: 7.3 Male: 52.8% Female: 47.2%	Not stated 12 months Not Applicable	US ($) Not stated	Wilcoxon tests performed to examine baseline intervention group differences. Fisher's exact	Dominant

First author, Year, Country of Population	*Study Design (Type of economic evaluation)*	*Patient population group*	*Description of Intervention & Comparator(s)*	*Intervention participants (No., mean age, gender (%), ethnicity (%))*	*Comparator participants (No., mean age, gender (%), ethnicity (%))*	*Study perspective, time horizon, discount rate*	*Currency & price year*	*Statistical analysis, sensitivity analysis*	*ICER or Net benefit / Net present value*
		between February 2004 and May 2007 from 4 hospitals providing asthma care	been in Emergency Department or inpatient with asthma. Followed at monthly intervals, with 57 meetings held during the study including asthma education, meals, and social interaction. **Com:** Traditional asthma care	Ethnicity: Not stated	Ethnicity: Not stated			test. Logarithmic regression used to examine time trends of asthma exacerbations. Not stated.	
Higgins et al, 1998, United States	Prospective before & after (CCA)	61 Paediatric asthma patients without a primary care provider identified during an acute asthma exacerbation by the Emergency Department staff at the	**Int:** Patients assigned a primary care provider and parents of patients had five 1 hour asthma education sessions.	No. 61 Mean age: 8.40 Male: 67.2% Female: 32.8% Caucasian: 50.9% African American: 38.6% Asian: 4.0% Hispanic: 2.0%	Not Applicable	Not stated 12 months Not Applicable	US ($) 1997	Paired t test comparing the means before and after the intervention. Not stated.	Not Applicable Intervention savings on resource use = $4845.29 Mean monthly hospital admissions: Before = 0.149, After = 0.007

First author, Year, Country of Population	*Study Design (Type of economic evaluation)*	*Patient population group*	*Description of Intervention & Comparator(s)*	*Intervention participants (No., mean age, gender (%), ethnicity (%))*	*Comparator participants (No., mean age, gender (%), ethnicity (%))*	*Study perspective, time horizon, discount rate*	*Currency & price year*	*Statistical analysis, sensitivity analysis*	*ICER or Net benefit / Net present value*
		South-eastern US military hospital from 01 July 1995 to 30 October 1995		(4 patients didn't state their race)					
Karnick et al, 2007, United States	Prospective RCT (CBA)	212 children aged 1 to 16 years old recruited from July 2000 to May 2001 from Mount Sinai Hospital's Emergency Department, inpatient units, and from referrals to paediatric pulmonologist for consultation	**Three interventions.** 1) Asthma education group: 20 to 30 minutes sessions and referral to primary care provider if more guidance needed 2) Reinforced education group: Same as group 1 plus further education through phone calls (minimum	1) No. 74 Mean age: 5.54 Male: 55% Female: 45% Non-Hispanic Black: 70% Hispanic: 30% 2) No. 68 Mean age: 5.13 Male: 66% Female: 34% Non-Hispanic Black: 65%	Not Applicable	Payer 1 year retrospectively & 9 months prospectively Not stated	US ($) 1998	Chi-squared or Fisher's test for categorical variables and ANOVA for continuous variables. Paired t test also used. Not stated.	Not stated

First author, Year, Country of Population	*Study Design (Type of economic evaluation)*	*Patient population group*	*Description of Intervention & Comparator(s)*	*Intervention participants (No., mean age, gender (%), ethnicity (%))*	*Comparator participants (No., mean age, gender (%), ethnicity (%))*	*Study perspective, time horizon, discount rate*	*Currency & price year*	*Statistical analysis, sensitivity analysis*	*ICER or Net benefit / Net present value*
			monthly calls) 3) Case management and reinforced education group: Same as group 2 plus case management services provided by a nurse practitioner / case manager	Hispanic: 35% 3) No. 70 Mean age: 5.71 Male: 59% Female: 41% Non-Hispanic Black: 64% Hispanic: 34% Other: 1%					
Lara et al, 2013, Caribbean	Prospective Before & After (CEA)	145 recruited children (0 to 17 years) with moderate to severe asthma from local health care clinics in two waves (January 2007 to August 2007 and February 2008	**Int:** *La red* – combined clinic and home based intervention adapted from Yes We Can program and Inner-City Asthma Study	No. 145 Mean age: 5.00 Male: 61.4% Female: 38.6% Hispanic/Puerto Rican: 100%	Not Applicable	Not stated 12 months Not Applicable	US ($) 2009	Monte Carlo Simulation.	Dominant

First author, Year, Country of Population	*Study Design (Type of economic evaluation)*	*Patient population group*	*Description of Intervention & Comparator(s)*	*Intervention participants (No., mean age, gender (%), ethnicity (%))*	*Comparator participants (No., mean age, gender (%), ethnicity (%))*	*Study perspective, time horizon, discount rate*	*Currency & price year*	*Statistical analysis, sensitivity analysis*	*ICER or Net benefit / Net present value*
		to December 2008)							
McCowan et al, 1997, United Kingdom	Prospective RCT (CCA)	2557 children aged 1 to 15 years with diagnosed asthma from Tayside GPs	**Int:** Individuals identified by GP practice, called for clinical review, and has guidelines for diagnosis & management of asthma inserted into their case records by an audit facilitator. **Com:** Standard medical care	No. 1288 Mean age: 7.67 Male: 55.4% Female: 44.6% Ethnicity: Not stated	No. 1269 Mean age: 7.8 Male: 59.6% Female: 40.4% Ethnicity: Not stated	Not stated 4 years Not stated	GBP (£) 1991	Not stated. Not stated.	Not Applicable Year 1: Int = £68,500 Con = £57,780. Year 2: Int = £62,300 Con = £53,910. Year 3: Int = £45,700 Con = £45,280. Year 4: Int = £43,550 Con = £44,960 No. of children with hospital admissions: Year 1: Int = 33 Con = 18. Year 2: Int = 24, Con = 25. Year 3: Int = 11, Con = 12. Year 4: Int = 9 Con = 14
Mogasale et al, 2013, Australia	Prospective Model (CEA)	Asthma patients	**Int:** Asthma clinical approach.	Not stated	Not stated	Healthcare 1 year	AUS ($) 2003	Monte Carlo Simulation.	Without time and travel costs: Scenario 2 =

First author, Year, Country of Population	*Study Design (Type of economic evaluation)*	*Patient population group*	*Description of Intervention & Comparator(s)*	*Intervention participants (No., mean age, gender (%), ethnicity (%))*	*Comparator participants (No., mean age, gender (%), ethnicity (%))*	*Study perspective, time horizon, discount rate*	*Currency & price year*	*Statistical analysis, sensitivity analysis*	*ICER or Net benefit / Net present value*
			Com: Current practice of asthma management			3%		Three scenarios: 1) Assumed intervention only 2) Assumed interventions, reduced ED visits and days off work 3) Assumed intervention, reduced ED visits, unscheduled GP visits, hospitalizations and days off work	$24,000 and Scenario 3 = $17,000. With time and travel costs: Scenario 2 = $30,000 and Scenario 3 = $20,000
Ryan et al, 2012, United Kingdom	Prospective RCT (CEA)	288 adolescents and adults with poorly controlled asthma from 32 practices recruited from 2008-2009. Prior to randomisation, both intervention and	**Int:** mobile phone based monitoring using an Asthma application with training in its use provided by practice nurse. **Com:** Standard paper based monitoring –	No. 145 Mean age: 46.60 Male: 34% Female: 66% White: 97% Non-White: 3%	No. 143 Mean age: 51.50 Male: 41% Female: 59% White: 99% Non-White: 1%	National Health Service 6 months Not Applicable	GBP (£) Not stated	Changes between groups using t-test, Mann-Whitney test. Trend over time examined using ANOVA and cost comparison using t-test. Per protocol sensitivity	Not stated

First author, Year, Country of Population	*Study Design (Type of economic evaluation)*	*Patient population group*	*Description of Intervention & Comparator(s)*	*Intervention participants (No., mean age, gender (%), ethnicity (%))*	*Comparator participants (No., mean age, gender (%), ethnicity (%))*	*Study perspective, time horizon, discount rate*	*Currency & price year*	*Statistical analysis, sensitivity analysis*	*ICER or Net benefit / Net present value*
		control groups received 30 minutes educational training by the practice asthma nurse on asthma, asthma treatment, inhaler technique, monitoring and personalised asthma action plan based on symptoms and peak flow.	twice daily recording of symptoms, drug use and peak flow					analysis including patients who completed all questionnaires at all time points.	
Smith et al, 2012, United Kingdom	Prospective RCT (CCA)	911 at-risk asthma patients with severe exacerbations recruited from 29 primary care practices in Norfolk between November 2006 and May 2009	**Int:** GP practices had visible electronic alerts on computerised records to flag at-risk asthma patients. Training provided to staff and ongoing training received through telephone and	No. 14 practices, 457 patients Mean age: 46.40 Male: 37.2% Female: 62.8% Ethnicity: Not stated	No. 15 practices, 454 patients Mean age: 44.60 Male: 40.2% Female: 59.8% Ethnicity: Not stated	National Health Service 1 year Not Applicable	GBP (£) 2007-2008	Odds-ratios, Mann-Whitney test, ICCs, random-effects negative-binomial models producing rate-ratios. Not stated	Not applicable Mean change in annual level of resource use: Int = £60.23 and Con = £149.14 Moderate-severe asthma exacerbation: Int

First author, Year, Country of Population	*Study Design (Type of economic evaluation)*	*Patient population group*	*Description of Intervention & Comparator(s)*	*Intervention participants (No., mean age, gender (%), ethnicity (%))*	*Comparator participants (No., mean age, gender (%), ethnicity (%))*	*Study perspective, time horizon, discount rate*	*Currency & price year*	*Statistical analysis, sensitivity analysis*	*ICER or Net benefit / Net present value*
			newsletters formats after activation of alerts. **Com:** Usual care with annual practice based asthma reviews in nurse-led clinics with follow-ups in secondary care outpatient clinics and emergency primary and secondary care for those who need it.						= 53.6% and Con = 46.5%
Tai et al, 2011, United States	Prospective Cohort (CBA)	School children with asthma	**Int:** School based health clinics nationwide including disease management and self-care monitoring skills	Not stated	Not stated	Societal Not stated 3%	US ($) 2006	Not stated. Not stated.	Not stated

First author, Year, Country of Population	*Study Design (Type of economic evaluation)*	*Patient population group*	*Description of Intervention & Comparator(s)*	*Intervention participants (No., mean age, gender (%), ethnicity (%))*	*Comparator participants (No., mean age, gender (%), ethnicity (%))*	*Study perspective, time horizon, discount rate*	*Currency & price year*	*Statistical analysis, sensitivity analysis*	*ICER or Net benefit / Net present value*
			Com: Traditional medical services						
Turcotte et al, 2014, United States	Prospective Before & After (CCA)	170 children recruited younger than 15 years old living in Lowell, Massachusetts with a diagnosis of asthma. Families recruited between September 2009 and February 2011 with final assessments done 11-12 months after recruitment.	**Int:** Environmental assessor walked through the homes to assess presence of triggers. Visits ranged from 4 to 9 during the year depending on need for education, remediation and outside contract work.	No. 170 Mean age: 6.08 Male: 59% Female: 41% Black: 5%, White: 12%. Asian: 15%, Hispanic: 53%, Other: 15%	Not Applicable	Not stated 1 year Not Applicable	US ($) Not stated	Wilcoxon rank sum test analysing the change in scores for high-risk participants. Not stated.	Not Applicable Net savings from intervention: 4 week = $38,522; 6 months = $394,332 and 12 months = $821,304 Decrease in occurrence: Hospitalization = 8, Emergency department = 29, Doctor visit = 76
Willems et al, 2007, the Netherlands	Prospective RCT (CUA)	Asthma outpatients: (53 adults and 56 children) from Medical Respiratory Department and	**Int:** Nurse led telemonitoring – portable asthma monitor at home allowing patients to monitor spirometry	No. Adults (26) Children (29) Mean age: Adults (45.65), Children (10.57)	No. Adults (27), Children (27) Mean age: Adults (45.90),	Healthcare & societal 1 year Not Applicable	Euro (€) 2002	Bootstrap simulation. ANCOVA used if normally distributed.	Health care perspective = €15,366/QALY gained. Societal perspective = €31,035/QALY gained.

First author, Year, Country of Population	*Study Design (Type of economic evaluation)*	*Patient population group*	*Description of Intervention & Comparator(s)*	*Intervention participants (No., mean age, gender (%), ethnicity (%))*	*Comparator participants (No., mean age, gender (%), ethnicity (%))*	*Study perspective, time horizon, discount rate*	*Currency & price year*	*Statistical analysis, sensitivity analysis*	*ICER or Net benefit / Net present value*
		the Department of Paediatrics at the University Hospital Maastricht with severity stages I to III from the GINA guidelines. Recruited between January 2003 and January 2004.	results and transfer with a modem to nurses' computer every month. **Com:** Regular outpatient care – for stable asthma, 3 to 6 monthly check ups by lung specialist or paediatrician. In case of exacerbations, additional care provided by GP and/or outpatient care.	Male: Adults (42.3%), Children (72.4%) Female: Adults (57.7%), Children (27.6%) Ethnicity: Not stated	Children (10.85) Male: Adults (33.3%), Children (55.6%) Female: Adults (66.7%), Children (44.4%) Ethnicity: Not stated			One way sensitivity analysis testing two cost components.	

Abbreviations: *ANCOVA = Analysis of Covariance; ANOVA = Analysis of Variance; AQLQ = Asthma Quality of Life Questionnaire; AUS = Australian; CBA = Cost Benefit Analysis; CCA = Cost Consequences Analysis; CEA = Cost Effectiveness Analysis; Com. = Comparator; CUA = Cost Utility Analysis; ED = Emergency Department; GBP = Great British Pound; GINA = Global Initiative for Asthma; GP = General Practitioner; HEPA = High-Efficiency Particulate Air; ICCs = Intra-cluster correlation coefficient; ICER = Incremental Cost Effectiveness Ratio; Int. = Intervention; No. = Number; QALY = Quality Adjusted Life Year; RCT = Randomised Control Trial; US = United States.*

2.4.2 Cost effectiveness of 15 additional papers

Two thirds of the studies (10 studies) were a mixture of CEA, CUA or CBA studies, with the remaining third (5 studies) being CCA studies. Out of the five CEA studies, two studies found the intervention evaluated to be dominant (the intervention was less costly and more effective) compared to the comparator (Flores et al., 2009, Lara et al., 2013), two studies found the intervention to be cost-effective (the Incremental Cost Effectiveness Ratio (ICER) was lower than the stated willingness to pay threshold) (Atherly et al., 2009, Mogasale and Vos, 2013) and one didn't report their ICER (Ryan et al., 2012).

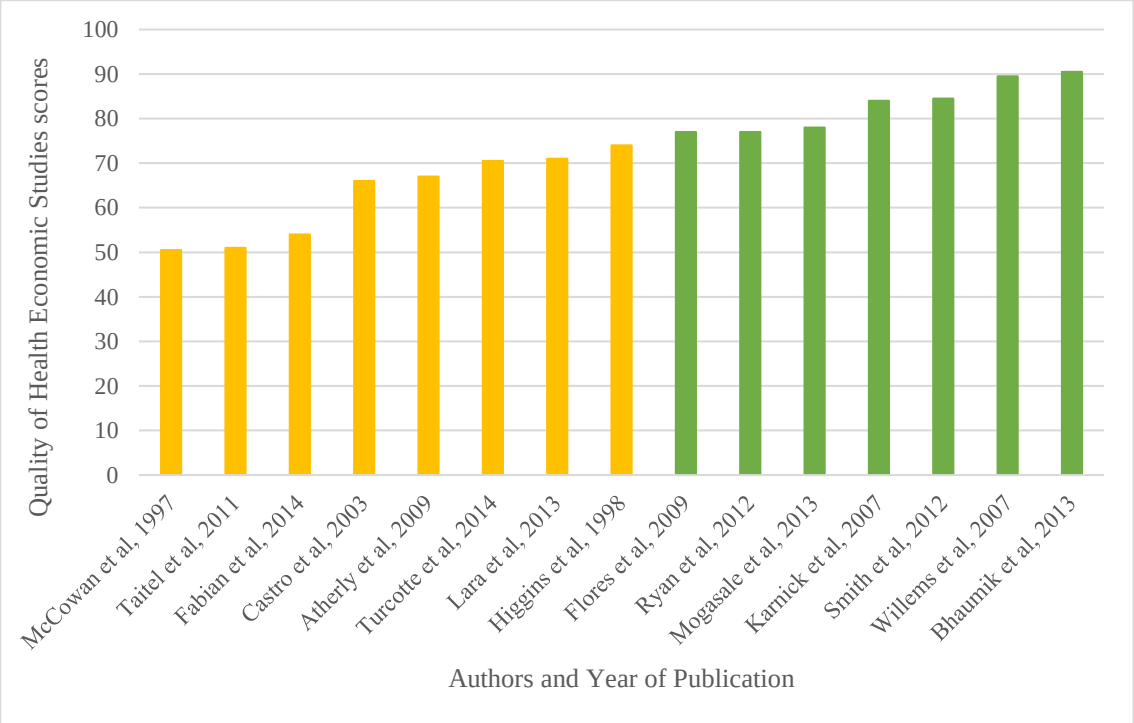
The two dominant studies had the same time horizons of 1 year, but differed in their country of population with one based in the United States (Flores et al., 2009) and the other based in the Caribbean (Lara et al., 2013). The two studies which stated that the interventions were cost effective (Atherly et al., 2009, Mogasale and Vos, 2013), both had varied time horizons (3 months and 1 year respectively), perspectives (societal and healthcare respectively), and thresholds. The stated threshold for Atherly et al. (2009) was AUS $50,000/DALY, whereas Mogasale and Vos (2013) didn't state the willingness to pay threshold. The final CEA study that didn't report an ICER stated that the intervention of a mobile phone self-monitoring system was not cost-effective (Ryan et al., 2012). This was due to there being no significant differences between the intervention (mobile phone technology) and the control group (paper based monitoring) in the clinical outcomes and self-efficacy, and the healthcare costs being the same with an additional increase in the cost of the intervention components.

The only CUA study (Willems et al., 2007) presented with a cost effective ICER had a time horizon of 1 year based on a societal and healthcare perspective separately. Only one CBA study (Bhaumik et al., 2013) out of three CBA studies produced positive net present values for the adjusted cost savings for year 1, 2, and 3, meaning that the benefits outweighed the costs and the intervention should be implemented. The five CCA studies did not present an ICER value, and so therefore were not compared for cost effectiveness. However, where available their cost and outcome results are displayed in **Table 4**.

2.4.3 Quality assessment for the 15 additional papers

The QHES checklist score (Yong and Shafie, 2014) varied across the 15 additional studies found, although the variation was only seen in the moderate and high quality categories. None of the studies scored within the poor quality range (25% to 49%) or the extremely poor quality range (< 25%). Eight studies scored within the range of fair quality (50% to 74%) (McCowan et al., 1997, Fabian et al., 2014, Castro et al., 2003, Atherly et al., 2009, Turcotte et al., 2014, Lara et al., 2013, Higgins et al., 1998, Tai and Bame, 2011), with three being borderline for either poor quality; 50.5% and 51% respectively (McCowan et al., 1997, Tai and Bame, 2011) or high quality; 74% (Higgins et al., 1998). The remaining seven studies (Flores et al., 2009, Ryan et al., 2012, Mogasale and Vos, 2013, Karnick et al., 2007, Smith et al., 2012, Willems et al., 2007, Bhaumik et al., 2013) scored within the range of high quality (>74%). **Figure 11** below shows the quality scores for the 15 additional studies and **Appendix IV** shows the table of scores.

Figure 11: Quality assessment for the 15 additional studies found post-2012 and in addition to Yong and Shafie, 2014



*Full table of the QHES criteria and scoring system can be found in **Appendix I**

Out of the included studies, there were two model based studies, where one was a discrete event simulation model simulating 1 million children and different health outcomes over

a range of interventions (Fabian et al., 2014), and the other was a simple decision tree model with an intervention and comparator arm developed from trial data (Mogasale and Vos, 2013). As two studies were model-based, the Phillips checklist (Philips et al., 2004) was also used to provide a further in-depth review of the quality. Fabian et al. (2014) provided a sound quality for the majority of the assessment categories, however reference to cycle length, internal consistency or methodological, structural and heterogeneity uncertainty was not mentioned. Mogasale and Vos (2013) also provided a good quality assessment overall, but was lacking in areas considering cycle length and uncertainties. There were also some areas of the quality assessment where clarity could have been improved, usually around justifications.

2.4.4 Methods used to estimate and value costs for all 64 papers

Most of the papers were transparent about the range of resources that were estimated, however amongst these papers, not all reported the associated unit cost, and so the finer details of how these resources were estimated were missed **(see Appendix II)**. Most papers included asthma-related hospitalizations (72%) and emergency department visits (70%) as resources that were measured, with physician visits (58%), other healthcare professional visits (28%), lost productivity (38%) and medication use (44%) being other resources most commonly identified. All resources, were appropriately chosen in line with the studies perspectives.

The resource use data was often gathered using multiple methods, meaning that amongst the included papers, about two-thirds would estimate the resources by using more than one method. This often depended on what type of resource use was being estimated, where quite commonly those papers who wanted to capture hospital-related costs, patients' quality of life and patients' loss of productivity costs were obtained from different sources.

With awareness of additional methods that was often used to estimate resources in each individual paper, data was mostly gathered from medical or computerised records (19%) for hospital related costs (Bratton et al., 2001, Bunting and Cranor, 2006, Castro et al., 2003, Doan et al., 1996, Levenson et al., 1997, van der Meer et al., 2011, Runge et al., 2006, Ryan et al., 2012, Shelledy et al., 2009, Shelledy et al., 2005, Smith et al., 2012, Steuten et al., 2007, Tschopp et al., 2005, Wood and Bolyard, 2011), wage rates by

employers or case managers for loss in productivity (22%) (Bhaumik et al., 2013, Bolton et al., 1991, Bunting and Cranor, 2006, Flores et al., 2009, Gallefoss and Bakke, 2001, Ghosh et al., 1998, van der Meer et al., 2011, Mogasale and Vos, 2013, Polisena et al., 2007, Runge et al., 2006, Steuten et al., 2007, Sullivan et al., 2005, Tai and Bame, 2011, Willems et al., 2007) and by patient or parent self-reported data (80%) for also gathering information about loss in productivity and quality of life (Bunting and Cranor, 2006, Castro et al., 2003, Drummond et al., 1994, Flores et al., 2009, Lindberg et al., 2002, van der Meer et al., 2011, Runge et al., 2006, Schermer et al., 2002, Shelledy et al., 2005, Steuten et al., 2007, Sullivan et al., 2002, Tschopp et al., 2002, Willems et al., 2007). Claims, billing or reimbursement data (25%) was often used for those countries who operate on healthcare insurance systems to also capture hospital-related costs (D'Souza et al., 2010, Greineder et al., 1999, Johnson et al., 2003, Rossiter et al., 2000, Suh et al., 2000, Sullivan et al., 2005, Tinkelman and Wilson, 2004, Bolton et al., 1991, Willems et al., 2007, Wood and Bolyard, 2011, Chan and Wang, 2004, Fabian et al., 2014, Gallefoss and Bakke, 2001, Gordois et al., 2007, Kattan et al., 2005, Sullivan et al., 2002). Costing manuals for healthcare were mostly used to gather the unit costs of resources amongst the papers; such as the Dutch Drug Compendium, 2000 and the Dutch Manual for Costing in Economic Evaluations (Kamps et al., 2004) and the Pharmacy price listing (Higgins et al., 1998).

For the papers who reported the methods used to estimate the resource use in more detail, (the extra detail including the unit costs and more information about what sources were used and calculations performed to estimate the resource use), the bottom-up approach (78%) was generally a more popular method used to estimate and value the resource-use costs including most of the intervention component costs, as opposed to the top-down approach (Anderson et al., 2004, Bolton et al., 1991, Bratton et al., 2001, Drummond et al., 1994, Franco et al., 2007, Higgins et al., 1998, Johnson et al., 2003, Karnick et al., 2007, Lucas et al., 2001, Rossiter et al., 2000, Shelledy et al., 2009, Shelledy et al., 2005, Tai and Bame, 2011). The bottom-up approach is defined as the individual's healthcare service use aggregated and the top-down approach is where the total healthcare service costs are divided by activity days (Chapko et al., 2009).

The methods used to estimate the lost productivity also varied with the variations including the human capital approach; each hour lost at work per patient (Runge et al.,

2006, Sullivan et al., 2005, Schermer et al., 2002), the friction cost method; each hour lost at work until the employer replaces the patient who is unable to work (Steuten et al., 2007, Willems et al., 2007), or using the caregivers income multiplied by the midpoint of the family's income (Flores et al., 2009). Other studies, (Bunting and Cranor, 2006, Kamps et al., 2004) stated lost productivity as an outcome measure, but the approach taken to calculate this was not specified. On occasions, reference to where the values were taken from to conduct the calculation was also mentioned, e.g. Federal Statistics Office (Tschopp et al., 2002, Tschopp et al., 2005).

The methods used to estimate the intervention components' resource use was not always clearly stated, with all of the necessary individual components needed to form the successful running of the intervention and the costing behind this, not often reported. Staff costs, program materials and training were the most commonly reported intervention component costs, however, only some studies stated the unit costs of the components (**see Appendix II)**. Only a select few papers took into account any associated travel costs involved with the intervention (Gallefoss and Bakke, 2001, Ghosh et al., 1998, Kattan et al., 2005, van der Meer et al., 2011, Rhee et al., 2012, Runge et al., 2006), and some studies reimbursed participants for taking part in their research (Atherly et al., 2009, Flores et al., 2009, Rhee et al., 2012, Turcotte et al., 2014, Wood and Bolyard, 2011). Likewise, with estimating the wider resource use, some papers were more detailed with the micro-costing of the intervention components (which were then summed) than others (see **Appendix V** for breakdown of micro-costing).

2.4.5 Methods used to estimate and value outcomes (1990 to January 2012)

The outcomes measured across the 64 papers varied widely, and this is depicted in **Appendix III,** with multiple data collection methods sometimes used within each study. The hospital visits and emergency department visits were the most frequently stated resource use, and they were also the most common type of outcomes measured. Over two-thirds (46 papers or 45 papers respectively) identified the emergency department visits or hospitalizations, followed by approximately one-third (26 papers and 29 papers respectively) investigating quality of life and physician (GP) visits. Other papers focused on reporting a wide range of other outcomes, of which some included intensive care admissions (Franco et al., 2007, Levenson et al., 1997, Shelledy et al., 2005, Turcotte et

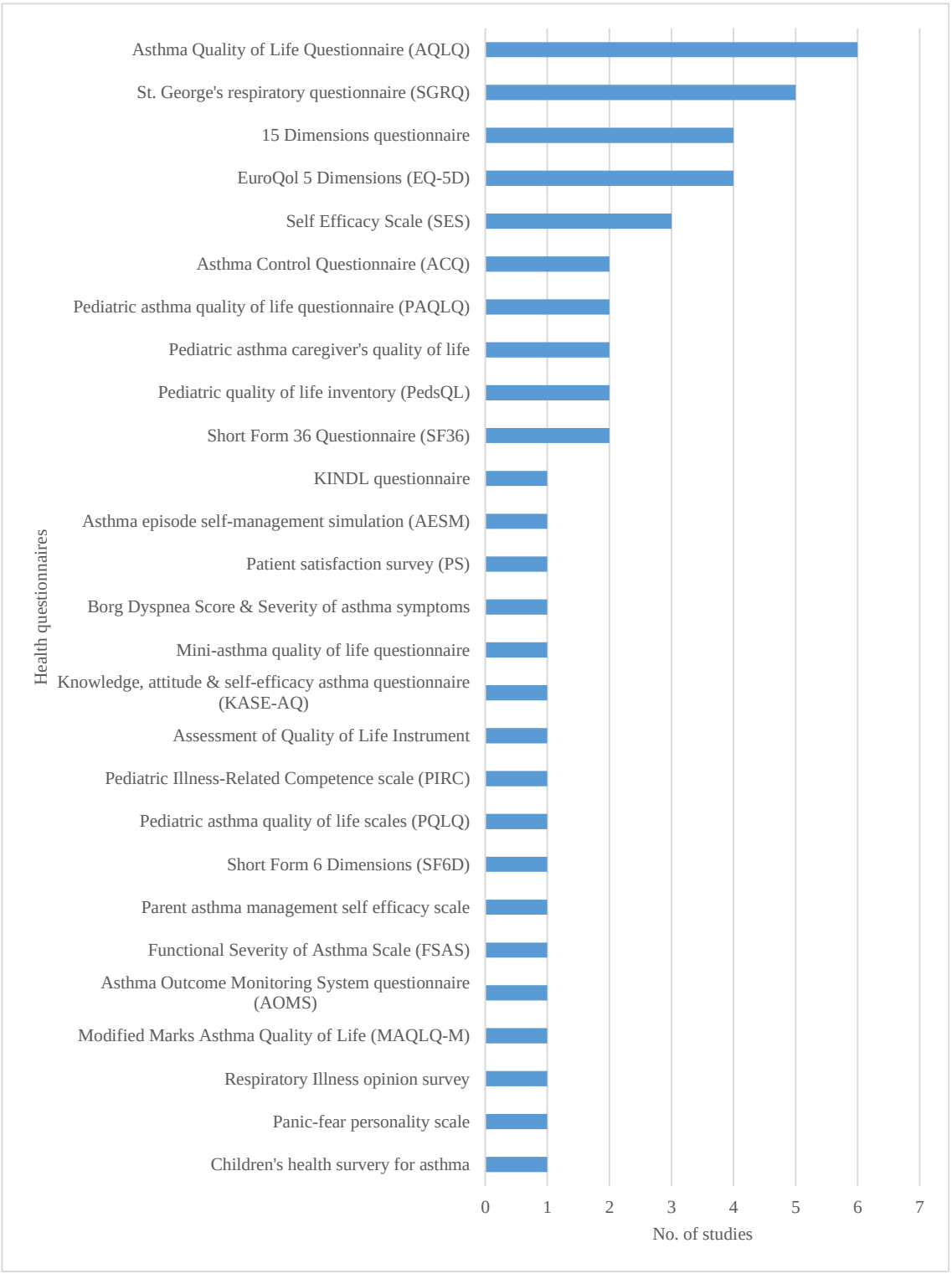
al., 2014), frequency of exacerbations and symptoms (Flores et al., 2009, McCowan et al., 1997, Ng et al., 2006, Ryan et al., 2012, Tagaya et al., 2005), asthma knowledge (Atherly et al., 2009, Chan and Wang, 2004, Lucas et al., 2001, Polisena et al., 2007), peak expiratory flow (Chan and Wang, 2004, Franco et al., 2007, Ghosh et al., 1998, Kauppinen et al., 1998, Kauppinen et al., 1999, Kauppinen et al., 2001, Lindberg et al., 2002, McLean et al., 2003, Neri et al., 1996, Runge et al., 2006, Tagaya et al., 2005), forced expiratory volume (Bunting and Cranor, 2006, Franco et al., 2007, Gallefoss and Bakke, 2001, Kauppinen et al., 1998, Kauppinen et al., 1999, Kauppinen et al., 2001, Lindberg et al., 2002, Neri et al., 1996, Runge et al., 2006, Schermer et al., 2002, Shelledy et al., 2009, Willems et al., 2007), force vital capacity (Franco et al., 2007, Gallefoss and Bakke, 2001, Kauppinen et al., 1998, Kauppinen et al., 1999, Kauppinen et al., 2001, Lindberg et al., 2002, Neri et al., 1996, Runge et al., 2006, Shelledy et al., 2009, Willems et al., 2007) and medications (Franco et al., 2007, Karnick et al., 2007, Kattan et al., 2005, Polisena et al., 2007, Runge et al., 2006, Taitel et al., 1995, Tinkelman and Wilson, 2004, Watanabe et al., 1998).

There was a wide selection of health questionnaires used to collect data in the studies, and this is shown in **Figure 12**. Most of the questionnaires used to capture quality of life and other outcome measures were patient self-report, where this data was often collected at face to face visits (Franco et al., 2007, Gallefoss and Bakke, 2001, Kamps et al., 2004, Kauppinen et al., 1998, Kauppinen et al., 1999, Kauppinen et al., 2001, Lara et al., 2013, Polisena et al., 2007, Ryan et al., 2012, Sullivan et al., 2005, Woods et al., 2012) or telephone interview sessions (Anderson et al., 2004, Bolton et al., 1991, Bratton et al., 2001, Donald et al., 2008, Flores et al., 2009, Greineder et al., 1999, Karnick et al., 2007, Kattan et al., 2005, Lucas et al., 2001, Mogasale and Vos, 2013, Ng et al., 2006, Sullivan et al., 2002, Watanabe et al., 1998, Woods et al., 2012). Other options of completing questionnaire data was by parent-reported questionnaires (Lara et al., 2013, Lindberg et al., 2002, Rhee et al., 2012, Woods et al., 2012), caregivers' questionnaires (Sullivan et al., 2005) or case managers self-reported questionnaires (Bhaumik et al., 2013, Xu et al., 2010). In addition, some of the questionnaires were posted to the participant (Bratton et al., 2001, Ryan et al., 2012). Within the different types of health questionnaires, some included generic questionnaires (such as; the EuroQol-5 Dimensions 3L (EQ-5D 3L) (Lindberg et al., 2002, van der Meer et al., 2011, Steuten et al., 2007, Willems et al., 2007), Short Form 36 Questionnaire (SF-36) (Lucas et al., 2001, Shelledy et al., 2009),

Short Form 6 Dimensions (SF-6D) (Willems et al., 2007) and 15 Dimensions (15D) (Kauppinen et al., 1998, Kauppinen et al., 1999, Kauppinen et al., 2001, McLean et al., 2003)), and more disease- specific questionnaires (such as; the Asthma Quality of Life Questionnaire (AQLQ) (Castro et al., 2003, Chan and Wang, 2004, Franco et al., 2007, Schermer et al., 2002, Tschopp et al., 2005, Willems et al., 2007) and St. Georges Respiratory Questionnaire (SGRQ) (Gallefoss and Bakke, 2001, Kauppinen et al., 1998, Kauppinen et al., 1999, Kauppinen et al., 2001, Shelledy et al., 2009)), with the most common being the AQLQ, followed by the SGRQ and in joint third the EQ-5D and 15D. The studies which used the EQ-5D and SF-6D converted the scores into utility values and used these to estimate QALYs. Other studies which didn't estimate QALYs used total and/or overall mean scores from the health questionnaires in their analysis.

Patient diaries were also used in several of the studies to collect data (Chan and Wang, 2004, Ghosh et al., 1998, Kamps et al., 2004, Lindberg et al., 2002, McLean et al., 2003, Schermer et al., 2002, Tagaya et al., 2005), as well as medical records (Anderson et al., 2004, Doan et al., 1996, Drummond et al., 1994, Higgins et al., 1998, McCowan et al., 1997, Neri et al., 1996, Runge et al., 2006, Ryan et al., 2012, Shelledy et al., 2005, Smith et al., 2012, Willems et al., 2007) and claims data (Bunting and Cranor, 2006, D'Souza et al., 2010, Greineder et al., 1999, Johnson et al., 2003, Rossiter et al., 2000, Suh et al., 2000, Sullivan et al., 2002, Taitel et al., 1995) to gather information. A small number of studies additionally addressed airway responsiveness (Kauppinen et al., 1998, Kauppinen et al., 1999, Kauppinen et al., 2001) and the peak expiratory flow (Chan and Wang, 2004, Franco et al., 2007, Ghosh et al., 1998, Kauppinen et al., 1998, Kauppinen et al., 1999, Kauppinen et al., 2001, Lindberg et al., 2002, McLean et al., 2003, Neri et al., 1996) of patients. Therefore, histamine was used to estimate the former (airway responsiveness) and a peak expiratory flow meter was used to address the latter (peak expiratory flow) in these studies. There were other lung function tests that were used to estimate the forced expiratory volume and forced vital capacity and this was measured by spirometry.

Figure 12: Different health questionnaires used in the studies



2.5 Discussion

This systematic review updated and extended previous work that evaluated the cost effectiveness of non-pharmacological asthma interventions with databases searched from 1990 until 2012 (Yong and Shafie, 2014). Due to Yong and Shafie (2014) having an applied focus on cost effectiveness, the methodologies used in the estimation of costs and outcomes in the studies found was not described or critiqued in their systematic review. Therefore, this systematic review explored both cost effectiveness and methods used to estimate costs and outcomes from 1990 until January 2016.

2.5.1 *Main findings*

In general, the additional studies found were mostly educational and self-management based interventions with almost half having interventions that were deemed cost effective or dominant. These findings were in line with Yong and Shafie (2014). On the other hand, the quality of studies have since improved with the additional studies presenting with fair (50%-74%) to high (>74%) quality. Multiple methods were often used to gather resource use data with self-report being the most common, the bottom-up approach being the most common estimation method of resource use gathered, and health related questionnaires being a common outcome measure with AQLQ and EQ-5D being the most common HRQL questionnaires.

2.5.2 *Comparison with other studies*

Earlier systematic reviews of asthma interventions also highlighted the importance of the quality assessment in studies (Willems et al., 2006, Campbell et al., 2008, Ismaila et al., 2013, Persson and Ghatnekar, 2003). One study in particular believed their peak flow monitoring intervention was cost effective, however, this could not be confirmed due to the low quality of the study (Willems et al., 2006). This review shows that the quality of studies has much improved since then, with nearly 50% of the studies found post 2012 presenting with high quality. The improvement in the quality of studies observed, stems from an earlier systematic review, which explored the quality of health economic asthma intervention studies (Campbell et al., 2008). For a like for like comparison, the mean QHES score for policy interventions from Campbell et al. (2008), (equivalent to non-pharmacological interventions in this present systematic review) was 61.4 for the 14 studies that this applied to. In comparison, the mean QHES score for the studies in Yong

and Shafie (2014) post-2008, was 75.6 (for the 8 studies that this applied to), and the mean QHES score for the additional studies identified in this review post-2012 was 75.1 (for the 7 studies that this applied to). Therefore, it is evident that there is an improvement in quality scores from the studies identified in Campbell et al. (2008) (mean QHES score = 61.4 for studies before 2008) through to Yong and Shafie (2014) (mean QHES score = 75.6 for studies 2008-2012) and this present review study (mean QHES score = 75.1 for studies 2012-2014).

Although improvement has been noticed in the quality of the studies, some still have inadequate follow up which can reduce validity and generalizability (Woolard et al., 2004). It was previously acknowledged that a short time horizon was inadequate for chronic conditions (Campbell et al., 2008), with a time horizon of 3 months or less considered to be unacceptable (Feenstra et al., 2002). The additional studies found in this review presented with one study having a time horizon of 3 months (Atherly et al., 2009), and others longer at between 6 months and 10 years.

As different cost perspectives are used amongst the included studies in this review, it becomes difficult to compare the total costs associated with each intervention. An earlier review noted that the author's definitions of direct medical costs, direct non-medical costs and indirect costs sometimes varied, where costs assigned to direct non-medical costs should have been assigned to indirect costs (Willems et al., 2006). Previous literature discusses that a societal perspective is important to synthesize the evidence and gain a proper understanding on peak flow monitoring interventions (Willems et al., 2006, Drummond et al., 2015, Jonsson, 2009). However, perspectives chosen can differ from country to country and the definitions of societal perspective can also vary.

It was surprising that only about a quarter of papers included lost productivity as an outcome measure. Due to asthma being a chronic condition, it is thought that more papers would have discussed lost productivity, and the possible implications that this may have on presenteeism and/or absenteeism. However, if such items, such as lost productivity have not been collected, then routinely available data, (e.g. from medical notes) can be used as an alternative as a way of applying the findings (Smith et al., 2012). With patients who have asthma attacks where they are often not well enough to continue at work or

with their usual activities, it is important to include nonmedical resource use and productivity costs in studies (Ramsey et al., 2015).

In all of the included studies in this review, the intervention details were often reported, but the detail surrounding the costs of conducting the interventions with the associated unit costs were limited. Three studies provided comprehensive details about how they estimated the intervention costs, including the breakdown of the intervention components, their associated unit costs and the methods chosen to estimate such costs (Willems et al., 2007, van der Meer et al., 2011, Rhee et al., 2012). The common approach between all three was a microcosting approach. Difficulties can sometimes occur with this approach when prices for certain resources are not always available from various data sources, leaving room for customization (Raftery, 2000).

From the 26 studies which also incorporated quality of life as an outcome measure, there were over 20 different questionnaires that were used to measure this. Many of the questionnaires used to analyse quality of life were more specific to asthma, but there did not appear to be a preferred measure that was used across the studies. The EQ-5D-3L questionnaire (five dimensions with 3 levels: no problems, moderate problems, extreme problems) was used across a number of studies, but often used alone and not in conjunction with another quality of life questionnaire. As discussed by Yong and Shafie (2014), EQ-5D-3L might not be the best tool to use for quality of life in asthma, as it is not seen as sensitive enough to detect differences in HRQOL particularly in people with mild asthma. However, there have been recent developments of a new EQ-5D-5L questionnaire which includes the same five dimensions but with 5 levels: no problems, slight problems, moderate problems, severe problems or extreme problems (Herdman et al., 2011). The newly developed EQ-5D-5L tool may be more suitable as it was designed to be more sensitive and reduce ceiling effects. This has been confirmed in several studies which have shown increased reliability, sensitivity and validity (Janssen et al., 2013, Herdman et al., 2011).

2.5.3 Strengths and limitations

A comprehensive search was conducted using a variety of different databases in order to capture a breadth of studies for this review. Bias was reduced by including two reviewers in the screening, data extraction and quality assessment processes. The methods used to

estimate both costs and outcomes of all studies found between 1990 and 2016 were critically assessed for non-pharmacological intervention studies. This time period shows that a vast array of studies have been encompassed, stretching back to when the earliest asthma guideline was introduced (Bousquet et al., 2007). The included studies help to understand how asthma interventions and methodologies chosen have evolved over the years, with discussions leading to recommendations for future practice. A limitation of this review is that only English language studies were included in this review with restrictions placed during the database search, and therefore it is not possible to acknowledge how many non-English studies have been excluded from this review. It is therefore apparent that due to this selection bias, additional studies may have been relevant for inclusion in this review.

2.5.4 Directions for future research

In light of the above, there are many areas for which focus is required when conducting an asthma study. The main recommendations are to use time horizons greater than 3 months to ensure adequate follow up, to include all relevant costs and benefits that have been accounted for as asthma is a chronic condition, (particularly the high cost drivers (Ramsey et al., 2015)) and to conduct a micro-costing approach where possible. For economic evaluations where QALYs are estimated, the EQ-5D-5L can be used as a generic measure. However, even though this has been proven in earlier studies to show positive results in terms of increased sensitivity and validity compared to the EQ-5D-3L, due to it being a relatively new questionnaire, it may be advisable to use this in conjunction with a more established disease specific questionnaire. Due to the difficulties that arise in economic evaluations and to ensure the comparability across different countries and decision makers (Wilkinson et al., 2016), it may be useful to adhere to an international reference case (Bill and Melinda Gates Foundation, 2014, Wilkinson et al., 2016), which is a useful guide from the planning stages of research through to reporting findings and completion. Future research should also ensure that the appropriate guidelines and checklists are adhered to, such as the TiDieR checklist (Hoffmann et al., 2014), the CHEERS statement (Husereau et al., 2013), CONSORT statement (Schulz et al., 2010) and the COMET initiative (COMET initiative, 2011-2017) for ease of replicability of both the intervention and control groups by clinicians or researchers looking to implement or expand research ideas respectively. The TiDieR checklist provides a minimum number of items, which are recommended to use when describing

an intervention. The CHEERS checklist (Husereau et al., 2013) provides detailed recommendations for reporting of health economic evaluations from what should be included in the title and abstract through to describing any conflicts of interest. The CONSORT statement, is similar to the CHEERS statement, except the reporting guideline recommendations are for reporting randomized trials. Finally, the COMET initiative allows people to identify the 'core outcome sets', which are an agreed set of standardized outcomes that represent the recommended minimum outcomes that should be measured and reported for a specific condition in clinical trials. For asthma studies, core outcomes for measuring quality of life have not yet been identified, but there are some existing instruments which are used as supplemental (standardized and used in relation to the aim of the study) (Wilson et al., 2012). All of the above checklists and statements, will in turn aid the comparability of studies.

This systematic review also highlights that less than half of the papers focused on quality of life as an outcome measure, measured it prospectively at set time points over the time horizon period. Though the most common time horizon being 12 months, the follow ups varied from 2-4 times during the year. As asthma attacks can occur at sporadic intervals, quality of life could be measured more frequently in future research to capture the true variation for asthmatics, as otherwise such attacks could be missed leading to inaccurate estimation.

2.6 Conclusions

In summary, the additional 15 studies included were of fair to high quality. In alliance with the previous review, most of the additional studies found had dominant or cost effective interventions which were educational or management based. The methods used to estimate costs and outcomes were varied, with the bottom-up approach being the most common approach. However, the reporting of unit cost values were lacking amongst some studies, with only a few studies providing detailed micro-costing methodologies for the intervention components. The most common method of collecting outcome results was through patient self-reported data, coupled with medical or claims records and telephone or face to face visits. For future studies, a thorough description of methods used in all components of the study is needed, including reporting of unit costs and a common quality of life measure to provide more comparability.

As noted in this review, there were many quality of life tools identified in the included papers, with very few papers using the same quality of life tools. This shows that a general consensus of quality of life tools used across asthma studies is yet to be reached. It was also noted that the follow up time points to assess quality of life in these studies were quite varied occurring at fixed time points during the year. Due to these fixed time points, it is possible that the changes in quality of life associated with potential hospital admissions or A&E attendances due to an asthma attack could have been missed. Therefore, an attempt to address this issue was conducted in the following chapter where different quality of life instruments were used to estimate quality of life in patients with more acute asthma. **Chapter 3** provides a thorough overview of a cohort observational study design developed to investigate the quality of life of acute asthmatics when presenting in hospital. Patients were followed up for a period of 8 weeks. Full details of the study design will be provided, including inclusion criteria, outcome measures and statistical analysis. The study was registered on ClinicalTrials.gov with the identification number as NCT02771678.

CHAPTER 3

ESTIMATING THE LOSS IN QUALITY OF LIFE ASSOCIATED WITH AN ASTHMA-RELATED CRISIS EVENT (ESQUARE): METHODOLOGY

"What we observe is not nature itself, but nature exposed to our method of questioning."

(Werner Karl Heisenberg, German physicist)

Preface

The studies included in the synthesis of the systematic review, included a variety of different study designs. Some were randomised controlled trials, prospective/retrospective cohort studies, or model based studies. Part of the conclusions from the previous systematic review **(CHAPTER 2)** related to different quality of life measures and showed that it was necessary to agree on a single quality of life tool to enable comparability between studies. The importance of this is that when conducting economic evaluations and deciding on which health product is more cost effective, a common quality of life tool enables decisions to be made on a level playing field. It was also recommended that future research should adhere to guidelines and checklists that are appropriate for the study design, as this will also improve the comparability of studies and provide a good base for other clinicians and researchers to implement and expand on in the future.

In light of the conclusions from the previous chapter, this chapter **(CHAPTER 3)** will investigate the quality of life in acute asthmatics by using different quality of life measures. The particular focus will be on acute asthmatics who present to A&E or are admitted to hospital following an asthma attack (referred to as an asthma-related crisis event). As previously discussed, asthma is a chronic condition, and occurrence of an attack can be sporadic. With previous literature measuring quality of life at set time points (e.g. baseline, 6 months and 12 months), and the assumption of linear interpolation, the probability of capturing the full changes in quality of life associated with an asthma attack

is small. Therefore, investigating quality of life at a point where a chronic episode is occurring (Mason et al., 2014), may allow us to better understand the condition and provide an extended way of measuring quality of life in asthmatics. Better understanding of a chronic episode, will in turn lead to better estimations when conducting economic evaluations.

The research study detailed in this chapter has an observational study design. There are three main types of observational studies, (cohort, cross-sectional and case-control), and a brief description of these are detailed below.

Cohort study

A prospective cohort study follows a patient population group over a period of time to establish whether an outcome has been reached (Euser et al., 2009, Song and Chung, 2010). In this type of study, patients are recruited before the outcomes have been expressed in any one of the patients. The researchers then assess the variables that might have an influence on the outcome of interest.

On the other hand, a retrospective cohort study already has a set of data that has been collected over a period of time (Euser et al., 2009, Song and Chung, 2010). Therefore the outcomes of interest are already identified from the dataset, but the data is examined historically to investigate how the patients developed the outcomes, as the initial baseline would still remain free from the outcome of interest.

Cross-sectional study

A cross-sectional study collects data from a population group at a single point in time (Levin, 2006).

Case-control study

This type of study is usually less costly than a cohort study and quick to conduct due to a smaller sample size (Song and Chung, 2010). Cases are identified by having the outcome of interest (e.g. particular condition) and are matched with controls who are from the same population group but are free from the outcome of interest with a risk to exposure (bmj,

2017). It is always conducted retrospectively as the outcome of interest is investigated historically (Song and Chung, 2010).

In light of the main observational studies described above, a prospective cohort study approach was taken for this research study in order to compare participants' quality of life over a fixed time period. This approach allows the outcome measures to be closely monitored making it easier to estimate the occurrence of an asthma-related crisis event and examine how quality of life corresponds with these outcome measures chosen. The downfall is that a large sample size is required in order to allow for the inevitable loss to follow up and to ensure enough participants are recruited into the study to provide valid conclusions. However, large sample sizes has cost implications.

This chapter will highlight the aims and objectives of this prospective cohort study, the recruitment approach, the study methods, data management and analysis. The three main research questions that this study aims to address are:

What is the loss in quality of life associated with an asthma-related crisis event?

To what extent does this loss vary depending upon which patient reported outcome measures is used?

What is the comparative performance of different generic and/or disease-specific questionnaire(s) when they are used to assess quality of life in acute asthmatics?

*The findings in r*elation to thes*e questions are addressed in chapters 4 and 5 respectively, and the methods for both are outlined below.*

3.1 Aims and Objectives of study

Some of the studies which were included in the systematic review **(Chapter 2)** measured quality of life using either generic or disease-specific questionnaires. The most commonly used generic questionnaires were the EQ-5D and the 15 Dimensions (15D) (Willems et al., 2007, van der Meer et al., 2011, Kauppinen et al., 1999, Kauppinen et al., 2001, Kauppinen et al., 1998, Steuten et al., 2007, Lindberg et al., 2002, Tagaya et al., 2005,

McLean et al., 2003). Several studies found their mean changes in utility values held statistical significant difference (Lindberg et al., 2002, van der Meer et al., 2011, Willems et al., 2007). One study stated that their QALY estimates might have been more accurate if they had included more follow up time points (van der Meer et al., 2011).

Often studies estimated quality of life at specific time points, such as baseline, 4 months, 8 months and 12 months (Willems et al., 2007). **Figure 13** shows an example of four utility values estimated from measuring quality of life at four different time points during one year, with the assumption of linear interpolation. However assuming linear interpolation in between these time points may not be adequate for estimating episodic quality of life as indicated in other studies (Mason et al., 2014, Franklin et al., 2017, Jakovljević et al., 2015, Fowler et al., 2014, Insinga et al., 2007, Barton et al., 2011). It is known that asthma attacks are unpredictable, and if quality of life is assessed between specific time points (e.g. baseline and 4 months), then the total QALY score could potentially be underestimated if the individual has had an attack in between these points, but has somewhat or wholly recovered by the point of the 4 month measurement, (see **Figure 14** as an example). Equally, if the asthma attack occurs at the 4 month time point, but is short-lived, then the use of linear interpolation may mean that the total QALY score is underestimated. Either way there is a potential for the utility estimation, QALY and cost-effectiveness to be incorrect. Thus, it is possible that treatments could be recommended for provision when they are not in fact cost effective, or even maybe not recommended when they are in fact cost effective.

Figure 13: Assumption of linear interpolation amongst four utility values at 4 time points during one year

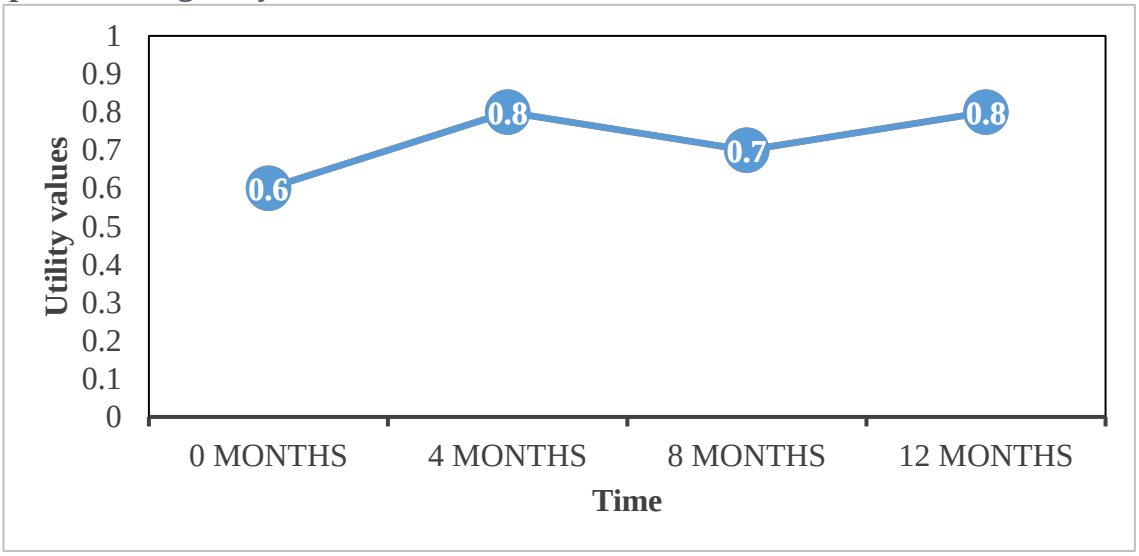
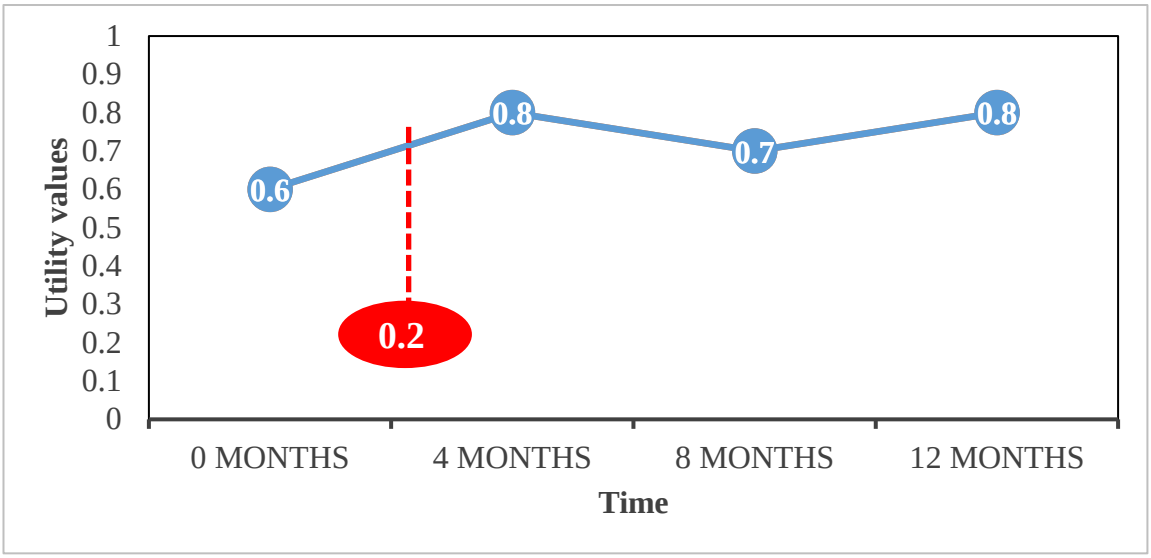


Figure 14: An asthma-related crisis event (utility value of 0.2) that could be missed at the two month time point



A recent study addressed the importance of this when exploring the utility decrement associated with an asthma attack requiring hospitalization in children (Franklin et al., 2017). However, the literature did not provide a suitable utility decrement for children, and so an alternative adult utility decrement was used instead (Lloyd et al., 2007, Luskin et al., 2014) . This study used three health related quality of life questionnaires to collect data at two time points (baseline and week 4), to estimate the mean change in quality of life (Lloyd et al., 2007). However the patients were recruited from outpatient clinics or primary care offices and not at time of the asthma attack, and so the asthma attack period was not closely monitored (Lloyd et al., 2007).

Therefore, due to the gap in the evidence highlighted above, the aim of this study was to estimate the loss associated with an asthma-related crisis event more regularly over a shorter time period, and to compare the performance of several instruments in order to see if one would be preferred over another. For this study, the definition of an asthma-related crisis event was patients who attended the A&E department or were admitted to hospital due to an asthma attack that they were unable to control themselves, and therefore required medical attention.

The idea was to estimate the loss in quality of life more accurately by using different quality of life methods through patient reported outcome measures (PROMs) and to assess the mean changes between more regular time points over a period of 8 weeks.

Several research questions are pertinent in this prospective cohort study, which this thesis aims to address in chapters 4 and 5. The questions detailed below help to better understand the quality of life surrounding the asthma-related crisis event and possible implications of this on the patients' productivity.

The research questions of interest for this study are as follows:

1) When did the asthma-related crisis event peak (e.g. on route to hospital, after 2 hours in hospital)?

2) What are the mean quality of life scores, utility values, and peak flow and symptom scores for patients reporting these at weekly, monthly and daily time points during the 8-week study?

3) What is the loss in quality of life associated with an asthma-related crisis event?

4) What is the relationship, (if any), between the demographic variables (e.g. age, gender, smoking status etc.) and utility estimates (EQ-5D-5L, AQL-5D and TTO)?

5) What is the productivity loss & out of pocket cost associated with an asthma-related crisis event?

6) What is the comparative performance of different generic and/or disease-specific questionnaire(s) when they are used to assess quality of life in acute asthmatics?

   a. With respect to convergent validity:

      i. What is the correlation between the utility values for EQ-5D-5L, AQL-5D and TTO?

   b. With respect to discriminative validity:

      i. Are there any differences between the three PEF groups (<50% best / predicted PEF, 50-75% best / predicted PEF and >75% best / predicted PEF) and utility values?

      ii. Are there any differences between patients' reporting asthma improvement (if any) at week 4 compared to baseline and the utility values?

   c. With respect to responsiveness:

i. What is the sensitivity to change between patients' reporting asthma improvement (if any) at week 4 compared to baseline and the utility values?

Chapter 4 will discuss research questions one to five, and chapter 5 will discuss research question 6.

3.2 Study participants & sample size

Acute asthma participants were recruited from three hospital sites; Norfolk and Norwich University Hospital (NNUH) (primary site), Queen Elizabeth Hospital Birmingham (secondary site), and Aberdeen Royal Infirmary (tertiary site) from 11th May 2016 until the 31st May 2017. All three hospital sites had staggered commencement for screening and recruitment in 2016 due to different times of the approval process, where Norwich, Aberdeen and Birmingham commenced recruitment in May, August and November respectively. Participants were screened for eligibility and considered for inclusion into the study if they met the inclusion criteria displayed in **Table 5.**

One of the quality of life questions that I asked participants to complete was called the time trade off (TTO). The sample size was chosen to reflect the same size as that used in previous literature when using the TTO valuation approach and other similar quality of life measures (Perez et al., 1997, Hamilton et al., 2015, Stiggelbout et al., 1995). Originally, the aim was to recruit 100 participants informed from the literature above. However, due to the large unforeseen number of participants who did not complete the study due to withdrawals or loss to follow up, the sample size was increased to recruit more than 100 participants, with 200 being the limit of participants recruited. The age range of the included sample (18 years and older) was chosen based on the knowledge that children might have difficulties with the TTO task. The TTO can be challenging for children to understand and provide realistic answers because they may lack the cognitive skills needed to evaluate the state of their health (Thorrington and Eames, 2015).

A post-hoc power calculation was conducted to determine the power required to compare the mean difference between two different time points which is large enough to detect a difference. The effect size, sample size, and standard deviation difference were all taken

into account to estimate the power for a one-sample t-test to account for the paired nature of the data. The standard deviation difference and sample (N) used in **Table 22** to test for significance between AQLQ baseline and AQLQ week 8, was also used to estimate the post-hoc power calculation. The minimal important difference (MID) for the AQLQ was reported as 0.5 (Juniper et al., 1993). Therefore, based on a MID of 0.5, N of 65 and the standard deviation of the difference between the two time points of 1.5, the estimated power was 75%. This indicates that the total sample size for this study based on a power calculation of 75%, would be 65. To take into account the potential loss to follow up, with a 50% drop out rate, the estimated total sample size required based on the AQLQ overall data from **Table 22**, would be (65 / 0.5)= 130 participants. This would give confidence in determining whether a MID exists in the mean difference.

Table 5: Eligibility criteria

Inclusion	Exclusion
18 years old and older; male or female	Younger than 18 years old
Attended A&E or admission to hospital following an asthma attack	Did not attend A&E or get admitted to hospital following an asthma attack
Has asthma alone, or asthma with Chronic Obstructive Pulmonary Disease (COPD) or asthma with a respiratory infection; main diagnosis is asthma.	Main diagnosis is not asthma
Speaks English	Does not speak English
Not in need of help from carer/guardian to complete questionnaires	In need of help from carer/guardian to complete questionnaires
Not hypoxaemic	Remains hypoxaemic despite oxygen therapy
Not participated in the study before	Has participated in the study before
Able to give informed consent	Impaired capacity to consent

3.3 Participant recruitment approach

Recruitment from the NNUH was done primarily by myself (chief investigator) and another researcher when cover was required. For the other two hospital sites in Birmingham and Aberdeen, research nurses and the principal investigator conducted recruitment. As patient's were attending hospital in an acute state, initial treatment was provided to the patient first, before study recruitment was allowed. The researchers would then give the patient's a participant information sheet (PIS) **(Appendix VIa)** if they met the inclusion criteria.

Participants were recruited as early as possible into the study from when they presented at hospital with their acute asthma attack (either A&E, short stay units or the respiratory wards). This was to ensure that the baseline data capturing the participant's quality of life was recorded as close as possible to their acute event to enable accurate estimation in loss in quality of life. Failure to do this, would risk underestimating the loss in quality of life if the patient was nearer recovery (Dritsaki et al., 2017). An earlier acute asthma study also recruited participants from A&E departments who were able to verbally consent (Goodacre et al., 2014).

Once participants were consented into the study, the original consent form **(Appendix VIb)** was filed in the medical notes, a copy was given to the patient and a copy was kept for the researcher's file. A patient and General Practitioner (GP) details form was also completed for contact details for the duration of the study. A written letter notified the participants' GP **(Appendix VIc)** of their inclusion in the study, and this was accompanied with a copy of the PIS.

3.4 Follow up

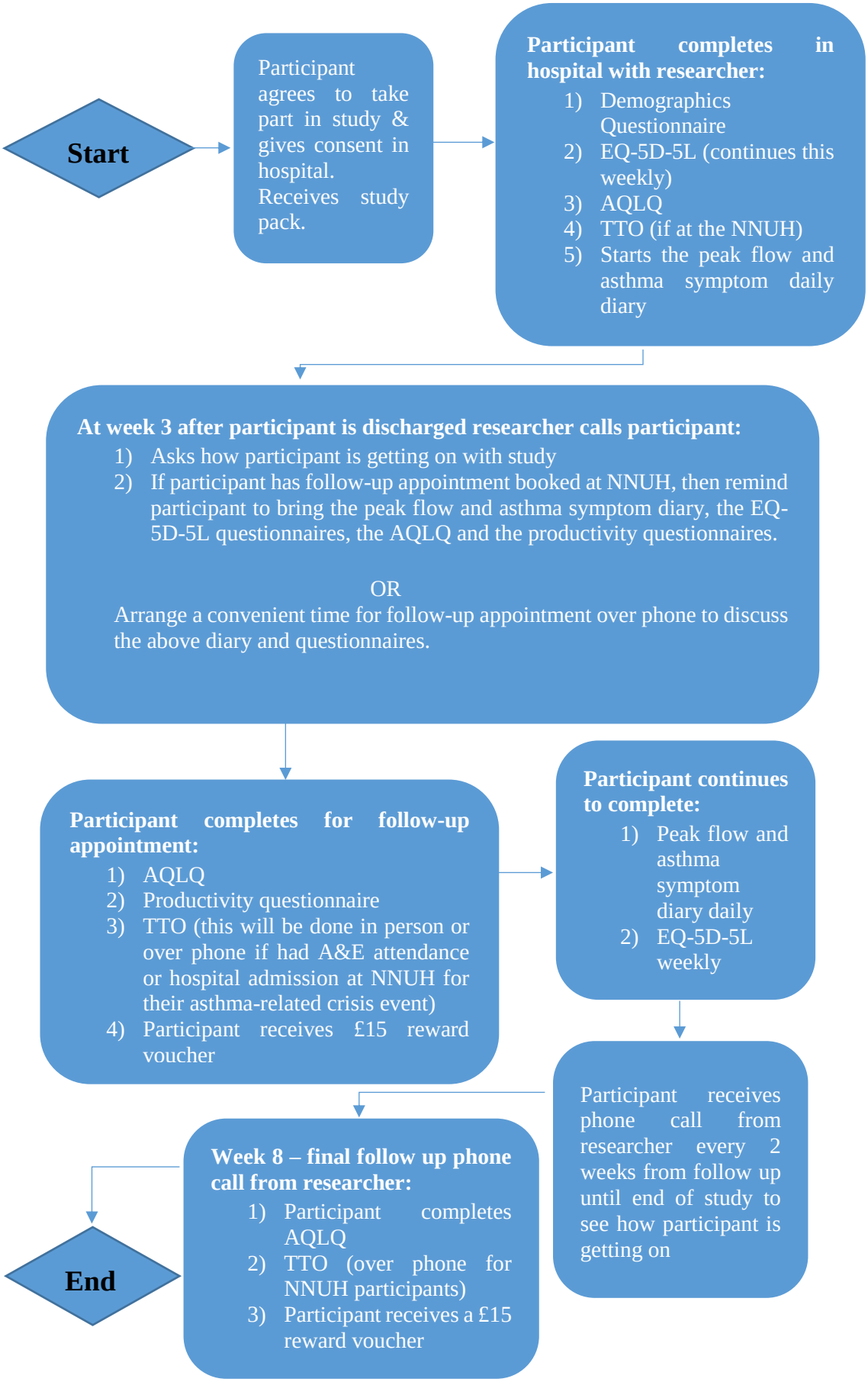
Participants were consented into the study and followed up for a period of 8 weeks. During this time period, the participants were asked to complete questionnaires at different time points; some daily, some weekly and some monthly. Upon consent, participants were asked to complete baseline questionnaires and received a pack of questionnaires in hospital for the first 4 weeks (week 1 to week 4) of the study **(see section 3.5 for further information on outcomes)**. Face to face or telephone follow ups were also conducted at 4 weeks and 8 weeks. These were chosen in order to correspond with

the routine follow up times of 4 and / or 8 weeks at the primary site. Accordingly, the plan was to hold face to face appointments at this site at these times. If the participants were recruited from the primary site, then follow ups at 4 weeks or 8 weeks, may have been delivered in conjunction with their routine follow-up appointment at approximately 4 weeks after they were discharged from hospital following their acute event. However, in some circumstances, this was not always possible due to the participants not attending their appointments or the appointments not being scheduled to align with the 4 and 8 week follow up points. Therefore, in these circumstances, the follow-ups were conducted over the telephone. Similarly, in the secondary and tertiary hospital sites, the follow-ups were conducted over the telephone at 4 weeks and 8 weeks by the chief investigator.

In addition to these follow-ups, the participants also received telephone calls at 3 weeks and 6 weeks to see how they were progressing with the study and to remind them about the upcoming follow-up appointments or telephone calls in the coming weeks. During the week 3 call, participants were asked if they were happy to continue with the study, and if so, the chief investigator (I) posted out the second pack of questionnaires to the participants for the last 4 weeks (week 5 to week 8) of the study. Freepost envelopes were provided in both packs of questionnaires – the first received in hospital, and the second posted out at 3 weeks – to allow the participant to post back all of the questionnaires from the study. Participants also received 'love2shop' vouchers to thank them for their time in contributing to the research study. A total of £30 was given to the participants if they completed the study; £15 was posted to them with the 2nd study pack of questionnaires and a further £15 was posted to them after receipt of all of the completed questionnaires.

The study process is displayed in **Figure 15;** a flow chart of the stages of the study from consent through to the end of the 8 week study period.

Figure 15: Flow chart of events for study design



3.5 Outcome measures

There were several questionnaires and forms included in this study that were completed by the research team and participants. Below **Table 6** shows each questionnaire and the form in which it was completed at different time points of the study.

Table 6: Questionnaires and forms completed during the study

Questionnaires/ Forms	**Baseline**	**Week 1**	**Week 2**	**Week 3**	**Week 4**	**Week 5**	**Week 6**	**Week 7**	**Week 8**
Researcher with participant completion									
Case Report Form 1	X								
Consent form	X								
Patient and GP details form	X								
Case Report Form 2					X				
Case Report Form 3									X
Time Trade Off	X				X				X
Participant completion									
Demographics questionnaire	X								
EuroQol-5 Dimensions-5 Level Questionnaire	X	X	X	X	X	X	X	X	X
Asthma Quality of Life Questionnaire	X				X				X

Questionnaires/ Forms	**Baseline**	**Week 1**	**Week 2**	**Week 3**	**Week 4**	**Week 5**	**Week 6**	**Week 7**	**Week 8**
Peak flow and symptoms diary	Completion of this diary was requested every day from baseline through to week 8								
Productivity Questionnaire					X				

3.5.1 Case Report Forms

These forms were completed at baseline (visit 1), week 4 (visit 2) and week 8 (visit 3), and gathered some basic information about the participant. At the initial visit (Case Report Form 1), the following information was captured:

- Height and weight (the height is useful to predict the PEF)
- Asthma history (last occurrence of having an asthma attack, A&E attendance, hospital admission and intensive care record)
- Current asthma medications
- Clinical observations (PEF recordings, respiratory rate, heart rate and oxygen levels; useful for the severity of the asthma attack)
- Comorbidities
- TTO

The other two case report forms (visit 2 and visit 3), were follow-ups to capture any data that might have changed. Both forms recorded the following:

- Adverse events
- Any changes in asthma medications
- Any new comorbidities
- Any changes in smoking status
- TTO

3.5.2 Demographics questionnaire

This questionnaire **(Appendix VId)** was completed by the participant at baseline to gather their general characteristics. The following data was captured:

- Age

- Gender
- Smoking status
- Ethnicity
- Highest level of education
- Employment status
- Peak of asthma-related event
- Route of entry into hospital
- Number of asthma related A&E attendances and hospital admissions in the last year
- List of medications before current asthma-related crisis event

3.5.3 EuroQol-5 Dimensions 5 Levels (EQ-5D-5L)

This questionnaire **(Appendix VIe)** was requested for completion by the participant at weekly intervals, with the first completed at baseline. The EQ-5D-5L is a generic questionnaire composed of five different categories (domains) of overall well-being: mobility, self-care, usual activities, pain/discomfort, and anxiety/depression. There are five different levels to choose from within each category, which describes health on the day the questionnaire is completed. The five levels are no problems, slight problems, moderate problems, severe problems, extreme/unable problems. Each participant ticked one of these levels from each of the five domains that best described their health on the day they completed the questionnaire. In addition, there was also a Likert scale which is called an EQ Visual Analogue Scale (VAS), ranging from 0 (worst possible health) to 100 (best possible health). Each participant recorded a value between these two points which best described their health on the day they completed the questionnaire.

The EQ-5D-5L value set was developed, based on the responses of, individuals of the general population in England using TTO and discrete choice experiment methods (Devlin et al., 2016, van Hout et al., 2012, NICE, 2017). The EQ-5D is a widely used questionnaire and is recommended by NICE for use in economic evaluation studies (Drummond et al., 2015). When the participants completed the questionnaire and ticked a level on each of the five different domains, their responses were converted into a utility score for use in economic evaluations. The utility scores can range from -0.281 to 1.000, providing worse then dead values to full health values respectively (Mulhern et al., 2017).

For this study, the EQ-5D-5L value set from Devlin et al. (2016) was used. However, this valuation set is currently not recommended by NICE, as highlighted from a recent position statement (NICE, 2017), and once further research has been conducted, (which has been laid out by NICE), then the position statement will be reviewed later in August 2018.

3.5.4 Asthma Quality of Life Questionnaire (AQLQ)

Each participant was asked to complete the AQLQ questionnaire **(Appendix VIf)** three times (baseline, week 4 and week 8). The AQLQ is a disease specific questionnaire that consists of 32 asthma-related questions, with answers based on the last 2 weeks when completing the questionnaire. The participant had 7 different response choices for each question ranging from 1 (e.g. all of the time) to 7 (e.g. none of the time). The 32 questions are grouped into four categories, which are symptoms, emotions, activities and environment. AQLQ scores can be estimated as an overall score and also as a score corresponding to the four categories mentioned.

This instrument was developed by a combination of unstructured interviews with clinicians and asthmatics discussing items important to asthma patients, of which 150 items were identified. Following this, a wider asthma subject population was studied to help identify which items were the most important during an item reduction phase in order to create the 32 item AQLQ (Juniper et al., 1992).

3.5.5 Justification for choosing the EQ-5D-5L and AQLQ

The EQ-5D-5L and the AQLQ were chosen based on the lack of evidence in the literature for a disease-specific HRQL instrument for asthma patients that can be used to inform economic evaluations. However, previous literature shows an earlier development of a generic preference-based measure that can be used specifically for asthma patients in economic evaluations (Young et al., 2011). This developed instrument is called the AQL-5D and uses an algorithm to translate the disease-specific HRQL (AQLQ) responses, into a utility score. This utility score can then be used in economic evaluations. Even though this measure was designed alongside supporting psychometric criteria, it is still a new measure and requires applied testing. This is highlighted by the recommendation that disease-specific HRQL instruments should be used in conjunction with generic HRQL

instruments (Drummond et al., 2005). With awareness of this, and the fact that NICE recommends the use of EQ-5D in economic evaluations, a decision was made to use the AQLQ, (which can later be converted into AQL-5D for utility scores), and the EQ-5D-5L.

The expanded version of the EQ-5D (5L), was chosen as opposed to the EQ-5D-3L because it is thought that this would provide more sensitivity for the outcome responses (van Reenen and Janssen, 2015). The AQL-5D also has 5 dimensions, which corresponds with the EQ-5D-5L. Therefore, both the EQ-5D-5L and the AQL-5D seem useful for comparisons in economic evaluation studies. In light of the above, and based on the fact that the AQL-5D can be derived from the AQLQ, both the EQ-5D-5L and the AQLQ were used in this study to identify which questionnaire would be more appropriate to use when estimating HRQL in asthmatics.

3.5.6 Peak flow and symptoms diary

This diary **(Appendix VIg)** included recording the PEF and symptom severity of each participant during the study. The participants were asked to record their PEF morning and evening on a daily basis, and to also record their symptom severity in relation to the following three questions from the Royal College of Physicians (RCP) (Thomas et al., 2009):

1. Have you had difficulty sleeping because of your asthma?
2. Have you had your usual asthma symptoms during the day (cough, wheeze, breathlessness, chest tightness)?
3. Has your asthma interfered with your usual activities (e.g. housework, childcare, work, school etc.)?

The above three questions were answered on a scale between 0 (no symptoms) and 3 (severe symptoms).

PEF readings and asthma symptoms are a regular way of monitoring how well controlled a patient's asthma symptoms are (British Thoracic Society. Scottish Intercollegiate Guidelines Network, 2016, Pearson and Bucknall, 1999). By asking participants to record these daily, it helped to visualise the trajectory of asthma recovery in more detail throughout the 8 week study period.

3.5.7 Productivity questionnaire

A societal perspective is often regarded as a better approach in health economics compared to a healthcare perspective, as the estimations take account of all or broader costs and benefits. To ignore the wider costs that have been included in this study (e.g. implications with time off work), would be ignoring the opportunity cost, and therefore, would risk an inaccurate conclusion of the intervention being cost effective (Drummond et al., 2015). Additionally, this aspect is not currently being collected in the ARRISA study, so therefore, exploring these wider costs is also a good opportunity. Therefore, whilst in the process of collecting information that would inform the benefit part of the societal perspective (quality of life), it seemed appropriate to also collect information around productivity in this acute asthma group during the same asthma-related crisis event period. This would take account of some of the productivity costs associated with the event, and would enable other studies to use this information as well in order to better estimate the asthma-related crisis event. However, it is also important to note that there is a minor risk of double counting in relation to productivity, because participants were not asked to ignore income effects when valuing their health (Drummond et al., 2015). This means that QALYs might have captured the benefits or loss associated with changes in productivity.

The productivity questionnaire **(Appendix VIh)** was adapted from the Work Productivity and Activity Impairment (WPAI) questionnaire (Margaret Reilly Associates. Inc., 2013), where permission was granted for adaptation, because some of the original questions were not completely appropriate for this study. For example, the questions were more relatable to the participant if the productivity questionnaire asked the participants questions relating to events that happened since or before, their asthma-related crisis event. Since the participants were asked to complete this questionnaire at week 4 of the study, the questions phrased were often based on the last four weeks as opposed to the past seven days as stated in the WPAI. I did not change questions from the WPAI questionnaire that were phrased around how the participants' asthma crisis event had impacted them on their working, studying, or activity patterns. Additional questions also included were as follows:

1. Compared to your asthma state when you were in hospital approximately 4 weeks ago, how would you rate your asthma now? (Responses included: Very good, Good, Moderate, Poor, Very poor)
2. Do you think you have completely recovered from when you were in hospital approximately 4 weeks ago? (Responses included: Yes, No)
3. If you are in employment (paid work), have you returned to work yet? (Responses included: Yes, No, Do not work)
4. Since your last asthma-related A&E attendance or hospital admission have you bought any extra products (e.g. prescriptions, allergy-free bedding, cleaning products, food items) or used an additional service (e.g. a visit to a complementary therapist) to that which you would normally buy/use e.g. in the four weeks prior to your asthma-related A&E attendance or hospital admission?

The additional questions above are useful for further understanding of the productivity losses associated with an asthma-related crisis event. Questions 1 and 2 are related to question 2 of the SF-36 questionnaire (Ware and Sherbourne, 1992), which has previously been used to assess responsiveness (Walters and Brazier, 2005), and asked:

"Compared to one year ago, how would you rate your health in general" (Responses included: much better now than one year ago, somewhat better now than one year ago, about the same as one year ago, somewhat worse now than one year ago, much worse now than one year ago).

Both questions 1 and 2, (added on in addition to the WPAI questionnaire), were important as they enabled the assessment of responsiveness to be conducted and provided the opportunity of detecting the sensitivity to change when compared against other questionnaires included in the study.

The latter questions 3 and 4, allowed a more in depth assessment of the productivity loss. Although, if the participant is unfortunate to have more than one asthma-related crisis event within a short period of time, then dependent on the additional products purchased in the first instance, they may not be purchased again if a second event was to occur.

3.5.8 Time trade off (TTO)

The TTO was chosen as an alternative method to estimate utilities, which will later enable a comparison between the EQ-5D-5L and AQL-5D. Both the EQ-5D-5L and AQL-5D used the TTO in the valuation of health states, so this seemed to be an appropriate alternative for comparability purposes. Also, in addition to the other alternative direct elicitation techniques (e.g. standard gamble and discrete choice experiments), the TTO was favoured for several other reasons which involved thinking about the acute asthma patient group that were recruited into the study. Given that the participants recruited were acute patients and I had already planned to ask them to complete a number of questionnaires, I thought that the TTO would be an easier and faster choice for the participants to comprehend in a short time frame without burdening them. It might have also enabled the benefit to be differentiated from loss associated with co-morbidities. I also designed the TTO using a macro and presented this to the patients on my laptop, which provided a good visual and aided the explanations of the TTO.

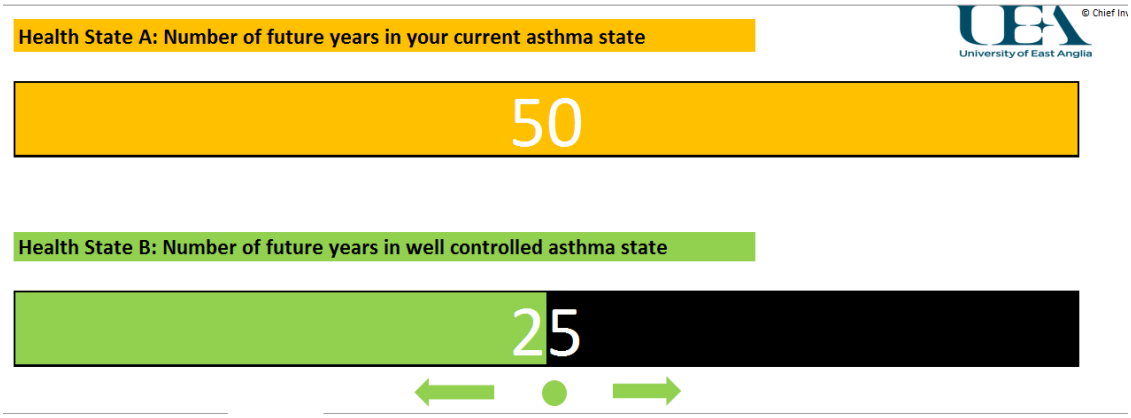
The TTO method used was slightly different to the normal statements used where the two options are typically *the condition of interest* and *full health*. In this case, the two options were *current asthma health state* (as the condition of interest) and *well controlled asthma* (as an alternative to full health). It is not unusual to use a different anchor comparator state compared to the more common "full health" state for the TTO. Alternative phrasing such as, "a comparator health state with no health problems", or wording such as, "excellent health", or "healthy" or in fact using the 11111 valuation from the EQ-5D as the comparator can also be used (Shah et al., 2016b). However, the use of these utilities in valuation studies may cause difficulties when comparing across studies and countries. It is therefore argued that for full comparability, there should be consistency in the upper anchor by having QALYs anchored at full health (Brazier et al., 2007, Shah et al., 2016b). However, these two options ("current asthma health state" and "well controlled asthma") were chosen for this study to reflect the quality of life of the asthma-related crisis event and to use terms that the participant was more familiar with. Most importantly, it is the loss in quality of life that was of specific interest and with this approach it was not necessary for the participant to imagine they had no asthma or no comorbidities. The hypothesis was that as the participants' were recovering from the event, the TTO utility score would be higher and eventually reach a ceiling effect (where they would not be willing to reduce their life expectancy) of utility 1.0 if the participant had completely

recovered from the asthma-related crisis event. Thus it would be possible to identify whether the patient had recovered by week 8. Conversely, if an EQ-5D score of 1 was not reached at this point it would be unclear whether this was because the patient had not recovered or there was another co-morbidity present.

Even though this study was already addressing quality of life using the questionnaires mentioned above, (e.g. EQ-5D-5L and AQLQ), and by asking a question in the productivity questionnaire (see section 3.5.7 question 2), it was interesting to see if the participants' responses differed at all when using the TTO method as well. The TTO had an advantage over using the quality of life questionnaires (such as the EQ-5D) because it was able to identify when the participant was returning or had returned back to their well-controlled asthma state (i.e. no symptoms or attacks, and they would not be willing to reduce their life expectancy in order to improve their asthma). The EQ-5D-5L and the AQLQ gave overall utility and scores respectively, but was not able to identify if the participant was back to their well-controlled state. However, implications can arise if participants are not willing to trade fewer years of well controlled asthma compared to their current asthma health state (even when worse), by considering other life factors, such as family when valuing their health (Dolan and Roberts, 2002).

The iterative process was informed by using the life expectancies of the general population (Office for National Statistics, 2017b), assuming that when asthma is well controlled then the individual should have the same life expectancy as someone who is a healthy individual (dependent of other comorbidities) (Papaioannou et al., 2015). With respect to the average life expectancy chosen based on each participant's age, the incremental movements during the TTO process was by 10% of the average life expectancy. This was to ensure that each participant, (regardless of their age), would have the same number of increments before either reaching their maximum or minimum trade off. An example of the developed macro for the TTO is shown below in **Figure 16** representing a TTO example for a 35 year old female who has an average life expectancy of 85 years (i.e. 50 years remaining). For this study, the iterative questioning began at mid-point (in this case 25 years) with the upper and lower arrows being moved by the increment of 5 (10% of remaining life expectancy) dependent on the response of the participant.

Figure 16: TTO for a participant aged 35 years old



The TTO was only conducted at the primary site because it was imperative to provide a face to face consultation at baseline. This was deemed important because the initial interaction between the interviewer and respondent has been shown to improve data quality (Attema et al., 2013).

Mixed approaches were used for the follow-up TTO conducted at week 4 and week 8 of the study due to the scheduled timing of the routine hospital follow-up appointments or if participants did not attend their appointments. Consistency in approaches was maintained as much as possible because the literature states that different TTO approaches could lead to different responses. (Attema et al., 2013, Norman et al., 2010). The alternative approach to conducting the TTO face to face was over the telephone instead. It was hoped that having the initial face to face consultation received at baseline would help participants remember the image displayed on the laptop (**Figure 16**) and the reasoning behind this. This was confirmed by participants during the telephone follow-ups. It was difficult to know if the participants' had completed their weekly EQ-5D-5L or monthly AQLQ before the time point at which the TTO was conducted as a specific time to complete these was not instructed. Therefore, an exact order of the completion of these questionnaires was unknown.

An alternative approach to the conventional TTO approach mentioned above, was considered, as the comparative baseline health state was a chronic health state. This chronic health state can be considered as a temporary health state, due to the health state lasting less than 1 year (Wright et al., 2009). Therefore, a chained TTO can be another approach to value temporary health states (Stoniute et al., 2017). However, in this

particular situation, the chained TTO approach was not deemed suitable, due to also requiring an anchor state as well, which should be considered as worse than the temporary health state, but not worse than death (Stoniute et al., 2017).

3.5.9 Piloting Questionnaires

The EQ-5D-5L, AQLQ, Peak flow and symptom diary, TTO and productivity questionnaire, were all piloted before the study commenced, and prior to ethical approval. Six patients from one asthma outpatient clinic were asked to provide feedback on these questionnaires. The feedback focused on the length of time it took to complete the questionnaires, the ease of understanding the questionnaires, and whether the patients thought that completing the questionnaires regularly over an 8 week time period was feasible given the acute health state that the recruited patients would be in. The feedback received from piloting the questionnaires was positive, and no concerning issues were raised. Therefore, there were no amendments made to the questionnaires.

3.5.10 Where should utility values come from?

There has been much literature discussing where utility values should come from. For example, should they come from the patient, the general population, proxy, (on behalf of patients through carers) or even health professionals (Dolan et al., 1996, Rowen et al., 2015). Much of the literature discusses whether the patient or the general population values matter for valuing the health states. Some suggest that the patient should value the health states based on their experience of the condition and therefore will be able to provide a more accurate picture (Nord et al., 1999). Although this may be true, patients who have the condition may not be as willing to trade life years for healthier years if they have adapted to their condition and are able to overlook the extent of its effects. However, there has been much discussion on the impact of chronic conditions, previous illness experience and the valuation of TTO, where controversies lie in both directions (Sayah et al., 2016).

Alternatively, those of the general population who have not been directly exposed to experiencing the health state may provide an inaccurate response due to not fully understanding the impact of the hypothetical health state. However, others suggest that the general population should be involved in valuing the health states because they have

a role in allocating scarce resources through the taxes they pay due to the healthcare system being publicly funded (Drummond et al., 2005). Because an asthma event is such an acute event, the general population may have difficulties in providing a true valuation, as they may struggle with identifying with specific health states. Buckingham (1993) stated a similar issue where they thought asking a 20 year old individual to imagine how they would value their health state at 70 years old would require a heavy amount of imagination. Whereas, asking a 70 year old about their health state and its importance at their age would provide more accuracy. With these accounts taken into consideration, and for the purpose of this study, patient completion and values were used for the TTO.

3.5.11 Adverse events

Adverse events for all participants were recorded during the study. This information was collected from the participant during the follow-ups at week 4 and week 8 of the study. Serious adverse events (such as hospitalizations), were recorded appropriately by completing a serious adverse event form and notifying the relevant Research & Development and sponsor team members.

3.6 Prospective analysis plan

Flow of participants:

The number of participants across all three hospital sites will be combined to produce an overall consort diagram. The diagram will include the following information:

- The number of participants assessed for eligibility
- The number of participants (and proportions) excluded from assessment and their reasons for exclusion
- The number of participants recruited from the hospitals from A&E attendance and hospital admission
- The number of participants (and proportions) who were lost to follow up or had withdrawn from the study

Data assessment:

The data will be entered into Microsoft Excel (2016) by the chief investigator (myself). Ten percent of the data will be entered twice by another researcher to check for any errors or discrepancies. Once double data entry is completed, the number of errors/discrepancies

will be identified. Assuming the error rate is <10% then these will then be considered in order to assess if any corrections are required to the original dataset. The dataset will then be locked by the chief investigator.

Statistical software:

The data will be entered into Microsoft Excel and statistical analysis will be conducted using either Microsoft excel or STATA v.12.

Baseline demographic characteristics:

A description of the baseline characteristics will be described from information obtained from the demographics questionnaire and other baseline quality of life questionnaires. The average age, height and weight will be reported, and the proportions of gender, ethnicity, smoking status, highest level of education, and employment status will also be reported. In addition, bar charts will be produced to depict the average number of participants who had the peak of their asthma-related crisis event either before, on route to hospital or in hospital. A bar chart will also be constructed to show the average number of participants who had different routes of entry into hospital (e.g. drove, by ambulance, by GP referral, or by nurse practitioner referral).

Quality of life statistical characteristics:

The baseline statistics for each of the quality of life baseline questionnaires (EQ-5D-5L, AQLQ, AQL-5D, and TTO) will also be reported. The statistics that will be tabulated will include means, standard deviations, ranges, response rates, floor and ceiling effects, (where floor effects mean that a high proportion of participants have the lowest score on the observed variable, and ceiling effects mean that a high proportion of participants have the maximum score on the observed variable). This display of statistics at baseline, will also be repeated at week 4 and week 8 to compare any changes. If there is a suggestion of ceiling effects or floor effects at baseline for the utility values, then these participants will be explored by using the time of when the asthma-related event peaked and regression analysis. If any statistically significant differences are found between the utility data and the peak of their asthma-related event occurring before A&E attendance or hospital admission, then the data will be re-analysed after removing these participants from the dataset.

Distribution of the data:

The dataset will be explored to see if the assumptions of normality hold. Histograms, Q-Q plots, and skewness / kurtosis tests will be conducted to see if there is a normal distribution. This is important to observe, as different statistical techniques will be used if the dataset satisfies either a normal or non-normal distribution.

Missing data:

There are different types of missing data definitions, and missing data are often described as missing completely at random (MCAR), missing at random (MAR) or missing not at random (MNAR). If data is MCAR, then the probability that the data is missing is not dependent on the observed or unobserved data. This therefore means that the observed data is representative of the sample distribution of the outcomes in the overall population.

If the data is said to be MAR, then the probability of having missing data is independent on unobserved values, having taken account of observed data i.e. any systematic differences can be explained by observed variables. If the data is MNAR, then the probability of having missing data is dependent on unobserved data. Different methods can be used to analyse the data, depending on the assumptions taken in relation to missing data.

To assess which assumption in relation to missing data was more appropriate the following analyses were undertaken. Firstly, missing data descriptions will include tabulating the proportions of missing data for each utility outcome measure. Secondly, the patterns of missing data will be observed to identify where the missing data is likely to be concentrated, and at which time points they occur. Thirdly, logistic regression analysis will be used to see if there are any predictors of missing data for each of the utility outcomes by using the baseline demographic variables as indicators.

If the missing data is associated with observed predictors of missingness, then the data is assumed to be either MAR or MNAR. If the missing data is not associated with any predictors of missingness, then the data is also assumed to be MCAR or MNAR. If the data satisfies an assumption of MCAR, then the approaches that can be used to analyse

the data include complete case analysis (CCA) and available case analysis (ACA). CCA is often regarded as a useful benchmark starting point in the analysis. However, it is also known to be inefficient in studies which have follow up data, as any participant that misses a data follow up point, will have to be excluded from the analysis. Alternatively, ACA can be used which provides a stronger dataset for analysis due to including all participants, regardless of any potential missing data. However, due to all the available data being used, the ACA can lead to a limitation of using different sample sizes and groups of participants for different analyses in the dataset.

If missing data is assumed to be MAR then the missing data can be imputed via a technique called multiple imputation (MI), where the observed data is used to predict the missing values. MI can be used to impute values into the missing data points (with focus on ensuring that the missing utility values are correctly imputed). STATA can be used to do this taking account of the predictors of missingness. Chained equations (MICE) can be used to implement this in STATA, using a code such as 'mi impute chained' or 'ice' package (Faria et al., 2014). MICE is known to accommodate non-normality well and large datasets with many variables having missing data (Faria et al., 2014). Alternatively, a likelihood-based model (i.e. multi-level model given hierarchical structure), can also be used if the model assumes MAR, conditional on the variables included (Faria et al., 2014). If the dataset does indicate that the data is MAR, then the most likely method would be to choose the likelihood-based model based on the dataset having a hierarchal structure.

Primary analysis:

The mean utility values (for EQ-5D-5L, AQL-5D and TTO), mean scores, (EQ VAS, AQLQ overall, AQLQ symptoms, AQLQ activity, AQLQ emotional, AQLQ environmental), and standard deviations will be tabulated at each time point of the study. The mean differences, confidence intervals and p-values will be displayed for statistical tests between baseline and week 8, baseline and week 4, and week 4 and week 8.

If normality assumptions hold, then paired t-tests (2-sided) will be conducted to test for statistical significant differences between the mean values. However, if the dataset shows evidence of non-normality, then Wilcoxon-signed rank tests will be used to test statistical significance. Scatter plots will be used to visually display the mean utility and score

results at the different time points for the EQ-5D-5L, AQL-5D, TTO, EQ VAS, peak expiratory flow and symptoms score. QALYs will be estimated using the utility loss results associated with an asthma-related crisis event from the EQ-5D-5L, AQL-5D and TTO. QALYs will be estimated using the area under the curve approach and linear interpolation. The mean differences in utility between the time points mentioned above, will be used to estimate QALYs using different scenarios.

Secondary analysis:

Additional descriptive information (N, %, SD) relating to the number of adverse events, average length of stay, number of medications, changes in comorbidities and changes in smoking status throughout the study will also be included.

If the data set is MAR then the relationship of the EQ-5D-5L, AQL-5D and TTO will be assessed against the demographic variables using a multi-level hierarchical model due to the dataset having a multi-level structure (responses at weekly intervals [level 1], participants [level 2] and hospitals [level 3]). Quadratic models will also be considered if there is evidence of non-linearity. Non-linearity can be assessed by observing the trajectories of the utility values for the first few participants at the different time points. If the lines observed between time points (e.g. EQ-5D-5L weekly time points from baseline to week 8) for each participant are not linear, then this confirms evidence of non-linearity.

Productivity loss associated with an asthma-related crisis event will also be estimated using the human capital approach and average weekly earnings taken from the office for national statistics. The productivity loss will take account of time lost from work and be based on a complete case analysis. Additional products purchased due to having an asthma-related crisis event will also be considered and will be asked in the questionnaire at week 4 of the study. As the reported cost of each product is requested these values will be summed to estimate the total out of pocket cost.

3.7 Data management

All research data was anonymised by assigning each consented participant with an identification (ID) number (e.g. 001) and site number (e.g. 01). Personal data was kept separate from the main research data to avoid any identification from the research data. The case report forms and questionnaires were stored in a folder in the secure respiratory research office in the Norfolk and Norwich University Hospital (NNUH). In addition, there was also a master site file holding the necessary documentation, some of which included protocols (superseded and current), regulatory approvals, screening logs, enrolment logs and delegation logs. This was also stored in the secure respiratory research office at the NNUH. The other sites kept a site file containing their documentation in a secure office located on their hospital premises. The files were kept abreast; both electronically and as a hard-copy.

The data was collected through paper-based questionnaires and entered into Microsoft Excel software packages and stored on the University of East Anglia's server. The Microsoft excel documents were encrypted with a secure entry password for security and data protection measures. This was done in accordance with Good Clinical Practice and the Data Protection Act, 1998. Once the study ended, the excel spreadsheet was cleaned and manipulated for analysis, and the anonymised hard copies were archived for a further 10 years.

3.8 Statistical analysis

Random participant ID numbers were generated from using the Microsoft excel random number formula for the purpose of double data entry. Double data entry was conducted for 10% of the data collected across all sites to check for accuracy by another researcher. This process found a few discrepancies which were cross-checked against the original hardcopies and any errors were corrected for the final database used for analysis. Due to the very small number of errors found across the 10% checked (approximately 0.003), the spreadsheet did not warrant any further data entry checks.

Every effort was made to reduce missing data, by double checking the questionnaires at baseline before leaving the participant's bedside, and ensuring the participants were fully informed and knew what they had to do during baseline and again at the follow-up phone

calls. Due to the large amount of participants who were lost to follow up and / or had missing data within questionnaires returned, the complete case analysis (listwise deletion; removing all data for a participant with one or more missing values) data set is reasonably smaller. Therefore, data was analysed using available cases (pairwise deletion; maximizes the use of all available data for each pair of variables considered in the analysis) in the first instance, meaning that there was a different sample size (N) for each statistical test conducted. Complete case analysis was also used afterwards to aid in comparability of the data points.

After retrieving the results based on available case analysis, the data was then analysed by using a technique called multi-level modelling for the EQ-5D-5L, AQL-5D and TTO utilities. Missing data was accounted for by using the multi-level modelling technique coupled with the maximum likelihood estimation. This technique is discussed further in **Chapter 4**.

There are several other approaches that could have been considered to handle the missing data. One option could be to use a mean substitution, where the mean is calculated from all observations in a variable for that particular time point and imputed to replace the missing value (Kang, 2013). A second option could be to take the last value within an observed variable before the missing data occurs, and impute the last observed data value in place of the missing data (Hamer and Simpson, 2009). A third option could be to substitute the missing values by using a method called multiple imputation. The missing data is predicted by using the variables and existing data set, and replacing the missing values with the prediction whilst formulating imputed data (Sinharay et al., 2001).

The values retrieved from three quality of life questionnaires (EQ-5D-5L, AQLQ and TTO) were converted into utility values (values of a stated health state). The EQ-5D-5L utility values were estimated from a value set based on the England population (Devlin et al., 2016). The AQL-5D utility values were estimated using an algorithm based on the AQLQ (Yang et al., 2011). The TTO utility values were estimated based on the participants' reaching a point of indifference. For example, going back to **Figure 16**, if the participant reached a point of indifference and chose health state B at 20 years of well controlled asthma, then the utility value would be 20 ÷ 50 (comparator health state ÷ remaining life expectancy) = 0.4; i.e. a loss in utility of 0.6. It should be noted that by the

method adopted we inherently assumed the asthma state will not be considered worse than death, and therefore only positive TTO scores can be obtained.

From the above utility conversions from the three questionnaires, the mean difference between the 8 week follow-up and baseline score was calculated to estimate the loss associated with a crisis event. The time points in between, from baseline to follow-up and the peak flow and symptoms scores, will also help to provide a more accurate estimation of the trajectory of this loss associated with a crisis event; i.e. assess whether linear interpolation is an appropriate assumption. The level of correlation (convergent validity) between the quality of life methods was tested as a way of assessing the appropriateness of the measures used. However, because generic and condition-specific measures were used in this study, the utility scores may not correlate strongly due to these differences in valuation and estimation techniques. In addition, the productivity questionnaire was used, to estimate the loss of productivity, by attaching the average hourly wage to estimate time off work. Further details of the statistical techniques used for the above analyses are detailed in **Chapter 4 and Chapter 5**. Microsoft excel and STATA packages were used for all analyses.

3.9 Ethics approval

This study was originally reviewed by the Proportionate Review Sub-Committee by the North West – Greater Manchester West Research Ethics Committee on 4th December 2015 under the REC reference 15/NW/0961. They decided on 'no opinion' on the account of ethical issues surrounding recruitment of A&E patients. Following this, it was then reviewed by the Cambridge South Research Ethics Committee under the REC reference 16/EE/0023. After attending the NHS Research Ethics Committee meeting on 28th January 2016, the committee decided upon 'provisional opinion' based on the information and documentation received. They provided advisory points and also required further clarifications and justifications on several points. The main issue was surrounding the recruitment of A&E patients as previously highlighted from the initial proportionate review, where they were concerned about the practicalities, chance of uptake, and ethics around approaching patients in the A&E department. A response was written to Cambridge South committee to address all points raised, with particular mention of liaisons with an A&E clinical director, a consultant in the acute medical unit and the Asthma UK Centre for Applied Research patient and public involvement (PPI) group.

These members supported our approach to recruitment in A&E, but only after the critical 1st hour had passed, the patient was free from hypoxaemia, and the patient was not in resuscitation. Shortly after responding to their request for further information and clarification, they awarded 'favourable opinion' on 29th March 2016. All ethics letters can be found in **Appendix VIi**.

Due to this being a multi-site study the National Health Service (NHS) site approvals took place in stages and granted local approvals once all necessary checks were completed. The Norfolk and Norwich University Hospital NHS Foundation Trust awarded their permission on 26th April 2016, the Aberdeen Royal Infirmary NHS Grampian awarded their permission on 11th May 2016, and the University Hospital Birmingham NHS Foundation Trust awarded their permission on 31st October 2016. Further minor amendments were made once the study had started recruitment. These included slight changes to the PIS for the Aberdeen site (a slight change in wording at the request of the site principal investigator), and an increase in the number of participants permitted for recruitment. Both changes were appropriately actioned with approvals made from the health research authority. All documents relating to this study can be found in **Appendix VI**. This study is registered with ClinicalTrials.gov and can be identified through this number: NCT02771678.

3.10 Summary

In conclusion, this study will address the current gap in the literature where there is a general assumption of linear interpolation in between time points when measuring HRQL. As asthma attacks can occur sporadically from triggers and unknown factors, it can be difficult to measure HRQL at the particular time point of the attack. Current studies that measure quality of life at set points (such as baseline, 6 months and 12 months), may be missing the quality of life implications of an acute asthma attack that causes an A&E attendance or hospital admission to occur. Therefore, they may be underestimating the loss in quality of life for asthmatics if the patient has somewhat or wholly recovered by the next time point. As an alternative method, this study will estimate the loss associated with an asthma-related crisis event. This will be useful for future studies, as they can count the number of crisis events that occur and attach the utility loss to them. This may in turn change the outcome and provide a different value when estimating what constitutes

best value for money. This approach is particularly of use where routine data sources are used and utility scores are not available / could not be elicited e.g. ARRISA.

This chapter comprehensively details the study design for acute asthmatics and their quality of life associated with either an A&E attendance or hospital admission. It provides in-depth details of the aims and recruitment process for this study, and outlines the outcome measures and statistical approach taken. This study forms the basis of the next two chapters, as further analysis is conducted to answer specific research questions, which were mentioned at the beginning of this chapter:

What is the loss in quality of life associated with an asthma-related crisis event?

To what extent does this loss vary depending upon which patient reported outcome measures is used?

What is the comparative performance of different generic and/or disease-specific questionnaire(s) when they are used to assess quality of life in acute asthmatics?

The next couple of chapters will provide further detail to the above and highlight the importance of this work. The next immediate chapter, **chapter 4**, will provide the descriptive results for this study, and will answer the first two research questions above.

CHAPTER 4

ESTIMATING THE LOSS IN QUALITY OF LIFE ASSOCIATED WITH AN ASTHMA-RELATED CRISIS EVENT (ESQUARE): RESULTS FROM A COHORT STUDY

"I found myself in the resuscitation suite of my local hospital on 10 occasions, and took myself to casualty at least 40 times in those first few years…..I was so sick of being sick, I wanted to die."

(Celeste Abrahams; written by Trish Lesslie, 2005)

Preface

The previous chapter provided the methodology for the prospective cohort study design which was developed to address the research questions focused on estimating the change in quality of life associated with an asthma-related crisis event. This study was a multi-site study and was aimed at an adult population group, (18 years and over), who were attending A&E or were admitted to hospital due to having an asthma attack. The main aim of the study was to estimate the loss in quality of life associated with an asthma-related crisis event – A&E attendance or hospital admission – and so the time horizon of the study was 8 weeks. Routine hospital follow-up appointments are usually scheduled approximately 4 weeks after an asthma hospital admission. However, some patients are scheduled more follow-up appointments following their initial 4 week follow-up, because they require further clinical support from their hospital admission. Therefore, it seemed appropriate to have a time horizon of 8 weeks to capture the quality of life in this patient group. The 8 weeks allowed for additional observation time from the patient's crisis event, and the time horizon was not too long to be burdensome for the patient's to complete the questionnaires. Informed consent was obtained in hospital and a variety of outcome measures were used to capture quality of life. This chapter will describe and discuss the results of this study in order to address the research questions outlined in **Chapter 3**:

1) When did the asthma-related crisis event peak (e.g. on route to hospital, after 2 hours in hospital)?

2) What are the mean quality of life scores, utility values, and peak flow and symptom scores for patients reporting these at weekly, monthly and daily time points during the 8-week study?

3) What is the loss in quality of life associated with an asthma-related crisis event?

4) What is the relationship, (if any), between the demographic variables (e.g. age, gender, smoking status etc.) and utility estimates (EQ-5D-5L, AQL-5D and TTO)?

5) What is the productivity loss & out of pocket cost associated with an asthma-related crisis event?

This chapter will give a brief background into health related quality of life for asthmatics and state the hypotheses. There will be more focused methods with statistical analysis pertinent for answering the above research questions. Then the results will proceed, with details about the recruitment process, mean estimations at different time points, multi-level modelling and missing data. The discussion and conclusion sections will follow and conclude this chapter by discussing the results and draw on earlier studies for comparison.

4.1 Background

Health related quality of life (HRQL) can impact people differently. Some conditions can have prolonged disturbance in quality of life (e.g. cancer, stroke, or diabetes) (Megari, 2013), other conditions can be more episodic, (e.g. epilepsy, bipolar disorder, or angina) (Kudo et al., 2001, Young and Melander, 2013), and furthermore, some conditions can have a combination of both prolonging and episodic disturbance in their quality of life.

Quality of life in people with asthma can be episodic and a combination of both prolonging and episodic disturbance. Some people are labelled as difficult asthma or are severe and uncontrolled, (Barnes and Woolcock, 1998) even though there is much discussion in the literature about ways to encourage and maintain well-controlled asthma (British Thoracic Society. Scottish Intercollegiate Guidelines Network, 2016, Ring et al., 2015, Juniper et al., 2006). Asthma attacks can occur amongst these groups of people, and can be a regular occurrence for some, and are for others far and few between.

Nevertheless, asthma attacks negatively impact a person's quality of life, and they can cause death (Royal College of Physicians, 2014).

As mentioned in **Chapter 3**, there is a need to estimate quality of life more closely because of how quality of life data is currently captured in most studies, (i.e. at set time points, such as Willems et al. (2006)), as otherwise biased estimations in QALYs could occur (Dritsaki et al., 2017). Initial estimations in HRQL should be captured as early as possible (Dritsaki et al., 2017), which is why the baseline point for this study was when the participant was in hospital, shortly after admission or attendance to A&E, subject to the participant meeting the inclusion criteria as mentioned earlier in **Table 5**.

Quality of life can be measured using different questionnaires, (generic or disease-specific) (Herdman et al., 2011, Brazier et al., 2002, Brazier et al., 2007, Horsman et al., 2003), or even by direct elicitation methods in health (Gafni, 1994, Attema et al., 2013), and so a mixture of these techniques were used in this study. It was useful to use a mixture of questionnaires and techniques, as it enabled comparability across PROMs, which was particularly important for the research questions addressed in C**hapter 5**. The hypotheses for this study were as follows:

- An improvement in quality of life will be seen after baseline (the asthma-related crisis event) in all quality of life questionnaires.
- Participants will show the minimal important difference in quality of life between baseline and week 4 of the study for the EuroQol-5 Dimensions-5 Level questionnaire (EQ-5D-5L) and the Asthma Quality of Life Questionnaire (AQLQ). The minimal important difference (MID) for the EQ-5D-5L and AQLQ have been estimated to be 0.063 (McClure et al., 2017) and 0.5 (Juniper et al., 1993) respectively. The MID can be defined as: "the smallest difference in score in the domain of interest which patients perceive as beneficial and which would mandate, in the absence of troublesome side effects and excessive cost, a change in the patient's management" (Jaeschke et al., 1989). The MID for the EQ-5D-5L is an estimate based on the same methodology that was first proposed to estimate the MID for the EQ-5D-3L (Luo et al., 2010) – instrument-defined MID estimation (average of the absolute difference in the index scores between the baseline health state (the first measured time point in a study), and all of the single level transitions from baseline). The MID for the AQLQ was calculated

by using the global ratings of change in conjunction with changes from different quality of life scores (Juniper et al., 1993).

The next section will expand on the methods described in Section 3, by providing more analytical detail for the statistical analysis specific to answering the research question for this chapter.

4.2 Methods

As detailed in **Chapter 3**, patients were recruited from three hospital sites in the United Kingdom. Participants were required to meet a specific inclusion criteria, which included being 18 years old and over, and either attending A&E or being admitted to hospital due to experiencing an asthma exacerbation (significant flare up of asthma symptoms). Once consented, participants completed several quality of life questionnaires over a period of 8 weeks. These included completion of the following:

- Peak flow and symptom diary (daily)
- EQ-5D-5L (weekly)
- AQLQ (monthly)
- TTO (monthly)

Other questionnaires, such as the demographics and productivity questionnaires were completed at baseline and week 4 respectively. **Chapter 3, section 3.5** provides a more detailed overview of each outcome measure, and **Chapter 3, section 3.7** gives reference as to how each questionnaire was converted into utilities for use in economic analysis. Ethical approval was granted for this study by the Cambridge South NHS Research Ethics Committee (REC reference 16/EE/0023).

4.2.1 Statistical analysis

As mentioned previously in **Chapter 3, section 3.2**, the sample size was informed from a combination of previous literature and the nature of the TTO design. The target sample size was 100 participants, but after several months of recruitment, the retention rate was 50%. Therefore, the sample size was increased to account for this with allowance of up

to 200 participants granted by the NHS ethics committee. A post-hoc power calculation was conducted to show that the sample size was sufficient for this study.

Baseline and descriptive characteristics were performed using Microsoft Excel (2016) and STATA (version 12) packages. Available case analysis was used to perform statistical analysis and missing data descriptive statistics were detailed. Complete case analysis was also used in some instances for a more robust comparison. Demographic characteristics were explored through means and percentages to display the averages and proportions respectively. Tables and graphs were used as necessary to illustrate these statistics. Adverse events, changes in asthma medications, changes in comorbidities and changes in smoking status at week 4 and week 8 of the study were also presented. The mean values of the peak flow and symptom scores were also displayed graphically.

The quality of life scores from the questionnaires were converted into utility values where appropriate. Mean values and standard deviations for each of the follow up time points were presented graphically and within tables. Some variables presented with normal distributions (mainly the demographics data) and others with non-normal distributions (mainly the outcome variables). Therefore, due to the outcome data not satisfying the assumptions of normality for the use of parametric tests, non-parametric tests were used in the analysis. However, it should be noted that prior research has also confirmed that non-parametric tests (e.g. Wilcoxon-Mann-Whitney test), have been shown to be less powerful than parametric tests (e.g. t-tests, ANCOVA), for non-normal distribution data where simulation methods were used to draw these conclusions (Vickers, 2005, Fagerland, 2012). Despite this, this was not the case for this cohort study data set when checking and testing the data with parametric and non-parametric tests.

The mean change between scores and utility values were tested by using Wilcoxon's signed-rank teste at the 5% statistical level. Confidence intervals and p-values were also noted in these tables. The minimal important difference for the EQ-5D-5L has been reported as 0.063 (McClure et al., 2017) and for the AQLQ, it has been reported as 0.5 (Juniper et al., 1993). Therefore, both the p-values and minimal importance differences for EQ-5D-5L and the AQLQ were taken into consideration in the analysis.

Response rates, floor and ceiling effects (e.g. for the EQ-5D-5L, a floor effect would be defined as 'extreme problems/unable to' in all of the 5 domains; 55555, and a ceiling effect would be defined as 'no problems' in all of the 5 domains; 11111) were also tabulated at different time points of the study (baseline, week 4 and week 8), to identify those participants who had completed at that time point, and those with the lowest or highest levels of utility or scores chosen for their corresponding health states.

Multi-level modelling was performed to demonstrate the relationships that occurred amongst the utility values. These models are useful for analysing grouped data which are clustered at different levels; in particular hierarchal data (Goldstein et al., 2002). An example of the hierarchal relationship for this study is displayed in **Figure 40**. Missing data is also accounted for by using this method and by taking into account, the maximum likelihood estimation that also provides an output with this method (Schminkey et al., 2016). Variables taken from the baseline demographics questionnaire, were used to build up the model in a step-wise way for each utility measurement. Such variables included, smoking status, employment status and highest level of education. The base case for these variables (to enable comparison), were smoker, unemployed and school leaver respectively.

To build the model using a step-wise approach, a null model with a random intercept was explored initially, followed by a random intercept fixed slope model, then a random slope model and finally a random polynomial model. Each of these base models were assessed to identify which model was the best model, by graphing the relationships (e.g. box plots, scatter plots and Q-Q plots), and producing log likelihood ratio tests. Once the best structural base model was identified, the factors predictive of missingness were added into the model. Following this, the other explanatory variables were added into the model separately using a step-wise approach to determine which variables fitted the model more strongly. The model with the strongest explanatory variable fitted was used to build on the model, fitting only those explanatory variables that had an impact on the model until a preferred, parsimonious model was achieved. This preferred model was used to estimate the disutility of an asthma attack.

Additionally, bootstrapping was also conducted to estimate the disutility of an asthma attack to check the stability of the results, since it estimates confidence intervals of a

population mean by resampling some data from a larger dataset randomly with replacement. Dummy variables were then added to this model to explore the impact of baseline quality of life on the disutility estimate. Finally, as the missing data patterns are explored and missing data proportions are tabulated, the final preferred parsimonious models were further improved by using an additional method called multiple imputation. This method increases the robustness of the results as it replaces the missing data from the available case dataset with values, and this in turn reduces the standard error and increases the precision of the estimations. The disutility of asthma attack was also estimated using the multiple imputed model.

The human capital approach (Walter and Zehetmayr, 2006) was used to estimate the productivity loss associated with an asthma-related crisis event, as absences from work associated with the event are likely to be short-term. Other methods such as the friction cost method, involves the organization potentially training someone so that their initial production level is restored (Drummond et al., 2015). This could take days, weeks or even months depending on the job description. Therefore, the human capital approach was deemed more appropriate for this study. Data from the office for national statistics average weekly earnings (Office for National Statistics, 2017c) was used, and multiplied by the average hours missed from work (Office for National Statistics, 2017a, Francis, 2017), to estimate the cost of the time lost at work from having the asthma-related crisis event. The latter data took into account the average hours worked in a week in the UK, including part-time work. This value was then added to the average cost of any additional products bought out-of-pocket by participants that were not normally purchased prior to the asthma-related crisis event. This provided an overall estimate of indirect and out of pockets costs associated with an asthma-related crisis event.

4.3 Results

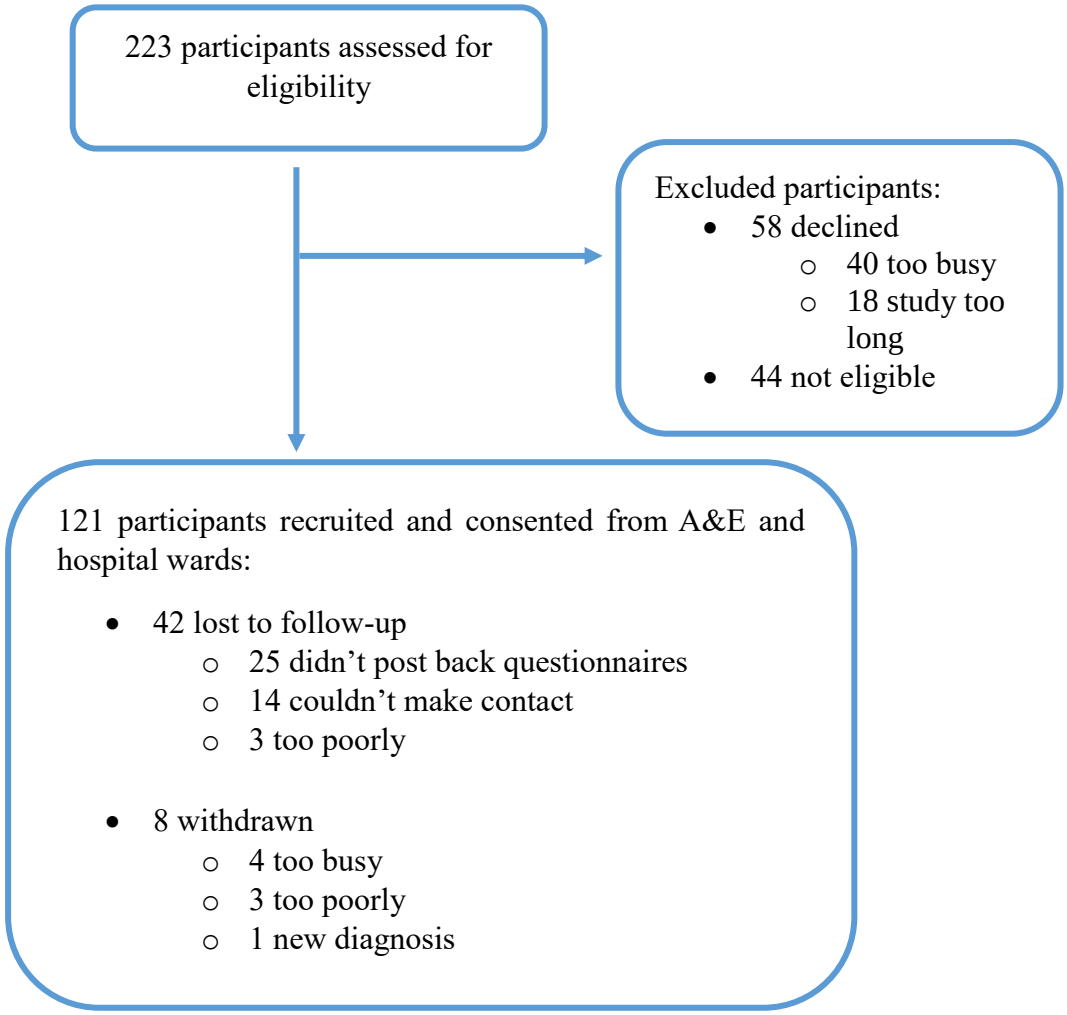
The results in this section, will aim to address all that was outlined in **Chapter 4, section 4.2.1;** the statistical analysis section of the methods section. The data collected was checked for accuracy, by entering 10% of the collected data again into Microsoft excel, and cross checking. The reported errors from the double data entry were very small (0.003). Nevertheless, these were corrected for accuracy.

4.3.1 Recruitment

Across all three hospital sites, a total of 223 participants were screened for eligibility into the study (**Figure 17**). The eligibility criteria for this study was previously highlighted in **Table 5**. Of those participants assessed, 58 participants declined (26.0%), because they were either too busy (40 participants), or the study duration was too long (18 participants). In addition, 44 participants were not eligible (19.7%).

The total number of participants who were recruited and consented into the study were 121 (**Figure 17**). From the recruited total, 42 participants were lost to follow up (34.7%), where 25 participants did not post back the questionnaires that they were asked to complete over the 8 week time period, 14 participants could not be reached from their contact telephone numbers provided and 3 participants were too poorly. A further 8 participants withdrew from the study (6.6%) because they were either too busy, (4 participants), too poorly, (3 participants), or were newly diagnosed with a different condition and not considered asthmatic anymore, (1 participant).

Figure 17: Recruitment flow diagram



4.3.2 Demographics

The characteristics of the 121 participants recruited and consented at baseline are depicted in **Table 7**. The mean age of the participants was 49.68 years old, with 26.45% male and 73.55% female. The majority of the participants were of 'white' ethnicity (95.83%), with 0.83% of 'mixed white and black' ethnicity and the remaining 3.33% of 'white other' ethnicity. Most of the participants either never smoked (42.50%), or were ex-smokers (40.83%). Only 15.00% were smokers, and a small proportion of participants were non-smokers (1.67%). The latter proportion of participants who were non-smokers, were often those who rarely smoked, i.e. smoked in a social capacity. During the study, some participants changed their smoking status (N = 4, 3.31%), where 3 participants (75%) became ex-smokers and 1 participant (25%) reverted back to being a smoker. A high proportion of participants were those who had 'school' (leaving age of 16 years old) as

their highest level of education (47.06%), and this was followed by 'college' (typically 16 years old and older) (33.61%) and 'degree' (typically 18 years old and older) (19.33%). The participants' employment status were varied with 27.50% full time, 15.83% part time, 28.33% retired, 7.50% stay at home parents, 3.33% student and 17.50% unemployed. The characteristics of adult asthmatics recruited in this study, were considered representative of the population as they were comparable to other studies, such as those in the UK (Pavord et al., 2017, Gibbison et al., 2013) and United States (Mirabelli et al., 2013).

Table 7: Baseline characteristics

Demographics	**N = 121**
Age (mean, years)	49.68
Height (mean, cm)	167.22
Weight (mean, kg)	85.54
Gender (%)	
Male	26.45
Female	73.55
Ethnicity (%)	
White	95.83
Mixed White and Black	0.83
White Other	3.33
Smoking Status (%)	
Never	42.50
Non-Smoker	1.67
Smoker	15.00
Ex-Smoker	40.83
Highest Level of Education (%)	
School	47.06
College	33.61
Degree	19.33
Employment status (%)	
Full-time	27.50
Part-time	15.83
Retired	28.33
Stay at home parents	7.50
Student	3.33
Unemployed	17.50

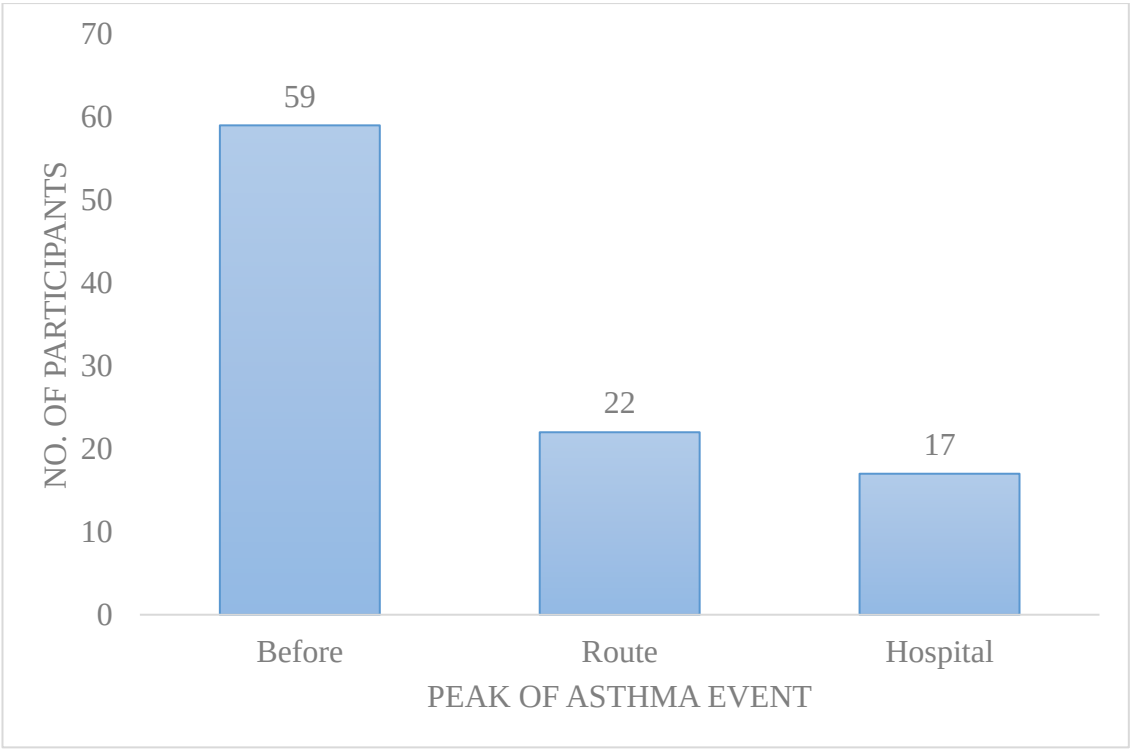
During this study, there were some non-responses from participants at times when the participants' were asked to complete questionnaires. The remainder of this section **(Chapter 4, section 4.3.2)** and **Chapter 4, section 4.3.3** represents statistics based on available data and complete data. **Chapter 4, section 4.3.4** will go into more depth and will provide results which account for missing data statistics.

At baseline, the participants' completed a demographics questionnaire which included the following question:

When did your asthma-related event peak (e.g. on route to hospital, after 2 hours in hospital)?

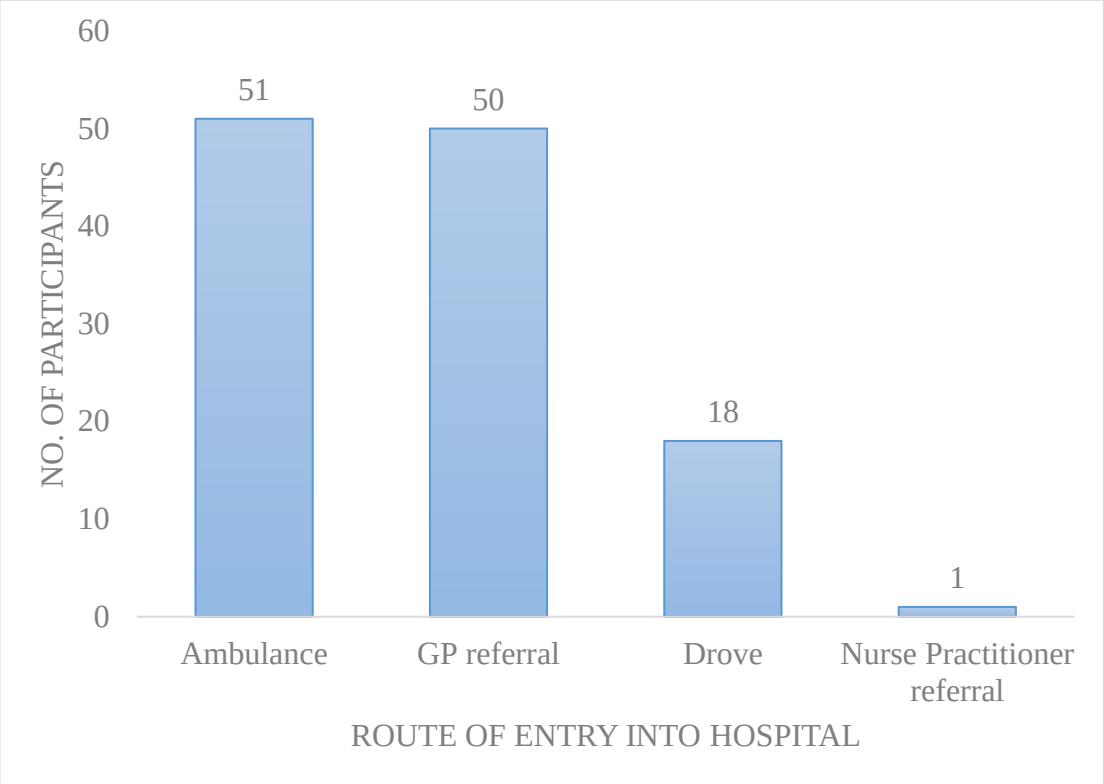
There were 98 responses (81%), and the point at which their asthma symptoms were at their worst varied (**Figure 18**). For the majority, (59 participants), the peak of their asthma symptoms being their worst was before arriving in hospital. Being en-route to hospital (22 participants) and whilst in hospital (17 participants) were the two other categories that followed this as being the point at which the participants' asthma symptoms peaked.

Figure 18: The point at which the asthma event was at its worst for participants



The two most common modes of entry into hospital were by ambulance (51 participants and GP referral (50 participants) (**Figure 19**), with driving to hospital (18 participants) or being referred by a nurse practitioner (1 participant) being the two least common modes.

Figure 19: The route of entry into hospital for the asthma-related crisis event



For this study, the average length of stay for the participants' was 4.64 days. The average number of A&E attendances in the last year was 0.66 (SD = 1.76) and the average number of hospital admissions in the last year was 0.74 (SD = 1.95). A small percentage of the participants recruited (N= 8; 6.61%), had an adverse event (in this case a hospitalization), during the study.

All participants' were taking medication for their asthma, with 55 participants' (45%) taking more than 2 medications and 57 participants' (47%) taking 2 medications. Over 30 different asthma medications were noted across the participants' recruited, and the average number of medications taken by participants' were 2.82 (SD = 1.41) at baseline. Most participants also had several other comorbidities, which varied widely, and this averaged to be 1.91 (SD = 1.49) across all those recruited.

During the study, at weeks 4 and weeks 8, participants were asked whether they had any changes to their asthma medications or comorbidities since the beginning of the study. Approximately a third of participants (N = 35; 28.92%), had changes made to their medications, and only 3 participants (2.48%), had changes to their comorbidities.

4.3.3 Patient reported outcome measure results

Participants were asked to complete a number of PROMs at different points over the 8 week time period. The EQ-5D-5L, AQL-5D and TTO were all converted into utility values and the EQ VAS, AQLQ overall, AQLQ symptoms domain, AQLQ activity domain, AQLQ emotional domain, and AQLQ environmental domain remained as score values. The EQ VAS scores can range from 0 to 100, with 0 (the worst possible health state you can imagine) and 100 (the best possible health state you can imagine). The AQLQ overall and corresponding domain scores can range from 1 to 7, with 1 being the worst category and 7 the best. The response rates, floor and ceiling effects, (the lowest possible value and the highest possible value respectively) are shown in **Table 8**, **Table 9**, and **Table 10** for baseline, week 4 and week 8 time points respectively.

Table 8: Baseline statistics for each quality of life questionnaire

Item	N	Mean	SD	Range	Response rates	Floor effects	Ceiling effects
EQ-5D-5L (utility)	120	0.635	0.274	-0.102 to 1.00	99.2%	0.00%	8.30%
EQ VAS score	120	45.7	19.3	5.00 to 90.0	99.2%	0.00%	0.00%
AQLQ overall score	120	3.28	0.963	1.18 to 5.30	99.2%	0.00%	0.00%
AQLQ Symptoms score	121	2.81	1.06	0.00 to 5.50	100.0%	0.83%	0.00%
AQLQ Activity score	121	3.51	1.05	0.00 to 5.82	100.0%	0.83%	0.00%
AQLQ Emotional score	121	3.14	1.51	0.00 to 7.00	100.0%	0. 83%	4.10%
AQLQ Environmental score	121	4.04	1.52	0.00 to 7.00	100.0%	0.83%	1.70%
AQL-5D (utility)	118	0.608	0.128	0.450 to 0.935	97.5%	0.00%	0.00%
TTO (utility)	112	0.626	0.277	0.100 to 1.00	100.0% *	0.00%	18.8%

*The response rate is based on the denominator being 112 due to only the participants based at the Norfolk and Norwich University Hospital (NNUH) being asked the TTO questions. All of the other response rates for the PROMS were based on the denominator being 121 as this was the total number recruited across all hospital sites where each participant was asked to complete PROM questionnaires.
Ranges for PROMs: EQ-5D-5L (-0.281 to 1); EQ VAS (0 to 100); AQLQ (0 to 7); AQL-5D (0 to 1); TTO (0 to 1).

Table 9: Week 4 statistics for each quality of life questionnaire

Item	N	Mean	SD	Range	Response rates	Floor effects	Ceiling effects
EQ-5D-5L (utility)	71	0.740	0.264	-0.005 to 1.00	58.7%	0.00%	15.5%
EQ VAS score	73	65.9	21.42	11.00 to 100.00	60.3%	0.00%	4.11%
AQLQ overall score	70	4.09	1.48	1.47 to 6.94	57.9%	0.00%	0.00%
AQLQ Symptoms score	85	3.34	2.12	0.00 to 7.00	70.2%	17.65%	1.18%
AQLQ Activity score	85	3.32	2.00	0.00 to 7.00	70.2%	14.12%	4.71%
AQLQ Emotional score	85	3.36	2.27	0.00 to 7.00	70.2%	16.67%	7.06%
AQLQ Environmental score	85	3.63	2.34	0.00 to 7.00	70.2%	16.67%	4.71%
AQL-5D (utility)	70	0.687	0.173	0.450 to 1.00	57.9%	0.00%	2.90%
TTO (utility)	87	0.820	0.264	0.000 to 1.00	77.7%*	2.30%	51.7%

*The response rate is based on the denominator being 112 due to only the participants based at the Norwich hospital site (NNUH) being asked the TTO questions. All of the other response rates for the PROMS were based on the denominator being 121 as this was the total number recruited across all hospital sites where each participant was asked to complete PROM questionnaires.
Ranges for PROMs: EQ-5D-5L (-0.281 to 1); EQ VAS (0 to 100); AQLQ (0 to 7); AQL-5D (0 to 1); TTO (0 to 1).

Table 10: Week 8 statistics for each quality of life questionnaires

Item	N	Mean	SD	Range	Response rates	Floor effects	Ceiling effects
EQ-5D-5L (utility)	65	0.725	0.292	-0.215to 1.00	53.7%	0.00%	21.5%
EQ VAS score	65	68.06	21.91	5.00 to 100.00	53.7%	0.00%	4.69%
AQLQ overall score	65	4.48	1.50	1.47 to 7.00	53.7%	0.00%	3.08%
AQLQ Symptoms score	66	3.64	2.22	0.00 to 7.00	54.5%	16.67%	3.03%
AQLQ Activity score	66	3.68	2.13	0.00 to 7.00	54.5%	16.67%	3.03%
AQLQ Emotional score	66	3.72	2.39	0.00 to 7.00	54.5%	16.67%	10.61%
AQLQ Environmental score	66	3.91	2.33	0.00 to 7.00	54.5%	16.67%	7.58%
AQL-5D (utility)	64	0.737	0.176	0.450 to 1.00	52.9%	0.00%	7.80%
TTO (utility)	80	0.787	0.295	0.000 to 1.00	71.4%*	5.00%	51.3%

*The response rate is based on the denominator being 112 due to only the participants based at the Norwich hospital site (NNUH) being asked the TTO questions. All of the other response rates for the PROMS were based on the denominator being 121 as this was the total number recruited across all hospital sites where each participant was asked to complete PROM questionnaires.
Ranges for PROMs: EQ-5D-5L (-0.281 to 1); EQ VAS (0 to 100); AQLQ (0 to 7); AQL-5D (0 to 1); TTO (0 to 1).

There was some evidence of floor effects in **Table 8** for the baseline statistics, but the EQ-5D-5L utility, AQLQ emotional and environmental scores and the TTO utility showed evidence of ceiling effects. The TTO utility had the highest percentage of 18.8% for ceiling effects. The baseline response rates ranged from 97.5% to 100.0%. For the statistics at week 4 shown in **Table 9**, the ceiling effects approximately doubled and trebled for the EQ-5D-5L utility and TTO utility respectively, which may suggest that the participants' health was improving and they had recovered from their asthma crisis event. The response rates had reduced and ranged from 57.9% to 77.7%. For the week 8 statistics shown in **Table 10**, the ceiling effects continued to increase for the EQ-5D-5L, and had begun to stabilise for the TTO. There was, however, a spiked increase seen in the ceiling effects for the AQL-5D utility. The response rates had lowered very slightly to range between 53.7% and 71.4%. Higher percentages of floor effects were observed for the AQLQ symptoms, activity, emotional and environmental scores at week 4 and 8. However, the AQLQ overall score and AQL-5D utility value were both absent from floor effects at these time points. This suggests that the participant's triggers were beginning to affect them again.

After considering the evidence of ceiling effects observed for utility in the baseline statistics (**Table 8**), I explored the EQ-5D-5L and TTO utility values further in relation to the peak of the asthma event data.

The table below (**Table 11**) shows that 10 participants had a ceiling effect at baseline for the EQ-5D-5L, and 20 participants had a ceiling effect at baseline for the TTO. The majority of these participants (70% for the EQ-5D-5L, and 55% for the TTO) had the peak of their asthma event occur before they either attended A&E or were admitted to hospital.

Table 11: Number of participants with ceiling effects at baseline for eq-5d-5l and TTO and their corresponding peak of asthma event

Peak of asthma event	**No. of participants with an EQ-5D-5L baseline utility of 1.000**	**No. of participants with a TTO baseline utility of 1.000**
Before A&E attendance / admission to hospital	7	11
On route to A&E attendance / admission to hospital	2	4
In hospital	1	5
Total	10	20

Following this, I used regression analysis to explore the relationship between the EQ-5D-5L and TTO baseline utility values and the peak of the asthma event data, since these two utility variables were reporting ceiling effects for a proportion of participants. **Table 12** below shows that there were no statistically significant differences found between the peak of the asthma event data (before or on route to A&E attendance or hospital admission) and the baseline TTO utility values. However, the sample size (N) was small, and the R-squared value was 0.0041, which indicates that the model doesn't represent goodness of fit. **Table 13** below also shows that there are no statistically significant differences found between the peak of the asthma event data and the baseline EQ-5D-5L utility values. Likewise, as above, the sample size (N) for **Table 13**, was small and the R-squared value was 0.0031, which indicates that the model doesn't represent goodness of fit.

Table 12: Regression analysis to show the baseline TTO utility value compared to the peak of the asthma-related crisis event

TTO utility (N=108)	Coefficient	Standard error	P-value	95% Confidence interval
Intercept	0.6031	0.0701	0.000	(0.4641,0.7422)
Before*	0.0162	0.0776	0.835	(-0.1377,-0.1701)
On route*	0.0556	0.0931	0.552	(-0.1290,0.2401)

*Hospital was the comparator

Table 13: Regression analysis to show the baseline EQ-5D-5L utility value compared to the peak of the asthma-related crisis event

EQ-5D-5L utility (N=116)	Coefficient	Standard error	P-value	95% Confidence interval
Intercept	0.6742	0.0675	0.000	(0.5404, 0.8080)
Before*	-0.0431	0.0746	0.565	(-0.1909,0.1048)
On route*	-0.0431	0.0900	0.632	(-0.2213,0.1350)

*Hospital was the comparator

The relationship between the baseline EQ-5D-5L utility values and the peak of the asthma event data, and between the TTO utility values and the peak of the asthma event data were explored using regression analyses. Both regressions showed no statistically significant differences between the utility values and the peak of the asthma event data.

Even though 10 participants had a ceiling effect in the EQ-5D-5L utility values at baseline, none of the participants had a ceiling effect for the EQ VAS scores at baseline.

Therefore, given the non-statistically significant result, it was not necessary to exclude the participants at baseline who had demonstrated ceiling effects in the EQ-5D-5L and TTO utility values.

The data set had missing data throughout the study as previously noted in **Table 8** to **Table 10**. The majority of the missing data was found in the PROMs, where participants either did not post back their questionnaires (loss to follow up), or did post back their questionnaires with missing data (patient non-response). To highlight the percentage of missing data in the PROMs, the tables below provide this information for the EQ-5D-5L, EQ VAS, AQLQ overall scores, AQL-5D and the TTO.

For the EQ-5D-5L questionnaires, a large amount of missing data was visible from the second time point (at week 1). **Table 14** shows that 33.06% of the EQ-5D-5L data points were missing by week 1, compared to 0.83% missing at baseline. Between week 1 and week 8, the missing values for the EQ-5D-5L (missing overall utility values) ranged between 33.06% and 47.11%.

Table 14: Missing data descriptive statistics for the EQ-5D-5L questionnaire at all time points

Follow-up points	Missing Values (%)	SD	Range
Baseline	0.83	0.274	-0.102 – 1.00
Week 1	33.06	0.264	-0.102 – 1.00
Week 2	38.02	0.233	0.030 – 1.00
Week 3	38.84	0.248	0.000 – 1.00
Week 4	41.32	0.264	-0.005 – 1.00
Week 5	46.28	0.235	0.092 – 1.00
Week 6	46.28	0.249	0.108 – 1.00
Week 7	47.11	0.232	0.108 – 1.00
Week 8	47.11	0.294	-0.215 – 1.00

The missing data values for the EQ VAS were very similar to the missing data values for the EQ-5D-5L, probably because the EQ VAS is part of the EQ-5D-5L questionnaire. **Table 15** shows the missing values were very low at baseline for the EQ VAS, (0.83%), and rose to 33.06% at week 1. This peaked to 47.11% missing data for weeks 7 to week 8.

Table 15: Missing data descriptive statistics for the EQ VAS scores at all time points

Follow-up points	Missing Values (%)	SD	Range
Baseline	0.83	19.26	5 - 90
Week 1	33.06	19.88	10 - 100
Week 2	38.02	20.70	10 - 100
Week 3	38.02	18.95	10 - 100
Week 4	39.67	21.42	11 – 100
Week 5	45.45	18.94	10 – 100
Week 6	46.28	19.33	30 – 100
Week 7	47.11	18.76	30 - 100
Week 8	47.11	22.03	5 - 100

For the AQLQ overall scores and the AQL-5D values (missing overall utility values), the missing data percentages were also very similar with 0.83% and 2.48% missing at baseline for the AQLQ overall score (**Table 16**) and AQL-5D utility values (**Table 17**) respectively. Both the AQLQ overall score and the AQL-5D utility values had missing values of 42.15% at week 4. At week 8, the AQLQ overall score and the AQL-5D utility values had 46.28% and 47.11% missing data respectively.

Table 16: Missing data descriptive statistics for the AQLQ overall scores at all time points

Follow-up points	Missing Values (%)	SD	Range
Baseline	0.83	0.96	1.18 – 5.30
Week 4	42.15	1.48	1.47 – 6.94
Week 8	46.28	1.50	1.47 – 7.00

Table 17: Missing data descriptive statistics for the AQL-5D utility values at all time points

Follow-up points	Missing Values (%)	SD	Range
Baseline	2.48	0.128	0.45 – 0.935
Week 4	42.15	0..173	0.45 – 1.00
Week 8	47.11	0.176	0.45 – 1.00

The TTO also showed the same pattern as the other PROMs for missing data. However, at week 4 and week 8 time points (**Table 18**), the missing data percentages were much lower, with 28.10% and 33.88% missing for week 4 and week 8 respectively. The reason for the lower missing value percentages in the TTO at week 4 and week 8 could be because the participant completed this with the researcher (for those who were not lost to follow up), either in person at a routine follow-up appointment or over the phone. The baseline TTO was missing for some participants, as those who were recruited at the hospital sites in Birmingham and Aberdeen were not asked the TTO. Therefore, the response rate could be higher if the participants in Birmingham and Aberdeen were asked. In comparison, the EQ-5D-5L and the AQLQ, showed much higher missing values after baseline, and this could be because the participants were completing this away from the researcher (e.g. at home), and therefore the researcher was not able to double check completion of the questionnaires in presence of the participant.

Table 18: Missing data descriptive statistics for the TTO utility values at all time points

Follow-up points	Missing Values (%)	SD	Range
Baseline	7.44	0.277	0.100 – 1.00
Week 4	28.10	0.264	0.000 – 1.00
Week 8	33.88	0.295	0.000 – 1.00

As seen above, there is a substantial amount of missing data amongst the EQ-5D-5L, AQL-5D and TTO. Further tests were performed to explore this missing data further by observing the patterns of missing data and identifying whether there were any predictors of this missing data. This exploration was informed by LEMMA (Bristol) and Faria et al. (2014). **Table 19** shows the highest frequencies of the missing data patterns. The first row indicates that all variables considered here were reported for 42 participants out of all who were recruited. However, the second row shows that the EQ-5D-5L, AQL-5D and TTO variables were reported at baseline for 18 participants, with the remaining variables showing missing data. Each row following on from this, shows a different pattern of missing data, but with lower frequencies.

Table 19: Patterns of missing data

	Pattern														
Frequency	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15
42	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1
18	1	1	1	0	0	0	0	0	0	0	0	0	0	0	0
12	1	1	1	1	0	1	0	0	0	0	0	0	0	0	0
7	1	1	1	1	0	0	0	0	0	0	0	0	0	0	0
4	1	1	0	0	1	0	0	0	0	0	0	0	0	0	0

Variables: (1) EQ-5D-5L baseline (2) AQL-5D baseline (3) TTO baseline (4) TTO week 4 (5) EQ-5D-5L week 1 (6) TTO week 8 (7) EQ-5D-5L week 2 (8) EQ-5D-5L week 3 (9) EQ-5D-5L week 4 (10) AQL-5D week 4 (11) EQ-5D-5L week 5 (12) EQ-5D-5L week 6 (13) EQ-5D-5L week 7 (14) EQ-5D-5L week 8 (15) AQL-5D week 8

Note: the 1 and 0 in the table are defined as observed (1) and missing (0).

The visualization of the missing data points, was followed by logistic regression to explore whether the probability of missing data was associated with any baseline demographic variables at different time points (**Table 20)**. The demographic variables were tested separately, one by one to see if there was any association with each of the utility variables at different time points. Most regressions produced statistically significant results ($p < 0.05$) between the age variable and missing data utility variables, except for the missing data on TTO at week 4 of the study. This implies that there was additional missing data points for every year of being older. In addition, some of the

smoking status and employment status categorical variables, showed statistically significant results ($p<0.05$) for some of the utility variables. This implied that there was more additional missing data points if the participant was a smoker compared to being an ex-smoker. The variables, gender, ethnicity and highest education status did not show any association with levels of missing data amongst the utility values at different time points.

Table 20: Logistic regression for missingness of utility values at different time points on baseline demographic variables

	Odds ratio in logistic regression for missing data (95% CI)											
	Missing data on TTO week 4	Missing data on EQ-5D-5L week 1	Missing data on TTO week 8	Missing data on EQ-5D-5L week 2	Missing data on EQ-5D-5L week 3	Missing data on EQ-5D-5L week 4	Missing data on AQL-5D week 4	Missing data on EQ-5D-5L week 5	Missing data on EQ-5D-5L week 6	Missing data on EQ-5D-5L week 7	Missing data on EQ-5D-5L week 8	Missing data on AQL-5D week 8
Age	1.02 (0.99-1.04)	1.05 * (1.02-1.07)	1.03* (1.01-1.06)	1.05* (1.02-1.07)	1.04* (1.02-1.07)	1.03* (1.01-1.05)	1.04* (1.01-1.06)	1.03* (1.01-1.05)	1.03* (1.01-1.05)	1.03* (1.01-1.05)	1.02* (1.00-1.05)	1.03* (1.01-1.05)
Gender Male	1.56 (0.60-4.03)	0.92 (0.39 – 2.17)	0.97 (0.41-2.27)	1.03 (0.45-2.37)	1.08 (0.47-2.48)	1.24 (0.54-2.85)	0.91 (0.40-2.07)	0.82 (0.36-1.83)	0.97 (0.43-2.18)	1.01 (0.45-2.28)	1.01 (0.45-2.28)	0.61 (0.27-1.37)
Ethnicity White	§	391ǂ	144ǂ	175 ǂ	162ǂ	102ǂ	345ǂ	248ǂ	248ǂ	235ǂ	102ǂ	235ǂ
White other	§	556ǂ	684ǂ	314ǂ	301ǂ	211ǂ	239ǂ	634ǂ	634ǂ	623ǂ	870ǂ	623ǂ
Smoking status Never	0.56 (0.23-1.40)	0.78 (0.32-1.89)	0.45 (0.19-1.08)	0.66 (0.28-1.56)	0.73 (0.32-1.71)	0.62 (0.27-1.43)	0.68 (0.30-1.56)	0.77 (0.34-1.71)	0.65 (0.29-1.45)	0.83 (0.38-1.85)	0.71 (0.32-1.57)	0.71 (0.32-1.57)
Non-smoker	0.26 (0.01-4.47)	1ǂ	1ǂ	1ǂ	1ǂ	1ǂ	1ǂ	1ǂ	1ǂ	1ǂ	1ǂ	1ǂ

	Odds ratio in logistic regression for missing data (95% CI)											
	Missing data on TTO week 4	Missing data on EQ-5D-5L week 1	Missing data on TTO week 8	Missing data on EQ-5D-5L week 2	Missing data on EQ-5D-5L week 3	Missing data on EQ-5D-5L week 4	Missing data on AQL-5D week 4	Missing data on EQ-5D-5L week 5	Missing data on EQ-5D-5L week 6	Missing data on EQ-5D-5L week 7	Missing data on EQ-5D-5L week 8	Missing data on AQL-5D week 8
Smoker	0.51 (0.15-1.70)	0.26 * (0.08-0.81)	0.45 (0.14-1.45)	0.18* (0.06-0.58)	0.20* (0.06-0.64)	0.15* (0.05-0.51)	0.17* (0.05-0.56)	0.22* (0.07-0.73)	0.20* (0.06-0.67)	0.24 (0.07-0.79)	0.22 (0.07-0.73)	0.22 (0.07-0.73)
Employment status Part-time	0.46 (0.13-1.61)	0.55 (0.16-1.87)	0.48 (0.15-1.55)	0.34 (0.10-1.10)	0.27* (0.08-0.90)	0.25* (0.07-0.84)	0.36 (0.11-1.16)	0.33 (0.10-1.08)	0.33 (0.10-1.08)	0.33 (0.10-1.08)	0.26* (0.08-0.88)	0.30* (0.09-0.99)
Retired	0.88 (0.28-2.77)	0.77 (0.26-2.27)	1.41 (0.48-4.19)	0.78 (0.27-2.24)	0.78 (0.27-2.24)	0.70 (0.25-1.94)	0.92 (0.33-2.51)	0.64 (0.24-1.71)	0.64 (0.24-1.71)	0.64 (0.24-1.71)	0.64 (0.24-1.71)	0.82 (0.31-2.18)
Stay at home parents	0.54 (0.11-2.71)	0.26 (0.06-1.19)	0.87 (0.18-4.19)	0.30 (0.07-1.37)	0.30 (0.07-1.37)	0.35 (0.08-1.57)	0.40 (0.09-1.79)	0.46 (0.10-2.04)	0.46 (0.10-2.04)	0.46 (0.10-2.04)	0.71 (0.16-3.18)	0.81 (0.18-3.60)
Student	0.81 (0.07-9.01)	0.32 (0.04-2.65)	0.43 (0.05-3.54)	0.38 (0.05-3.08)	0.38 (0.05-3.08)	0.43 (0.05-3.54)	0.50 (0.06-4.04)	0.57 (0.07-4.59)	0.57 (0.07-4.59)	0.57 (0.07-4.59)	0.57 (0.07-4.59)	0.65 (0.08-5.21)
Unemployed	0.54 (0.16-1.85)	0.64 (0.19-2.14)	0.71 (0.22-2.24)	0.61 (0.19-1.96	0.61 (0.19-1.96)	0.87 (0.27-2.81)	0.67 (0.22-2.06)	0.93 (0.30-2.88)	0.93 (0.30-2.88)	0.76 (0.25-2.33)	0.76 (0.25-2.33)	0.87 (0.29-2.63)
Highest level of education Degree	0.82 (0.25-2.70)	1.39 (0.48-4.01)	1.37 (0.46-4.10)	1.39 (0.48-4.01)	1.39 (0.48-4.01)	1.39 (0.48-4.01)	1.53 (0.53-4.43)	1.18 (0.42-3.30)	1.18 (0.42-3.30)	1.3 (0.46-3.65)	0.99 (0.35-2.76)	1.18 (0.42-3.30)

	Odds ratio in logistic regression for missing data (95% CI)											
	Missing data on TTO week 4	Missing data on EQ-5D-5L week 1	Missing data on TTO week 8	Missing data on EQ-5D-5L week 2	Missing data on EQ-5D-5L week 3	Missing data on EQ-5D-5L week 4	Missing data on AQL-5D week 4	Missing data on EQ-5D-5L week 5	Missing data on EQ-5D-5L week 6	Missing data on EQ-5D-5L week 7	Missing data on EQ-5D-5L week 8	Missing data on AQL-5D week 8
School	0.66 (0.26-1.70)	2.22 (0.93-2.53)	1.38 (0.58-3.24)	1.44 (0.62-3.32)	1.33 (0.58-3.06)	1.06 (0.47-2.41)	1.17 (0.52-2.66)	1.12 (0.50-2.53)	1.12 (0.50-2.53)	1.24 (0.55-2.80)	1.12 (0.50-2.53)	1.04 (0.46-2.35)

*statistically significant $p < 0.05$

§ convergence not achieved

ǂ confidence interval not reported

ǂǂ omitted due to predicting failure perfectly

Reference cases for gender (female); ethnicity (Mixed white and black); smoking status (ex-smoker); employment status (full-time); highest education (college)

The results above show that age is definitely a predictor of missingness for the majority of the utility values, where in some cases smoking status and employment status are also associated. This confirms that the data cannot be assumed to be MCAR due to observations of statistical significance i.e. data is associated with observed values. Therefore the data could be MAR or MNAR. Whilst missing data could be MNAR, for the purposes of this analysis it was assumed to be MAR.

The utility data (EQ-5D-5L, AQL-5D and TTO), was further explored to assess whether the data was normally distributed. Histograms, Q-Q plots and skewness / kurtosis tests were conducted to explore the normality distributions. All utility data at the different time points showed evidence of non-normality. The EQ-5D-5L weekly time point data showed histograms that were left-skewed, with the corresponding Q-Q plots showing the data to be non-normally distributed as it deviates from the solid normal line (**Figure 20** - **Figure 28**). For the AQL-5D, the first baseline time point shows evidence of right-skewed data, with the following two data points at week 4 and 8 beginning to show a more bimodal relationship (**Figure 29** - **Figure 31**). Again, the data points for the AQL-5D deviate from the normal distribution line on the Q-Q plots. Lastly, the TTO utility data shows a bimodal relationship for baseline and left skewed data for week 4 and week 8, indicating non-normality (**Figure 32** - **Figure 34**). The Q-Q plots for the TTO also confirm this non-normality assumption.

Figure 20: Histogram and Q-Q plot to show the distribution for participants completing the EQ-5D-5L at baseline

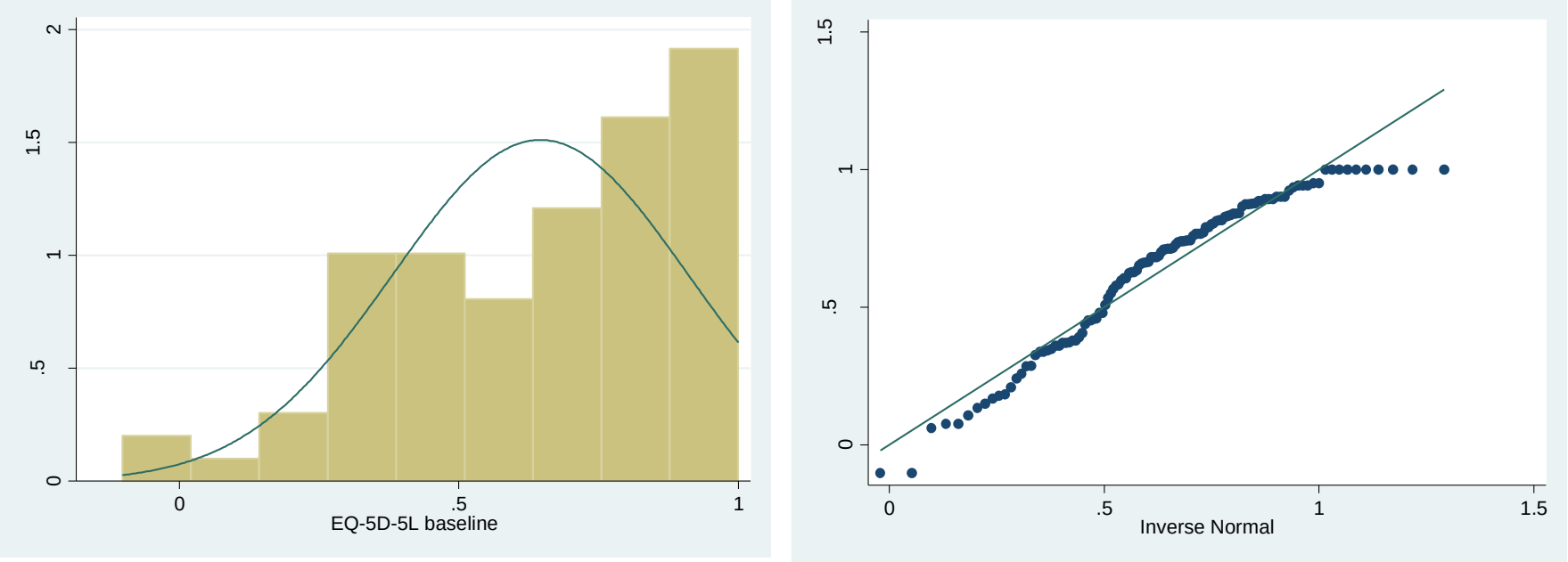
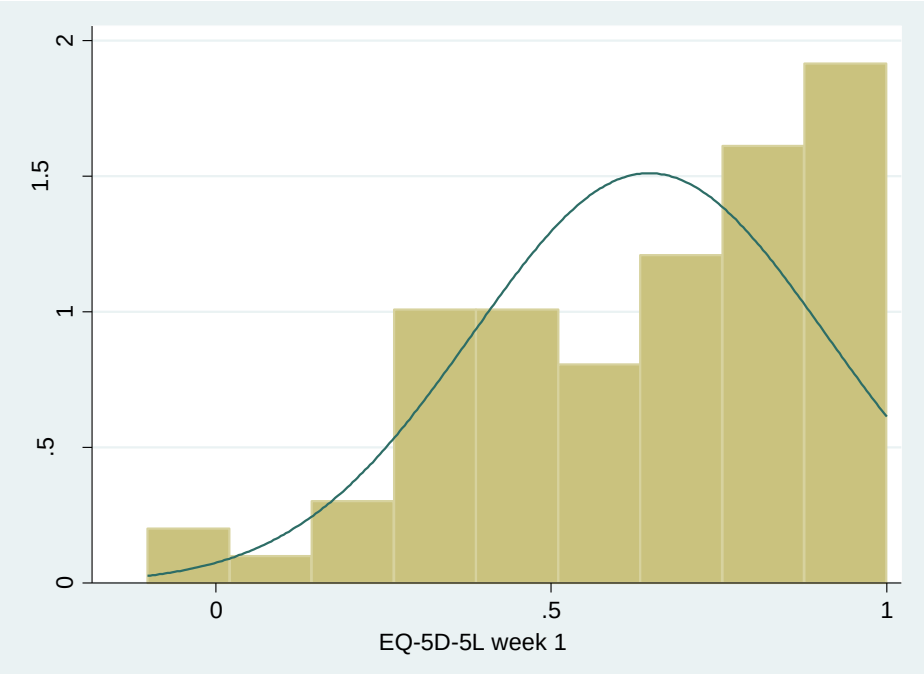


Figure 21: Histogram and Q-Q plot to show the distribution for participants completing the EQ-5D-5L at week 1



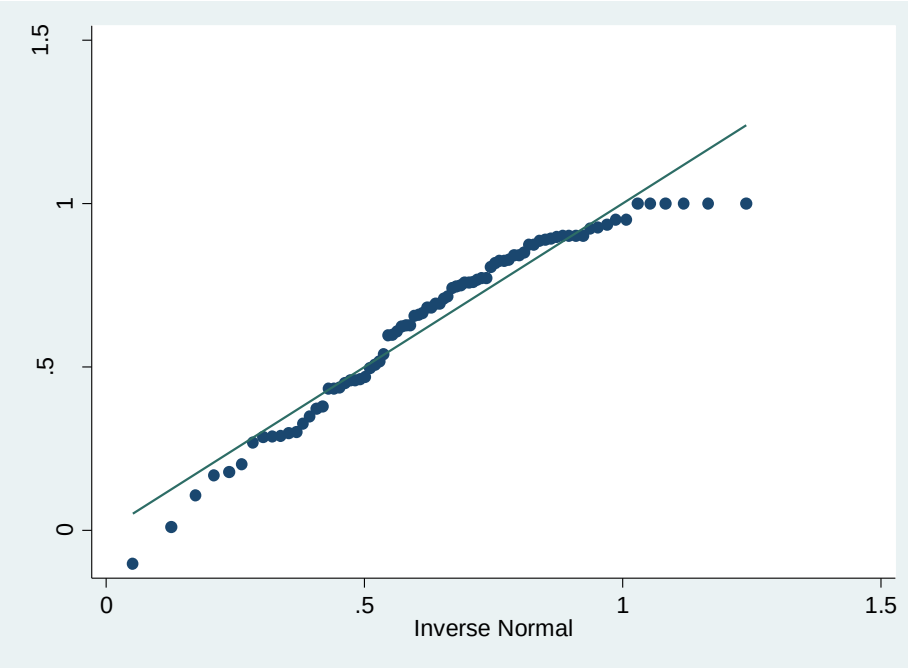


Figure 22: Histogram and Q-Q plot to show the distribution for participants completing the EQ-5D-5L at week 2

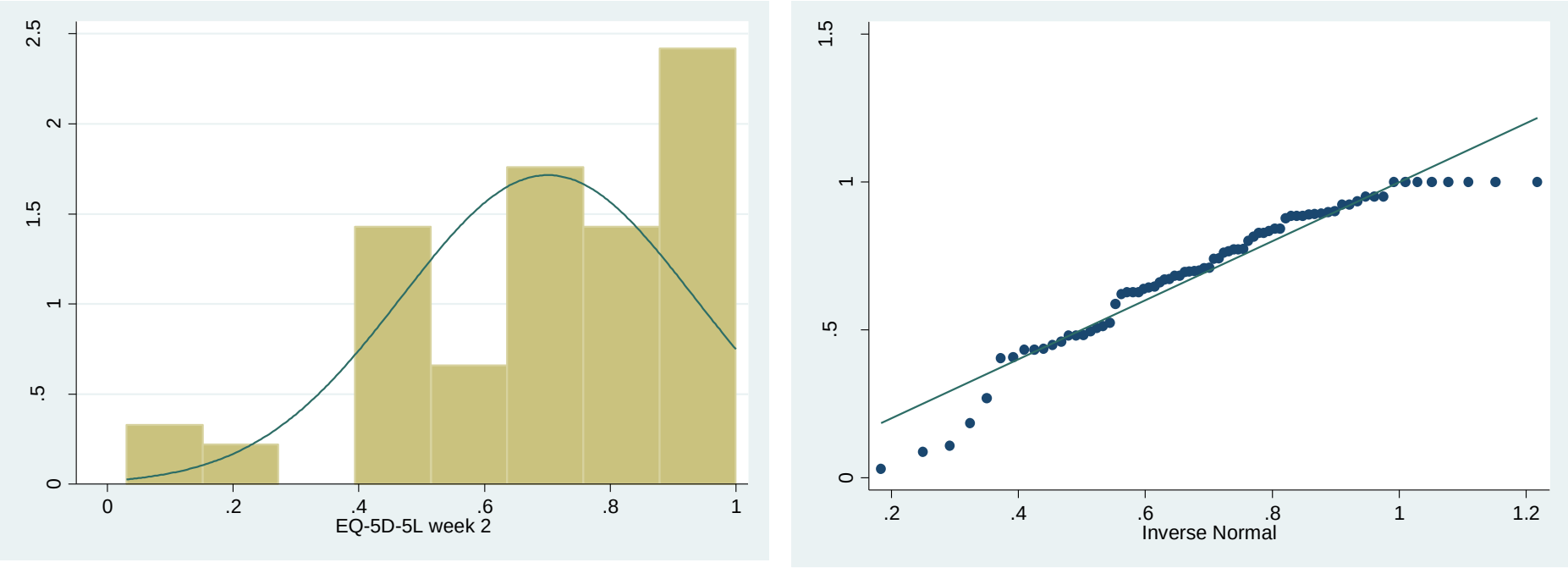


Figure 23: Histogram and Q-Q plot to show the distribution for participants completing the EQ-5D-5L at week 3

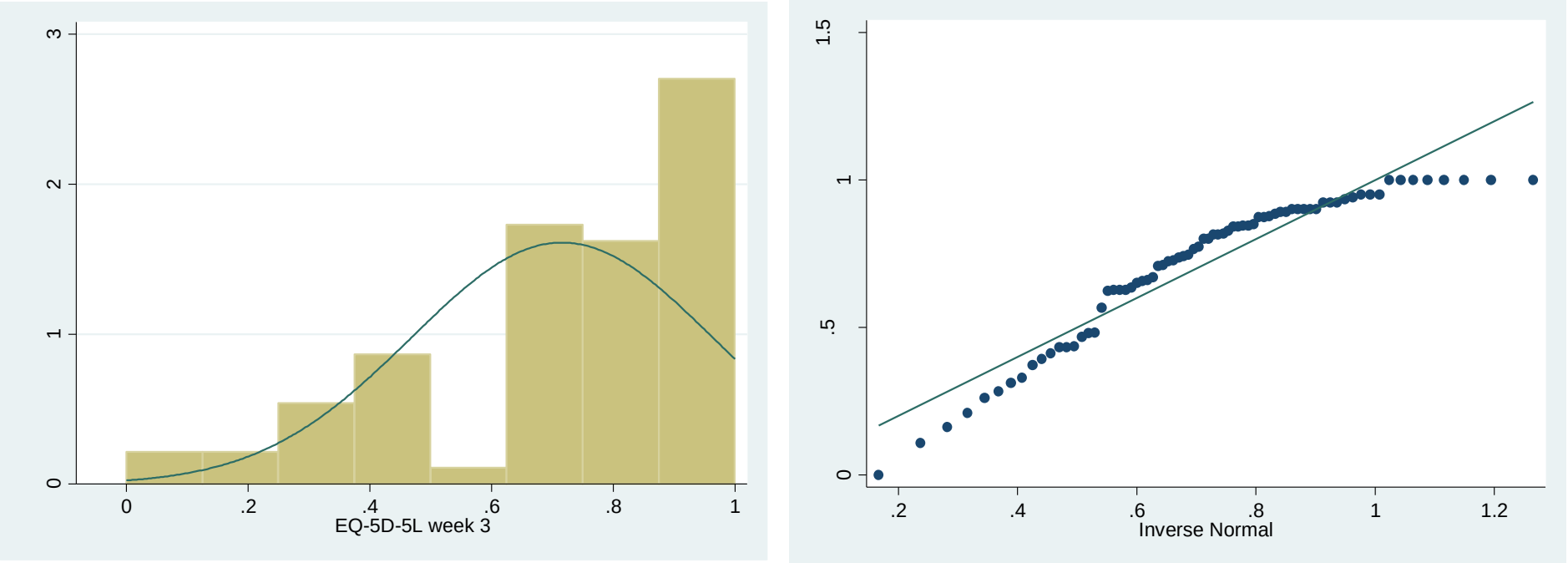
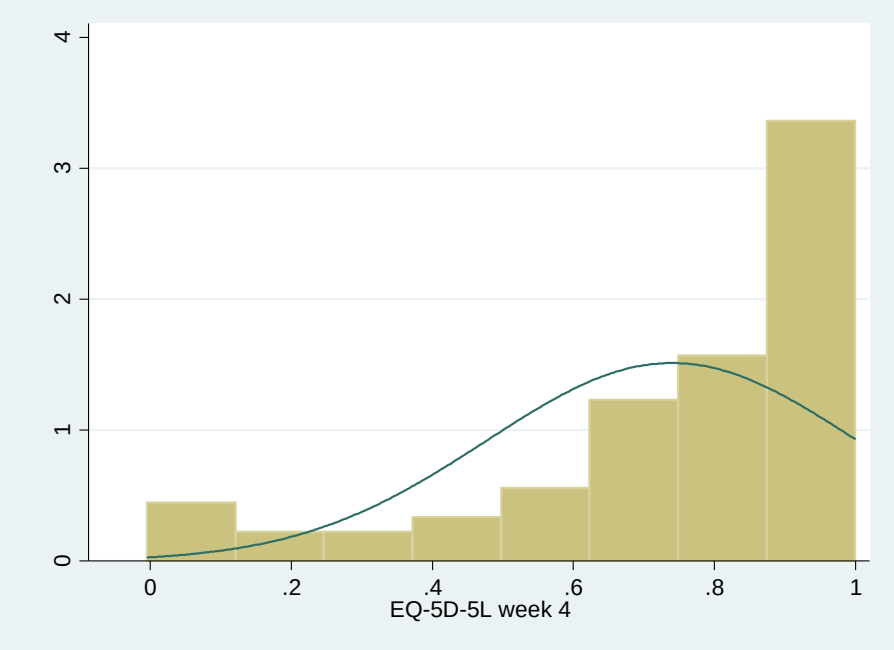


Figure 24: Histogram and Q-Q plot to show the distribution for participants completing the EQ-5D-5L at week 4



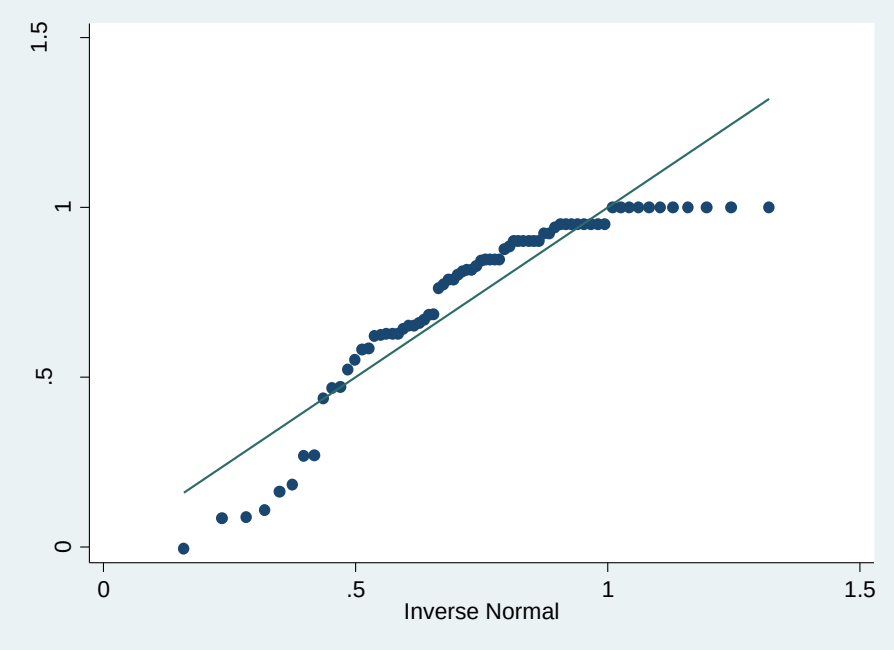
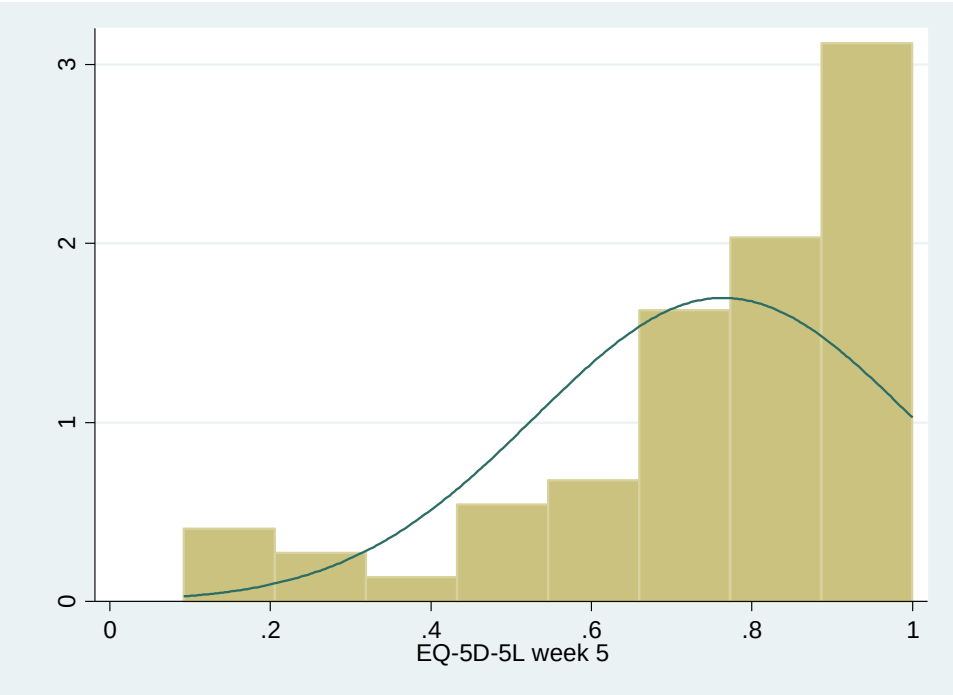


Figure 25: Histogram and Q-Q plot to show the distribution for participants completing the EQ-5D-5L at week 5



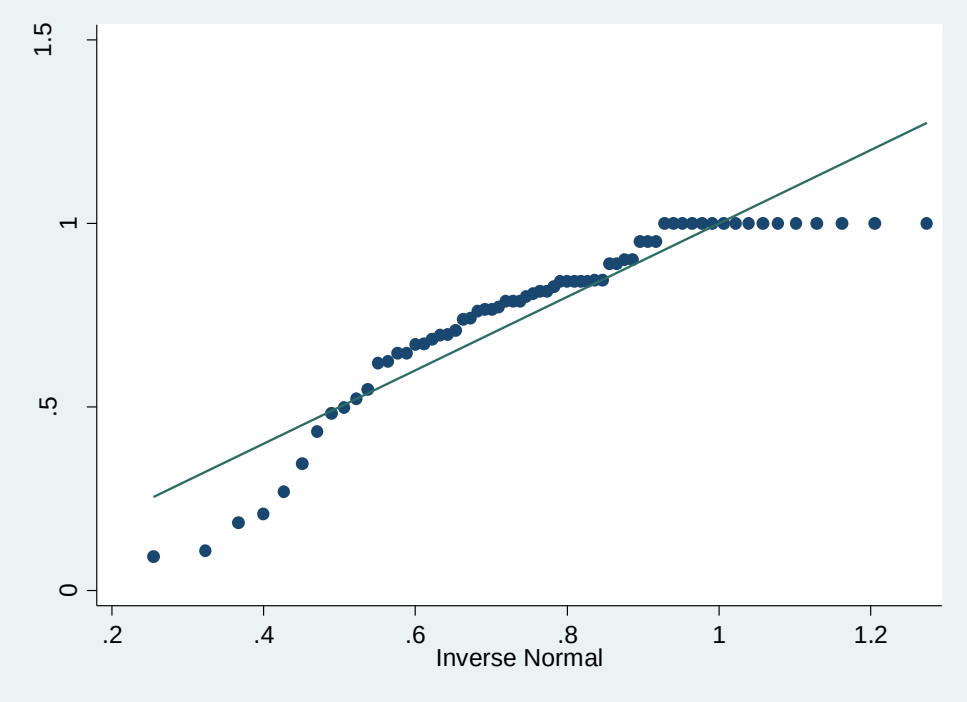


Figure 26: Histogram and Q-Q plot to show the distribution for participants completing the EQ-5D-5L at week 6

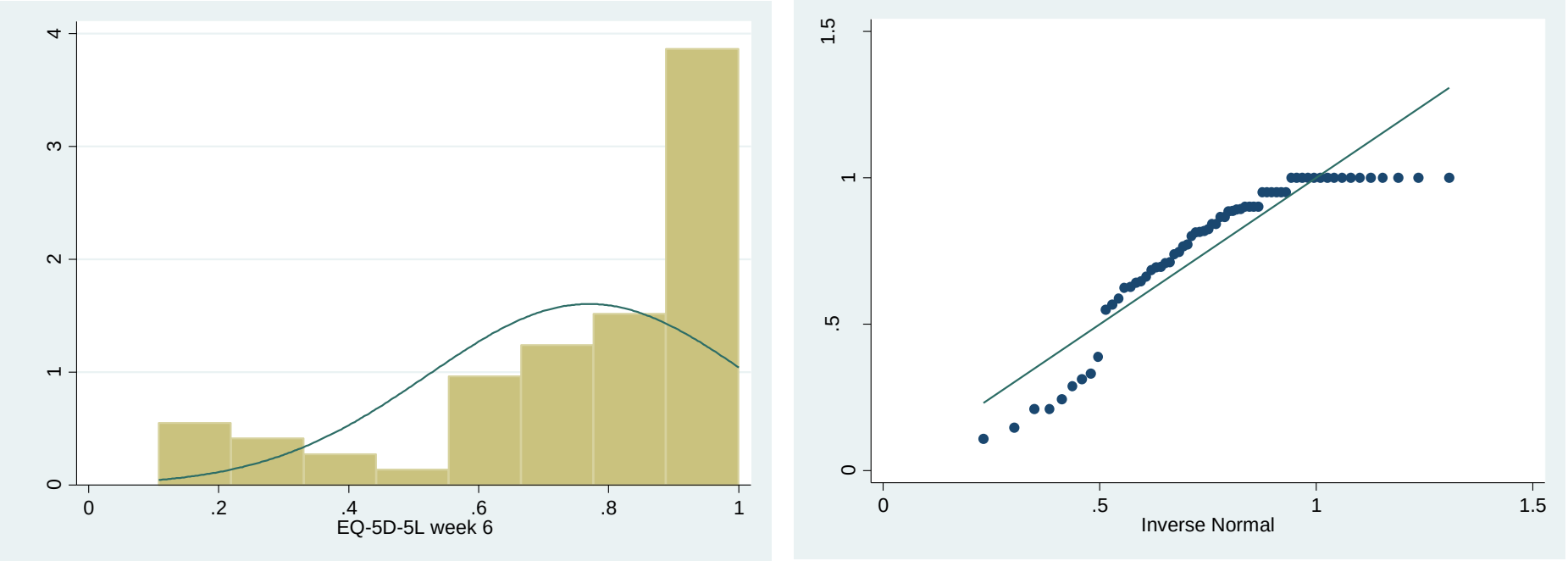
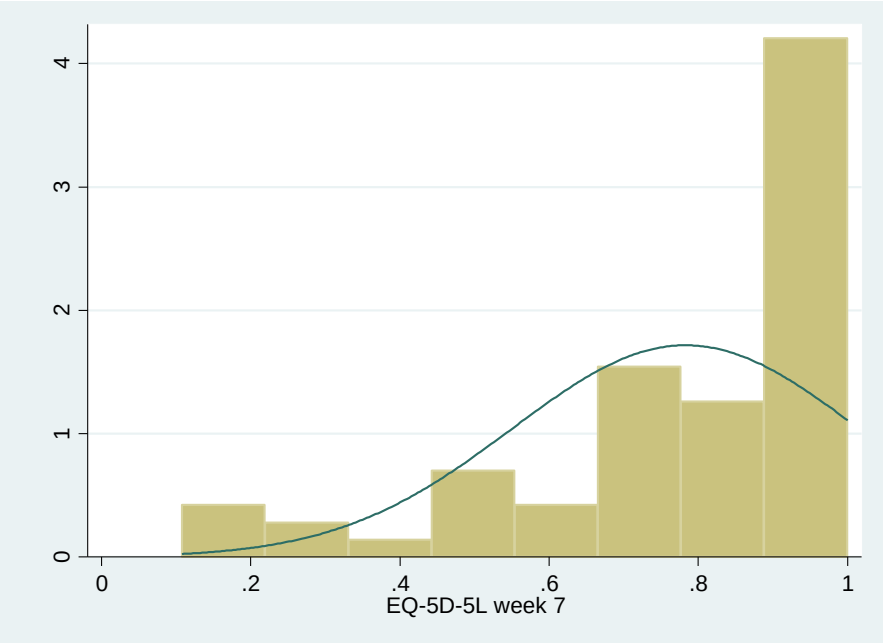


Figure 27: Histogram and Q-Q plot to show the distribution for participants completing the EQ-5D-5L at week 7



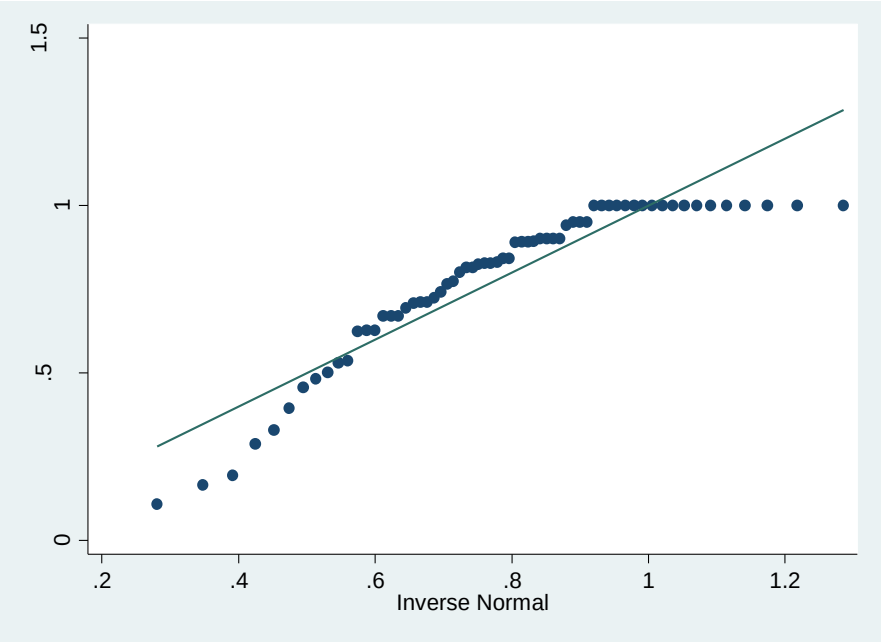


Figure 28: Histogram and Q-Q plot to show the distribution for participants completing the EQ-5D-5L at week 8

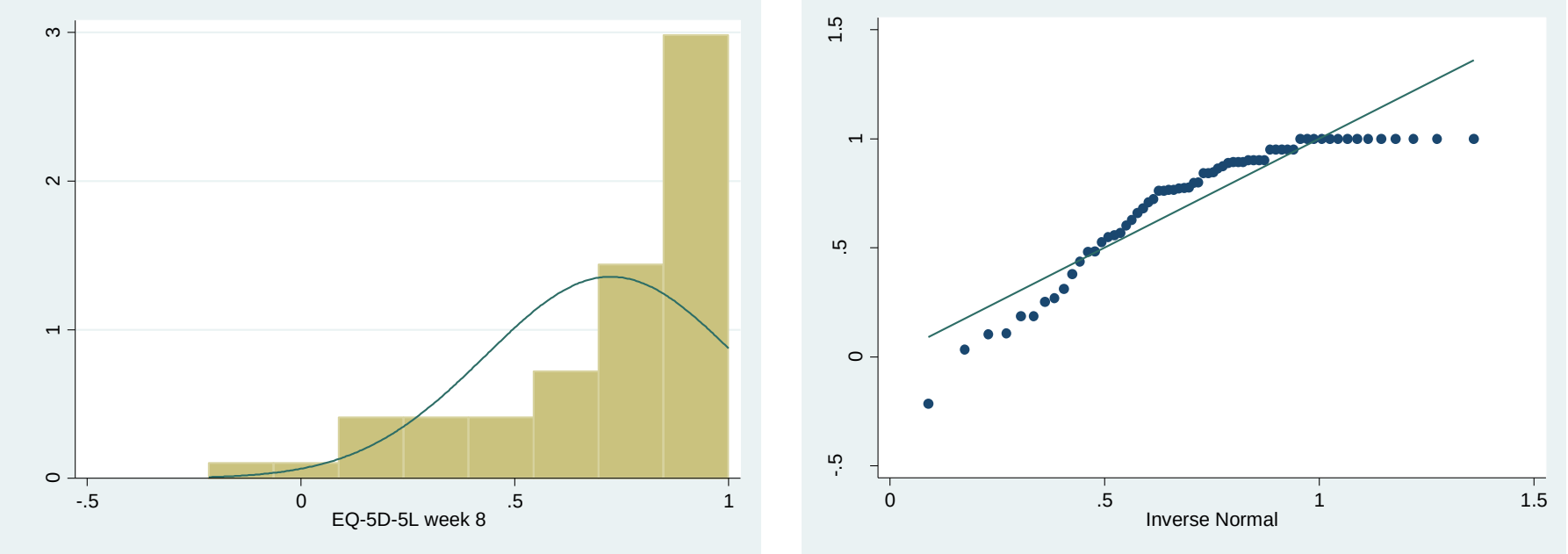
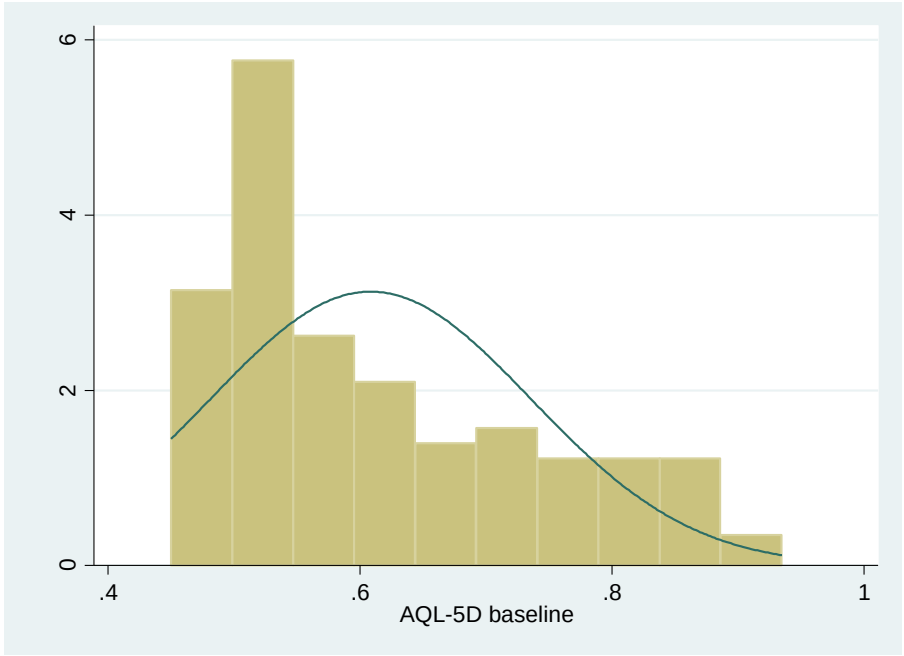


Figure 29: Histogram and Q-Q plot to show the distribution for participants completing the AQL-5D at baseline



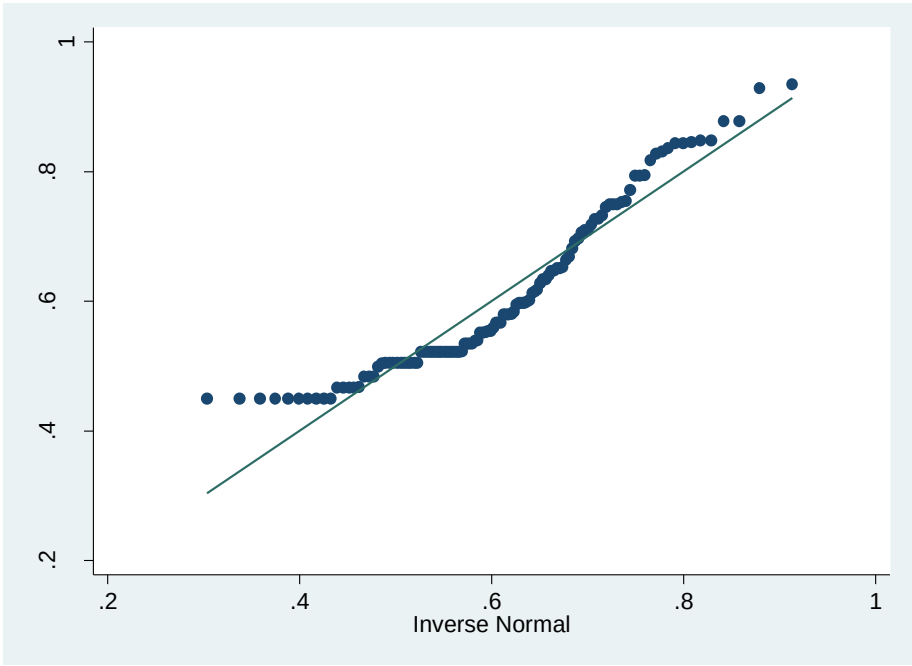
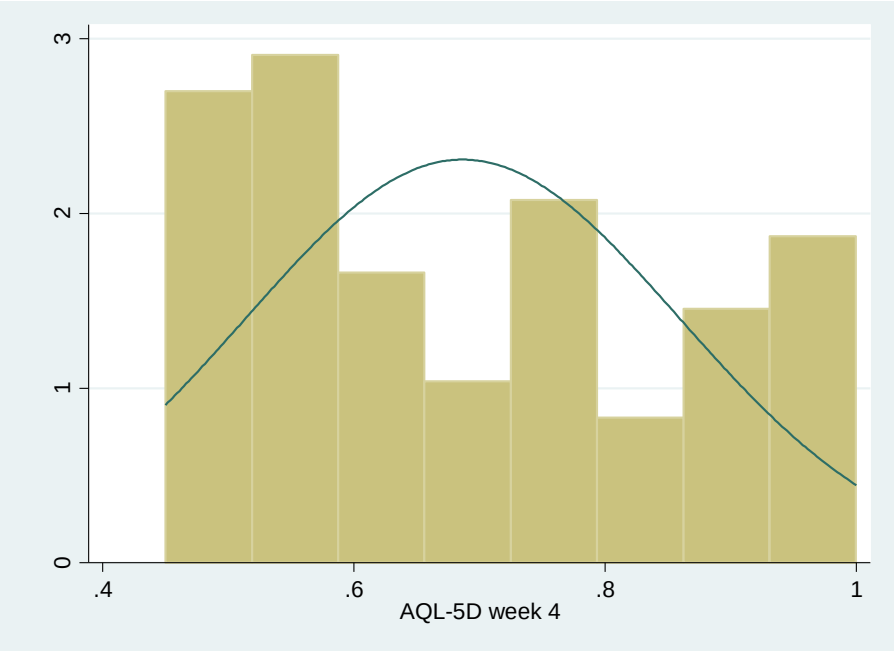


Figure 30: Histogram and Q-Q plot to show the distribution for participants completing the AQL-5D at week 4



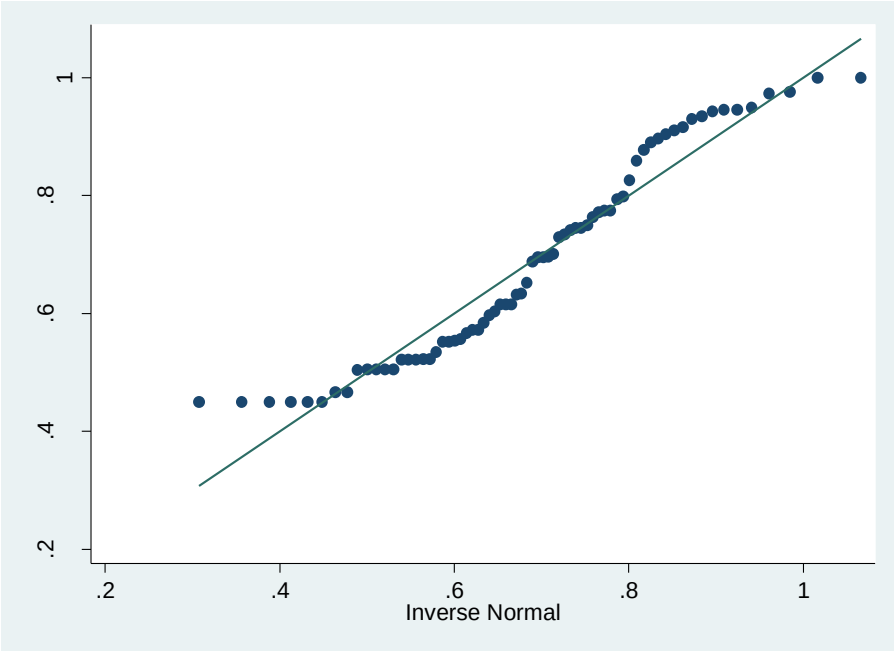


Figure 31: Histogram and Q-Q plot to show the distribution for participants completing the AQL-5D at week 8

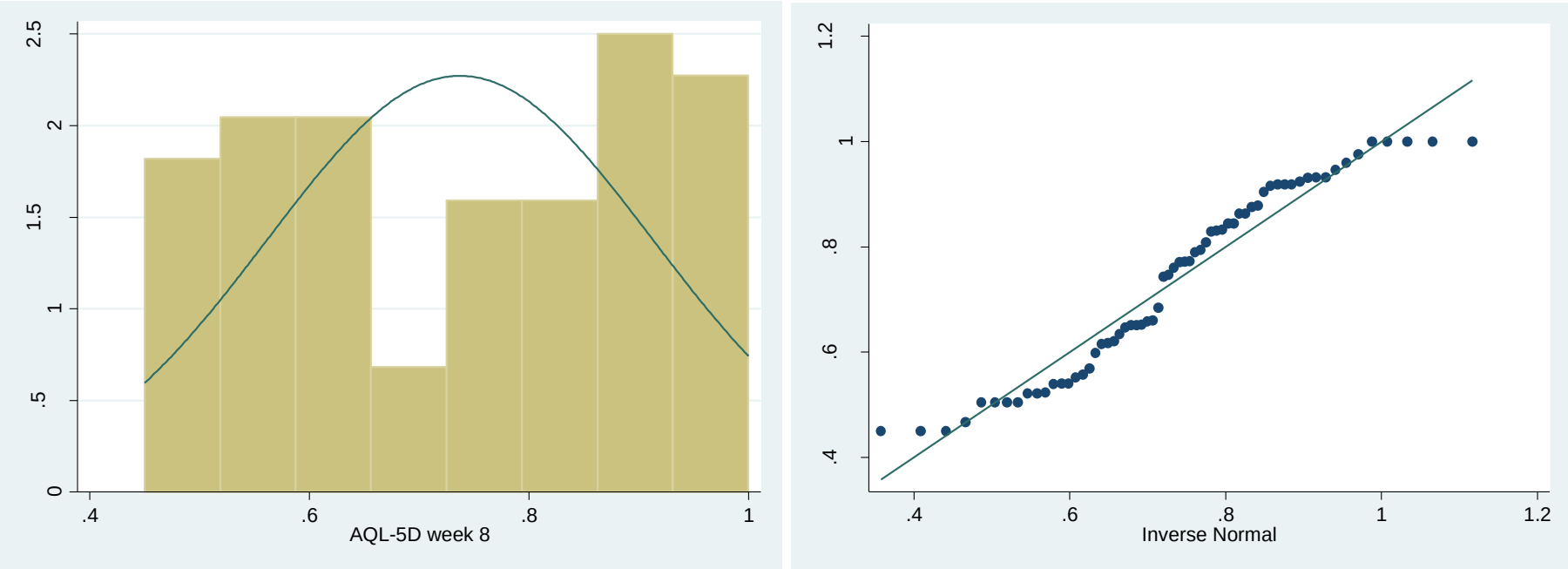
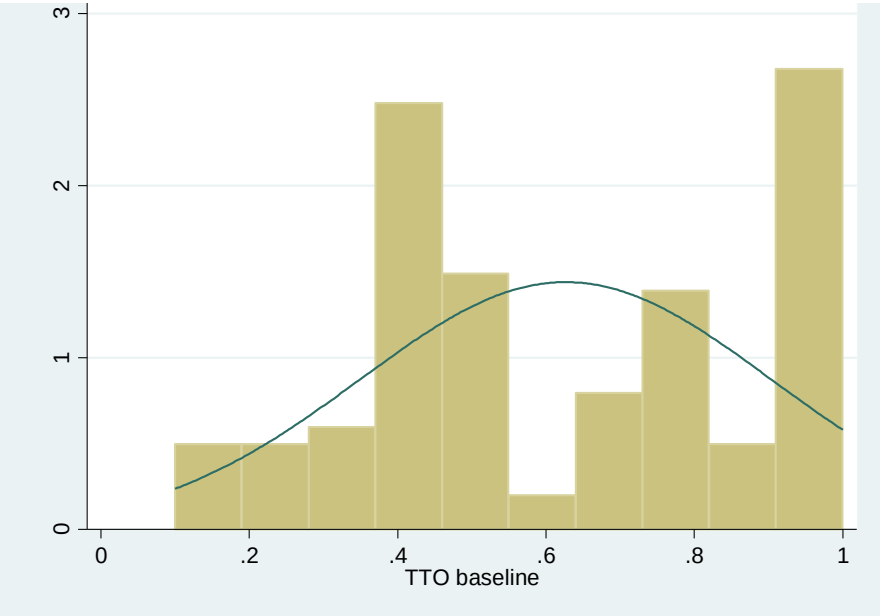


Figure 32: Histogram and Q-Q plot to show the distribution for participants completing the TTO at baseline



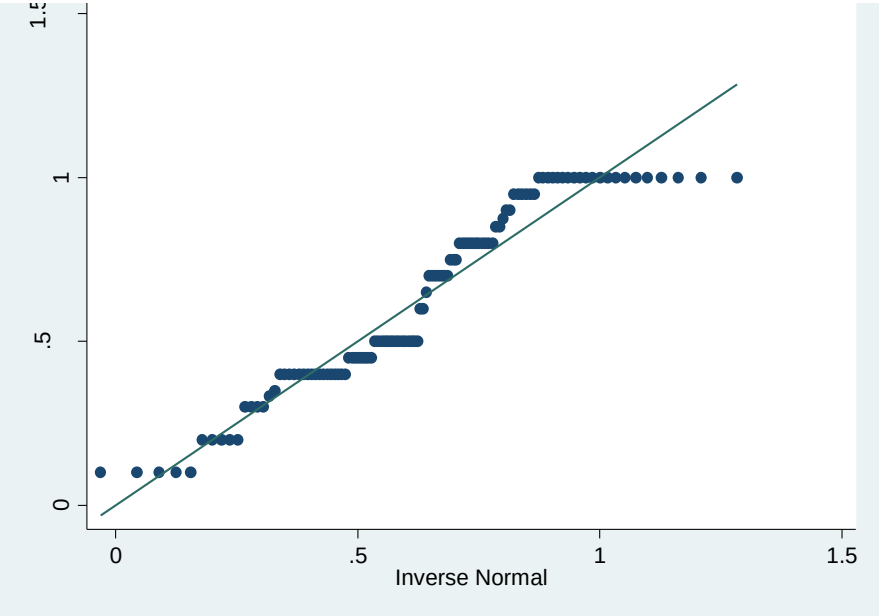
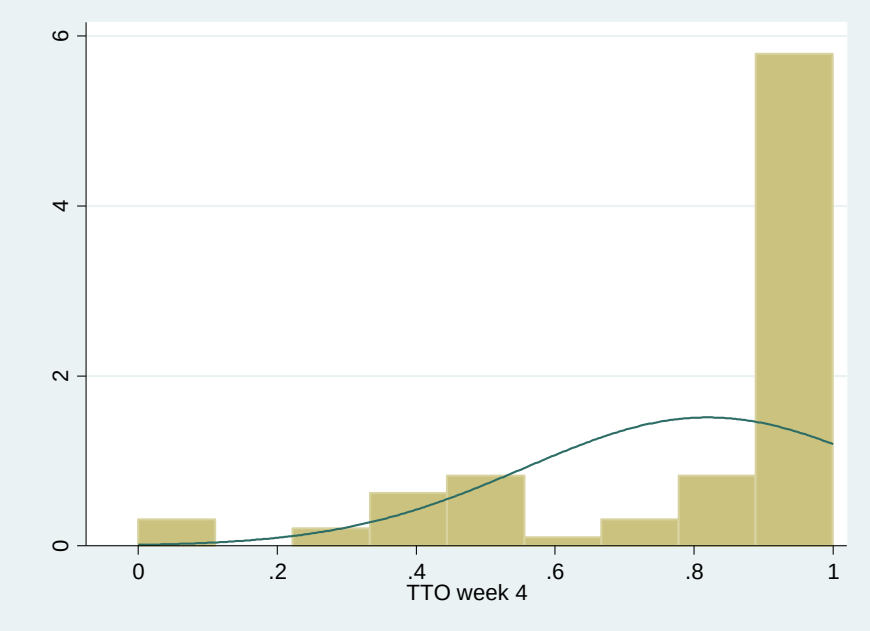


Figure 33: Histogram and Q-Q plot to show the distribution for participants completing the TTO at week 4



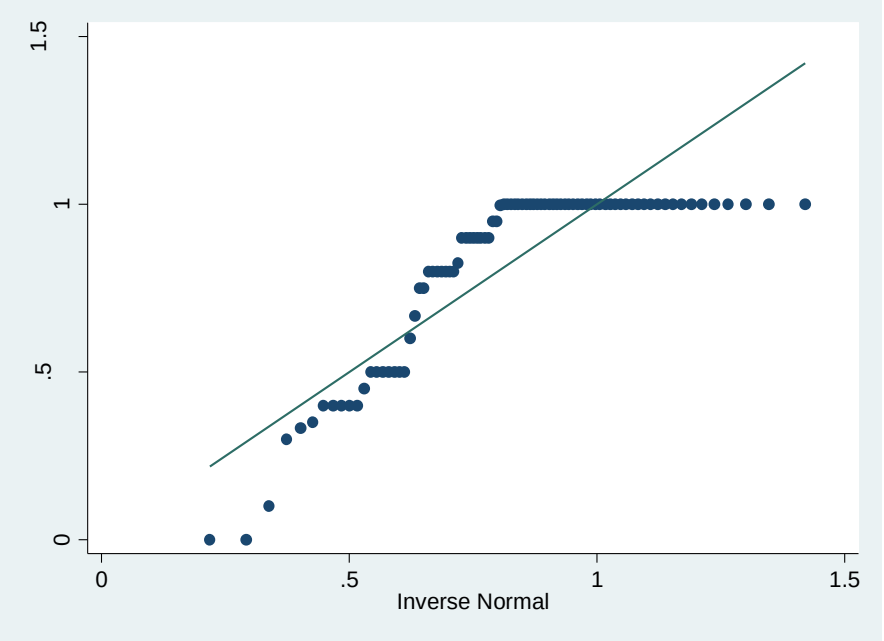
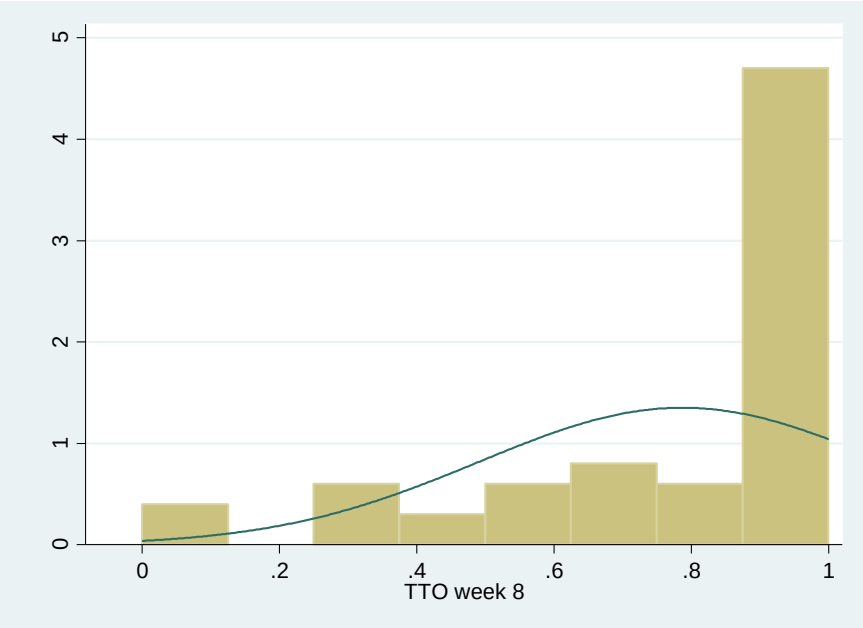
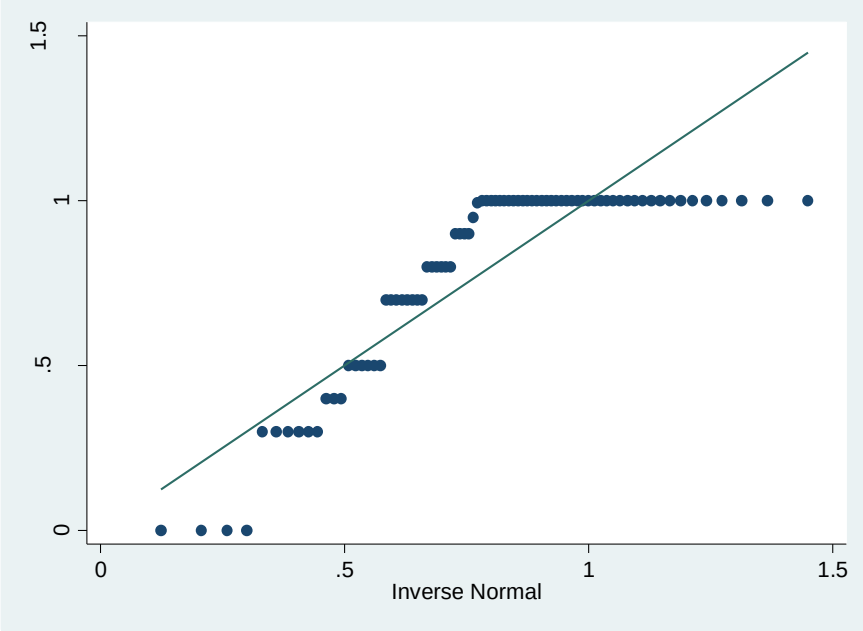


Figure 34: Histogram and Q-Q plot to show the distribution for participants completing the TTO week 8





Additionally, the skewness / kurtosis test provided further confirmation that the utility data was not normally distributed as shown by the Chi^2 test statistic being $p<0.05$ for all variables (**Table 21**). This finding suggests one should reject the hypothesis that the variables are normally distributed.

Table 21: Skewness / Kurtosis test to explore the normality assumptions of the utility variables at different time points

Variable	*Observations*	*Pr (Skewness)*	*Pr (Kurtosis)*	*Adj Chi^2 (2)*	*Prob > Chi^2*
EQ-5D-5L baseline	120	0.0036	0.3898	8.25	0.0162
EQ-5D-5L week 1	81	0.0151	0.6418	5.83	0.0542
EQ-5D-5L week 2	75	0.0035	0.3175	8.36	0.0153
EQ-5D-5L week 3	74	0.0013	0.6132	9.11	0.0105
EQ-5D-5L week 4	71	0.0001	0.1504	13.39	0.0012
EQ-5D-5L week 5	65	0.0002	0.0812	13.36	0.0013
EQ-5D-5L week 6	65	0.0003	0.2727	11.59	0.0030
EQ-5D-5L week 7	64	0.0003	0.1452	12.16	0.0023
EQ-5D-5L week 8	64	0.0003	0.1512	12.39	0.0020
AQL-5D baseline	118	0.0013	0.2450	10.09	0.0064
AQL-5D week 4	70	0.2690	0.0000	17.33	0.0002
AQL-5D week 8	64	0.7739	0.0000	25.61	0.0000
TTO baseline	112	0.7991	0.0000	29.84	0.0000
TTO week 4	87	0.0000	0.0648	18.84	0.0001
TTO week 8	80	0.0000	0.2419	14.35	0.0008

Skewness / Kurtosis test used to test for normality in data

All variables show the Chi^2 statistic as $p < 0.05$, which suggests to reject the hypothesis that the variables are normally distributed.

The mean utility values, score values and their associated standard deviations for these questionnaires are displayed in **Table 22** for the available cases. All of the questionnaires apart from the AQLQ activity domain, AQLQ emotional domain and the AQLQ environmental domain had statistically significantly different scores at the 1% level when the Wilcoxon-signed rank test were conducted between baseline and week 8.

Graphical representations of these aforementioned utility values and scores are displayed in **Figure 35** and **Figure 36** for the available case analysis, where the *N* changes over the weekly time points as illustrated in **Table 22**. Both the mean utility values and EQ VAS scores progress by increasing in the same direction whilst tapering off at the end of the 8 weeks.

The mean PEF shown in **Figure 37**, also shows an increase in values over the course of the 8 weeks, but this progression is not as linear as the utility values and EQ VAS scores have illustrated. **Figure 38** highlights the mean symptoms scores, (sleeping, symptoms and activities), which were recorded daily over the 8 weeks by the participants. The y-axis of this graph represents the severity of the symptoms, (1 = mild, 2 = moderate and 3 = severe). On average, by approximately half a week after the asthma-related crisis event, difficulties in sleeping had reduced from moderate severity to mild severity. The severity of symptoms and difficulties doing activities had reduced from moderate to mild severity by approximately 7 days from when the asthma-related crisis event had occurred. Approximately half of the recruited participants completed both the PEF and symptom diary over the 8 week period.

Table 22: Mean utility values and scores at weekly time points shown between baseline and week 8

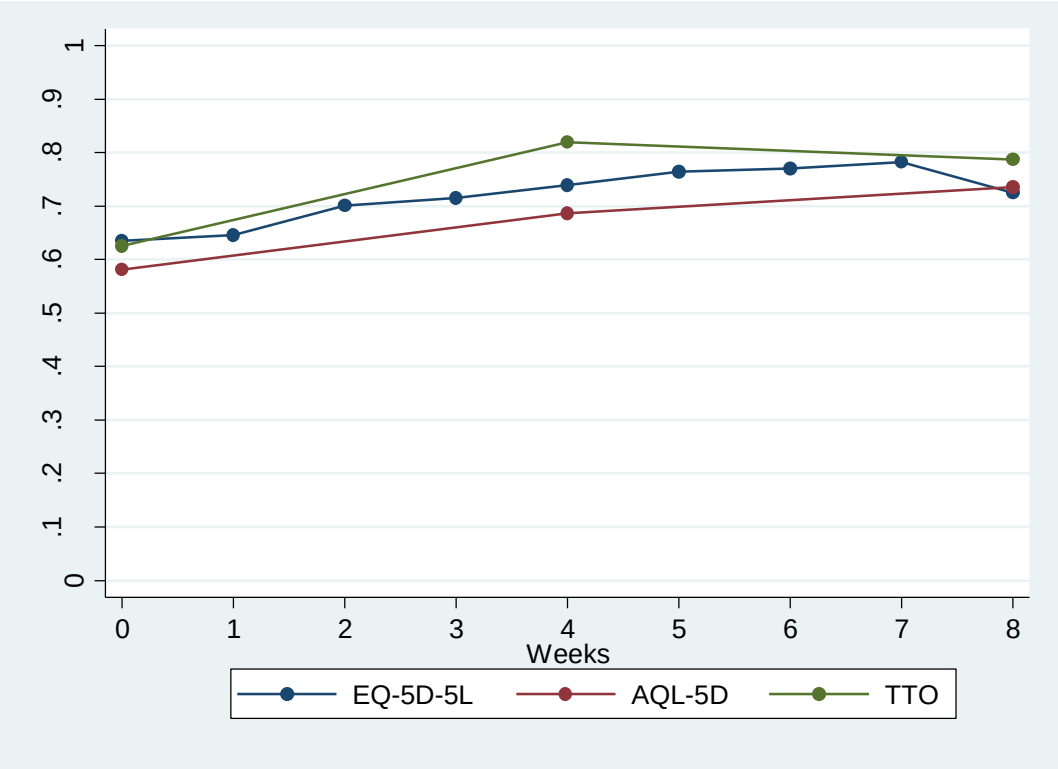
	Baseline (Mean ± SD)	***Week 1 (Mean ± SD)***	***Week 2 (Mean ± SD)***	***Week 3 (Mean ± SD)***	***Week 4 (Mean ± SD)***	***Week 5 (Mean ± SD)***	***Week 6 (Mean ± SD)***	***Week 7 (Mean ± SD)***	***Week 8 (Mean ± SD)***	***p Value***
EQ-5D-5L	**N = 120** 0.64 ± 0.27	**N = 81** 0.65± 0.26	**N = 75** 0.70 ± 0.23	**N = 74** 0.72 ± 0.25	**N = 71** 0.74 ± 0.26	**N = 65** 0.76 ± 0.24	**N = 65** 0.77± 0.25	**N = 64** 0.78 ± 0.23	**N = 64** 0.72 ± 0.29	**N = 64** P < 0.007**
EQ VAS	**N = 120** 45.68 ± 19.26	**N = 81** 57.70 ± 19.88	**N = 75** 60.79 ± 20.70	**N = 75** 63.21 ± 18.95	**N = 73** 65.95 ± 21.42	**N = 66** 68.09 ± 18.94	**N = 65** 68.75 ± 19.33	**N = 64** 71.56 ± 18.76	**N = 64** 67.88 ± 22.03	**N = 64** P < 0.000**
AQLQ overall	**N = 120** 3.28 ± 0.96				**N = 70** 4.09 ± 1.48				**N = 65** 4.48 ± 1.50	**N = 65** P < 0.000**
AQLQ Symptoms	**N = 121** 2.81 ± 1.06				**N = 85** 3.33 ± 2.12				**N = 66** 3.64 ± 2.22	**N = 66** P < 0.003**
AQLQ Activity	**N = 121** 3.51 ± 1.05				**N = 85** 3.32 ± 2.00				**N = 66** 3.68 ± 2.13	**N = 66** P < 0.044*
AQLQ Emotional	**N = 121** 3.14 ± 1.51				**N = 85** 3.36 ± 2.27				**N = 66** 3.72 ± 2.39	**N = 66** P < 0.041*
AQLQ Environmental	**N = 121** 4.04 ± 1.52				**N = 85** 3.63 ± 2.34				**N = 66** 3.91 ± 2.33	**N = 66** P < 0.089
AQL-5D	**N = 118** 0.61 ± 0.13				**N = 70** 0.69 ± 0.17				**N = 64** 0.74 ± 0.18	**N = 62** P < 0.000**
TTO	**N = 112** 0.63 ± 0.28				**N = 87** 0.82 ± 0.26				**N = 80** 0.79 ± 0.30	**N = 80** P < 0.000**

Wilcoxon signed-rank test shown for the mean change between baseline and week 8.

**p-value < 0.01 therefore statistically significant at the 1% level.

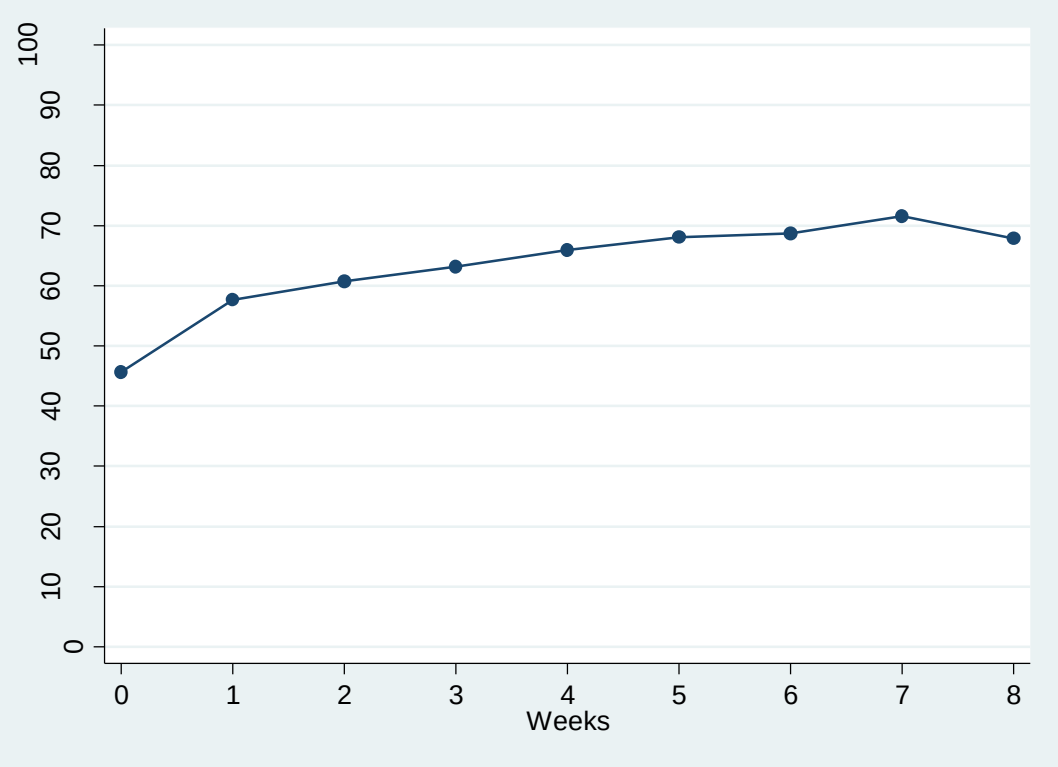
*p-value < 0.05 therefore statistically significant at the 5% level.

Figure 35: Mean utility values for the EQ-5D-5L, AQL-5D and TTO at weekly time points



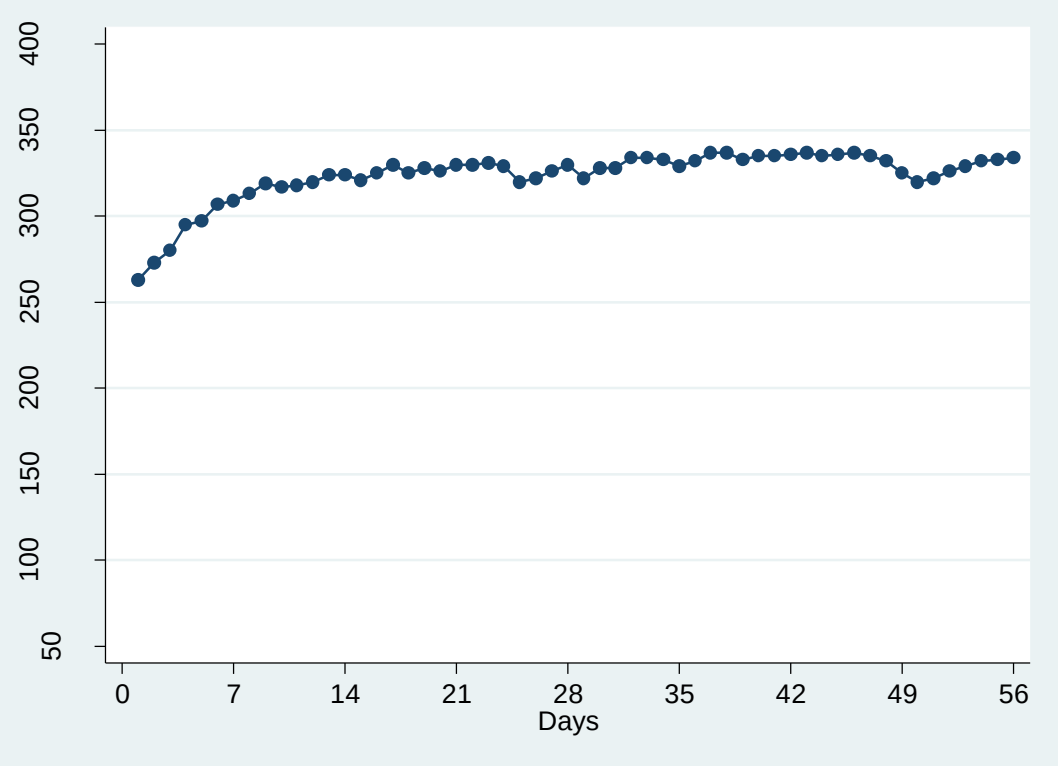
Note: Different N at each time point for each measure

Figure 36: Mean EQ VAS scores at weekly time points



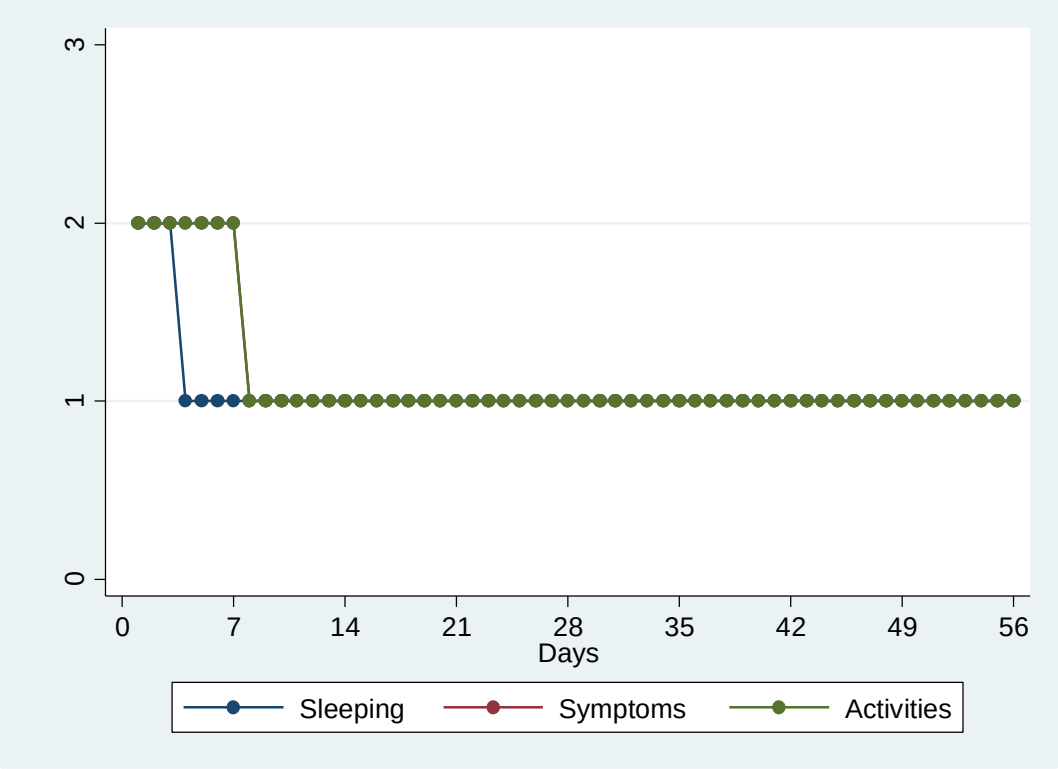
Note: Different N at each time point for each measure

Figure 37: Mean Peak Expiratory Flow at daily time points



From the above graph in **Figure 37**, the mean PEF indicates variability in the measurements from baseline (263) to week 8 (334) of the study. The mean change from these two time points (baseline and week 8) was 63.97, with a strong statistical significant difference at the 5% level. However, the participants' mean best PEF and mean predicted PEF, was 377 and 490 respectively, and so it is clear that by week 8 of the study, the participants were not back to their best or predicted PEF values. This indicates that the study time period of 8 weeks, was not long enough for the participants to reach their best or predicted PEF values again, as recorded at baseline.

Figure 38: Mean scores for difficulties sleeping, symptoms and activities at daily time points



y-axis: 0 = no symptoms, 1 = mild symptoms, 2 = moderate symptoms, 3 = severe symptoms

Daily, weekly, and monthly data were collected over the 8 weeks from different PROM questionnaires. Three key time points, (baseline, week 4 and week 8), were compared using Wilcoxon signed-rank tests to test for differences in the mean rank and p-values. The mean changes in the PROM scores, (EQ-5D-5L, EQ VAS score, AQLQ overall score, AQL-5D, and the TTO), were all statistically significant at the 1% level between baseline and week 8 (**Table 23**), where there was an improvement in quality of life from baseline. Likewise, for the PROMs observed between baseline and week 4, they were also all statistically significant at the 1% level (**Table 24**), with an improvement in quality of life from baseline. However, for the PROM scores where the comparison was between week 4 and week 8, only two of them remained statistically significantly different at the 5% level, and this was the AQLQ overall score and AQL-5D (**Table 25**). There was no statistical significant difference identified in the other PROMS in **Table 25**. This indicated that most of the loss associated with an asthma-related crisis event occurred during the first four weeks. The mean differences between the time points shown for the EQ-5D-5L utility values (**Table 23** and **Table 24**) and the AQLQ overall scores (**Table**

23, **Table 24** and **Table 25**), also highlighted that they exceeded the minimal important difference.

Most of the loss in quality of life is seen by 4 weeks, as represented in **Table 24**. If estimating the QALY loss associated with an asthma-related crisis event for preference-based measures from this table (over a 4 week period, assuming linear interpolation), then the loss associated would be as follows:

$$EQ-5D-5L = \frac{1}{2} \times 0.127 \times \frac{4}{52} = 0.005\ QALYs$$

$$AQL-5D = \frac{1}{2} \times 0.099 \times \frac{4}{52} = 0.004\ QALYs$$

$$TTO = \frac{1}{2} \times 0.170 \times \frac{4}{52} = 0.007\ QALYs$$

If estimating the QALY loss associated with an asthma-related crisis event for preference-based measures from **Table 23** (over a 8 week period, assuming linear interpolation), then the loss associated would be as follows:

$$EQ-5D-5L = \frac{1}{2} \times 0.086 \times \frac{8}{52} = 0.007\ QALYs$$

$$AQL-5D = \frac{1}{2} \times 0.154 \times \frac{8}{52} = 0.012\ QALYs$$

$$TTO = \frac{1}{2} \times 0.132 \times \frac{8}{52} = 0.010\ QALYs$$

As the aforementioned three tables were data based as available cases, the next three tables provided the same analytical information on mean changes but by using complete case analysis. Using data points from the same participants over the 8 week time period enables better comparability between the considered time points of interest.

The data tables representing the complete case analysis, showed similar outputs to the available case analysis. However, the differences were that the EQ-5D-5L only showed a statistical significant difference at the 5% level in **Table 26** and **Table 27**, for the mean changes between baseline and week 8, and baseline and week 4 respectively.

In addition, the TTO had a slightly lower mean change for between baseline and week 4 (**Table 27**), with a statistical significance at the 5% level as opposed to the 1% level as previously estimated in the available case analysis table (**Table 24**). None of the PROMs showed statistical significance for the last mean change between week 4 and week 8 in **Table 28**. Despite these differences, the majority of the loss associated with an asthma-related crisis event for the complete case analysis data was during the first four weeks of the study, which was in line with the available case analysis data. Therefore, the QALY loss estimations associated with an asthma-related crisis event, over the four week period, assuming linear interpolation, are displayed below.

$$EQ-5D-5L = \frac{1}{2} \times 0.067 \times \frac{4}{52} = 0.003\ QALYs$$

$$AQL-5D = \frac{1}{2} \times 0.114 \times \frac{4}{52} = 0.004\ QALYs$$

$$TTO = \frac{1}{2} \times 0.117 \times \frac{4}{52} = 0.005\ QALYs$$

$$EQ-5D-5L = \frac{1}{2} \times 0.073 \times \frac{8}{52} = 0.006\ QALYs$$

$$AQL-5D = \frac{1}{2} \times 0.153 \times \frac{8}{52} = 0.012\ QALYs$$

$$TTO = \frac{1}{2} \times 0.141 \times \frac{8}{52} = 0.011\ QALYs$$

As highlighted from above, the QALY losses associated with an asthma-related crisis event for the preference-based measures, were very similar in value for both the available case analysis and complete case analysis data sets.

Table 23: Mean changes in utility and score values between baseline and week 8 (available case analysis)

Outcome measure	N	Baseline Mean (SD)	8 weeks Mean (SD)	Mean difference (95% CI)	P-value
EQ-5D-5L (utility)	64	0.639 (0.267)	0.725 (0.294)	0.086 (0.153 to 0.019)	0.007**
EQ VAS (score)	64	48.81 (18.58)	67.88 (22.03)	19.06 (25.69 to 12.44)	<0.001**
AQLQ overall (score)	65	3.20 (0.955)	4.48 (1.50)	1.28 (1.60 to 0.963)	<0.001**
AQL-5D (utility)	62	0.582 (0.120)	0.736 (0.178)	0.154 (0.196 to 0.112)	<0.001**
TTO (utility)	80	0.655 (0.273)	0.787 (0.295)	0.132 (0.201 to 0.063)	<0.001**

Wilcoxon signed-rank test
**p-value <0.01 therefore statistically significant at the 1% level

Table 24: Mean changes in utility and score values between baseline and week 4 (available case analysis)

Outcome measure	N	Baseline Mean (SD)	4 weeks Mean (SD)	Mean difference (95% CI)	P-value
EQ-5D-5L (utility)	71	0.613 (0.275)	0.740 (0.264)	0.127 (0.193 to 0.061)	<0.001**
EQ VAS (score)	73	47.38 (20.08)	65.95 (21.42)	18.56 (23.40 to 13.72)	<0.001**
AQLQ (score)	70	3.16 (0.980)	4.09 (1.48)	0.929 (1.19 to 0.666)	<0.001**
AQL-5D (utility)	69	0.589 (0.126)	0.687 (0.174)	0.099 (0.134 to 0.063)	<0.001**
TTO (utility)	87	0.650 (0.278)	0.820 (0.264)	0.170 (0.243 to 0.097)	<0.001**

Wilcoxon signed-rank test
**p-value <0.01 therefore statistically significant at the 1% level

Table 25: Mean changes in utility and score values between week 4 and week 8 (available case analysis)

Outcome measure	N	4 weeks Mean (SD)	8 weeks Mean (SD)	Mean difference (95% CI)	P-value
EQ-5D-5L (utility)	59	0.745 (0.255)	0.720 (0.302)	-0.025 (-0.033 to 0.082)	0.710
EQ VAS (score)	61	67.41 (20.31)	68.51 (22.13)	1.10 (4.60 to 2.41)	0.575
AQLQ (score)	57	4.23 (1.52)	4.52 (1.55)	0.291 (0.536 to 0.046)	0.017*
AQL-5D (utility)	56	0.700 (0.179)	0.740 (0.181)	0.040 (0.078 to 0.002)	0.044*
TTO (utility)	76	0.813 (0.268)	0.794 (0.290)	-0.019 (-0.047 to 0.086)	0.488

Wilcoxon signed-rank test
*p-value <0.05 therefore statistically significant at the 5% level

Table 26: Mean changes in utility and score values between baseline and week 8 (complete case analysis)

Outcome measure	N	Baseline Mean (SD)	8 weeks Mean (SD)	Mean difference (95% CI)	P-value
EQ-5D-5L (utility)	44	0.658 (0.271)	0.732 (0.270)	0.073 (0.152 to 0.006)	0.036*
EQ VAS (score)	44	49.55 (19.25)	68.52 (21.06)	18.98 (26.71 to 11.25)	<0.001**
AQLQ overall (score)	44	3.08 (0.863)	4.41 (1.45)	1.33 (1.74 to 0.923)	<0.001**
AQL-5D (utility)	44	0.580 (0.116)	0.733 (0.173)	0.153 (0.202 to 0.104)	<0.001**
TTO (utility)	44	0.701 (0.274)	0.842 (0.260)	0.141 (0.235 to 0.048)	0.002**

Wilcoxon signed-rank test
**p-value <0.01 therefore statistically significant at the 1% level
*p-value < 0.05 therefore statistically significant at the 5% level

Table 27: Mean changes in utility and score values between baseline and week 4 (complete case analysis)

Outcome measure	N	Baseline Mean (SD)	4 weeks Mean (SD)	Mean difference (95% CI)	P-value
EQ-5D-5L (utility)	44	0.658 (0.271)	0.725 (0.276)	0.067 (0.152 to 0.018)	0.051*
EQ VAS (score)	44	49.55 (19.25)	66.70 (21.31)	17.16 (23.73 to 10.59)	<0.001**
AQLQ (score)	44	3.08 (0.863)	4.10 (1.44)	1.025 (1.38 to 0.667)	<0.001**
AQL-5D (utility)	44	0.580 (0.116)	0.694 (0.175)	0.114 (0.158 to 0.069)	<0.001**
TTO (utility)	44	0.701 (0.274)	0.818 (0.262)	0.117 (0.222 to 0.013)	0.014*

Wilcoxon signed-rank test
**p-value <0.01 therefore statistically significant at the 1% level
*p-value <0.05 therefore statistically significant at the 5% level

Table 28: Mean changes in utility and score values between week 4 and week 8 (complete case analysis)

Outcome measure	N	4 weeks Mean (SD)	8 weeks Mean (SD)	Mean difference (95% CI)	P-value
EQ-5D-5L (utility)	44	0.725 (0.276)	0.732 (0.270)	0.006 (0.065 to 0.052)	0.842
EQ VAS (score)	44	66.70 (21.31)	68.52 (21.06)	1.82 (6.12 to 2.48)	0.522
AQLQ (score)	44	4.10 (1.44)	4.41 (1.45)	0.306 (0.617 to 0.006)	0.072
AQL-5D (utility)	44	0.694 (0.175)	0.733 (0.173)	0.039 (0.085 to 0.007)	0.126
TTO (utility)	44	0.818 (0.262)	0.842 (0.260)	0.024 (0.092 to 0.043)	0.279

Wilcoxon signed-rank test

I also wished to observe the results of the dataset when all the participants who had showed evidence of ceiling effects at baseline for the utility data (**Table 8**) were removed from the dataset. This was because of ceiling effects potentially indicating that these participants were 'healthy' at baseline, and would therefore have a potential to bias the results in loss in quality of life associated with an asthma-related crisis event. In this instance, the evidence of ceiling effects could have arisen because the measures might not have fully captured the problems associated with an asthma crisis event or, for the TTO, less problems could have arisen that were not deemed to be of such value that the participant would be willing to reduce their life expectancy.

For comparison purposes, the mean changes in utilities and scores will be compared for available cases. When observing the mean changes between baseline and week 8, the values when ceiling effects were removed (**Table 29**) compared to the full dataset (**Table 23**), were generally lower at baseline, (with the exception of the VAS score), and lower and week 8. However, the statistical significance was still strong for all outcome measures, with only the EQ-5D-5L having a slightly weaker statistical significance when ceiling effects were removed **(Table 29**) compared to the full dataset (**Table 23**).

Likewise, when comparing the mean changes between baseline and week 4, the values when ceiling effects were removed (**Table 30**) were lower at baseline and week 4 compared to the full dataset (**Table 24**). All the statistical significance for the outcome measures were the same for both datasets, showing statistical significance at the 1% level. Similarly, when comparing the mean changes between week 4 and week 8, the values when ceiling effects were removed (**Table 31**), were lower at baseline and week 4, compared to the full dataset (**Table 25)**. However, when ceiling effects were removed, there was no statistical significance for the mean changes between week 4 and week 8 for the AQL-5D (**Table 31**), compared to the full dataset when there was statistical significance (**Table 25**).

Overall, the mean differences between weeks were only slightly different, with some of them being slightly higher or lower when the available cases had the ceiling effects removed. For example, the mean change between baseline and week 4 for the EQ-5D-5L when ceiling effects were removed was 0.163 (**Table 30**) compared to the mean change

for the full dataset being 0.127 (**Table 24**). Therefore, there was only a 0.036 difference between datasets and statistical significance remained strong at the 1% level.

Table 29: Mean changes in utility and score values between baseline and week 8 without ceiling effects (available case analysis)

Outcome measure	N	Baseline Mean (SD)	8 weeks Mean (SD)	Mean difference (95% CI)	P-value
EQ-5D-5L (utility)	45	0.595 (0.262)	0.674 (0.312)	0.079 (0.168 to 0.009)	0.052*
VAS (score)	46	48.89 (17.77)	65.39 (22.91)	16.50 (24.65 to 8.35)	0.000**
AQLQ overall (score)	46	3.06 (0.859)	4.24 (1.46)	1.18 (1.52 to 0.847)	0.000**
AQL-5D (utility)	45	0.562 (0.103)	0.714 (0.175)	0.152 (0.201 to 0.102)	0.000**
TTO (utility)	58	0.551 (0.221)	0.744 (0.299)	0.194 (0.274 to 0.113)	0.000**

Wilcoxon signed-rank test
*p-value <0.05 therefore statistically significant at the 5% level
**p-value <0.01 therefore statistically significant at the 1% level

Table 30: Mean changes in utility and score values between baseline and week 4 without ceiling effects (available case analysis)

Outcome measure	N	Baseline Mean (SD)	4 weeks Mean (SD)	Mean difference (95% CI)	P-value
EQ-5D-5L (utility)	51	0.557 (0.265)	0.720 (0.253)	0.163 (0.241 to 0.084)	0.000**
VAS (score)	53	47.25 (19.76)	64.57 (21.80)	17.32 (23.23 to 11.41)	0.000**
AQLQ (score)	48	3.00 (0.923)	3.91 (1.49)	0.911 (1.21 to 0.613)	0.000**
AQL-5D (utility)	48	0.563 (0.111)	0.664 (0.168)	0.101 (0.145 to 0.057)	0.000**
TTO (utility)	64	0.549 (0.230)	0.792 (0.272)	0.244 (0.325 to 0.163)	0.000**

Wilcoxon signed-rank test
**p-value <0.01 therefore statistically significant at the 1% level

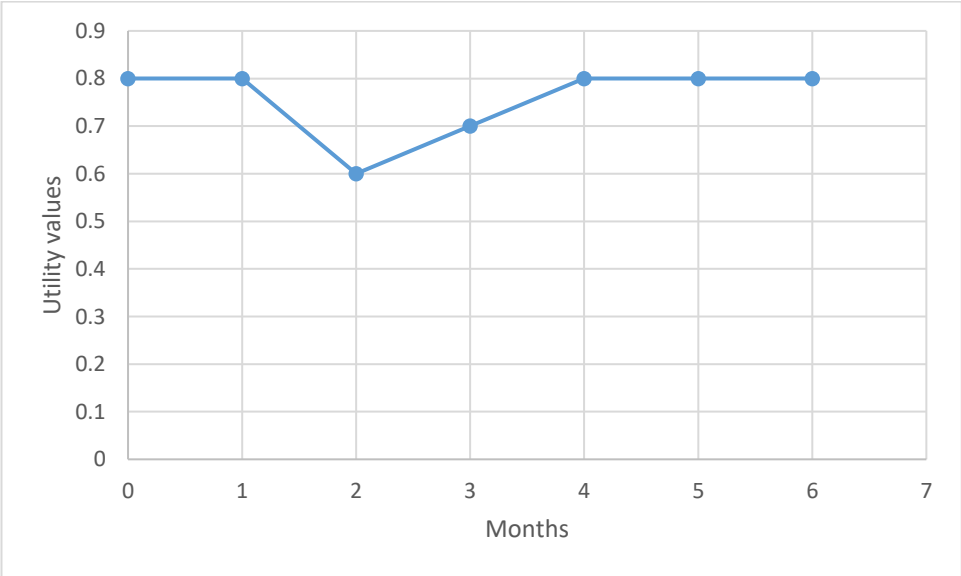
Table 31: Mean changes in utility and score values between week 4 and week 8 without ceiling effects (available case analysis)

Outcome measure	N	4 weeks Mean (SD)	8 weeks Mean (SD)	Mean difference (95% CI)	P-value
EQ-5D-5L (utility)	41	0.732 (0.235)	0.670 (0.324)	-0.063 (0.233 to 0.011)	0.222
VAS (score)	44	66.93 (20.36)	66.32 (22.98)	-0.614 (4.90 to 3.67)	0.765
AQLQ (score)	38	4.05 (1.53)	4.25 (1.54)	0.202 (0.471 to 0.068)	0.014*
AQL-5D (utility)	38	0.689 (0.175)	0.715 (0.182)	0.026 (0.072 to 0.021)	0.309
TTO (utility)	54	0.781 (0.277)	0.751 (0.294)	-0.031 (-0.048 to 0.109)	0.466

Wilcoxon signed-rank test
*p-value <0.05 therefore statistically significant at the 5% level

Figure 39 below, provides an example of a possible asthma-related crisis event happening once in a six month period (at two months), where it takes 2 months for the participant to recover back to the same health state as before the crisis event.

Figure 39: Example of EQ-5D-5L utility values captured over 6 months with one asthma-related crisis event



The total QALYs in this example could be estimated in several ways. For example,

1) By estimating the total QALYs based on scores at two time points, (baseline and 6 months):

$$0.8 \times \frac{6}{12} = 0.40 \text{ QALYs}$$

2) By estimating the total QALYs based on scores at each time point at every month using linear interpolation:

$$\left(0.8 \times \frac{1}{12}\right) + \left(\frac{1}{2} \times (0.6 + 0.8) \times \frac{1}{12}\right) + \left(\frac{1}{2} \times (0.6 + 0.7) \times \frac{1}{12}\right) + \left(\frac{1}{2} \times (0.7 + 0.8) \times \frac{1}{12}\right) + \left(0.8 \times \frac{1}{12}\right) + \left(0.8 \times \frac{1}{12}\right) = 0.0667 + 0.0583 + 0.0542 + 0.0625 + 0.0667 + 0.0667 = 0.3751 \text{ QALYs}$$

3) By estimating the total QALYs at two time points, (baseline and 6 months), and taking account of the asthma-related crisis event in between using the mean EQ-5D-5L utility loss estimated in this study (mean difference in utility value taken from **Table 23**):

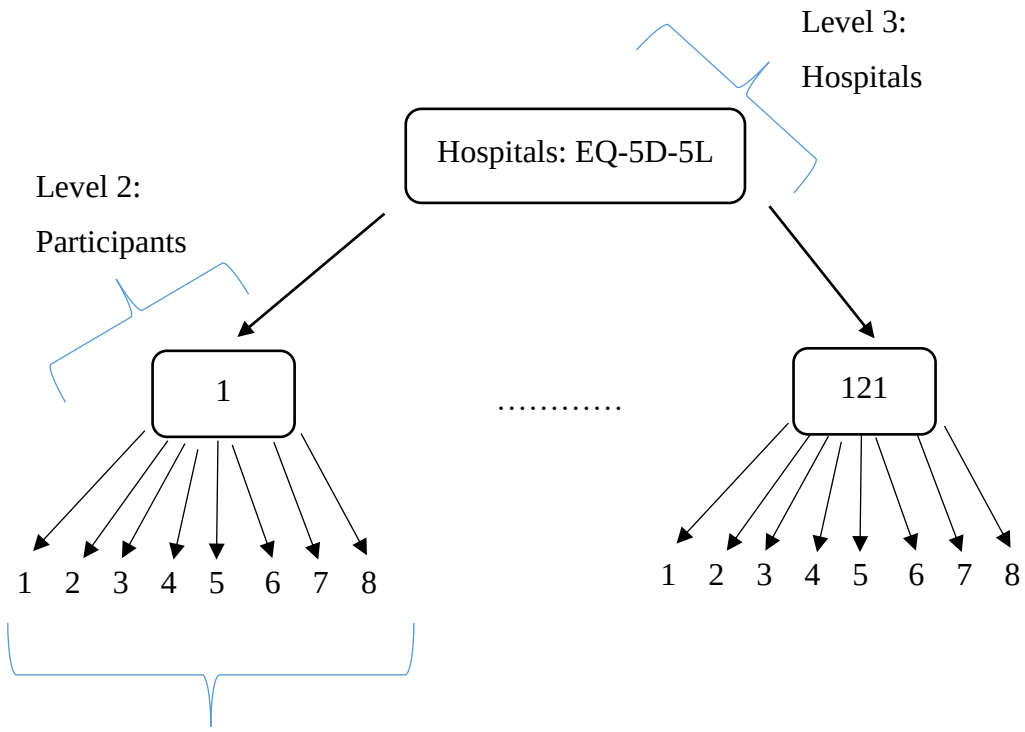
$$\left(0.8 \times \frac{6}{12}\right) - \left(\frac{1}{2} \times 0.086 \times \frac{2}{12}\right) = 0.4 - 0.0072 = 0.3928\ QALYs$$

From the above three estimation scenarios, option 1 is overestimated, as it doesn't take account of the asthma-related crisis event. Option 2, has a more accurate estimation of the QALYs by estimating the QALYs at each month and adding the values together. Option 3 takes a different approach, by estimating the QALYs at two time points (baseline and 6 months), and subtracting the total QALY estimation from the utility loss associated for an asthma-related crisis event.

Measuring quality of life at multiple time points is more accurate because the participant's quality of life is captured more regularly (option 2). However, due to practicality issues, it may not always be possible to ask participant's to complete quality of life questionnaires on such a regular basis. Therefore, an alternative can be used, (option 3), where the average utility loss associated with an asthma-related crisis event (taken from this study) is used alongside the number of asthma-related crisis events that have occurred in the time period for the estimation, assuming the recovery period is 2 months.

As noted, throughout this study there were many repeated measures observed using different PROMs. For example, the EQ-5D-5L questionnaires were asked to be completed at weekly intervals over an 8 week time period, and the AQLQ and TTO were asked to be completed monthly over 8 weeks. The level of repetition within the PROMS and participants observed forms a hierarchal structure as demonstrated in **Figure 40**. However, only two levels were represented in this hierarchal structure, (participants and responses at intervals), because the participant data was combined from across the 3 hospitals.

Figure 40: Multivariate responses presented in a hierarchal structure for EQ-5D-5L



To reflect on the hierarchal structure observed in this study, a multi-level modelling approach was conducted, (following the learning environment for multilevel methodology and applications [LEMMA] online course guidance from the University of Bristol), which aims to make the data more generalizable to a wider population. This approach was taken because it was assumed that the probability that the data is missing is MAR. The approach taken was to first identify the most appropriate model structure to

estimate the EQ-5D-5L, AQL-5D and TTO utility and disutility estimates using the model selection process outlined in **Table 32**.

Table 32: Model selection process

Choosing base model	Run each of the below models separately: • Null model (Random intercept) • Random Intercept fixed slope model • Random slope model • Random polynomial model
	Conduct a log likelihood ratio test between two models to help identify the best model. For example: • Null model and random intercept fixed slope model Or • Random intercept fixed slope model and random slope model
Adding the predictors of missingness to the base model	Once selected best base model, add the predictors of missingness to that model
Adding remaining covariates to the model	Add the best remaining covariate to the model (i.e. if it has stronger statistical significance and a higher log likelihood ratio compared to the other remaining covariates): • Model with predictors of missingness + best remaining covariate
	Add the next best remaining covariate to the model: • Model with predictors of missingness + best remaining covariate + next best remaining covariate
	Adding of the best remaining covariates continues until no further covariates need to be added and a parsimonious model has been achieved.

Firstly, by reshaping the EQ-5D-5L data into a long format, the data can be visualized in a box plot, as shown in **Figure 41**. The box plot shows that there are varying differences amongst the EQ-5D-5L data, due to the lengths of the box and whisker plots and their minimum and maximum values at each time point. The median time point generally increases across the 8 weeks, and some outliers are observed from week 3 to week 8.

Figure 41: Box plot to show the spread of the EQ-5D-5L at weekly time points

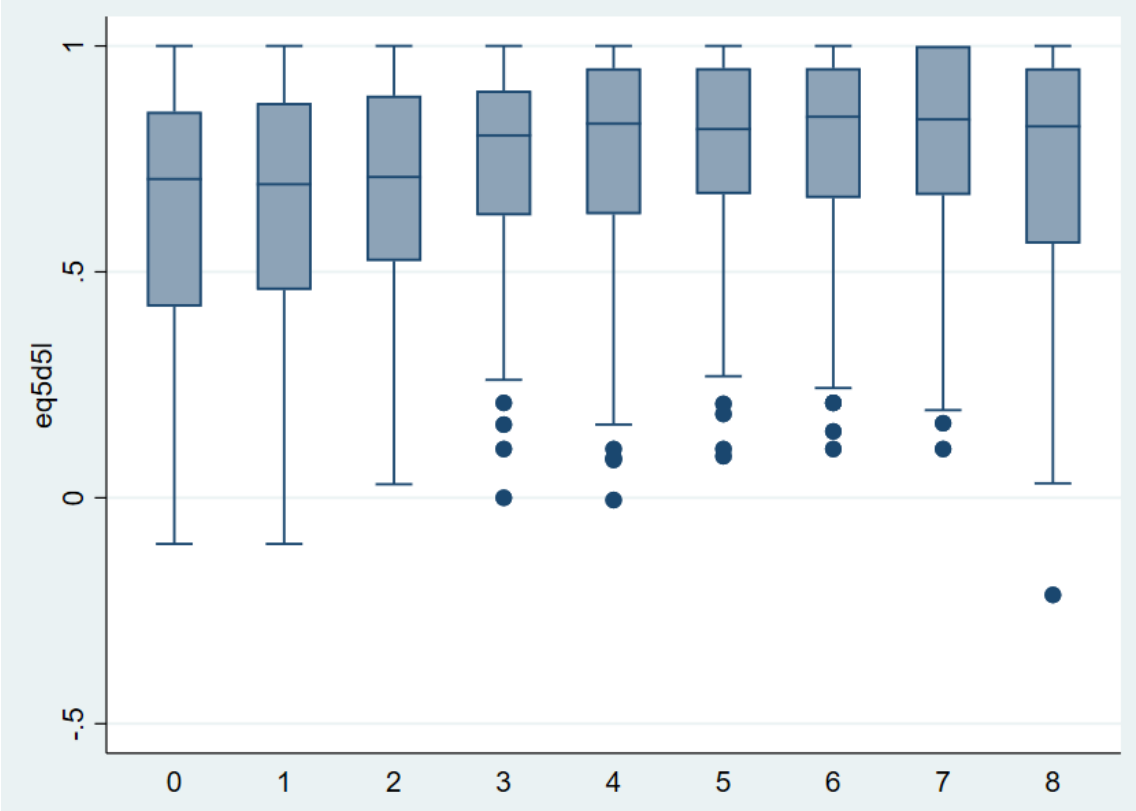


Table 33: Null model (random intercept) for EQ-5D-5L

EQ-5D-5L	Coefficient	Standard error	z	P > |z|	95% confidence interval
Intercept	0.6935	0.0215	32.33	0.000	0.6514 to 0.7355

Log likelihood: 179.99

The null model in **Table 33** illustrates that the intercept coefficient is 0.6935 for the EQ-5D-5L with strong statistical significance and a log likelihood of 179.99. The scatter plot in **Appendix VIII Figure 44** shows the EQ-5D-5L at weekly time points with the null model fitted. The Q-Q plot shown in **Appendix VIII Figure 45** shows there is non-linearity around the predicted fitted values from the null model as the points deviate from the solid line.

Table 34: Random intercept, fixed slope model for EQ-5D-5L

EQ-5D-5L	Coefficient	Standard error	Z	P>|z|	95% CI
Week	0.0153	0.0023	6.71	0.000	0.0108 to 0.0197
Intercept	0.6527	0.0221	29.50	0.000	0.6093 to 0.6961

Log likelihood = 201.68

The random intercept model in **Table 34** illustrates that the intercept coefficient is 0.6527 and the week coefficient is 0.0153 both with strong statistical significance and a log likelihood of 201.68. The scatter plot in **Appendix VIII Figure 46** shows the EQ-5D-5L at weekly time points with the random intercept model fitted. This model shows a more sloped fitted line in comparison to the null model. **Appendix VIII Figure 47** shows there is non-linearity around the predicted fitted values from the random intercept model, as the points deviate from the solid line. A log likelihood ratio test was conducted between the null model and random intercept model which showed a value of 43.38 with strong statistical significance.

Table 35: Random slope model for EQ-5D-5L

EQ-5D-5L	Coefficient	Standard error	Z	P>|z|	95% CI
Week	0.0161	0.0034	4.67	0.000	0.0093 to 0.0228
Intercept	0.6516	0.0222	29.31	0.000	0.6080 to 0.6951

Log likelihood = 221.52

The random slope model in **Table 35** illustrates that the intercept coefficient is 0.6516 and the week coefficient is 0.0161 both with strong statistical significance and a log likelihood of 221.52. The scatter plot in **Appendix VIII Figure 48** shows the EQ-5D-5L at weekly time points with the random slope model fitted. This model shows a more sloped fitted line in comparison to the null model, but a more relaxed slope is assumed in comparison to the random intercept model. **Appendix VIII Figure 49** shows there is non-linearity around the predicted fitted values from the random slope model, as the points deviate from the solid line. A log likelihood ratio test was conducted between the random intercept model and the random slope model which showed a value of 39.68 with strong statistical significance. This indicates that the random slope model is a slightly better fit

compared to the random intercept model. Additionally, the log likelihood value has also increased from the null model to the random slope model.

Table 36: Random polynomial model for EQ-5D-5L

EQ-5D-5L	Coefficient	Standard error	Z	P>|z|	95% CI
Week	0.0454	0.0076	5.99	0.000	0.0306 to 0.0603
Week^2	-0.0039	0.0009	-4.33	0.000	-0.0056 to -0.0021
Intercept	0.6288	0.0228	27.54	0.000	0.5841 to 0.6736

Log likelihood = 230.75

The random polynomial model in **Table 36** illustrates that the intercept coefficient is 0.6288, the week coefficient is 0.0454 and the week^2 coefficient is -0.0039 with strong statistical significance and a log likelihood of 230.75. The scatter plot in **Appendix VIII Figure 51** shows the EQ-5D-5L at weekly time points with the random polynomial model fitted. **Appendix VIII Figure 50** shows there is non-linearity around the predicted fitted values from the random polynomial model, as the points deviate from the solid line. A log likelihood ratio test was conducted between the random slope model and the random polynomial model which showed a value of 18.45 with strong statistical significance. This indicates that the random polynomial model is a much more improved model compared to the random intercept and random slope models. Additionally, the log likelihood value has also largely increased from the null model to the random polynomial model, indicating that the latter random polynomial model has the better model structure. Therefore, the explanatory variables were used to build upon the random polynomial model in a stepwise approach, and **Table 37** summarises the results, which led to choosing the random polynomial model as the best base model.

Table 37: A summary of identifying the best model for the EQ-5D-5L

No. of steps leading to model improvement	Type of model	Log Likelihood value	Log likelihood ratio test (Previous model vs current model)
1	Null model (Random intercept)	179.99	-
2	Random Intercept fixed slope model	201.68	43.38 (Null model vs random intercept fixed slope model)
3	Random slope model	221.52	39.68 (Random intercept fixed slope model vs random slope model)
4	Random polynomial model	230.75	18.45 (Random slope model vs random polynomial model)
5	Random polynomial model + predictors of missingness	239.22	-
6	Random polynomial model + predictors of missingness + gender	240.16*	-
7	Random polynomial model + predictors of missingness + ethnicity	240.68*	-
8	Random polynomial model + predictors of missingness + education status	240.83*	-

*There was no statistical significant difference when adding the covariates. Therefore, the model at step 5 is the preferred parsimonious model.

The model below shows the preferred parsimonious model including the factors predictive of missingness. No other explanatory variables improved the model.

Table 38: Random polynomial model including explanatory variables providing the best model fit for the EQ-5D-5L

EQ-5D-5L	Coefficient	Standard error	Z	P>|z|	95% CI
Week	0.0471	0.0076	6.20	0.000	0.0322 to 0.0620
Week^2	-0.0040	0.0009	-4.45	0.000	-0.0057 to -0.0022
Age centered	-0.0009	0.0018	-0.50	0.616	-0.0044 to 0.0026
Ex smoker ⋕	-0.1342	0.0658	-2.04	0.041	-0.2632 to 0.0052
Never smoked ⋕	-0.1001	0.0663	-1.51	0.131	-0.2300 to 0.0298
Non smoker ⋕	0.0571	0.1850	0.31	0.758	-0.3054 to 0.4196
Full time ǂ	0.2088	0.0618	3.38	0.001	0.0877 to 0.3299
Part timeǂ	0.1768	0.0702	2.52	0.012	0.0392 to 0.3143
Retired ǂ	0.1614	0.0750	2.15	0.031	0.0144 to 0.3084
Home ǂ	0.1389	0.0911	1.52	0.127	-0.0397 to 0.3175
Student ǂ	0.2369	0.1246	1.90	0.057	0.0072 to 0.4811
Intercept	0.5762	0.0663	8.70	0.000	0.4463 to 0.7061

Log likelihood = 239.22

Dummy variables comparators: ǂ Unemployed, ⋕ Smoker

The model above in **Table 38** shows that on average the baseline EQ-5D-5L utility value is 0.5762, increasing by 0.0471 each week for someone who is unemployed and a smoker. Additionally, bootstrapping could also be considered to estimate the disutility of an asthma attack. This is a method which is used to estimate confidence intervals of a population mean by resampling some data from a larger dataset randomly with replacement. It is appropriate to use a bootstrap method to check the stability of the results. **Table 39** below shows the EQ-5D-5L QALY disutility for someone who has an asthma attack over 8 weeks. The QALY disutility was estimated by using the EQ-5D-5L time points at baseline, week 4 and week 8, using the algebra below.

$U_t = B_0 + B_1.t + B_2.t^2$

Utility scores at weeks 0, 4 and 8

$U_0 = B_0$

$U_4 = B_0 + B_1.4 + B_2.4^2$

$U_8 = B_0 + B_1.8 + B_2.8^2$

Average Utility in weeks 0-8

$$\bar{U} = \frac{1}{2}\left(\frac{U_0+U_4}{2} + \frac{U_4+U_8}{2}\right) = \frac{U_0}{4} + \frac{U_4}{2} + \frac{U_8}{4}$$

$$= \frac{B_0}{4} + \frac{B_0+4B_1+16B_2}{2} + \frac{B_0+8B_1+64B_2}{4}$$

$= B_0 + 4.B_1 + 24.B_2$

Average Disutility in weeks 0-8 (assuming week 8 is 'normal')

$U_{D^-} = U_8 - \bar{U} = (B_0 + 8.B_1 + 64.B_2) - (B_0 + 4.B_1 + 24.B_2)$

$= 4.B_1 + 40.B_2$

QALY disutility

$Q_{D^-} = \frac{8}{52}(4.B_1 + 40.B_2)$

Table 39: EQ-5D-5L QALY disutility using bootstrapping

EQ-5D-5L	Coefficient	Standard error	T	P>|t|	95% CI
QALY disutility	0.0045	0.0020	2.31	0.021	0.0007 to 0.0084

Table 40 shows the EQ-5D-5L disutility estimate when exploring the impact of baseline utility. This estimate does not hugely differ from **Table 39**.

Table 40: EQ-5D-5L QALY disutility using bootstrapping: exploring the impact of baseline quality of life on the disutility estimate

EQ-5D-5L	Coefficient	Standard error	T	P>|t|	95% CI
QALY disutility	0.0044	0.0020	2.23	0.025	0.0005 to 0.0083

Multiple imputation is an additional method that can be used to increase the robustness of the results as it replaces the missing data from the available case dataset with values, and this in turn reduces the standard error and increases the precision of the estimations. Therefore, the EQ-5D-5L QALY disutility was estimated using the same polynomial model as estimated in **Table 38**, but with the additional consideration of multiple imputation. **Table 41** shows that the QALY disutility is 0.0075 compared to the bootstrap QALY disutility observed as 0.0045 in **Table 39**.

Table 41: EQ-5D-5L QALY disutility using multiple imputation

EQ-5D-5L	Coefficient	Standard error	T	P>|t|	95% CI
QALY disutility	0.0075	0.0027	2.77	0.006	0.0021 to 0.0128

The AQL-5D utility values were explored in the same way as the EQ-5D-5L by estimating the most appropriate hierarchal model to estimate the values needed to estimate the disutility of an asthma attack over an 8 week time period. Firstly, the AQL-5D data was visually displayed using the box plots as observed in **Figure 42.** The box plot showed that the median time points had gradually increased over the 8 weeks. All time points had the same minimum values, but a smaller range of values were observed at baseline compared to week 4 and week 8 which had larger ranges with the maximum utility value reaching 1.0.

Figure 42: A box plot to show the distribution of AQL-5D across 8 weeks.

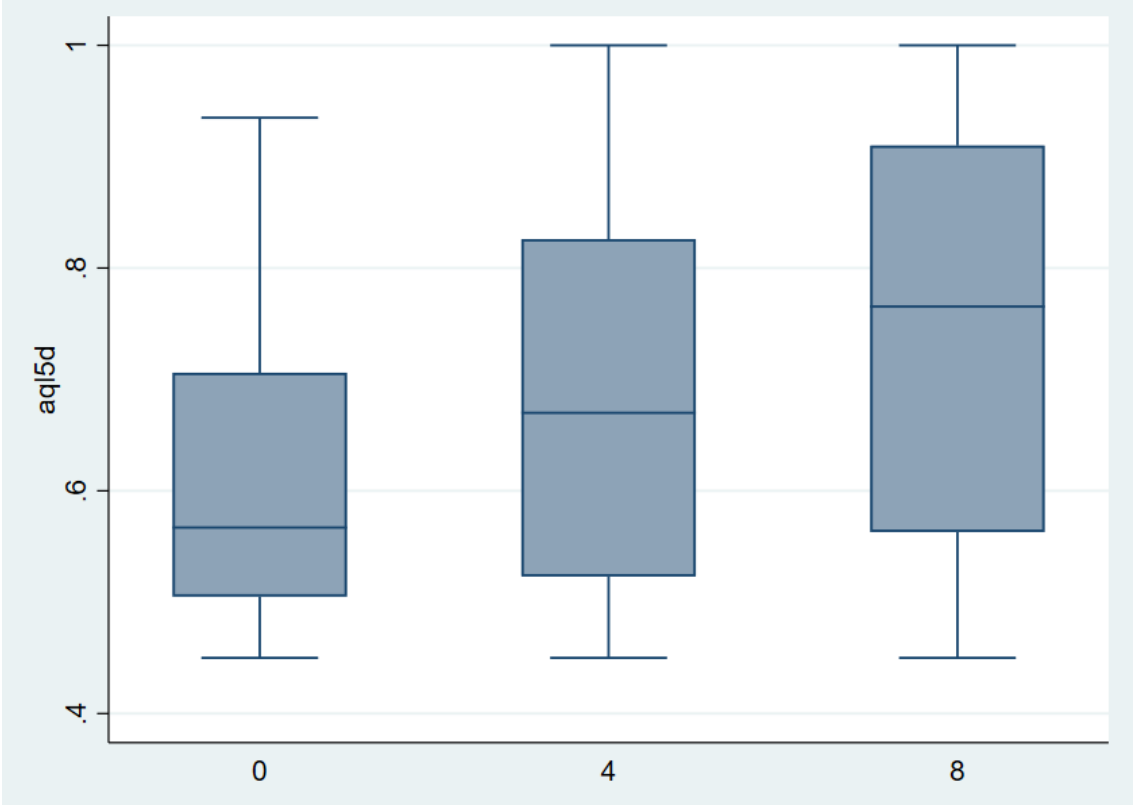


Table 42: Null model for AQL-5D

AQL-5D	Coefficient	Standard error	Z	P>|z|	95% CI
Intercept	0.6602	0.0124	53.45	0.000	0.6360 to 0.6844

Log likelihood = 115.52

The null model in **Table 42** illustrates that the intercept coefficient is 0.6602 for the AQL-5D with strong statistical significance and a log likelihood of 115.52. The scatter plot in **Appendix VIII Figure 52** shows the AQL-5D at monthly time points with the null model fitted. The Q-Q plot shown in **Appendix VIII Figure 53** shows there is some non-linearity around the predicted fitted values from the null model as the points deviate slightly from the solid line.

Table 43: Random intercept, fixed slope model for AQL-5D

AQL-5D	Coefficient	Standard error	Z	P>|z|	95% CI
Week	0.0174	0.0022	8.01	0.000	0.0132 to 0.0217
Intercept	0.6122	0.0135	45.27	0.000	0.5857 to 0.6388

Log likelihood = 142.08

The random intercept model in **Table 43** illustrates that the intercept coefficient is 0.6122 and the week coefficient is 0.0174 both with strong statistical significance and a log likelihood of 142.08. The scatter plot in **Appendix VIII Table 54** shows the AQL-5D at monthly time points with the random intercept model fitted. This model shows a more sloped fitted line in comparison to the null model. **Appendix VIII Figure 55** shows there is non-linearity around the predicted fitted values from the random intercept model, as the points deviate from the solid line. However, the fit is better compared to the null model. A log likelihood ratio test was conducted between the null model and random intercept model which showed a value of 53.12 with strong statistical significance.

Table 44: Random slope model for AQL-5D

AQL-5D	Coefficient	Standard error	Z	P>|z|	95% CI
Week	0.0176	0.0024	7.27	0.000	0.0129 to 0.0224
Intercept	0.6123	0.0118	52.00	0.000	0.5892 to 0.6353

Log likelihood = 148.83

The random slope model in **Table 44** illustrates that the intercept coefficient is 0.6123 and the week coefficient is 0.0176 both with strong statistical significance and a log likelihood of 148.83. The scatter plot in **Appendix VIII Figure 56** shows the AQL-5D at monthly time points with the random slope model fitted. This model shows a more sloped fitted line in comparison to the null model, but a more relaxed slope is assumed in comparison to the random intercept model. **Appendix VIII Figure 57** shows there is non-linearity around the predicted fitted values from the random slope model, as the points deviate from the solid line. There is more non-linearity observed in this model compared to the other null and random models. A log likelihood ratio test was conducted between

the random intercept model and the random slope model which showed a value of 13.49 with strong statistical significance. This indicates that the random slope model is a much better fit compared to the random intercept model. Additionally, the log likelihood value has also increased from the null model to the random slope model.

Table 45: Random polynomial model for AQL-5D

AQL-5D	Coefficient	Standard error	Z	P>|z|	95% CI
Week	0.0272	0.0073	3.71	0.000	0.0128 to 0.0417
Week^2	-0.0013	0.0009	-1.39	0.163	-0.0030 to 0.0005
Intercept	0.6085	0.0121	50.15	0.000	0.5847 to 0.6323

Log likelihood = 149.75

The random polynomial model in **Table 45** illustrates that the intercept coefficient is 0.6085, the week coefficient is 0.0272 and the week^2 coefficient is -0.0013 with strong statistical significance for the intercept and week variable. The log likelihood was 149.75. The scatter plot in **Appendix VIII Figure 58** shows the AQL-5D at monthly time points with the random polynomial model fitted. **Appendix VIII Figure 59** shows there is non-linearity around the predicted fitted values from the random polynomial model, as the points deviate from the solid line. A log likelihood ratio test was conducted between the random slope model and the random polynomial model which showed a value of 1.84. However, there was no statistical significant difference observed from the log likelihood ratio test and from the week^2 variable. Therefore, the explanatory variables were used to build upon the random slope model in a stepwise approach, and **Table 46** summarises the results, which led to choosing the random slope model as the best base model.

Table 46: A summary of identifying the best model for the AQL-5D

No. of steps leading to model improvement	Type of model	Log Likelihood value	Log likelihood ratio test (Previous model vs Current model)
1	Null model (Random intercept)	115.52	-
2	Random Intercept fixed slope model	142.08	53.12 (Null model vs random intercept fixed slope model)
3	Random slope model	148.83	13.49 (Random intercept fixed slope model vs random slope model)
4	Random polynomial model	149.75	1.84 (Random slope model vs random polynomial model)*
5	Random slope model + predictors of missingness	156.12	-
6	Random slope model + predictors of missingness + gender	156.96**	-
7	Random slope model + predictors of missingness + ethnicity	156.68**	-
8	Random slope model + predictors of missingness + education status	155.36**	-

*No statistical significance observed, so random slope model preferred.

****** There was no statistical significant difference when adding the covariates. Therefore, the model at step 5 is the preferred parsimonious model.

The model below shows the preferred parsimonious model with the included explanatory variables for the AQL-5D.

Table 47: Random slope model including explanatory variables providing the best model fit for the AQL-5D

AQL-5D	Coefficient	Standard error	Z	P>|z|	95% CI
Week	0.0178	0.0024	7.36	0.000	0.0131 to 0.0226
Age centered	-0.0004	0.0010	-0.46	0.642	-0.0023 to 0.0014
Ex smoker ǂ	-0.1150	0.0361	-3.18	0.001	-0.1858 to -0.0442
Never smoked ǂ	-0.0809	0.0361	-2.24	0.025	-0.1515 to -0.0102
Non smoker ǂ	-0.1646	0.0944	-1.74	0.081	-0.3496 to 0.0204
Full time ǂǂ	-0.0229	0.0342	-0.67	0.504	-0.0900 to 0.0442
Part time ǂǂ	-0.0299	0.0387	-0.77	0.440	-0.1058 to 0.0460
Retired ǂǂ	0.0108	0.0420	0.26	0.797	-0.0715 to 0.0931
Home ǂǂ	-0.0500	0.0496	-1.01	0.313	-0.1471 to 0.0471
Student ǂǂ	-0.0501	0.0676	-0.74	0.458	-0.1826 to 0.0824
Intercept	0.7106	0.0369	19.26	0.000	0.6382 to 0.7829

Log likelihood = 156.12

Dummy variables comparators: ǂ Smoker, ǂǂ unemployed

The model above in **Table 47** shows that on average the baseline AQL-5D utility value is 0.7106, increasing by 0.0178 monthly for someone who is a smoker and unemployed.

Additionally, bootstrapping could also be considered to estimate the disutility of an asthma attack. **Table 48** below shows the AQL-5D QALY disutility for someone who has an asthma attack over 8 weeks. The QALY disutility was estimated by using the AQL-5D time points at baseline, week 4 and week 8.

Table 48: AQL-5D QALY disutility using bootstrapping

AQL-5D	Coefficient	Standard error	T	P>|t|	95% CI
QALY disutility	0.0110	0.0016	7.07	0.000	0.0079 to 0.0140

Table 49 shows the AQL-5D disutility estimate when exploring the impact of baseline utility. This estimate does not differ from **Table 48**.

Table 49: AQL-5D QALY disutility using bootstrapping: exploring the impact of baseline quality of life on the disutility estimate

AQL-5D	Coefficient	Standard error	T	P>|t|	95% CI
QALY disutility	0.0110	0.0016	6.75	0.000	0.0078 to 0.0142

Multiple imputation is an additional method that can be used to increase the robustness of the results as it replaces the missing data from the available case dataset with values, and this in turn reduces the standard error and increases the precision of the estimations. Therefore, the AQL-5D QALY disutility was estimated using the same random slope model as estimated in **Table 47**, but with the additional consideration of multiple imputation. **Table 50** shows that the QALY disutility is 0.0096 compared to the bootstrap QALY disutility which is observed as 0.0110 in **Table 48**.

Table 50: AQL-5D QALY disutility using multiple imputation

AQL-5D	Coefficient	Standard error	T	P>|t|	95% CI
QALY disutility	0.0096	0.0018	5.23	0.000	0.0057 to 0.0135

The TTO utility values were explored in the same way as the EQ-5D-5L and AQL-5D by estimating the most appropriate hierarchal model to estimate the values needed to

estimate the disutility of an asthma attack over an 8 week time period. Firstly, the TTO data was visually displayed using the box plots as observed in **Figure 43.** The box plot showed that the median time points had increased from baseline to week 4 and week 8. The minimum values varied, with baseline holding the lowest minimum value, followed by week 8 and week 4. However, there were some anomalies in the data set observed at week 4 and week 8.

Figure 43: A box plot to show the distribution of TTO across 8 weeks.

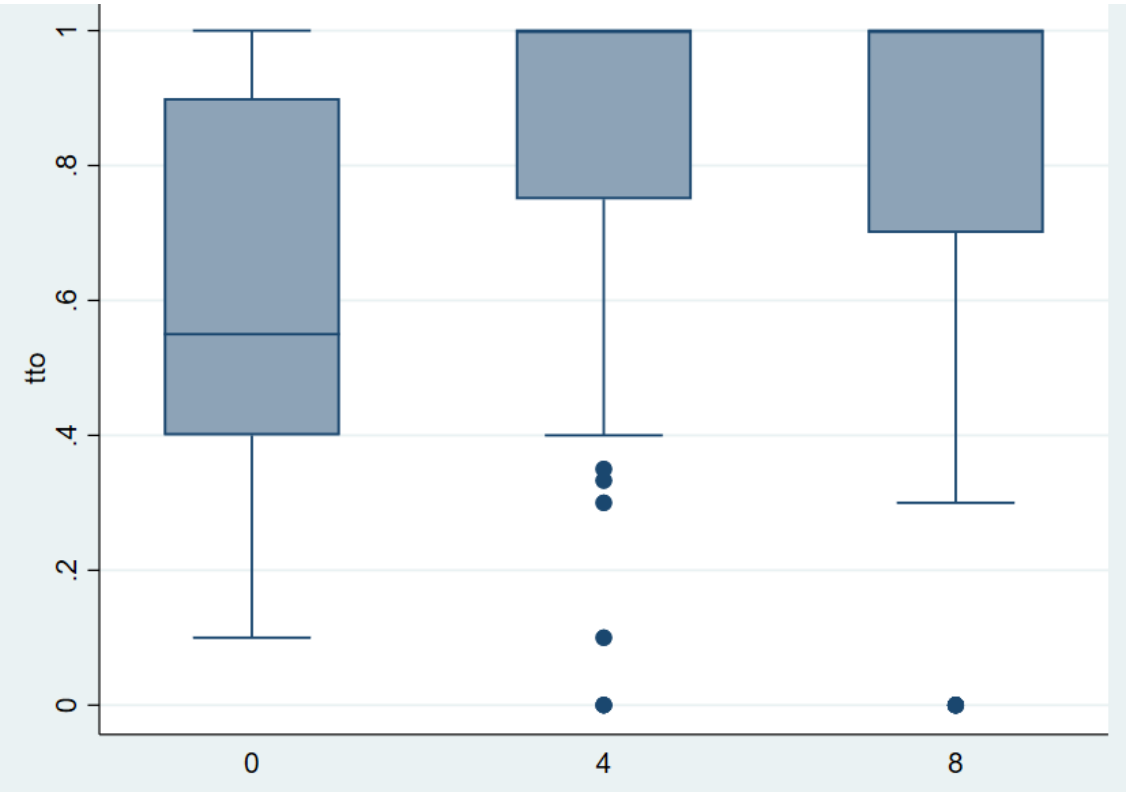


Table 51: Null model for TTO

AQL-5D	Coefficient	Standard error	Z	P>|z|	95% CI
Intercept	0.7247	0.0214	33.86	0.000	0.6827 to 0.7666

Log likelihood = -41.41

The null model in **Table 51** illustrates that the intercept coefficient is 0.7247 for the TTO with strong statistical significance and a log likelihood of -41.41. The scatter plot in

Appendix VIII Figure 60 shows the TTO at monthly time points with the null model fitted. The Q-Q plot shown in **Appendix VIII Figure 61** shows there is some non-linearity around the predicted fitted values from the null model as the points deviate slightly from the solid line.

Table 52: Random intercept, fixed slope model for TTO

AQL-5D	Coefficient	Standard error	Z	P>|z|	95% CI
Week	0.0203	0.0043	4.69	0.000	0.0118 to 0.0288
Intercept	0.6555	0.0256	25.61	0.000	0.6053 to 0.7057

Log likelihood = -30.88

The random intercept model in **Table 52** illustrates that the intercept coefficient is 0.6555 and the week coefficient is 0.0203 both with strong statistical significance and a log likelihood of -30.88. The scatter plot in **Appendix VIII Figure 62** shows the TTO at monthly time points with the random intercept model fitted. This model shows a more sloped fitted line in comparison to the null model. **Appendix VIII Figure 63** shows there is non-linearity around the predicted fitted values from the random intercept model, as the points near the tail ends deviate from the solid line. However, the fit is better compared to the null model. A log likelihood ratio test was conducted between the null model and random intercept model which showed a value of 21.06 with strong statistical significance.

Table 53: Random slope model for TTO

AQL-5D	Coefficient	Standard error	Z	P>|z|	95% CI
Week	0.0203	0.0044	4.61	0.000	0.0117 to 0.0289
Intercept	0.6555	0.0243	26.98	0.000	0.6079 to 0.7031

Log likelihood = -30.16

The random slope model in **Table 53** illustrates that the intercept coefficient is 0.6555 and the week coefficient is 0.0203 both with strong statistical significance and a log likelihood of -30.16. The scatter plot in **Appendix VIII Figure 64** shows the TTO at monthly time points with the random slope model fitted. This model shows a more sloped fitted line in comparison to the null model, but a more relaxed slope is assumed in comparison to the random intercept model. **Appendix VIII Figure 65** shows there is non-linearity around the predicted fitted values from the random slope model, as the points deviate from the solid line. A log likelihood ratio test was conducted between the random intercept model and the random slope model, which showed a value of 1.44 without a strong statistical significant difference. Additionally, the log likelihood value has also increased from the null model to the random slope model.

Table 54: Random polynomial model for TTO

AQL-5D	Coefficient	Standard error	Z	P>|z|	95% CI
Week	0.0725	0.0149	4.85	0.000	0.0432 to 0.1018
Week^2	-0.0067	0.0018	-3.65	0.000	-0.0103 to -0.0031
Intercept	0.6275	0.0250	25.08	0.000	0.5785 to 0.6766

Log likelihood = -23.69

The random polynomial model in **Table 54** illustrates that the intercept coefficient is 0.6275, the week coefficient is 0.0725 and the week^2 coefficient is -0.0067 with strong statistical significance for the intercept and week variable. The log likelihood was -23.69. The scatter plot in **Appendix VIII Figure 66** shows the TTO at monthly time points with the random polynomial model fitted. **Appendix VIII Figure 67** shows there is non-linearity around the predicted fitted values from the random polynomial model, as the points deviate from the solid line. A log likelihood ratio test was conducted between the random slope model and the random polynomial model which showed a value of 12.94 with strong statistical significance. The log likelihood ratio is higher in this model but has a stronger statistical significance compared to the previous random slope model. Additionally, the log likelihood value has also increased from the null model to the random polynomial model, indicating that the latter random polynomial model has the better model structure. Therefore, the explanatory variables were used to build upon the

random polynomial model in a stepwise approach, and **Table 55**, summarises the results, which led to choosing the random polynomial model as the best base model.

Table 55: A summary of identifying the best model for the TTO

No. of steps leading to model improvement	Type of model	Log Likelihood value	Log likelihood ratio test (Previous model vs current model)
1	Null model (Random intercept)	-41.41	-
2	Random Intercept fixed slope model	-30.88	21.06 (Null model vs random intercept fixed slope model)
3	Random slope model	-30.16	1.44 (Random intercept fixed slope model vs random slope model)
4	Random polynomial model	-23.69	12.94 (Random slope model vs random polynomial model)
5	Random polynomial model + predictors of missingness	-18.98	-
6	Random polynomial model + predictors of missingness + gender	-18.52*	-
7	Random polynomial model + predictors of missingness + ethnicity	-18.63*	-
8	Random polynomial model + predictors of missingness + education status	-18.75*	-

* There was no statistical significant difference when adding the covariates. Therefore, the model at step 5 is the preferred parsimonious model.

The model below shows the preferred parsimonious model with the included explanatory variables for the TTO.

Table 56: Random polynomial model including explanatory variables providing the best model fit for the TTO

TTO	Coefficient	Standard error	Z	P>|z|	95% CI
Week	0.0716	0.0149	4.80	0.000	0.0424 to 0.1009
Week^2	-0.0067	0.0018	-3.64	0.000	-0.0102 to -0.0031
Age centered	0.0041	0.0017	2.39	0.017	0.0007 to 0.0075
Ex smoker ǂ	0.0374	0.0649	0.58	0.564	-0.0897 to 0.1646
Never smoked ǂ	0.0096	0.0667	0.14	0.886	-0.1212 to 0.4122
Non smoker ǂ	0.0699	0.1746	0.40	0.689	-0.2724 to 0.4122
Full time ǂǂ	0.0303	0.0637	0.47	0.635	-0.0947 to 0.1552
Part time ǂǂ	0.0902	0.0751	1.20	0.229	-0.0569 to 0.2374
Retired ǂǂ	-0.0899	0.0768	-1.217	0.242	-0.2404 to 0.0606
Home ǂǂ	0.1318	0.0899	1.47	0.143	-0.0445 to 0.3080
Student ǂǂ	0.0599	0.1216	0.49	0.622	-0.1785 to 0.2983
Intercept	0.5996	0.0663	9.05	0.000	0.4698 to 0.7295

Log likelihood = -18.98

Dummy variables comparators: ǂ Smoker, ǂǂ Unemployed

The model above in **Table 56** shows that on average the baseline TTO utility value is 0.5996, increasing by 0.0716 monthly for someone who is of average age, a smoker and unemployed.

Additionally, bootstrapping could also be considered to estimate the disutility of an asthma attack. **Table 57** below shows the TTO QALY disutility for someone who has an asthma attack over 8 weeks. The QALY disutility was estimated by using the TTO time points at baseline, week 4 and week 8.

Table 57: TTO QALY disutility using bootstrapping

TTO	Coefficient	Standard error	T	P>|t|	95% CI
QALY disutility	0.0031	0.0045	0.70	0.485	-0.0057 to 0.0119

Table 58 shows the TTO disutility estimate when exploring the impact of baseline utility. This estimate does not differ from **Table 57**.

Table 58: TTO QALY disutility using bootstrapping: exploring the impact of baseline quality of life on the disutility estimate

TTO	Coefficient	Standard error	T	P>|t|	95% CI
QALY disutility	0.0031	0.0047	0.67	0.505	-0.0061 to 0.0123

Multiple imputation is an additional method that can be used to increase the robustness of the results as it replaces the missing data from the available case dataset with values, and this in turn reduces the standard error and increases the precision of the estimations. Therefore, the TTO QALY disutility was estimated using the same polynomial model as estimated in **Table 56**, but with the additional consideration of multiple imputation. **Table 59** shows that the QALY disutility is 0.0035 compared to the bootstrap QALY disutility observed as 0.0031 in **Table 57**.

Table 59: TTO QALY disutility using multiple imputation

TTO	Coefficient	Standard error	T	P>|t|	95% CI
QALY disutility	0.0035	0.0033	1.05	0.297	-0.0031 to 0.0101

4.3.5 Productivity loss

Participants were asked to complete the productivity questionnaire at week 4 of the study. Out of the total number of participants recruited (N = 121), 47 participants (38.84%) did not post back their productivity questionnaires. For those that completed the questionnaire, participants varied in their responses relating to how they thought their asthma was at four weeks compared to when they were in hospital four weeks ago. When asked to respond either 'yes' or 'no', 36.37% (N = 44) thought they hadn't recovered from when they were in hospital four weeks ago, and 24.79% (N = 30) thought they had. Therefore, this meant that 59.5% of respondents $(44 \div 74)$ thought they hadn't recovered from when they were in hospital four weeks ago, and 40.5% of respondents $(30 \div 74)$ thought they had. However, a further question showed more variation in the breakdown of the responses, when asked to rate their asthma at four weeks compared to how they were when in hospital by using options of poor, moderate, good and very good. Nine participants (7.44%), reported that their asthma was in a poor condition compared to when they were in hospital 4 weeks ago, 28 (23.14%) reported that their asthma was in a moderate condition, 20 (16.53%) reported that their asthma was in a good condition and 17 (14.05%) reported that their asthma was in a very good condition.

From completion of the demographics questionnaire, it was found that 33 participants were in full-time employment (27.50%) and 19 participants were in part-time employment (15.83%) out of the 121 participants recruited. However, out of the 52 participants in employment, only 33 participants responded to the productivity questionnaire at week 4 of the study. Of those who responded to the productivity questionnaire, 21 participants (17.35%) had returned back to work by week 4 of the study and 12 participants (9.92%) had not returned back to work. On average, the number of hours worked per week (for those only in employment) before the asthma-related crisis event was 36.10 hours (N=24 respondents), and the average number of hours worked per week (for those only in employment) after the asthma-related crisis event was 25.11 hours (N=23 respondents). Assuming that these average number of hours worked per week applied to each of the four weeks, the productivity loss in working hours per week was:

$$36.10 - 25.11 = 10.99\ hours$$

Taking into account the average weekly earnings (£503.00) (Office for National Statistics, 2017c) and the average number of hours worked in a week in the UK (31 hours reduced by part-time work) (Office for National Statistics, 2017a, Francis, 2017), this estimated to a total of £713.29 lost in productivity over the four weeks since their asthma-related crisis event for those in employment (see equation below).

$$\frac{(10.99\ hours\ \times 4\ weeks)}{31\ hours} \times £503.00 = £713.29$$

However, since the proportion of participants in employment was 43.33% (27.50% + 15.83%), the average productivity loss per person is $£713.29\ \times 0.4333 = £309.07$.

In addition to the above, 13 participants (10.74%) had purchased additional products after their asthma-related crisis event, that they would not have otherwise purchased prior to their event. From the 13 participants, this averaged out to be £95.74 per participant for the additional products, which included items such as; allergy free pillows, allergy free duvets, and humidifiers. In this case, the whole cost of the additional aforementioned items were considered in the out-of-pocket costs due to participants only purchasing new pillows and duvets because of their asthma-related crisis event.

Since 13 participants reported purchasing additional products, out of the 74 respondents of the productivity questionnaire, the above cost is weighted accordingly. This means that the additional out of pocket costs per person is:

$$£95.74\ x\ \frac{13}{74} = £16.82$$

Therefore, in total, the average societal loss in the first four weeks per person was:

$$£309.07\ + £16.82 = £325.89$$

4.4 Discussion

This study explored the quality of life in people with acute asthma who attended A&E or were admitted to hospital with an asthma attack. The aim of this study was to identify the loss in quality of life associated with these events, by asking the participants to complete several PROMs over a period of 8 weeks at different time points. The PEF and symptom diary was asked to be completed daily, the EQ-5D-5L weekly, and the AQLQ and TTO monthly. The demographics questionnaire and productivity questionnaire were asked to be completed at baseline and week 4 of the study respectively. Values were converted into utility scores where appropriate and comparisons were made by statistical analysis.

4.4.1 Summary of findings

Within all three hospital sites, 121 participants were recruited into the study, with approximately 50% lost to follow up over the 8 week study time period. Most of the loss associated with an asthma-related crisis event occurred during the first four weeks of the study, as the statistical analysis demonstrated that there was a strong statistical significance for the mean changes between baseline and week 4 for all PROMs at the 1% level. The EQ-5D-5L and the AQLQ also exceeded their minimal important difference between baseline and week 4.

The best structural multi-level model for the EQ-5D-5L and the TTO was the random polynomial model, and for the AQL-5D it was the random slope model. These models were used to find the preferred parsimonious models by using stepwise methodology. When using multiple imputation on these models, the QALY disutilities associated with an asthma-related crisis event over an 8 week time period for the EQ-5D-5L, AQL-5D and TTO were 0.0075, 0.0096 and 0.0035 respectively.

Not all participants had completely recovered from their asthma-related crisis event by the week 4 time point. Just over a third thought they hadn’t completely recovered from their asthma-related crisis event, which corresponds with the responses from the TTO at week 8 of the study, as nearly a third had a utility value of less than 1. Nearly a quarter of the participants thought that their asthma was in a poor condition compared to when they were in hospital. Approximately a quarter of those who were in full-time or part-time employment (43.33%) hadn’t returned back to work by the week 4 time point. The

societal loss (loss of productivity plus out of pocket) averaged at £325.89 per person over the first four weeks.

4.4.2 Comparison with other studies

In comparison with an earlier study that analysed HRQL in asthmatics over a four week time period, their utility loss estimation for someone who was recruited at baseline from an outpatient clinic or in primary care, and was hospitalized with an acute asthma attack was 0.20 for the EQ-5D (Lloyd et al., 2007). However, for this current ESQUARE study the estimated utility loss over four weeks was 0.127 for the EQ-5D. It should be noted, that the earlier study EQ-5D estimation was based on the 3 level version (Lloyd et al., 2007), compared to this study being based on the 5 level version, where the 5 level aims to improve sensitivity (Herdman et al., 2011). It is interesting that the earlier study estimated a utility loss which was reasonably higher than that of this current study, however that could be a result of overestimation, as the patients were not experiencing an asthma attack at the point at which they were recruited into the study (Lloyd et al., 2007), or it could be due to differences in the valuation methods of the EQ-5D-3L and EQ-5D-5L. The patients were recruited from outpatient clinics and primary care, and even though every effort was made to recruit patients with an exacerbation history, all the patients recruited were not experiencing an exacerbation at the time of recruitment (Lloyd et al., 2007). For this study, if participants were asked to complete the HRQL questionnaires at week 8 only, and not in between this time point (i.e. at week 4), then the utility loss would have been overestimated. This assumption of overestimation is because most of the quality of life improvement was observed in the first four weeks of the study, with very small changes seen past this time point that were not statistically significantly different.

Additionally, the ceiling effects for the TTO were fairly high to begin with at baseline (18.8%), and then increased at week 4 and week 8 to 51.7% and 51.3% respectively. Even though the mean TTO utility value was close in value to the other PROMs at baseline, the high ceiling effect at baseline could be dependent on other factors as the TTO is more of a scenario-based question on number of life years compared to the other PROMs. For example, the participants' trade off may be dependent on marital status and age (Sayah et al., 2016), or it may be dependent on whether a particular medication will still be administered to them (Hyland et al., 2015), or it may be that the enjoyment of life through children, friends, and other social affairs has a greater impact and is of more importance

than their illness (Arnesen and Norheim, 2003). The steep rise in ceiling effect at week 4 and week 8 was expected, as with improvements in asthma quality of life, it was expected that the participants would not want to trade any life years.

For the multi-level models, the employment status was a predictor of the EQ-5D-5L estimation, and this is in line with other studies where being in employment and working full-time is associated with less symptoms and better quality of life compared to being unemployed (Taponen et al., 2017, Dimich-Ward et al., 2007). However, as stress can be a factor of asthma attacks, it has been found that over commitment at work can lead to poorer quality of life (Hartmann et al., 2017), and so striking a good work-life balance is essential.

4.4.3 Strengths and limitations

There are a number of strengths from this study. The participants were recruited over a whole year from three hospital sites, which enhanced the generalisability of the collected data. Data was entered by double entry for 10% of the collected data, with errors reported to be minimal (0.003), therefore enhancing the accuracy of the dataset. Another strength was that several PROMs were used in this study to gain a more comprehensive perspective on quality of life in people with acute asthma.

A number of limitations arose from this study. Firstly, the peak of the asthma-related crisis event occurred before attendance to A&E or admission to hospital for most participants, indicating that the initial decrease in quality of life (whether that be gradual or sudden), occurred before the baseline point in this study. Therefore, the true time point for those participants' who were at their worst before attending A&E or being admitted to hospital has not been recorded in this instance. Secondly, the retention rate for this study was problematic, with a large proportion of participants lost to follow up. The low retention rate could have been because the study time period was too long for participants to complete several questionnaires (Lloyd et al., 2007), or that a large number of asthmatics are often non-compliant (Gul and Ali, 2010, Mattei, 2012) with taking their medications, making compliance with a study less likely too. Thirdly, selection bias was reduced by visiting the hospital daily on weekdays, (both in A&E and on the hospital wards) during the recruitment period of one year, to capture as many potential participants as possible.

4.4.4 Recommendations for future

In light of the results given, the EQ-5D-5L and AQL-5D provide closely matched utility values based on a generic questionnaire and a disease specific questionnaire. However, there is some ambiguity over whether the EQ-5D-5L is appropriate to be used by NICE (NICE, 2017), and it is recommended that further research be conducted to explore whether the recent valuation set of the EQ-5D-5L (Devlin et al., 2016) should be adopted in the NICE reference case. NICE currently recommend that the utility values from the EQ-5D-5L should be mapped onto the EQ-5D-3L using a preferred mapping function (van Hout et al., 2012) for consistency until further review (NICE, 2017).

Nevertheless, future studies can benefit from this research by counting the number of asthma-related crisis events and assigning a QALY loss to each occurrence. For example, if using the EQ-5D-5L or the AQL-5D, the utility loss was 0.127 or 0.099 respectively over four weeks for an asthma related crisis event (**Table 24**), and so these values could be used in modelling. This could also be useful for use in previous studies, by expanding upon work already conducted. For example, an asthma study which investigated at-risk asthma by using registers in GP practices for their intervention (Smith et al., 2012), could estimate that the mean QALY loss per participant associated with crisis events for their intervention and control groups was 0.215 and 0.322 respectively using the EQ-5D-5L, and 0.168 and 0.251 respectively using the AQL-5D. The calculations for the intervention and control group mean QALY loss estimations are as follows using the EQ-5D-5L utility estimation loss first, followed by the AQL-5D utility estimation loss second:

$$QALY\ loss\ for\ intervention\ group: (15\ + 29) \times \left(\frac{1}{2} \times\ 0.127\ \times \frac{4}{52}\right) = 0.215$$

$$QALY\ loss\ for\ control\ group: (29\ + 37) \times \left(\frac{1}{2} \times 0.127\ \times\ \frac{4}{52}\right) = 0.322$$

$$QALY\ loss\ for\ intervention\ group: (15\ + 29) \times \left(\frac{1}{2} \times\ 0.099\ \times \frac{4}{52}\right) = 0.168$$

$$QALY\ loss\ for\ control\ group: (29\ + 37) \times \left(\frac{1}{2} \times 0.099\ \times\ \frac{4}{52}\right) = 0.251$$

Note, intervention group: hospitalisation for asthma exacerbation (N = 15) and A&E attendance for asthma exacerbation (N = 29).

Control group: hospitalisation for asthma exacerbation (N = 29) and A&E attendance for asthma exacerbation (N = 37).

Both equations show the addition of the number of hospitalizations and A&E attendances in 1 year multiplied by the area under the curve for asthma-related crisis events. By incorporating the utility loss value into estimations, this will enhance the area under the curve estimation when comparing a new intervention with another product or usual care, and may in fact alter the end result (i.e. the incremental cost effectiveness ratio).

Alternatively, the QALY loss estimated from the multi-level modelling over 8 weeks can be applied to modelling studies. The best models were a random polynomial model for the EQ-5D-5L and TTO, and a random slope model for the AQL-5D, and this was improved by using multiple imputation to increase the precision of the estimation and minimize standard error. The EQ-5D-5L, AQL-5D and TTO QALY losses were 0.00575, 0.0096 and 0.0035 respectively. These QALY losses can also be multiplied by the number of participants who have experienced an asthma-related crisis event.

Patients should be aware of how asthma-related crisis events can impede on daily activities, (both recreational and work-related). By acknowledging the amount of time it took for the participants in this study to recover from their asthma-related crisis event and their financial implications, patients should aim to maintain well-controlled asthma (e.g. by taking medications and using PAAPs) and reduce the risk of asthma attacks (e.g. by avoiding known triggers such as exposure to pets) (British Thoracic Society. Scottish Intercollegiate Guidelines Network, 2016).

Researchers and policy makers should take into account that this research is the first to explore quality of life in acute asthmatics associated with asthma-related crisis events in such depth. It provides useful estimations, which can be used in economic analyses to further the accuracy of results.

4.5 Conclusion

To conclude, this study aimed to estimate the QALY loss associated with asthma-related crisis events. These were defined as admission to hospital or attendance to A&E from having an asthma attack. Most of the loss associated with the asthma-related crisis events occurred within the first four weeks, causing loss in productivity, and showed strong statistical significant differences at the 1% level for all PROMs. The EQ-5D-5L and the AQL-5D showed closely matched utility values, which can be used to enhance research studies by using the loss in utility to estimate the QALY loss and assigning this to the number of asthma-related crisis events.

To consolidate these findings further, it would be useful to examine the comparative performance of these PROMs using psychometric techniques in order to inform future research about which instrument(s) might be used. Therefore, the available cases from this study, will be used to explore techniques such as, construct validity and responsiveness, in the next chapter.

CHAPTER 5

WHAT IS THE APPROPRIATENESS OF DIFFERENT PREFERENCE-BASED MEASURES IN ACUTE ASTHMATICS?

"Don't take something at face value, there are always new observations to be found"

Preface

The previous chapter outlined various estimates for the loss in quality of life associated with an asthma-related crisis event. This event was defined as those who attended A&E or were admitted to hospital following an asthma attack. A total of 121 participants were recruited from three hospital sites in the UK. They were asked to complete several PROMs over a period of 8 weeks, to investigate their quality of life associated with the crisis event. Descriptive statistics, wilcoxon signed-rank test, and multi-level modelling were used to explain the data set.

The participants recruited had mixed characteristics, with most of the estimated loss associated with the crisis events occurring during the first four weeks of the study. All PROMs showed strong statistical significant differences at the 1% level between the mean scores at baseline and week 4 of the study, with the EQ-5D-5L and AQLQ overall scores exceeding their minimal important difference threshold. Participants also lost productivity during those first four weeks and not all had returned back to work by the fourth week of the study. The EQ-5D-5L and the AQL-5D (converted into utility values from the AQLQ), showed closely matched utility values when observed.

However, it is necessary to investigate all preference-based measures further. This is to identify the nature of their relationship to each other and other associated variables, and also the strength that this bears, in order to provide further confirmation as to which instrument is appropriate to be used. Therefore, this chapter will seek to explore the

relationships between the preference-based measures by using psychometric techniques; in particular construct validity and responsiveness.

5.1 Background

PROMs are used widely in research as they are useful for capturing patient's perceptions for different diseases (Black, 2013). The PROMs can be disease-specific or generic questionnaires, and they can be conducted in different modes and at different time points (Weldring and Smith, 2013).

As seen earlier (**Chapter 2, Figure 12**) in my systematic review study (Crossman-Barnes et al., 2017), the use of PROMs in asthma is vast. It appears that there are many PROMs that can be used for asthma studies, such as the AQLQ, mini-AQLQ, SGRQ, and EQ-5D being the top common ones (Crossman-Barnes et al., 2017, Frew et al., 2013, Worth et al., 2014, Shah et al., 2016a). The AQLQ, mini-AQLQ and SGRQ are disease-specific questionnaires (questionnaires specifically tailored to a particular disease) and the EQ-5D is a generic questionnaire (questionnaire that can be used for many different diseases). Both the AQLQ and EQ-5D have been outlined previously in sections 1.6 and 1.7. The mini-AQLQ is a shortened version of the AQLQ composed of 15 questions and still encompasses the same four domains as used in the AQLQ (symptoms, activities, emotions and environment) (Juniper et al., 1999). Additionally, the AQLQ has been used to develop a preference-based measure (AQL-5D), as previously discussed in **Chapter 3.5.5**. The SGRQ is a 50 item questionnaire split into three domains (symptoms, activity and impacts), and can be used for people with asthma COPD, and bronchiectasis. As there are so many different PROMs available to use, it is important that there is transparency for their use and knowledge for which one is more appropriate. However, knowing what specific PROMs are appropriate for asthma are yet to be identified, and further research is warranted (Worth et al., 2014).

The testing of preference-based measures through psychometric techniques has been conducted before in many different diseases. Earlier asthma studies have conducted psychometric tests on a range of different PROMs (Globe et al., 2016, Nguyen et al., 2014, Bime et al., 2012, Nelsen et al., 2017, Apfelbacher et al., 2016, Kheir et al., 2008, van Bragt et al., 2014). To highlight a few examples, a previous study confirmed that the EQ-5D (3L) is valid and reliable for use on asthma patients after exploring its correlation

strength against other disease specific or generic questionnaires (e.g. to name a few, AQLQ, SF-36, SF-6D, SGRQ, and 15D). This helped clinicians form better decisions about HRQL in people with asthma (Pickard et al., 2008), however, a more recent qualitative study explored the use of the EQ-5D-5L in asthma patients and identified that the acceptability (defined as the ease of using an instrument) and content validity (defined as the ability of an instrument to appropriately represent the most important and relevant aspects of a concept), was poorly aligned (Whalley et al., 2018) compared to the AQL-5D and the asthma symptom diary (ASD). This demonstrates that further research is required to explore these discrepancies between studies. An earlier study also explored psychometric properties between several questionnaires in asthma patients, including the EQ-5D, SF-36 / SF-6D, SGRQ and TTO (Szende et al., 2004). Interestingly, after evaluating HRQL in asthmatics with different levels of disease control, Szende et al. (2004) indicated that the EQ-5D was better suited to the more severe asthma or poorly controlled asthma patient groups and the SF-6D was more suited to patients with milder or well controlled asthma. Furthermore, another study confirmed that when observing preference instruments, (rating scale (RS), SG, TTO, HUI3 and asthma symptom utility index (ASUI)), the SG showed no correlation with asthma severity markers (Moy et al., 2004), but the RS was significantly associated with all symptoms.

From assessing the literature discussed in these paragraphs above and throughout the thesis, it is evident that more research needs to be conducted to identify which instrument is more suitable for measuring quality of life in asthma patients. Therefore, based on the PROMs considered in my prospective cohort study, (**see chapters 3 & 4**), and the comparison of different instruments used by psychometric testing in the above literature, it appeared appropriate to use the three instruments, which could derive utilities as a comparison for the psychometric testing. The EQ-5D has been used in several studies already, however, the EQ-5D-5L warrants comparison since it has been recently developed. Furthermore, the AQL-5D has also been recently developed and comparisons amongst utility instruments have not currently been performed based on data from a critical asthma patient group. Finally, comparisons with the TTO are also limited, and in particular, since this TTO was modified, it also important for comparisons.

Validity, reliability, repeatability, sensitivity and responsiveness, are the common types of psychometric properties that all measurements should aim to satisfy to be able to be

clinically useful (Fayers and Machin, 2016). Since the prospective cohort study (**see chapter 3**), included patients where their quality of life status was expected to change over time and not remain a constant, then reliability and repeatability psychometric testing could not be performed (Fayers and Machin, 2016). Therefore, validity, sensitivity and responsiveness were considered, and these psychometric techniques are less well understood in this asthma patient group.

This study will aim to answer prior hypotheses relating to the construct validity and responsiveness of the data set by comparing the three preference-based measures (EQ-5D-5L, AQL-5D and TTO):

- High levels of correlations (Spearman's rank correlation coefficient > 0.5, (Cohen, 1988a)) are expected to be seen amongst all preference-based measures. (Convergent validity)

- Participants with a PEF of <50% of best/predicted are expected to have a poorer quality of life than those patients with PEF >50% of best/predicted. (Discriminative validity). This is due to medical information stating that those with a PEF of <50% of best /predicted will have life threatening or acute severe asthma, those with between 50% and 75% will have moderate acute asthma and those >75% will have good/very good asthma (British Thoracic Society. Scottish Intercollegiate Guidelines Network, 2016).

- All questionnaires would show improvements in asthma quality of life between baseline and week 4 of the study, with the responses to 'very good' and 'poor' showing greater changes at the extremities, as well as responses to 'yes' and 'no' also showing great changes at the extremities. (Responsiveness). These responses are taken from the productivity questionnaire where the participants are asked to complete this at week 4 of the study, and the questions relate to whether they feel their asthma has completely recovered since their A&E attendance or hospital admission. These questions are detailed further in the methods section of this chapter (**section 5.2.1**).

The following section will discuss the methods used in this chapter, by providing more detailed information on the statistical analysis and definitions of the psychometric techniques used. The results will then follow with many tables highlighting the validity and responsiveness results at different time points. Then, the chapter will close, discussing the results, providing future recommendations and conclusions.

5.2 Methods

This study also draws on data from the prospective cohort study, the methods for which were described in **Chapter 3**. The data set used is the same as that used in **Chapter 4** (the available cases), and the analysis for this chapter is described below. As the outcome variables were mostly non-normally distributed, non-parametric tests were used for the analysis.

5.2.1 Statistical analysis

The analysis for this study assessed the construct validity and responsiveness of the preference-based measures; EQ-5D-5L, AQL-5D and TTO. As mentioned previously in **Chapter 3, section 3.7**, the utility values for the EQ-5D-5L were estimated using the value sets based on England, and the AQLQ was converted into preference-based utility values based on an algorithm to form the AQL-5D.

Construct validity

Construct validity assesses whether the constructs of an instrument are measuring what it should be measuring (de Vet et al., 2015). Two forms of construct validity were considered; convergent and discriminative validity.

Convergent validity addresses the level of correlation between constructs and instruments. It shows whether the constructs or instruments that are being compared are related to each other as expected. These relations may be strong or weak correlations depending on the relationship expected between the constructs or instruments compared (Fayers and Machin, 2016).

The correlations for convergent validity have been assessed at baseline, week 4 and week 8 of the study. The Spearman's rank correlation coefficient was used to determine the correlations with statistical significance considered at the 5% level. Additionally, correlations were considered weak if < 0.3, moderate if 0.3 to 0.5 and strong if >0.5 (Cohen, 1988a).

Discriminative validity, (also known as known-groups validity), is another type of construct validity which has been considered in this analysis (Fayers and Machin, 2016). The groups tested are expected to differ between each other, and so a test is conducted to help discriminate against them. The analysis was conducted based on specific groups that were anticipated to provide different results between instruments at baseline. Three PEF groups were chosen to conduct this analysis (British Thoracic Society. Scottish Intercollegiate Guidelines Network, 2016):

- < 50% of the best/predicted PEF (life threatening or acute severe asthma)
- 50-75% of the best/predicted PEF (moderate acute asthma)
- > 75% of the best/predicted PEF (good/very good asthma)

The Kruskal-Wallis test statistic was used to conduct the test for discriminative validity across the instruments using the above three PEF subgroups. P-values were used to display the statistical significance.

In addition to the above, discriminative validity was also conducted to test between groups based on two questions asked in the productivity questionnaire which was completed at week 4 of the study. These questions were as follows:

Question (a): Compared to your asthma state when you were in hospital approximately 4 weeks ago, how would you rate your asthma now?

Answers to choose (a): Very good, Good, Moderate, Poor or Very Poor.

Question (b): Do you think you have completely recovered from when you were in hospital approximately 4 weeks ago?

Answers to choose (b): Yes, No.

The Kruskal-Wallis test was also used here to compare the answers to question (a) with the preference-based measures, where it was expected that there will be statistical significant differences between the change in the mean rank scores over a 4 week period in the good, moderate and poor categories. As none of the participants chose the last item, '*very poor',* this category was omitted from the groups. Likewise, the Kruskal-Wallis test was also used to compare the answers to question (b) against the preference-based measures, where it was expected that there will be strong statistical significant differences between both groups (change in mean rank scores over a 4 week period).

Responsiveness

This was an assessment of all of the quality of life questionnaires, including the PEF to detect any sensitivity to change (de Vet et al., 2015). Responsiveness should highlight whether the instruments are measuring the constructs as it should, e.g. by detecting whether an expected improvement or deterioration over a period of time is reflected in the scores for that instrument. Responsiveness was tested by using the responses of two anchor questions, which were incorporated into the productivity questionnaire (the same two questions as those used in the discriminative validity test above).

Responses to the above question (a) were used as an anchor and grouped into 4 categories. As none of the participants chose the last item, '*very poor',* this category was omitted from the groups. Responses to question (b) were grouped into 2 categories (Yes and No) for all questionnaires. Wilcoxon signed-rank tests were conducted to identify any significant changes in scores within each category, accompanied with effect size (ES) and standard response mean (SRM) calculations (Fayers and Machin, 2016).

Effect size (ES): $\frac{Mean\ change}{Standard\ deviation\ at\ baseline}$

Standardised Response Mean (SRM): $\frac{Mean\ change}{Standard\ deviation\ of\ change}$

The SRM helped to indicate how responsive the questionnaires were to change. Values ranging between 0.20 and 0.50 were considered small, 0.50 to 0.80 were considered moderate and greater than 0.80 were considered large (Cohen, 1988b).

The results for the construct validity and responsiveness will be presented in the following section below.

5.3 Results

The convergent validity for baseline, week 4 and week 8, are shown in **Table 60**, **Table 61** and **Table 62** respectively using Spearman's rank correlation coefficients for the preference-based measures. At baseline, the relationship between the EQ-5D-5L and the AQL-5D, showed statistical significant differences at the 1% level. The correlation

coefficients for the EQ-5D-5L and the TTO, and the AQL-5D and the TTO were not associated.

The convergent validity relationships highlighted at baseline had become stronger at week 4. The EQ-5D-5L and the AQL-5D remained having a strong statistical difference at the 1% level. The AQL-5D and the TTO had a better relationship at week 4, with a strong statistical difference at the 5% level.

The same statistical significant relationships were also observed for the convergent validity at week 8 of the study, as compared to the convergent validity relationships observed at week 4 of the study. Both the EQ-5D-5L and the AQL-5D, and the AQL-5D and the TTO showed the same relationship.

Table 60: Convergent validity at baseline using Spearman's rank Correlation coefficient

	EQ-5D-5L (utility)	AQL-5D (utility)	TTO (utility)
EQ-5D-5L (utility)	N = 120 1.0000		
AQL-5D (utility)	N = 118 **0.3888****	N = 118 1.0000	
TTO (utility)	N = 111 0.1287	N = 109 0.0864	N =112 1.000

Pairwise correlation coefficients displayed.
Correlation coefficients considered < 0.3 are weak, 0.3 to 0.5 are moderate and >0.5 are strong.
**p-value is < 0.01 therefore statistically significant at the 1% level.

Table 61: Convergent validity at week 4 using Spearman's rank Correlation coefficient

	EQ-5D-5L (utility)	AQL-5D (utility)	TTO (utility)	PEF
EQ-5D-5L (utility)	N = 71 1.0000			
AQL-5D (utility)	N =63 **0.5355****	N = 70 1.0000		
TTO (utility)	N = 62 0.1771	N = 62 **0.3027***	N =87 1.000	

Pairwise correlation coefficients displayed.
Correlation coefficients considered < 0.3 are weak, 0.3 to 0.5 are moderate and >0.5 are strong.
*p-value is < 0.05, **p-value is < 0.01 therefore statistically significant at the 5% level and 1% level respectively.

Table 62: Convergent validity at week 8 using Spearman's rank Correlation coefficient

	EQ-5D-5L (utility)	AQL-5D (utility)	TTO (utility)
EQ-5D-5L (utility)	N = 64 1.0000		
AQL-5D (utility)	N =61 **0.6260****	N = 64 1.0000	
TTO (utility)	N = 60 0.1871	N = 58 **0.3087***	N =80 1.000

Pairwise correlation coefficients displayed.
Correlation coefficients considered < 0.3 are weak, 0.3 to 0.5 are moderate and >0.5 are strong.
*p-value is < 0.05, **p-value is < 0.01 therefore statistically significant at the 5% level and 1% level respectively.

Three different types of discriminative validity tests were also conducted for the preference-based measures. The first discriminative validity test, shown in **Table 63**, was based on three PEF groups. The PEF groups were split into categories of different asthma severities; <50% of best/predicted PEF, 50%-75% of best/predicted PEF and >75% of best/predicted PEF (British Thoracic Society. Scottish Intercollegiate Guidelines Network, 2016). The lower proportion (<50% of best/predicted PEF), indicates that the participants are the furthest away from their best or predicated PEF, indicating that they are more poorly (have life threatening asthma or acute severe asthma) than the participants who have a PEF of >75% of their best or predicted PEF (good or very good asthma).

Most of the participants were within the 50-75% of best/predicted PEF category indicating that they had moderate acute asthma at baseline. Interestingly, at baseline some participants were in the third PEF category which indicated they had good/very good asthma based on their PEF being > 75% of their best/predicted value. Even though, most of the utility values were increasing as hypothesized from the lowest PEF group (< 50% of best/predicted PEF) to the highest PEF group (>75% of best/predicted PEF), the change was not very large and so the results showed no statistical significant differences between any of the preference-based measures displayed.

Table 63: Discriminative (Known-groups) Validity at baseline using three PEF subgroups against preference-based measures

	< 50% of best / predicted PEF Mean Rank	< 50% of best/predicted PEF N	50-75% of best/predicted PEF Mean Rank	50-75% of best/predicted PEF N	>75% of best/predicted PEF Mean Rank	>75% of best/predicted PEF N	P-value*
EQ-5D-5L utility	53.64	18	57.02	42	71.89	27	0.105
AQL-5D utility	53.36	18	56.45	42	68.96	26	0.223
TTO utility	49.91	16	58.11	40	56.70	28	0.713

Kruskal-Wallis test conducted and PEF split into three subgroups: <50% of PEF best / predicted = life threatening / acute severe asthma; 50-75% of PEF best/predicted = moderate acute asthma and >75% of best/predicted asthma for good/very good asthma (British Thoracic Society. Scottish Intercollegiate Guidelines Network, 2016).

*No statistical significant difference found for all PROMS between the three PEF subgroups.

The second discriminative validity test, shown in **Table 64**, compares how participants were at baseline when in hospital with how they felt at four weeks from their asthma-related crisis event. Most of the participants felt that their asthma had improved at four weeks compared to baseline, either moderately or very well, and very few rated their asthma as poor. All of the utility values either increased or decreased appropriately across the different recovery rates, and this was in line with earlier hypotheses. Both the EQ-5D-5L and the AQL-5D were statistically significantly different at the 1% level.

The third discriminative validity test, shown in **Table 65**, also related to the productivity questionnaire, and was a direct 'yes' or 'no' response to whether the participant thought that they had recovered from their asthma-related crisis event approximately four weeks ago. A higher proportion of responses were observed to be in the 'no' category. The discriminative validity in **Table 65**, was statistically significantly different at the 1% level for both the EQ-5D-5L and AQL-5D utility value.

Table 64: Discriminative (Known-groups) Validity at week 4 against preference-based measures

	Very good Mean Rank	Very good N	Good Mean Rank	Good N	Moderate Mean Rank	Moderate N	Poor Mean Rank	Poor N	P-value
EQ-5D-5L utility	54.57	15	43.25	18	32.21	26	8.89	9	**0.000**
AQL-5D utility	48.53	15	48.15	17	29.72	27	14.89	9	**0.000**
TTO utility	54.68	14	49.42	19	39.09	23	38.63	8	0.207

Kruskal-Wallis test conducted and split into four recovery rates where the participants were asked to rate their asthma at four weeks compared to their asthma at baseline (in hospital upon consent).

The P-values in bold are statistically significantly different at the 1% level.

Table 65: Discriminative (Known-groups) Validity at week 4 against preference-based measures

	Yes Mean Rank	Yes N	No Mean Rank	No N	P-value
EQ-5D-5L utility	45.18	25	32.21	43	**0.013**
AQL-5D utility	49.54	27	27.94	41	**0.000**
TTO utility	49.22	27	42.80	37	0.253

Kruskal-Wallis test conducted and split into two recovery response rates where the participants were asked to rate their asthma at four weeks compared to their asthma at baseline (in hospital upon consent).

The P-values in bold are statistically significantly different at the 1% level.

Two responsiveness tests were conducted, which also looked at the recovery rates and responses as to whether the participants had recovered from their asthma-related crisis event from approximately four weeks ago. The first responsiveness test is shown in **Table 66**, and this shows the results of the changes in means between baseline and week 4 based on the anchor question taken from the productivity questionnaire. As hypothesized, most of the utilities demonstrated sensitivity to change (which is highlighted from the SRM values). The range for the mean change from poor to very good groups in the EQ-5D-5L utility was from -0.276 to 0.221, for the AQL-5D from -0.0065 to 0.169, and for the TTO from -0.173 to 0.254. The TTO was the only preference-based measure which didn't have a large sensitivity to change in any of the four groups (poor, moderate, good and very good). Instead, moderate responsiveness was observed for the very good, good and moderate groups, with a small responsiveness observed for the poor group. The AQL-5D, showed large responsiveness to change for the very good and good groups, moderate responsiveness for the moderate group, and small responsiveness for the poor group. The EQ-5D-5L, showed large responsiveness for the good and poor groups, moderate responsiveness for the very good group and small responsiveness for the moderate group.

For the second responsiveness test, shown in **Table 67**, the responses to the recovery question asked in the productivity questionnaire are observed against the preference-based measures. It is clear that there is a large responsiveness to the 'yes' category for the AQL-5D utility value. However, both the EQ-5D-5L and the TTO had moderate responsiveness to the 'yes' category, and all of the preference-based measures had a small responsiveness for the 'no' category.

Table 66: Responsiveness of all preference-based measures between baseline and week 4

Items	N	Baseline (mean)	Week 4 (mean)	Mean change	SD at baseline	SD at change	ES	SRM	P value
EQ-5D-5L									
Very good	14	0.747	0.922	0.175	0.280	0.235	0.625	0.745 **	**0.011**
Good	17	0.585	0.807	0.221	0.325	0.233	0.680	0.948***	**0.000**
Moderate	24	0.630	0.724	0.094	0.265	0.239	0.355	0.393*	**0.031**
Poor	8	0.604	0.328	-0.276	0.148	0.268	-1.865	-1.030 ***	0.066
AQL-5D									
Very good	15	0.629	0.798	0.169	0.135	0.187	1.252	0.904 ***	**0.010**
Good	17	0.621	0.787	0.166	0.132	0.140	1.258	1.186 ***	**0.001**
Moderate	26	0.560	0.621	0.061	0.113	0.110	0.540	0.555 **	**0.023**
Poor	9	0.529	0.524	-0.005	0.107	0.019	-0.047	-0.263*	0.356
TTO									
Very good	14	0.679	0.932	0.254	0.250	0.329	1.016	0.772 **	**0.014**
Good	19	0.682	0.908	0.227	0.296	0.320	0.767	0.709 **	**0.013**
Moderate	23	0.598	0.787	0.189	0.297	0.348	0.636	0.543 **	**0.008**
Poor	8	0.881	0.708	-0.173	0.177	0.376	-0.977	-0.471*	0.468

Wilcoxon signed-rank test conducted and p-values in bold are statistically significant at the 5% level.
ES = Effect size (mean change / SD at baseline); SRM = Standardized response mean (Mean change / SD of change).
If SRM = 0.2 to 0.50 equals small, 0.50 to 0.80 equals moderate and 0.80 and above equals large.
*small change, small responsiveness
**moderate change, moderately responsive
***large change, largely responsive

Table 67: Responsiveness of all preference-based measures between baseline and week 4

Items	N	Baseline (mean)	Week 4 (mean)	Mean change	SD at baseline	SD at change	ES	SRM	P value
EQ-5D-5L									
Yes	25	0.641	0.810	0.169	0.317	0.221	0.533	0.765 **	**0.001**
No	43	0.613	0.701	0.088	0.253	0.308	0.348	0.286*	**0.054**
AQL-5D									
Yes	27	0.618	0.802	0.183	0.124	0.162	1.476	1.130 ***	**0.000**
No	17	0.566	0.614	0.049	0.123	0.103	0.398	0.476 *	**0.023**
TTO									
Yes	37	0.677	0.883	0.206	0.277	0.388	0.744	0.531 **	**0.007**
No	37	0.675	0.817	0.142	0.290	0.334	0.490	0.425 *	**0.007**

Wilcoxon signed-rank test conducted and p-values in bold are statistically significant at the 5% level.

ES = Effect size (mean change / SD at baseline); SRM = Standardized response mean (Mean change / SD of change).

If SRM = 0.2 to 0.50 equals small, 0.50 to 0.80 equals moderate and 0.80 and above equals large.

*small change, small responsiveness

**moderate change, moderately responsive

***large change, largely responsive

5.4 Discussion

This study used psychometric techniques to analyse the construct validity and responsiveness relationships between preference-based measures for people with acute asthma. The data used for this analysis was prospective cohort data collected from across three hospital sites in the UK from when people attended A&E or were admitted to hospital with acute asthma symptoms. This study analysed the observed findings by comparing the preference-based measures at three main time points during the study, which were baseline, week 4 and week 8.

5.4.1 Summary of findings

The correlations between the preference-based measures were mostly moderately to strongly correlated and had strengthened from time points at baseline, through to week 4 and week 8. At baseline, the EQ-5D-5L and the AQL-5D were statistically significant at the 1% level. As the study progressed, the TTO also showed more of a statistical significance at the 5% level at week 4 and week 8 of the study.

The discriminative validity comparing the three PEF with the EQ-5D-5L, AQL-5D and TTO showed no statistical significant differences across the groups, even though the utility values and scores were increasing as the proportion of PEF groups increased. However, statistical significant differences were observed at the 5% level in the two further discriminative validity tests. The latter tests observed responses at week 4 of the study to the participants' recovery rates from their asthma-related crisis event (A&E attendance or hospital admission due to their asthma). The TTO utility value didn't show statistical significance for both of the recovery rate tests.

The preference-based measures also demonstrated good levels of responsiveness when comparing the participants' responses to recovery rates at four weeks from when they had their asthma-related crisis event. Moderate (SRM statistic > 0.50) and large responsiveness (SRM statistic > 0.80) was mostly observed on average across the preference-based measures for both responsiveness tests. The level of responsiveness was the largest for participants' who felt their asthma had improved from when they were in hospital approximately four weeks ago, and in particular if they thought their asthma was good or very good in comparison to their asthma-related crisis event.

5.4.2 Comparison with other studies

It is not unusual for high levels of correlation to be observed between the AQLQ and the AQL-5D because, upon development of the AQL-5D, correlation tests were conducted between the AQLQ and the AQL-5D using rasch analysis coupled with psychometric techniques, equally displaying high levels of correlation (Young et al., 2011). The mini AQLQ has also been used in other asthma studies, such as, Thomas et al. (2009), where the royal college of physician three question scores were compared against the mini AQLQ, as opposed to the original AQLQ used in this study. Both of these questionnaires have been previously tested and have shown good measurement properties, (including reliability, responsiveness, construct validity and criterion validity), however, the original AQLQ performed the strongest overall (Juniper et al., 1999).

In this study, the correlation coefficients between the TTO and the EQ-5D-5L were much weaker compared to the EQ-5D-5L and the AQL-5D. Even as the study progressed, they stayed weak with no statistical significance. A previous cross-sectional study compared the TTO with the EQ-5D but had a higher correlation coefficient of 0.40, indicating a moderate correlation (Szende et al., 2004). However, there were several differences between that study (Szende et al., 2004), and this current study around the participant population group, the questioning of the TTO, and the number of levels on the EQ-5D. Nevertheless, the TTO correlations presented with lower correlations compared to the other preference-based measures for both studies, which potentially confirms the unsuitability for using the TTO (based on the format used in this study) in asthma measurement.

The other two discriminative validity tests observing the recovery rates of the participants at week 4 of the study presented strongly in both categories. The participants responded with either a ‘yes’ or ‘no’ if they thought they had recovered from their asthma-related crisis event, and then categorised their response ranging from ‘very good’ to ‘very poor’. The questionnaire that performed the best overall from this test was the AQL-5D. This finding was in line with an earlier study, which also assessed the construct validity with disease specific and generic questionnaires for people with asthma (McTaggart-Cowan et al., 2008). They encouraged responsiveness tests for the AQL-5D to consolidate their findings.

After reflecting on the analytical technique used to address responsiveness in this thesis, my interpretation of this is in line with other studies. For example, Shah et al. (2016a) also used an external reference anchor (in this case, question 1 from SF-12) to test sensitivity to change amongst the quality of life questionnaires. Additionally, Goranitis et al. (2016), also used an external anchor of how women felt their symptoms had changed. Similarly, with particular focus on non-normality data, other studies have also taken the same approach as I have done in this thesis by using the Wilcoxon signed-rank test for the p-values instead of the paired t-test (Goranitis et al., 2016, Goncalves et al., 2010).

When assessing the two responsiveness tests conducted in this study, (again using the recovery rates / questions from the participants at week 4 of the study), the AQL-5D performed the best as a measure of utility. The AQLQ has previously shown high levels of responsiveness in another asthma study at two different time points (Oga et al., 2003). As the AQL-5D is derived from the AQLQ, and it has been confirmed of their strong correlations in this study and others (Young et al., 2011), this shows promise for the AQL-5D as high levels of responsiveness was observed in this study.

5.4.3 Recommendation for the future

In light of the findings from this study, both the construct validity and responsiveness tests have confirmed which preference-based measures perform the best for the acute asthma population group for the criteria assessed. Overall, the AQL-5D and the EQ-5D-5L performed the best and should be considered for use in economic evaluations for asthma studies. Even though the AQL-5D is a recent development (Yang et al., 2011), previous literature and this current study have strongly confirmed its performance (McTaggart-Cowan et al., 2008, Young et al., 2011). Therefore, it is suggested that the disease-specific questionnaire, AQLQ, is used in asthma studies in order to estimate utilities using the AQL-5D.

However, given that NICE have emphasised using the EQ-5D in economic evaluations (Drummond et al., 2005, Drummond et al., 2015), this should still be considered. In this

study, it did not perform as strongly as the AQL-5D, but it was the second best option out of the utility measurements.

5.5 Conclusion

In conclusion, this study aimed to identify the relationships between the preference-based measures that were used in a prospective cohort study, which estimated the loss associated with an asthma-related crisis event. Psychometric techniques, in particular, convergent validity, discriminative validity and responsiveness were used in this analysis.

The EQ-5D-5L and the AQL-5D, illustrated moderate to strong correlations throughout all three time points at baseline, week 4 and week 8. They were both also able to discriminate against groups for productivity rates, with the AQL-5D performing slightly more strongly. Moderate to large changes were observed in the preference-based measures for the level of sensitivity to change for the recovery rate responses. However, the discriminative test indicated that the preference-based measures were not very good at discriminating against the three PEF groups, and the TTO showed weak correlations between the EQ-5D-5L and the AQL-5D.

Therefore, the results overall highlight that the AQL-5D and the EQ-5D-5L are well correlated and sensitive to change for participants who have had an asthma-related crisis event. From this study, the results suggest that the AQL-5D performed better overall, compared to the other preference-based measures. However, for the purposes of economic evaluation studies, and the fact that previous research recommends the use of the EQ-5D, both the EQ-5D-5L and the AQL-5D should be used in the future. Nevertheless, it is important to bear in mind that both of these questionnaires have been recently developed, and therefore further research is encouraged on a larger, more complete data set.

CHAPTER 6

FINAL DISCUSSION

"Research is creating new knowledge"

(Neil Armstrong, American astronaut)

Preface

This final chapter will discuss and conclude the findings from the whole thesis. It will begin with a summary of the main research findings, followed by contributions to the literature. Subsequently, there will be a discussion of the main strengths and limitations of the thesis, followed by a discussion of the implications and future directions.

6.1 Summary of main research findings

This thesis opened with an introduction chapter (**Chapter 1**), which provided some background on asthma and its impact on quality of life. The introduction described the scale of the problem (affects millions of people worldwide) and highlighted symptoms, (such as; breathlessness, wheezing, chest tightness and coughing), which can progressively worsen, reduce quality of life and impact healthcare resource use. Current literature shows that asthma can develop from a combination of genetic and environmental factors, and although it can be managed by medications and routine asthma reviews, when this does not happen asthma attacks are likely to occur. These attacks are the progressive worsening of symptoms and can be life threatening. Depending on the severity of the asthma attack, the reduction in quality of life can be substantial. There are many ways to measure quality of life through direct elicitation methods for use in economic evaluations, such as the TTO, standard gamble and EQ VAS. Alternatively, generic or disease specific questionnaires can also be used.

This thesis aimed to address several research questions around acute asthmatics and quality of life. The rest of this chapter will discuss the main research objectives of this thesis.

6.1.1 *Cost effectiveness of enhanced asthma management interventions from 2012 to January 2016*

The primary objective of the systematic review was to investigate the cost effectiveness of asthma management interventions in studies published after 2012, since a previous review had already addressed this for studies published between 1990 and 2012 (Yong and Shafie, 2014). However, since the secondary objective expanded the search to include studies between 1990 and 2016, there were some studies that were included in this systematic review, which could have been included previously in the Yong and Shafie (2014) review. Therefore, these additional studies and studies found post 2012, were included to address the primary objective.

The review found 15 new studies and showed that enhanced asthma management interventions were mostly cost effective, across the different types of economic evaluations included in the review. ICERs were either dominant or cost effective, and this was often reported for CEAs and the only reported CUA study. In comparison, Yong and Shafie (2014) also reported the studies to be cost effective for educational and environmental studies.

In addition, the quality of these 15 new studies were ranked moderate to high quality, with an average QHES score of those post 2012 as 75.1. This was also an improvement from previous studies, where Campbell et al. (2008) averaged with a QHES score of (Campbell et al., 2008) 61.4 for an equivalent group of studies. The average QHES score for Yong and Shafie (2014) was 75.6, which is very similar to the quality assessment of these studies found in this systematic review.

The above highlights that these interventions have shown a level of consistency over the years since 1990, due to the positive cost effectiveness results and increase in average study quality. Therefore, these interventions should be considered for use in practice, if they have not already been implemented.

6.1.2 *Methods used in estimating and evaluating both costs and outcomes for economic analyses*

The secondary objective of the systematic review, was to explore the methods used to estimate and evaluate costs and outcomes in the included studies. This objective was useful in determining how costs and quality of life can be assessed and what tools and methods can be used to derive the costs and quality of life. Out of the 64 studies assessed, the studies presented with heterogeneity across both costs and outcomes. The most commonly reported resource use were asthma-related hospitalizations, asthma-related accident and emergency visits, and physician visits, which were often recorded from medical records or patient self-reported data. Multiple methods were often used to estimate the resource use, due to different outcomes being reported. However, the detail in the reporting of the methods, was often limited, and lacking replicability, as unit costs and the approach taken to estimate costs (e.g. bottom-up or top-down), were not always clearly reported. Three different methods were also used to estimate productivity loss (human capital approach, friction cost method and caregiver multiplied by midpoint of family's income), which makes it difficult to compare across studies.

Likewise, comparability across the outcome measures is also challenging, because of differences in data collection methods, and quality of life questionnaires used across studies. Mixed methods were used, where patient self-report and face to face sessions were used in some instances or in conjunction with telephone sessions. The top four most commonly reported quality of life questionnaires from the studies were AQLQ, SGRQ, 15 Dimensions and EQ-5D. Seventeen quality of life questionnaires were only reported once across the 64 included studies.

Due to the heterogeneous nature of these studies, it is challenging to know what methods for costs and outcomes, and also what quality of life tool, is appropriate to use in the asthma population group. There is a lack of consistency in the reporting of these factors, where information is limited across some studies (e.g. microcosting of interventions), which leads to difficulties in the replicability of studies. Therefore, this review suggests using appropriate guidelines and checklists (e.g. TiDier statement, COMET initiative, CONSORT statement and international reference case), to ensure methods are reported sufficiently.

Additionally, this review highlighted that quality of life is often captured at set time points, such as baseline, 6 months and 12 months. There is potential for asthma related studies to underestimate or overestimate quality of life if captured in this way, due to asthma attacks occurring sporadically. Therefore, quality of life, (taking into account the asthma attacks), may be missed in between such large time points. This gap in the literature led to the development of a prospective observational cohort study, which aimed to address this problem. Several PROMs were used in this cohort study to estimate the loss associated with quality of life during an asthma-related crisis event, which was defined as an accident and emergency attendance or hospital admission.

6.1.3 *Peak of an asthma-related crisis event*

The objective was to identify when an asthma-related crisis event reached a peak and was at its worst. From the 121 participants recruited into this prospective cohort study, 98 responded to this question. It was identified that 60% of participants thought their asthma-related crisis event peaked before attending A&E or being admitted to hospital. On the other hand, 22% thought their asthma-related crisis event peaked on route and 17% thought their asthma-related crisis event peaked after attending A&E or being admitted to hospital. It could be inferred that those whose asthma-related crisis event peaked beforehand would have started to improve before they got to hospital, indicating that their perception of quality of life could possibly be higher than a participant whose peak was on route or in hospital. Likewise, when observing the mode of transport into hospital, participants who travelled via ambulance and had the peak of their asthma attack either before or on route to hospital, could have also improved in quality of life before reaching hospital. From these inferences, and after comparing the association between participants whose asthma-related crisis event peaked before A&E attendance or hospital admission, and baseline EQ-5D-5L and TTO (due to some ceiling effects being present here), there was no statistical significant differences found. However, whilst there is a possibility for quality of life to be somewhat improved before attending A&E or being admitted to hospital, if the peak of their event occurred beforehand, the sample size was too small to detect a difference. The possibility of improvement in quality of life may be because it takes on average, a long period of time to recover from an asthma-related crisis event (as highlighted below in the next research question). Therefore, the time between when an

asthma-related crisis event peaks before reaching hospital and attending A&E or being admitted to hospital maybe too small to make any significant impact.

6.1.4 *Loss in quality of life associated with an asthma-related crisis event*

Several outcome measures were used to estimate the loss in quality of life associated with an asthma-related crisis event from this prospective cohort study. Mean changes were reported for utility scores for the EQ-5D-5L, EQ VAS, AQLQ overall, AQL-5D and TTO between baseline and week 8, baseline and week 4, and week 4 and week 8 of the study. This study identified that when observing the available case dataset, the mean changes between the utilities and scores reported at baseline and week 8, and baseline and week 4 showed strong statistical significant differences at the 1% level. However, only the AQLQ overall score and AQL-5D showed statistical significant differences between week 4 and week 8.

Interestingly, some participants had ceiling effects at baseline in some of the outcome measures (EQ-5D-5L, AQLQ and TTO), suggesting that these participants had returned to a 'healthy' state by the time of recruitment into the study. However, when these participants were excluded from the dataset, and the mean changes were estimated again as above, the mean changes still showed statistical significance between the outcome measures, with very small differences in values between the full dataset and adjusted dataset.

Since the cohort study collected data at several different time points, (e.g. EQ-5D-5L weekly, AQLQ monthly and TTO monthly), these initial results allow alternative scenarios to be considered when assessing the loss in quality of life associated with an asthma-related crisis event. For example, the loss in quality of life could have also been assessed at a more granular level, by considering the area under the curve for the EQ-5D-5L at weekly time points, as opposed to baseline and week 8. This would in turn, produce a different, and potentially more accurate estimation of the loss associated with an asthma-related crisis event.

This research study is particularly important, as it will enable researchers to estimate the loss associated with an asthma-related crisis event in an alternative way, which can also

inform the estimation of QALY losses / gains. An example of a QALY loss estimation was conducted by using the mean change utility score estimated between baseline and week 8 for the EQ-5D-5L (0.086), applied to a hypothetical scenario. These techniques may improve cost effectiveness analyses findings by providing more granular estimations for asthma-related crisis events.

6.1.5 *The relationship between the demographic variables and the utility estimates (EQ-5D-5L, AQL-5D and TTO)*

The prospective cohort study dataset showed a non-normal distribution and a hierarchical structure. The missing data was assumed to be MAR, and therefore a multi-level model was conducted with inclusion of the covariates to estimate the utility loss. The EQ-5D-5L and TTO both showed to have the same best structural model, which was the random polynomial model, and the best structural model for the AQL-5D was a random slope model. The model build was improved by adding the covariates in a stepwise approach, until a preferred model was achieved. The EQ-5D-5L, AQL-5D and TTO models accounted for the strong predictors of missingness. This suggests that these variables may influence the utility estimates of people with acute asthma differently, depending on which approach is taken. It also shows the importance of taking into consideration these variables in future analysis, and shows potential areas for future research if subgroup comparisons are using these variables. The model was further improved by using bootstrapping and multiple imputation to estimate the disutilities associated with an asthma-related crisis event. The EQ-5D-5L, AQL-5D and TTO QALY disutilities were 0.0075, 0.0096 and 0.0035 respectively when using the preferred parsimonious model incorporated with multiple imputation.

6.1.6 *Productivity and out of pocket losses associated with an asthma-related crisis event*

The prospective cohort study, also identified productivity and out of pocket losses associated with an asthma-related crisis event, particularly during the four weeks after attending A&E or being admitted to hospital. The study found that the average productivity loss per person was £309.07, and the average out of pocket costs (additional products purchased due to having the asthma-related crisis event), per person was £16.82.

Not all participants reported that they were back to work after four weeks since their asthma-related crisis event.

These new findings can be used in future research to better estimate the costs associated with an asthma-related crisis event.

6.1.7 *The correlation between the EQ-5D-5L, AQL-5D and TTO utility values*

The three utility instruments that were used in the prospective cohort study were compared against each other to identify if there were any correlations between them. It was found that the EQ-5D-5L and AQL-5D showed statistical significance in their correlations at baseline, week 4 and week 8. Initially the correlations were moderate at baseline, and then this increased to strong correlations at week 4 and week 8. The AQL-5D and the TTO also were also weakly correlated at week 4 and week 8.

Therefore, the results indicate that the EQ-5D-5L and AQL-5D are the two instruments which show strong potential for being considered for economic evaluation studies in acute asthma research, due to the increasing strength in correlations during the study.

6.1.8 *The discriminative validity between the EQ-5D-5L, AQL-5D and TTO utility values*

Several discriminative validity tests were conducted to identify if the utility instruments (EQ-5D-5L, AQL-5D and TTO), were measuring what they were supposed to be measuring. Firstly, three PEF anchor markers were used, which were, < 50% of best / predicted PEF, between 50 and 75% of best / predicted PEF and > 75% of best / predicted PEF. Approximately two-thirds of participants were categorised into the < 50% of best / predicted PEF and between 50 and 75% of best / predicted PEF at baseline. None of the utility instruments showed statistical significance with the PEF groups. For the next two discriminative validity tests, the EQ-5D-5L and the ALQ-5D showed statistical significance for the responses to whether participants thought their asthma had recovered or not at week 4 of the study compared to baseline when having their asthma-related crisis event. About two-thirds of respondents, thought that they hadn’t recovered from their asthma-related crisis event at week 4.

The results show that it tends to take longer than 4 weeks to completely recover from an asthma-related crisis event, as not all of the respondents had returned to their optimum health by week 4 of the study. These results also imply that the EQ-5D-5L and the AQL-5D are better at measuring what they should be measuring in comparison to the TTO, as indicated from the statistical significance in the latter discriminative validity tests. Therefore, these two utility-based instruments (EQ-5D-5L and AQL-5D), initially appear to be best suited to asthma research.

6.1.9 *The responsiveness between the EQ-5D-5L, AQL-5D and TTO utility values*

Responsiveness tests were also conducted to test the sensitivity of the instruments. The test for the responsiveness was whether participants thought their asthma health had improved at week 4 of the study compared to when they attended A&E or were admitted to hospital. The EQ-5D-5L and the AQL-5D showed larger responsiveness compared to the TTO, with the AQL-5D slightly performing better than the EQ-5D-5L. The instruments were least sensitive at detecting participants' response of poor health, compared to very good, good and moderate health for deciding on how they thought their asthma was at week 4 of the study.

6.2 Contributions to the literature

Asthma characteristics, symptoms, effect on quality of life, and interventional treatments or therapies, are well documented in asthma studies. However, there are fewer asthma studies focusing on the impact of quality of life in those who have had attacks that lead to hospital admissions or A&E attendance. A couple of studies have acknowledged this gap in the literature (Lloyd et al., 2007, Luskin et al., 2014). The former study conducted a 4 week study by assessing quality of life on a moderate to severe asthma population group recruited from outpatient clinics and primary care (Lloyd et al., 2007). The latter study included patients with severe or difficult to treat asthma recruited from community physicians, managed care organisations, academic centres and group practices (Luskin et al., 2014). Both studies concluded that there were significant decreases in quality of life associated with these events. This thesis confirms the findings from these two studies,

and further improves on these conclusions because the quality of life measurement used is closer to the occurrence of the event, (asthma-related crisis event). The estimation of the asthma-related crisis event, is a similar approach as to an earlier study, which investigated recurrent cellulitis episodes and estimated QALY loss as a means to express QALY gains in the prevention of cellulitis recurrence (Mason et al., 2014). Therefore, this idea of QALY loss for the estimation of an asthma-related crisis event is a new contribution to the literature influenced from earlier techniques and approaches.

Another contribution of this thesis is from the findings from the PROMs for the asthma-related crisis event, both in terms of the loss in quality of life associated with the event and the psychometric findings for the appropriateness of the PROMs. Both the EQ-5D-5L and the AQL-5D are relatively new measures, so this contribution is of value.

This thesis has also introduced a novel approach of the TTO. Other studies have also adapted the TTO to suit their needs by the method of elicitation, the timeframe (either fixed or life expectancy), and the description of the hypothetical health state (Arnesen and Trommald, 2005).. On reflection, is it practical to ask participants to imagine their life years in a hypothetical state where an asthma-related crisis event continues for the remainder of their life expectancy? Will this be a stretch of their imagination? The main purpose of using the TTO in the way that it was used in this thesis, was to see if the participants' were back to their normal asthma state after their asthma-related crisis event, by not wanting to trade any life years. If the participants' did not trade any life years then their TTO utility would by 1.00. This was useful because it was not known what their normal asthma state was before their asthma-related crisis event, and the other PROMs would not have been able to provide this information, (decrements in scores on other scales could potentially have been due to the presence of co-morbidities).

6.3 Strengths and Limitations

This thesis contributes new research and findings to the literature on utility estimation for those experiencing an asthma crisis event. An initial observation of the vast array of asthma PROMs, coupled with outcome measurement from a limited number of time points, was highlighted in the systematic review. Following this, utility values and scores were provided from estimating the loss associated with an asthma-related crisis event, which can be used in future research. Identifying appropriate PROMs for asthma studies

was an additional strength. This thesis has added value and provided an awareness of how severe asthma can be, and widened the knowledge for more accurate estimations for quality of life in future studies.

Additional limitations to those already discussed, include the lack of ethnic diversity in the prospective cohort study data set. A very high percentage of participants were of white ethnicity (95.83%), even though one of the three study sites included Birmingham, which is known to be ethnically diverse (Office for National Statistics, 2012). The number of participants recruited from Birmingham was considerably smaller than the number of participants recruited in Norwich, as were the number of participants recruited from Aberdeen in comparison to those recruited from Norwich. It was unfortunate that due to timing and resource, recruitment of participants was not at the same rate in Birmingham and Aberdeen as the NNUH in Norwich. This was because of reliance on the research support staff at the Birmingham and Aberdeen hospitals, and due to their other commitments, time was often limited for them to dedicate time for recruitment at these sites. This impacted on the richness of the study data set, as the data wasn't equally reflective of participants from each city. Therefore, this also impacted the generalizability of the data in the UK.

Another limitation, is the number of questionnaires that the participants had to complete over the course of the 8 weeks, which increased the likelihood of missing data or lost to follow up. To ensure that all of the data points were completed, and to reduce the number of missing data points, it was required to actively check that the participants had completed everything that they needed to. This process is often feasible when face to face with the participant, and this proved to be mostly successful at baseline in the study. However, due to the nature of the study (with participants asked to complete questionnaires, daily, weekly and monthly for 8 weeks), and the lack of face to face appointments, (as this would be impractical and burdensome to participants), this limited the amount of active checking whilst face to face with the participant.

This leads to the next limitation of the study, which was related to the large loss to follow up. Participants either withdrew from the study or didn't post back questionnaires. Due to this loss to follow up, it would have benefited the results if the sample size was much larger than the original aim of 100 participants for estimating the loss in quality of life

associated with an asthma-related crisis event. Conversely, for comparing the PROMs using psychometric techniques, the sample size for the available case analysis was sufficient (Fayers and Machin, 2016).

Another limitation is that the novel TTO that I designed to reflect slightly different anchor points (well controlled asthma and current asthma health states), were different from the original design of the TTO from Dolan et al. (1996), as their anchor points were (full health and diseased health state). As a result, I was assuming that the novel approach anchor, 'well controlled asthma health state' did not include any other potential comorbidities that the participants might have had, and just focused on their asthma comorbidity. Therefore, the interpretation of the TTO from my novel approach, cannot be the same as the Dolan et al. (1996) approach, due to the former not being weighted to reflect the Dolan et al. (1996) approach which includes all comorbidities when taking into account the anchor of 'full health state'.

6.4 Potential areas for future research

There are a number of areas where future research could improve these findings further. Firstly, as mentioned previously in this thesis, the actual peak of the asthma crisis event occurred before attendance to A&E or admission to hospital for 60% of the recruited participants. Therefore, the true estimated loss in quality of life associated with an asthma-related crisis event could be higher than that estimated here. It would be interesting to see if that peak in the asthma event could be captured. A possible way to do this would be to follow people with asthma more closely by asking them to complete PROMs regularly, including when they had an asthma-related crisis event and thereafter. Asthma apps could potentially be a great way to incorporate a PROM, to make it easier for potential participants to complete them.

Secondly, estimating the cost of an asthma-related crisis event could also be an area of future research. The estimation could be categorised into three different groups of patients according to their PEF when the patient is having an asthma-related crisis event. For example, the cost could be estimated for those who had a PEF of < 50% of their best/predicted PEF (life threatening asthma), or a PEF of between 50% and 75% of their

best/predicted PEF (moderate acute asthma), or a PEF of > 75% of their best/predicted PEF (good/very good asthma).

Thirdly, another area of future research could be to estimate the minimal important difference for the AQL-5D. As this is a relatively new development, and it has proven its usefulness in this thesis and a previous study, there is potential for this measure to be used more widely in research. With this in mind, having a metric of the minimal important difference is important for relatability and comparability in future studies.

Fourthly, the findings reported in the thesis, and the above research ideas could be combined to enhance a previous study, which compared interventions to estimate cost-effectiveness in terms of e.g. hospital admissions. This would enable the researcher to identify whether alternative estimations for asthma-related crisis events, in terms of cost/QALY, enable comparisons with a more recognised threshold (NICE, 2013) and other studies.

Finally, a qualitative piece of research could be conducted amongst the participants who had experienced the asthma-related crisis events to find out from their perspective how they felt during the event, and their views about the aftercare post crisis event.

Future researchers might benefit from learning about the challenges that I encountered during this research journey and strategies that I found helpful for overcoming these. Therefore, I will discuss this in more detail below.

Conducting a systematic review is challenging in itself, and one of the main challenges lies in the creation of the search strings. These need to be carefully developed in order to ensure that the search is sufficiently capturing the amount of information needed in order to answer the research questions. One way of overcoming this challenge, is by seeking out other systematic reviews with similar research interests in order to get an idea of the search strings used in their reviews. These search strings can then be adapted to suit the systematic review that you are working on, with discussions with a specialist if uncertainty arises.

Additionally, there were many challenges that were involved with the design and development of the prospective cohort study through to recruiting patients. Acute asthma patients are a difficult patient group to conduct research on, and due to this there were ethical concerns about this research project. Initially, the NHS research ethics committee granted a provisional opinion on this research project as they had some ethical concerns, particularly around approaching acute patients in hospital with questionnaires and the timing of when the questionnaires would be distributed. To overcome this concern, discussions with the A&E clinical lead, asthma specialist nurse and a patient and public involvement group took place in order to identify the best practical way to approach the acute patients as early as possible. These discussions offered plausible alternatives, such as, approaching this patient group within an early timeframe of them presenting to hospital.

Recruiting the acute asthma patient group was challenging for two reasons. One of the reasons was due to needing to be made aware as soon as possible of patients attending A&E or being admitted to hospital. This was to ensure that as many patients as possible were approached as early as possible for the purpose of this study in order to maintain the accuracy of estimating the quality of life associated with an asthma-related crisis event as close to the event as possible. This recruitment procedure was challenging as it was not always easy to identify those groups of asthma patients who attended A&E or were admitted to hospital. Therefore, to overcome this challenge, I liaised with the A&E clinical lead and put up posters in the A&E department as a reminder for the staff to contact me if a suitable patient arrived fitting my inclusion criteria. For the hospital admissions, I liaised with the asthma specialist nurse and other respiratory nurses who were regularly involved in the daily triage of asthma patients. This enabled me to ensure that I was capturing the patients who had been admitted to hospital on a daily basis. The second reason was the challenge of loss to follow up for various reasons (e.g. too poorly or too busy). The retention rate was always going to be a challenge given the patient group recruited, however, I didn't expect the loss to follow up to be so large. To overcome this challenge, I sent an amendment to ethics and ask to increase the recruitment target number to account for this loss.

Overall, research brings challenges, but these challenges can be reduced with patience, willingness to learn and the right levels of expertise.

6.5 Conclusion

Overall, this thesis has investigated the quality of life in acute asthmatics, with a particular interest in their quality of life during an asthma-related crisis event (A&E attendance or hospital admission). Initially, a systematic review was conducted to explore the cost effectiveness of non-pharmacological asthma management interventions and identify the methodologies used to estimate costs and outcomes. Educational and environmental interventions were generally observed as being cost effective, which was in line with an earlier review, and the studies had also tended to improve in quality, compared to earlier studies. Due to also concluding that there were many PROMs used to measure quality of life, and that quality of life was mostly captured at set time points that were often months apart, a prospective cohort study was designed. The cohort study explored the loss in quality of life in people who had an asthma-related crisis event over 8 weeks. This study found most of the loss associated with an asthma-related crisis event to occur during the first four weeks of the study, with an estimated loss in EQ-5D-5L utility of 0.127 and AQL-5D utility of 0.099 (using available case analysis) for the two most appropriate tools for measuring quality of life in economic evaluations. When using multi-level modelling incorporated with multiple imputation, the QALY disutility was estimated to be 0.0075 and 0.0096 for the EQ-5D-5L and AQL-5D respectively over 8 weeks.

Of the preference-based measures, the EQ-5D-5L and the AQL-5D performed well, as evidenced by strong correlations and large levels of responsiveness and the TTO produced poor results for construct validity and responsiveness. Therefore, given the poor results from the TTO, I do not consider this to be suitable for this asthma population. However, I do consider the EQ-5D-5L and AQL-5D to be suitable given the results, and I would consider using both in future studies.

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Appendices

Appendix I: Adapted version of the QHES checklist by Yong and Shafie (2014)

No.	Questions / Criteria	Scoring system	Highest total score
1	Was the study objective presented in a clear, specific, and measureable manner?	Clear, specific, measurable = 7 Any two = 5 Any one = 2 None = 0	7
2	Were the perspective of the analysis (societal, third-party payer, etc.) and reasons for its selection stated?	(1) Perspective = 2 (2) Reasons = 2	4
3	Were variable estimates used in the analysis from the best available source (i.e., randomized control trial – best, expert opinion – worst)?	Randomized control trial = 8 Non-Randomized control trial = 7 Cohort Studies = 6 Case-control/case report/case series = 4 Expert opinion = 2	8
4	If estimates came from a subgroup analysis, were the groups pre-specified at the beginning of the study?	Yes = 1 No = 0	1
5	Was uncertainty handled by (1) statistical analysis to address random events, (2) sensitivity analysis to cover a range of assumptions?	(1) Statistical analysis = 4.5 (2) Sensitivity analysis = 4.5	9

No.	Questions / Criteria	Scoring system	Highest total score
6	Was incremental analysis performed between alternatives for resources and costs? *If the case is CBA, then the question shall ask "Was net monetary benefit / cost benefit ratio performed between alternatives for resources and costs?"*	Yes = 6 No = 0 *CCA type of economic evaluation = NA*	6
7	Was the methodology for data extraction (including the value of health states and other benefits) stated?	Yes = 5 No = 0	5
8	Did the analytic time horizon allow time for all relevant and important outcomes? Were benefits and costs that went beyond 1 year discounted (3% and 5%) and justification given for the discount rate?	If less than 1 year, only answer for the time horizon. Yes = 7, No = 0; If more than 1 year, done for (1) Time horizon = 3 (2) Cost discounting = 1 (3) Benefit discounting = 1 (4) Justification = 2	7
9	Was the measurement of costs appropriate and the methodology for the estimation of quantities and unit costs clearly described?	Done for (1) Appropriateness of cost measurement = 4 (2) Clear description of methodology for the estimation of quantities = 2 (3) Clear description of methodology for the	8

No.	Questions / Criteria	Scoring system	Highest total score
		estimation of unit costs = 2	
10	Were the primary outcome measure(s) for the economic evaluation clearly stated and did they include the major short-term? Was justification given for the measures/scales used?	Done for (1) Primary outcome clearly stated = 2 (2) Include major short-term outcome = 2 (3) Justification = 2	6
11	Were the health outcomes measures/scales valid and reliable? If previously tested valid and reliable measures were not available, was justification given for the measures/scales used?	Yes = 7 No = 0	7
12	Were the economic model (including structure), study methods and analysis, and the components of the numerator and denominator displayed in a clear, transparent manner?	If modelling study, done for (1) Economic model = 2 (2) Study methods = 1.5 (3) Analysis = 1.5 (4) Components of numerator = 1.5 (5) Components of denominator = 1.5 If not a modelling study, done for (1) Study methods = 2 (2) Analysis = 2 (3) Components of numerator = 2 (4) Components of denominator = 2	8

No.	Questions / Criteria	Scoring system	Highest total score
13	Were the choice of economic model, main assumptions, and limitations of the study stated and justified?	If modelling study, done (stated and justified) for (1) Economic model = 2 (2) Assumptions = 2.5 (3) Limitations = 2.5 If not a modelling study, done (stated and justified) for (1) Assumptions = 3.5 (2) Limitations = 3.5	7
14	Did the author(s) explicitly discuss direction and magnitude of potential biases?	(1) Direction = 3 (2) Magnitude = 3	6
15	Were the conclusions/recommendations of the study justified and based on the study results?	Yes = 8 No = 0	8
16	Was there a statement disclosing the source of funding for the study?	Yes = 3 No = 0	3

Appendix II: Resource use, intervention components and method of estimation across all studies

	Anderson et al, 2004	*Asis et al, 2004*	*Atherly et al, 2009*	*Bhaumik et al, 2013*	*Bolton et al, 1991*	*Bratton et al, 2001*	*Bunting et al, 2006*	*Castro et al, 2003*
Intervention resource use measured								
Staff costs	*		**	*	*	*	*	*
Program materials and/or equipment supplies		**	*	*	*	*	*	*
Education and training sessions		**	*	*	*	*	*	*
Operating costs of activities (including meetings)					*			
Travel costs								
Compensation for participants and/or personnel			**					
Overhead costs				*	*			
Wider resource use measured								
Hospital costs (including inpatient, outpatient and emergency visits)	**	**	*	*	*	**	*	*
Healthcare professional costs (including visits and calls)	**		*		*	**	*	*
Transportation costs								
Medication costs			*				*	*
Lost productivity costs			*	*	*		*	*
Miscellaneous expenses (e.g. mattress covers, pillow covers, air-conditioning, cleaning devices)								
Method of estimation								
Bottom-up approach		*	*	*			*	*
Top-down approach	*				*	*		

*****Reports item

**Reports item and unit cost

	Chan et al, 2004	***Doan et al, 1996***	***Donald et al, 2008***	***Drummond et al, 1994***	***D'Souza et al, 2010***	***Fabian et al, 2014***	***Flores et al, 2009***	***Franco et al, 2007***
Intervention resource use measured								
Staff costs	*	*	**	*	*		*	*
Program materials and/or equipment supplies	*	*	**	*	*		**	*
Education and training sessions	*	*	**	*	*		**	*
Operating costs of activities (including meetings)						*		
Travel costs								
Compensation for participants and/or personnel							**	
Overhead costs						*	**	
Wider resource use measured								
Hospital costs (including inpatient, outpatient and emergency visits)	*	**	*	*	*	**	*	*
Healthcare professional costs (including visits and calls)	*	**	*	*	*	**	*	*
Transportation costs								*
Medication costs	*		*	*	*	**	*	*
Lost productivity costs			*			*	*	*
Miscellaneous expenses (e.g. mattress covers, pillow covers, air-conditioning, cleaning devices)								
Method of estimation								
Bottom-up approach	*	*	*		*	*	*	
Top-down approach				*				*

*****Reports item

**Reports item and unit cost

	Gallefoss et al, 2001	***Ghosh et al, 1998***	***Gordois et al, 2007***	***Greineder et al, 1999***	***Higgins et al, 1998***	***Johnson et al, 2003***	***Kamps et al, 2004***	***Karnick et al, 2007***
Intervention resource use measured								
Staff costs	*	**	**	*	*	*	*	*
Program materials and/or equipment supplies	*	**	**	*	*	*	*	*
Education and training sessions	*	**	*	*	*	*	*	*
Operating costs of activities (including meetings)					*			*
Travel costs	*	**						
Compensation for participants and/or personnel								
Overhead costs								
Wider resource use measured								
Hospital costs (including inpatient, outpatient and emergency visits)	*	*	**	**	**	*	**	**
Healthcare professional costs (including visits and calls)	*	*	**	**	**	*	**	**
Transportation costs								
Medication costs	*		**		**		**	**
Lost productivity costs		*					**	
Miscellaneous expenses (e.g. mattress covers, pillow covers, air-conditioning, cleaning devices)								
Method of estimation								
Bottom-up approach	*	*	*	*			*	
Top-down approach					*	*		*

*****Reports item

**Reports item and unit cost

	Kattan et al, 2005	***Kauppinen et al, 1998***	***Kauppinen et al, 1999***	***Kauppinen et al, 2001***	***Lara et al, 2013***	***Levenson et al, 1997***	***Lindberg et al, 2002***	***Lucas et al, 2001***
Intervention resource use measured								
Staff costs	**	*	*	*	*	*	*	*
Program materials and/or equipment supplies	**	*	*	*	*	*	*	*
Education and training sessions		*	*	*	*	*	*	*
Operating costs of activities (including meetings)	**	*	*	*	*	*	*	*
Travel costs	**							
Compensation for participants and/or personnel								
Overhead costs								
Wider resource use measured								
Hospital costs (including inpatient, outpatient and emergency visits)	**	**	**	*	*	**	*	**
Healthcare professional costs (including visits and calls)	**	**	**	*	*			
Transportation costs		**						
Medication costs	**	*	**	*			*	
Lost productivity costs			**				*	*
Miscellaneous expenses (e.g. mattress covers, pillow covers, air-conditioning, cleaning devices)	*							
Method of estimation								
Bottom-up approach	*	*	*	*	*	*	*	
Top-down approach								*

*****Reports item

**Reports item and unit cost

	McCowan et al, 1997	*McLean et al, 2003*	*Meer et al, 2011*	*Mogasale et al, 2013*	*Neri et al, 1996*	*Ng et al, 2006*	*Polisena et al, 2007*	*Rhee et al, 2012*
Intervention resource use measured								
Staff costs	*	*	**	*	**	*	**	**
Program materials and/or equipment supplies	*	*	**	*	**	*	**	**
Education and training sessions	*	*	**	*	**	*	**	**
Operating costs of activities (including meetings)		*	**	*	**			
Travel costs			**					**
Compensation for participants and/or personnel								**
Overhead costs								
Wider resource use measured								
Hospital costs (including inpatient, outpatient and emergency visits)	**	**	*	**	**	**	**	*
Healthcare professional costs (including visits and calls)	**	**	*	**	**		**	*
Transportation costs				**				
Medication costs	**	**	*				**	
Lost productivity costs		**	*	**	**		**	
Miscellaneous expenses (e.g. mattress covers, pillow covers, air-conditioning, cleaning devices)								
Method of estimation								
Bottom-up approach	*	*	*	*	*	*	*	*
Top-down approach								

*****Reports item

**Reports item and unit cost

	Rossiter et al, 2000	***Runge et al, 2006***	***Ryan et al, 2012***	***Schermer et al, 2002***	***Shelledy et al, 2009***	***Shelledy et al 2005***	***Smith et al, 2012***	***Steuten et al, 2007***
Intervention resource use measured								
Staff costs	*	**	*	**	*	*	*	*
Program materials and/or equipment supplies	*	**	*	**	*	*	*	*
Education and training sessions	*	**	*	**	*	*	*	*
Operating costs of activities (including meetings)	*	**	*	**	*	*	*	
Travel costs		**						
Compensation for participants and/or personnel								
Overhead costs								*
Wider resource use measured								
Hospital costs (including inpatient, outpatient and emergency visits)	*	**	*	*	**	*	*	*
Healthcare professional costs (including visits and calls)	*	**	*	*	*	*	*	*
Transportation costs		**						
Medication costs	*	**		**		*	*	*
Lost productivity costs		**		**		*		*
Miscellaneous expenses (e.g. mattress covers, pillow covers, air-conditioning, cleaning devices)								
Method of estimation								
Bottom-up approach		*	*	*			*	*
Top-down approach	*				*	*		

*****Reports item

**Reports item and unit cost

	Suh et al, 2000	***Sullivan et al, 2005***	***Sullivan et al, 2002***	***Tagaya et al, 2005***	***Tai et al, 2011***	***Taitel et al, 1995***	***Tinkelman et al, 2004***	***Tschopp et al, 2002***
Intervention resource use measured								
Staff costs	*	*	**	*	*	*	*	*
Program materials and/or equipment supplies	*	*	**	*	*	*	*	*
Education and training sessions	*	*	**	*	*	*	*	*
Operating costs of activities (including meetings)	*	*	**	*	*		*	*
Travel costs								
Compensation for participants and/or personnel								
Overhead costs								
Wider resource use measured								
Hospital costs (including inpatient, outpatient and emergency visits)	*	**	**	*	*	*	*	*
Healthcare professional costs (including visits and calls)	*	**	**	*		*	*	*
Transportation costs						*		
Medication costs	*			*		*	*	*
Lost productivity costs					*	*		*
Miscellaneous expenses (e.g. mattress covers, pillow covers, air-conditioning, cleaning devices)			**			*		
Method of estimation								
Bottom-up approach	*	*	*	*		*	*	*
Top-down approach					*			

*****Reports item

**Reports item and unit cost

	Tschopp et al, 2005	***Turcotte et al, 2014***	***Westley et al, 1997***	***Willems et al, 2007***	***Wood et al, 2011***	***Woods et al, 2012***	***Xu et al, 2010***
Intervention resource use measured							
Staff costs	*	*	*	**	*	*	**
Program materials and/or equipment supplies	*	*	*	**	*	*	**
Education and training sessions	*	*	*	**	*	*	
Operating costs of activities (including meetings)	*	*					**
Travel costs							
Compensation for participants and/or personnel		**			**		
Overhead costs				**			
Wider resource use measured							
Hospital costs (including inpatient, outpatient and emergency visits)	**	**	**	**	*	*	**
Healthcare professional costs (including visits and calls)	**	**	**	**	*	*	**
Transportation costs							
Medication costs				**			**
Lost productivity costs	**			**			
Miscellaneous expenses (e.g. mattress covers, pillow covers, air-conditioning, cleaning devices)							
Method of estimation							
Bottom-up approach	*	*	*	*	*	*	*
Top-down approach							

*****Reports item

**Reports item and unit cost

Appendix III: Types of outcomes measured, data collection and estimation methods

	Anderson et al 2004	***Asis et al 2004***	***Atherly et al 2009***	***Bhaumik et al 2013***	***Bolton et al 1991***	***Bratton et al 2001***	***Bunting et al 2006***	***Castro et al 2003***
Outcomes measured								
Emergency departments (ED) visits	*	*			*		*	*
Hospitalization visits	*	*			*		*	*
Intensive care admissions								
Outpatient visits								
Physician (clinic) visits					*			
Frequency of exacerbations								
Symptoms							*	
Quality of Life			*	*		*	*	*
Psychiatric difficulties						*		
Lost productivity (children/parents/careg ivers)				*	*			*
Asthma Knowledge / education			*					
Forced Expiratory Volume (FEV)							*	
Forced Vital Capacity (FVC)								
Peak Expiratory Flow (PEF)		*	*					
Medications								
Prescriptions								
Airway responsiveness								
Disability weights								
Data collection methods								
Telephone interviews	*				*	*		
Face to Face visits								
Patient self-reported questionnaires		*	*			*	*	*
Parent-reported questionnaires								
Caregivers questionnaires								
Case managers self-reported questionnaires				*				
Patient diary								
Medical records	*							
Claims records							*	
Letters								
Previous reviews & studies								
Methods used to estimate outcomes								
Spirometry							*	
Peak Flow meter		*	*					
Histamine dosage								
QALYs								
DALYs								

	Chan et al 2004	Doan et al 1996	Donald et al 2008	Drummond et al 1994	D'Souza et al 2010	Fabian et al 2014	Flores et al 2009	Franco et al 2007
Outcomes measured								
Emergency departments (ED) visits		*	*		*	*	*	*
Hospitalization visits		*	*	*	*	*	*	*
Intensive care admissions								*
Outpatient visits		*						
Physician (clinic) visits			*	*	*	*		*
Frequency of exacerbations							*	
Symptoms			*	*		*		
Quality of Life	*		*					
Psychiatric difficulties								
Lost productivity (children/parents/caregivers)			*				*	*
Asthma Knowledge / education	*							
Forced Expiratory Volume (FEV)								*
Forced Vital Capacity (FVC)								*
Peak Expiratory Flow (PEF)	*		*					*
Medications	*	*	*	*	*	*		*
Prescriptions								
Airway responsiveness								
Disability weights								
Data collection methods								
Telephone interviews			*				*	
Face to Face visits								*
Patient self-reported questionnaires	*		*	*				*
Parent-reported questionnaires							*	
Caregivers questionnaires								
Case managers self-reported questionnaires								
Patient diary	*		*					
Medical records		*		*				
Claims records					*			
Letters								
Previous reviews & studies								
Methods used to estimate outcomes								
Spirometry								*
Peak Flow meter	*		*					*
Histamine dosage								
QALYs								
DALYs								

	Gallefoss et al 2001	Ghosh et al 1998	Gordois et al 2007	Greineder et al 1999	Higgins et al 1998	Johnson et al 2003	Kamps et al 2004	Karnick et al 2007
Outcomes measured								
Emergency departments (ED) visits		*		*	*	*	*	*
Hospitalization visits		*		*	*	*	*	*
Intensive care admissions								
Outpatient visits					*	*		*
Physician (clinic) visits					*	*	*	*
Frequency of exacerbations								
Symptoms	*						*	*
Quality of Life	*		*					
Psychiatric difficulties								
Lost productivity (children/parents/caregivers)							*	*
Asthma Knowledge / education								
Forced Expiratory Volume (FEV)	*							
Forced Vital Capacity (FVC)	*							
Peak Expiratory Flow (PEF)		*						
Medications							*	*
Prescriptions					*			
Airway responsiveness								
Disability weights								
Data collection methods								
Telephone interviews				*				*
Face to Face visits	*						*	
Patient self-reported questionnaires	*		*					
Parent-reported questionnaires								
Caregivers questionnaires								
Case managers self-reported questionnaires								
Patient diary		*					*	
Medical records					*			
Claims records				*		*		
Letters								
Previous reviews & studies								
Methods used to estimate outcomes								
Spirometry	*							
Peak Flow meter		*						
Histamine dosage								
QALYs			*					
DALYs								

	Katta n et al 2005	*Kauppine n et al 1998*	*Kauppine n et al 1999*	*Kauppine n et al 2001*	*Lar a et al 201 3*	*Levenso n et al 1997*	*Lindber g et al 2002*	*Luca s et al 2001*
Outcomes measured								
Emergency departments (ED) visits	*				*	*		*
Hospitalization visits	*				*	*		*
Intensive care admissions						*		
Outpatient visits								*
Physician (clinic) visits	*						*	*
Frequency of exacerbations								
Symptoms	*				*		*	
Quality of Life		*	*	*			*	*
Psychiatric difficulties								
Lost productivity (children/parents/caregivers)								*
Asthma Knowledge / education								*
Forced Expiratory Volume (FEV)		*	*	*			*	
Forced Vital Capacity (FVC)		*	*	*			*	
Peak Expiratory Flow (PEF)		*	*	*			*	
Medications	*					*		
Prescriptions	*							
Airway responsiveness		*	*	*				
Disability weights								
Data collection methods								
Telephone interviews	*							*
Face to Face visits		*	*	*	*			
Patient self-reported questionnaires		*	*	*			*	*
Parent-reported questionnaires					*		*	
Caregivers questionnaires								
Case managers self-reported questionnaires								
Patient diary		*	*	*			*	
Medical records								
Claims records								
Letters								
Previous reviews & studies								
Methods used to estimate outcomes								
Spirometry		*	*	*			*	
Peak Flow meter		*	*	*			*	
Histamine dosage		*	*	*				
QALYs								
DALYs								

	McCowan et al 1997	*McLean et al 2003*	*Meer et al 2011*	*Mogasale et al 2013*	*Neri et al 1996*	*Ng et al 2006*	*Polisena et al 2007*	*Rhee et al 2012*
Outcomes measured								
Emergency departments (ED) visits	*	*		*		*	*	*
Hospitalization visits	*	*		*		*	*	*
Intensive care admissions								
Outpatient visits	*						*	
Physician (clinic) visits	*			*		*	*	*
Frequency of exacerbations	*					*		
Symptoms								
Quality of Life		*	*					
Psychiatric difficulties								
Lost productivity (children/parents/caregivers)		*						
Asthma Knowledge / education							*	
Forced Expiratory Volume (FEV)					*			
Forced Vital Capacity (FVC)					*			
Peak Expiratory Flow (PEF)		*			*			
Medications							*	
Prescriptions	*							
Airway responsiveness								
Disability weights				*				
Data collection methods								
Telephone interviews				*		*		
Face to Face visits							*	
Patient self-reported questionnaires		*	*		*			
Parent-reported questionnaires								*
Caregivers questionnaires								
Case managers self-reported questionnaires								
Patient diary		*			*			
Medical records	*				*			
Claims records								
Letters								
Previous reviews & studies				*				
Methods used to estimate outcomes								
Spirometry					*			
Peak Flow meter		*			*			
Histamine dosage								
QALYs			*					
DALYs				*				

	Rossiter et al 2000	***Runge et al 2006***	***Ryan et al 2012***	***Schermer et al 2002***	***Shell-edy et al 2009***	***Shell-edy et al 2005***	***Smith et al 2012***	***Steuten et al 2007***
Outcomes measured								
Emergency departments (ED) visits	*	*	*			*	*	
Hospitalization visits		*	*			*	*	
Intensive care admissions						*		
Outpatient visits		*				*	*	
Physician (clinic) visits		*	*			*	*	
Frequency of exacerbations			*					
Symptoms				*			*	
Quality of Life		*	*	*	*			*
Psychiatric difficulties								
Lost productivity (children/parents/caregivers)		*				*		
Asthma Knowledge / education								
Forced Expiratory Volume (FEV)		*		*	*			
Forced Vital Capacity (FVC)		*			*			
Peak Expiratory Flow (PEF)		*		*	*			
Medications		*	*					
Prescriptions			*				*	
Airway responsiveness				*				
Disability weights								
Data collection methods								
Telephone interviews								
Face to Face visits			*					
Patient self-reported questionnaires			*	*	*			*
Parent-reported questionnaires								
Caregivers questionnaires								
Case managers self-reported questionnaires								
Patient diary				*				
Medical records		*	*			*	*	
Claims records	*							
Letters							*	
Previous reviews & studies								*
Methods used to estimate outcomes								
Spirometry		*		*				
Peak Flow meter		*		*				
Histamine dosage				*				
QALYs								*
DALYs								

	Suh et al 2000	***Sullivan et al 2005***	***Sullivan et al 2002***	***Tagaya et al 2005***	***Tai et al 2011***	***Taitel et al 1995***	***Tinkelman et al 2004***	***Tschopp et al 2002***
Outcomes measured								
Emergency departments (ED) visits	*			*	*	*	*	*
Hospitalization visits	*			*	*	*		*
Intensive care admissions								
Outpatient visits								
Physician (clinic) visits	*					*		
Frequency of exacerbations				*				
Symptoms		*	*				*	
Quality of Life								*
Psychiatric difficulties								
Lost productivity (children/parents/caregivers)								*
Asthma Knowledge / education								
Forced Expiratory Volume (FEV)								
Forced Vital Capacity (FVC)								
Peak Expiratory Flow (PEF)				*				
Medications				*		*	*	
Prescriptions	*							
Airway responsiveness								
Disability weights								
Data collection methods								
Telephone interviews			*					
Face to Face visits		*						
Patient self-reported questionnaires			*					*
Parent-reported questionnaires								
Caregivers questionnaires		*						
Case managers self-reported questionnaires								
Patient diary				*				
Medical records								
Claims records	*		*			*		
Letters								
Previous reviews & studies					*			
Methods used to estimate outcomes								
Spirometry								
Peak Flow meter				*				
Histamine dosage								
QALYs								
DALYs								

	Tschoop et al 2005	*Turcotte et al 2014*	*Watanabe et al 1998*	*Westley et al 1997*	*Willems et al 2007*	*Wood et al 2011*	*Woods et al 2012*	*Xu et al 2010*
Outcomes measured								
Emergency departments (ED) visits	*	*	*	*	*	*	*	*
Hospitalization visits	*	*	*	*	*	*	*	*
Intensive care admissions		*						
Outpatient visits	*		*					
Physician (clinic) visits		*	*	*		*		*
Frequency of exacerbations								
Symptoms								
Quality of Life	*	*			*			*
Psychiatric difficulties								
Lost productivity (children/parents/caregivers)	*		*		*		*	
Asthma Knowledge / education								
Forced Expiratory Volume (FEV)					*			
Forced Vital Capacity (FVC)					*			
Peak Expiratory Flow (PEF)					*			
Medications			*				*	*
Prescriptions			*					
Airway responsiveness								
Disability weights								
Data collection methods								
Telephone interviews			*				*	
Face to Face visits							*	
Patient self-reported questionnaires	*				*			*
Parent-reported questionnaires		*				*	*	
Caregivers questionnaires								
Case managers self-reported questionnaires			*					*
Patient diary								
Medical records	*				*			
Claims records	*							
Letters								
Previous reviews & studies								
Methods used to estimate outcomes								
Spirometry					*			
Peak Flow meter								
Histamine dosage								
QALYs					*			
DALYs								

Appendix IV: Quality assessment scores for the fifteen additional studies using the QHES checklist for the systematic review

QHES criteria no. (*)	*Atherly et al, 2009*	*Bhaumik et al, 2013*	*Castro et al, 2003*	*Fabian et al, 2014*	*Flores et al, 2009*	*Higgins et al, 1998*	*Karnick et al, 2007*	*Lara et al, 2013*	*McCowan et al, 1997*	*Mogasale et al, 2013*	*Ryan et al, 2012*	*Smith et al, 2012*	*Tai et al, 2011*	*Turcotte et al, 2014*	*Willems et al, 2007*
1	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7
2	2	4	0	4	0	0	4	0	0	2	2	2	2	0	2
3	8	6	8	4	8	6	8	6	8	8	8	8	6	6	8
4	0	0	0	1	0	0	1	0	0	0	0	0	0	0	1
5	4.5	4.5	4.5	4.5	4.5	4.5	4.5	4.5	0	9	9	4.5	0	4.5	9
6	6	6	0	0	6	0	0	0	0	6	0	6	0	0	6
7	5	5	5	0	5	5	5	5	0	5	5	5	5	5	5
8	7	7	0	5	7	7	7	7	0	0	7	7	0	7	7
9	6	6	2	6	8	8	8	6	8	8	6	6	8	8	8
10	6	6	4	0	6	4	4	6	4	0	4	6	0	4	4
11	0	7	7	0	7	7	7	7	7	7	0	7	0	7	7
12	4	8	8	4.5	4	8	8	5	2	8	8	8	2	4	8
13	3.5	7	3.5	7	3.5	3.5	3.5	3.5	3.5	7	7	7	7	7	3.5
14	0	6	6	0	0	6	6	3	0	0	3	0	6	0	6
15	8	8	8	8	8	8	8	8	8	8	8	8	8	8	8
16	0	3	3	3	3	0	3	3	3	3	3	3	0	3	0
Total	**67**	**90.5**	**66**	**54**	**77**	**74**	**84**	**71**	**50.5**	**78**	**77**	**84.5**	**51**	**70.5**	**89.5**

Appendix V: The resources, outcomes and methods used in the included papers in the systematic review

First author, Year, Country of Population	***Resource use (unit cost)***	***Method of estimating & valuing resources***	***Method of estimating intervention cost component***	***Cost results (Int. & Con.)***	***Types of outcomes measured***	***Method of estimating & valuing outcomes***	***Outcome results***	***Response rates***
Anderson et al, 2004, United States	Hospitalizations ($1575/day), Emergency visits ($685/visit), Follow-up visits ($50/visit)	Averaged from 6 local hospitals and the Colorado Hospital Association	Not stated	***Int.*** Before = $8122 After = $1588 (80% cost reduction) ***Control***: Before = $2915 After = $2376 (19% reduction)	Comparing annual rates of hospitalizations, emergency department (ED) visits and follow up visits	Telephone interviews were used to contact the parents of the children at Kunsberg to confirm whether the primary utilization of Denver Health medical services was continued. Audited asthma utilization from Denver Health medical records.	***Hospitalizations (per year/child):*** Pre-period (Int. = 0.95; Con. =0.94) Post-period: (Int. = 0.55; Con. = 0.89) p = 0.05. ***ED visits (per year/child):*** Pre-period (Int. = 1.1; Con. = 1.3) Post-period: (Int. = 0.5; Con. = 1.3) p = 0.04. ***Follow up visits (per year/child):*** Pre-period (Int. = 3.3; Con. = 2.0) Post period: (Int. = 0.8; Con. = 2.3) p = 0.01. *[At-risk subgroup for Intervention only. Hospitalizations (per days/year/child):*	Not stated

First author, Year, Country of Population	*Resource use (unit cost)*	*Method of estimating & valuing resources*	*Method of estimating intervention cost component*	*Cost results (Int. & Con.)*	*Types of outcomes measured*	*Method of estimating & valuing outcomes*	*Outcome results*	*Response rates*
							pre-period = 3.5. Post-period = 0.1 p < 0.01. Intensive care unit (ICU) (per days/year/child): pre-period = 1.0 post-period = 0. p < 0.004. ED visits (per days/year/child): pre-period = 2.1 post-period = 0.6. p = 0.02. Follow up visits (per days/year/child): pre-period = 6.8 post-period = 2.1. p = 0.02].	
Asis et al, 2004, United States	Mini wright peak flowmeter ($28); Asthma education program ($35); Emergency Room visits ($209); Hospitalization for asthma ($3102)	Peak flowmeter - based on average wholesale price; asthma education plans – based on literature; ER visits & hospitalizations – based on	Not stated	Program cost of peak flow plan = $63 per patient. Program cost of symptom based plan = $35 per patient	Reduction in the number of ER visits and hospitalizations caused from asthma exacerbations during the 6 month period	Patient questionnaires	***Peak flow management:*** Reduction in ER visits = 91%; Reductions in hospitalizations = 84%. ***Symptoms management:*** Reduction in ER visits = 0%; Reductions in	Not stated

First author, Year, Country of Population	*Resource use (unit cost)*	*Method of estimating & valuing resources*	*Method of estimating intervention cost component*	*Cost results (Int. & Con.)*	*Types of outcomes measured*	*Method of estimating & valuing outcomes*	*Outcome results*	*Response rates*
		Premier's perspective comparative database (provides detailed resource use for 1996 - 1997)					hospitalizations = 13%	
Atherly et al, 2009, United States	***Direct costs*** - medical service use (ED visits; hospitalizations; outpatient care; prescription drugs, peak flow devices). ***Indirect costs*** - lost productivity, school absences, waiting times in doctors.	Considered direct costs and indirect costs. Not clear - assuming surveys	Program costs included: compensation for students participants ($10), compensation for school personnel ($25 for teachers, $30 for school nurses, $50 program facilitators). Time spent by students (2.25 hrs per student), parents (0.42 hrs per parent), teachers (0.67 hrs per teacher), school nurses (1.01 per nurse), program	Intervention cost = $6500 per year. Or $30.37 per student	Asthma knowledge, measuring impact of program's knowledge, understanding of asthma disease process, self-management techniques, attitudes toward asthma, self-management behaviours, asthma related quality of life, health status	Surveys	***Baseline: In previous 4 weeks*** - any hospitalizations (Int = 2.54%, Con = 3.08%, p-value = 0.725). Any ED visits (Int = 5.08%, Con = 9.25% p = 0.082). ***Post intervention: In previous 4 weeks*** - any hospitalizations (Int = 1.27%, Con = 1.76% p = 0.667). Any ED visit (Int =3.39%, Con = 3.52% p = 0.937). Change in no. of asthma symptoms from post-intervention &	524 were included, but only 458 completed surveys. (87%)

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			facilitators (1.17 hrs per program facilitator). No. of hours spent by respondent/participant multiplied by average hourly wage earned				baseline (Int = -0.18, Con = 0.09 p = 0.125). Change in no. of days with asthma symptoms among those with symptoms at baseline (Int = -1.97 Con = 0.619, p = 0.008	
Bhaumik et al, 2013, United States	Ed visits, Hospitalizations, Missed days at work/school.	Costs collected from Children's financial database (including labour, supplies, overhead costs - depreciation & building costs, it did not include physician costs). No. of ED visits & hospitalizations extracted	Program costs obtained from clinical budget of the program (staff costs and cost of supplies were main components). The cost of instruction for each student per day was computed using the annual budget for the Boston school districts for money spent on instruction divided by the number of enrolled students	**Total cost savings: *Year 1 per patient*** (Int = $1780, Con = $436). ***Year 2 per patient*** (Int = $2305, Con = $746). ***Year 3 per patient*** (Int = $1873, Con = $1003)	Quality of life improvements - missed days from work/school for children and parents/caregivers.	Self-reported data recorded by CAI Case managers at baseline, 6 months and 1 year (only for intervention)	Reduction in proportion of patients hospitalized. ***Year 1*** (Int = 0.37 (p<0.001), Con = 0.09 p = 0.11) ***Year 2*** (Int = 0.43 (p < 0.001), Con = 0.12 p = 0.03) ***Year 3*** (Int = 0.43 (p<0.001), Con = 0.16 p = 0.003)	Not stated

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		from Children's administrative data. No. of missed days at work/school - self-reported data from CAI Case Managers	and divided by 180 (assuming 180 classes are held each year)					
Bolton et al, 1991, United States	ED visits, Physician visits; Hospitalizations	7 month sample of billing data was used. Average charges per emergency visit, per outpatient visit, and per hospital day were calculated. Appropriate cost-to-charge ratios were also used due to	Cost of developing program (incl. wages, overheads & materials) plus operating costs of day to day activities	***Per person per year.*** ED visits; Int = $408 Con = $1,036. Physician; Int = $281 Con = $351. Hospitalization; Int = $2,250 Con = $3,461. Total; Int = $2, 936 Con = $4, 849 p = 0.10	Asthma related visits (physician, Emergency Department (ED), Hospitalization). Limited Activity days	Both groups were interviewed every 4 months with a blinded telephone interview	***Mean per 100 persons. First 4 months:*** ED visits; Int = 68 Con = 220 p= 0.003. Physician visits; Int = 197 Con = 287 p = 0.35. Hospitalization; Int = 26 Con = 39 p = 0.4. Limited activity days; Int = 622 Con = 888 p = 0.03. ***Monthly average for 12 months:*** ED visits; Int = 16 Con = 39 p = 0.0005 Physician; Int = 46 Con = 58 p = 0.16.	Intervention follow-up = 93; Control follow-up 92

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		charges overestimating the actual cost. Wage rates used to calculate productivity costs					Hospitalization; Int = 7 Con = 10 p = 0.23. Limited activity days; Int = 161 Con = 246 p = 0.04	
Bratton et al, 2001, United States	Intensive care day charges with ventilator ($3,500); Intensive care day charges without ventilator ($2,000). Hospitalization day charges ($1,575), A+E visit ($600), "sick" visits ($135), "well" visits ($50).	Averaged 1996 data from six local hospitals and the Colorado Hospital Association. Survey report of 12 and 24 month healthcare contracts, medical records obtained from every provider seen. Medical records coded. A medical	Not stated	Before = $16,250. 1 year = $1,902. 2 years = $690. (P < 0.0001 between admission and 1 year)	Functional severity of asthma scale (FSAS), Paediatric asthma caregiver's quality of life questionnaire, Paediatric asthma quality of life scales (PQLQ), Paediatric illness-related competence scale (PIRC),	***Quality of Life:*** Postal questionnaires (completed by competent > 7 year olds, and families) at baseline, 12 and 24 months. If questionnaires were not returned in 'timely fashion' (proper time frame is not provided) then a follow up telephone call was provided requesting answers over	***Self-report:*** FSAS: Baseline = 16.5, 1 year = 9.5, 2 years = 8.3 (P < 0.0001). CQLQ: Baseline = 4.2, 1 year = 5.6, 2 years = 6.1 (P < 0.0001). PQLQ: Baseline = 4.4, 1 year = 5.8, 2 years = 6.1 (P < 0.0001). ***Medication:*** Corticosteroids: Baseline = 66% use; 1 year = 26% use; 2 years = 13% use. (P=0.0001). Corticosteroid dosage decreased to 0mg/day at 1 and 2 years follow up (P < 0.0001).	***Between Year 1 and Year 2 follow-up:*** one patient died. Medical record data: ***Year 1*** = 83/98; 84.7%; **Year 2** = 77/90; 85.6%. ***Questionnaire data: Year 1*** = 87/98; 88.8%; ***Year 2*** = 71/90; 78.9%

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		encounter utilization derived by summing weighted value assignments for hospital, emergency and office visits. The data was used to derive a medical encounter cost based on services used.				the phone. ***Psychiatric difficulties*****:** 5 point scale used to code for nonadherence, parent-child problems, child depression, child anxiety, and family problems (developed by the General Clinical Research Centre-Psychosocial Assessment Core Laboratory). Functional severity of asthma scale (FSAS) completed by parents at baseline, 12 and 24 months.		

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						Paediatric asthma CQLQ, Paediatric QLQ for those > 7 years old. Perceived illness - related competence scale (PIRC)		
Bunting et al, 2006, United States	Direct medical costs (the amount paid by the employer for asthma related visits including ED, hospitalizations, prescriptions drugs, MTM services, educator fees, and medication co-payment waivers) using the US Consumer Price Index for medical care; medical records. Indirect costs (cost to the employer - lost	Direct costs obtained from Consumer Price Index for medical care; medical records. Indirect costs calculated from patient self-reported data. For loss of productivity costs - hourly average rate was used provided by employers	Not stated	Combined absenteeism and presenteeism: Before = 66 hours gained/patient/year. $1230/patient/year savings in indirect costs. Cost saving: Direct = $725 per patient per year. Indirect = $1230 per patient per year.	Changes in Forced expiratory volume (FEV) over time, changes in severity and frequency of asthma symptoms at night and asthma attacks. How asthma had affected the patient's lives (Quality of life). Also investigated the number of ED visits, hospitalizations, and asthma related health care costs over time.	Self-reported Asthma Outcome monitoring system (AOMS), Questionnaires and FEV, and insurance claims records	***FEV:*** Baseline = 50% had normal FEV, 1 year or more = 75% had normal FEV. At baseline 17% were severe, at 1 year or more this reduced to 4%. ***Asthma questionnaire:*** Baseline = 28% patients were awakened 2 or more times per week in the night, at 1 year or more this reduced to 12%. Baseline = 35% indicated high frequency of asthma episodes of 2 or more times per	39 people (19%) dropped out.

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	work hours due to absence or presence) were identified though patient self-reported questionnaires						week, at 1 year or more this reduced to 16%. Baseline = 50% indicated low frequency of asthma episodes, increased to 75% at 1 year or more. ***272 observed before and 320 patients observed after.*** ED visits/100 patients/year: Before = 16.9, After = 1.9. Hospitalizations/100 patients/year: Before = 5.1, After = 1.9 Combined inpatient events/100 patients/year: Before = 22, After = 3.8.	
Castro et al, 2003, United States	Hospitalizations, ED visits, healthcare provider visits, nurse/paid caregiver, asthma medications, lost work/school days	Collected by patients and patients medical records.	Not stated	Intervention costs = $186. Total healthcare costs (Int = $5,726, Con = $12, 188 p = 0.03)	Readmission due to asthma, total readmissions, ED visits, Quality of Life, direct and indirect healthcare costs, lost school or work days and	Asthma Quality of Life Questionnaire at baseline, 6 months.	***Within 1 year of initial hospitalization:*** No. of asthma readmissions (Int = 21, Con = 42 p = 0.04). No. of readmissions not for	Not stated

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					cumulative number of days of hosp.		asthma (Int = 10, Con = 29 p = 0.19). No. of hospital days for asthma (Int = 53, Con = 129 p = 0.04). No. of ED visits (Int = 93, Con = 64 p = 0.52) No. of healthcare provider visits (Int = 166, Con = 157 p = 0.82) AQLQ change (Int = 1.4, Con = 1.2 p = 0.55)	
Chan et al, 2004, Southern Taiwan	Direct costs - included ER visits, hospitalizations, physicians' fees for outpatient clinic, pharmacist service, lab test, registration fee and drug costs. Costs based on reimbursement cost for healthcare services at hospital	Costs based on reimbursement cost for healthcare services at the hospital	Not stated	Currency = NT Drug cost per patient: Baseline= 1188 $NT, Intervention = 483 $NT. Lab test per patient: Baseline = 448 $NT, Intervention = 259 $NT. Healthcare costs per patient: Clinic visits: Baseline = 277	Cost of healthcare services. Asthma knowledge, quality of life, self-management, PEF variation, frequency of use of inhaled beta-2-agonists, and corticosteroids	CEA: Asthma quality of life questionnaire (AQLQ) at baseline and 3 month follow up. Peak expiratory flow was measured before intervention (used as baseline). Inhaled beta-2-agonists and	Asthma knowledge: Baseline = 5.1(1.0), Intervention = 9.2(1.5) (P < 0.05). AQLQ all categories had (P < 0.001). PEF variation (%): Baseline = 25.25, 1 month = 19.39 (P<0.001), 2 months = 13.52 (P<0.001), 3 months = 11.49 (P<0.001). Beta-2-agonist: Baseline = 0.86, 1 month =	55 (78.6%) people completed the questionnaires at baseline and follow-up. 25 of 55 (45.5%) completed the asthma diary chart

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				$NT, Intervention = 46 $NT. ER visits: Baseline = 865 $NT, Intervention 827 $NT. Hospitalisations: Baseline and Intervention = 0$NT. Pharmacist dispensing: Baseline = 102 $NT, Intervention = 68 $NT. Total cost per patient: Baseline = 2880$NT. Intervention = 1683 $NT. Mean drug cost per visit: Baseline = 535.80 $NT, Intervention = 385 $NT.		corticosteroids use and peak flow meter was recorded by patients daily in the asthmatic diary chart.	0.67 (P=0.276), 2 months = 0.33 (P=0.034), 3 months = 0.22 (P=0.039). Inhaled corticosteroids: Baseline = 1.77, 1 month = 1.70 (P=0.317), 2 months = 1.60 (P=0.157), 3 months = 1.50 (P=0.083)	
Doan et al, 1996,	Medical intensive care unit with	Inpatient hospitalizatio	Not stated	***1 Year before intervention:***	From the medical records information	From the medical	Not completely clear. After = 22%	From 21 patients: 7

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United States	mechanical ventilatory support ($6421), Medical intensive care unit without mechanical ventilatory support ($5761), Semiprivate room on a general medical floor ($2167), Emergency room visit for asthma ($1409), Office visit ($58), Chest radiograph ($69), Theophylline Serum Concentration ($51), Office Spirometry ($25)	n - multiplied number of days that the patient was hospitalized by the estimated charge to the patient for standard care per day. Emergency services - multiplied no. of visits by cost of standard care in an urban hospital emergency room. Outpatient services - all outpatient visits and laboratory tests. Medicine costs - summed costs of each		Hospitalization = $40,253; ER Services = $783; Outpatient services = $939; Medicine = $1091. ***1 year after intervention:*** Hospitalization = $1926; ER Services = $626; Outpatient services = $1203; Medicine = $1159	obtained: number, severity and duration of hospitalizations, ER visits, number of office and outpatient lab visits, number, frequency use and duration of antiasthma medications	records information obtained: number, severity and duration of hospitalization s, ER visits, number of office and outpatient lab visits, number, frequency use and duration of antiasthma medications	had hospitalizations. Before = 77% medication use; After = 66% medication use.	left and were excluded, therefore 14 patients treated in year 1. After this, 3 were lost to follow up and 9 patients remained

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		medication. Total cost of care - sum of costs of impatient hospitalizatio n, outpatient services, emergency visits and medications						
Donald et al, 2008, Australia	Cost of face to face session: $40.15 (mean time 66 minutes) + $36.50 (administration time 60 minutes) + $1.00 (Printing, postage and call costs) + $12.00 (Peak Expiratory Flow Meter) = $89.65. Cost of telephone based management: $57.29 per participant (average educator spent on all calls is	Cost of face to face sessions - used educators' hourly rate of $36.50, also used printing, call, postage costs and the Peak expiratory flow meter cost $12 each. The telephone intervention - cost of educators'	Mean time spent by educators' on calls (92 minutes) multiplied by the cost of 6 calls ($1.32).	Total costs of hospital readmissions: Int = $2,063.60 and Con. = $41,272	Self-efficacy and Asthma quality of life. Patients telephoned on a weekly basis to gather information about waking at night due to asthma, lost days from work/study due to asthma, use of oral corticosteroids, unplanned visits to the GP, ER attendance and hospital readmissions	Weekly telephone call regarding 5 questions about patients' wellbeing. Questionnaires administered at baseline, 6 months, 12 months (at 12 months those who had intervention could leave additional comments): Self-efficacy scale (SES);	MAQLQ-M: Intervention: baseline = 4.96; 12 months = 5.63; difference is clinically important = 0.67. Control difference = 0.06 - not clinically important. Repeated measures analysis SES: no significant difference between intervention & control = p > 0.9 or within groups across the three times points p= 0.52.	8 participants discontinue d within 6 months. (Int = 32/36, Con = 31/35) Further 3 participants discontinue d after.

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	92 minutes; cost of 6 calls = $1.32)	hourly rate, time spent and cost of call (standard local call rate is $0.22 per call). Hospital readmissions - average cost of 1 day hospital stay ($938) and average length of stay for admitted asthma patient (2.2 days).				Modified Marks Asthma Quality of Life (MAQLQ-M)		
Drummond et al, 1994, Scotland	Not stated	Extra postal questionnaire sent to patients after their third quarterly review. Costs to GPs were gathered from existing information.	Costs of integrated care stated as relevant staffing, material costs, savings to the changes in no. of hospital and GP consultations, and cost of administering integrated care.	Intervention seen to be cost saving on average by: £3.06 per patient per year for hospitals; £2.41 per patient per year for GPs; £39.52	The use of bronchodilators and oral steroids, the number of GP consultations and hospital admissions, sleep disturbance, restrictions on normal activity and psychological aspects on health. Self-efficacy	Clinical & medical record data and patient review questionnaires	***After 12 months:*** No. of bronchodilators prescribed: Int. = 10.1 Con = 10.6. No. of inhaled steroids prescribed: Int. = 6.4 Con = 6.5. No. of courses of oral steroids used: Int. = 1.6 Con = 1.6	Not stated

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		Health service costs were gathered from collaboration with Grampian Health Board		per patient per year for patients	scale (SES); living with asthma scale;		No. of general practice asthma consultations: Int. = 2.7 Con. = 2.5. No. of hospital admissions for asthma: Int. = 0.15. Con = 0.11. No. of nights disturbed: Int. = 2.4 Con. = 2.4. No. of days restricted activity/month: Int. = 5.7 Con. = 4.8. Psychological outcome: Anxiety: Int. = 6.5 Con. = 6.5; SES: Int. = 2.0 Con. = 2.0; Living with asthma scale: Int. = 2.9 Con = 2.9; Depression: Int. = 3.6 Con. = 3.6	
D'Souza et al, 2010, United States	Total amount paid for physician visits, hospitalizations, ER visits, prescription drugs	Medical and pharmacy claims data gathered this information for the study parameters	Not stated	Total co-payments for asthma-related medications: Int. = $192 Con = $158 P < 0.001. Total co-	No. of physician/hospitalizations/ER visits. No. of short acting canisters and oral corticosteroid prescriptions	Medical and pharmacy claims data gathered this information for the study	No. of inhaled corticosteroid prescription: Int. = 73.5% Con = 64.2% P = 0.007. No. of asthma-related outpatient visits in	Not stated

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		and outcomes		payments for non-asthma related medications: Int. = $313 Con = $262 P = 0.003 during the pre-index period. Asthma related monthly costs: Int. = $43 Con = $23 P=0.030; however monthly reduction was greater for Int. (-$15) compared to control (-$6). Overall baseline: Medical costs (Int = $224; Con = $155; p = 0.002) Pharmacy costs (Int = $145; Con = $113; p < 0.001) 12 months follow		parameters and outcomes	pre-index period: Int. = 1.68 Con = 1.25 P = 0.031. At baseline No. of physician visits: Int. = 1.38 Con. = 1.08 P =0.123. At follow up no. of physician visits: Int. = 1.20 Con. = 0.96 P=0.108. Baseline no. of SABA canisters: Int. = 1.72 Con. = 1.57 P=0.324. At follow up no. of SABA canisters: Int. = 1.76 Con. = 1.49 P=0.114.	

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				up Medical costs (Int = $170; Con = $229; p = 0.004) Pharmacy costs (Int. = $181; Con = $124 p < 0.01) Total overall costs (Int = $362; Con = $337; p = 0.276				
Fabian et al, 2014, United States	Asthma clinic visits ($156), ER visits ($638), Hospitalizations ($10,167). Cost of medications used daily per day: SABA low dose ICS ($4.05), SABA medium dose ICS ($6.46), SABA medium dose ICS+LABA ($8.20)	Costs taken from Massachusetts Medicaid Reimbursement Survey, the Medical Expenditure Panel Survey, and 2006 Agency for Healthcare Research and Quality	Not stated	Installation of kitchen fan: Cost savings for healthcare utilization = $175 per year per asthmatic. Maintaining an IPM program: Cost savings for $302 per year per asthmatic.	Symptom-days, medication use, hospitalizations, ER visits and clinic visits with prescribed oral steroid bursts, FEV1%	Not stated	Baseline model: Hospitalizations per year = 0.023, ER visits per year = 0.1, Serious events per year = 0.78. Many of the interventions had significant reductions in pollutant concentrations. The weatherization intervention had a significant increase in prevalence of damp homes. As a result of fix fans, replaced gas stoves,	Not stated

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							no oven for heat, no smoking HEFA filters, IPM, asthma symptom days and serious events including asthma hospitalizations, ER visits and clinic visits decreased.	
Flores et al, 2009, United States	Program costs, direct medical costs, indirect income costs from missed work days.	Medical costs taken from: Paediatric Health Information System (database of inpatient & selected outpatient data from North American paediatric hospitals that are affiliated with the Child Health Corporation of America).	The sum of costs for: personnel ($4555), PM stipend payments ($88), PM training sessions ($102 per session), supplies ($78.94/month), monthly meetings with PMs and intervention participants ($120.05 per meeting).	Intervention cost = $120.84 per child for first and final month of study.	Frequency of child's symptoms and asthma exacerbations. Missed school and work days. Scores on the Paediatric Quality of Life Inventory (PedsQL). Scores on Paediatric Asthma Caregiver's Quality of Life Questionnaire (PACQLQ). ED visits. Asthma hospitalizations. Scores on Patient Asthma Management Self-efficacy scale (PAMSES). Scores on Asthma Satisfaction survey.	Parent mentors phoned families monthly to collect data for 1 year. For families without telephone access, home visits were made. A blinded research assistant collected this through telephone interviews. Parent self-report	Intervention: significant reductions in rapid-breathing episodes, asthma exacerbations and ED visits. High participants experienced significant reductions in asthma exacerbations, missed school days, missed parental work days and ED visits and significant improvements in PedSQL scores. Control: reductions	From intervention group - 45 (40%) dropped out. From control group - 44 (41%) dropped out.

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		Missed work days: employed caregivers' missed worked days multiplied by midpoint of family's income.				collected child's frequency of asthma symptoms and exacerbations each month, missed school/work and parents' quality of life.	in coughing and difficulty breathing, with low participants having reductions only in coughing. Controls also had a reduction in missed school and parental work days, improvements in PedsQL and PACQLQ scores, with a significant improvement in the activity sub-score of the PACQLQ.	
Franco et al, 2007, Brazil	Direct and Indirect costs included: expenses with transportation, doctor visits, medication, therapeutically devices, diagnostic tests, ER visits, hospitalizations, intensive care admissions.	Average cost of day of asthma hospitalizatio n - includes average total direct costs, the number of total patients and the proportion of patients with asthma	Cost of public health system and for the ProAR were calculated using accounting procedures and depreciated as necessary.	Government annual costs of treatment per patient (median values): Cost of outpatient treatment: Before = $184; After = $359. Cost of hospital treatment: Before = $590; After = $0. Total annual	Asthma Quality of Life Questionnaire (AQLQ), Asthma Control Questionnaire (ACQ), lung function tests of forced vital capacity (FVC), and forced expiratory volume in 1 second (FEV1) and peak expiratory flow rate (PEF). Other outcomes included doctor's visits, medications, therapeutical devices	Questionnaires given at beginning of programme, 1 month, 3 months, 6 months, 9 months. The first 2 completed questionnaires were taken as a baseline before intervention.	Regular specialist visits (median value): Before = 0; After = 9. Spirometries performed: Before = 1; After = 2. Emergency/unsched uled visits: Before = 36; After =1. Hospitalizations: Before = 1; After = 0. Total AQLQ score: Before = 2;	64 out of 81 (79%) patients completed the study (3 patients died during the follow-up and 14 patients dropped out.

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		hospitalized per year and costs of asthma medications. The costs of ambulatory health care in The Programme for control of asthma and Allergic Rhinitis in Bahia (ProAR) (cost per patient / year) - total annual stable costs with current expenses, office and medical supplies, communications and staff, all divided by the total number of patients		costs: Before = $750; After = $363. Family annual costs of treatment and income (median values): Family income: Before = $2768; After = $3280. Family expenses with asthma: Before = $615; After =$74. Losses for patient and companion: Before = $0; After = $0. Total family costs: Before = $807; After = $74.	and diagnostic tests, ER visits and hospitalisations and intensive care admissions due to asthma. Effectiveness was measured by "hospitalisations avoided".	FEV, FEC and PEF, were monitored at baseline, 6 months and 12 months by patients performing tests	After = 4. ACQ scores: Before = 4; After =2. Percentage of FEV: Before = 69%; After = 76%. Percentage of PEF: Before = 45%; After = 66%. For ProAR no. of hospitalizations = 1; For usual treatment no. of hospitalizations = 85	

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		admitted. Variable costs - analysed individual expenses with diagnosis and treatment. Family costs - used the Asthma Family's cost questionnaire (AFCQ) before and after admission to ProAR.						
Gallefoss et al, 2001, Norway	Asthma education; peak flow; GP visits (NOK 91); pulmonary consultant visits; pharmaceuticals; physiotherapist sessions	Cost of asthma education - patient co-payments and reimbursement costs according to the National Health	Cost of asthma education = patient co-payments, reimbursement costs according to the fee schedule of the National Health Insurance (NHI) covering both group	Int = NOK 10,500 Con = NOK 16,000	Health related quality of life and symptom data for effectiveness measures	4 questions asked at baseline and 12 months from interviews from another source. A disease specific quality of life	SGRQ at 12 months (mean): Int.=20.2; Con.=36.5; p=0.0002 for CI. FEV change: Int. = 3.4%; Con. = -2.7%; p=0.043 for CI. Percentage of those answering: A better year: Int = 81%; Con. = 43%.	Not stated

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		Insurance (NHI). Cost of peak flow meter, the cost of premises and patient brochure - market prices. Cost of hospital asthma care - based on Norwegian Diagnosis Related Groups (DRG) reimbursement rates. GP visits, pulmonary consultant visits - based on NHI fee. Pharmaceuticals costs - Anatomical Therapeutic Chemical (ATC)	sessions and individual sessions.			instrument, St. George's respiratory questionnaire (SGRQ) was used consisting of 76 weighted items and completed at 12 months. Spirometry was used and measurements recorded before randomization and at 12 months follow up.	Symptom free days: Int. = 81%; Con. = 36%. Symptom free nights: Int. = 94%; Con. = 60%. No impact on daily life: Int. = 88%; Con. = 62%	

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		classification index based on monthly reports from the local pharmacies with the current market prices recorded for dispensing medications. Time employed - national hourly wage rate in NOK. Cost of leisure for those not employed - assumed zero. Number of absent days from work - valued based on national average daily wage rate in NOK.						

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		Patients' travel costs for medical care - bus fares from patients' residence.						
Ghosh et al, 1998, India	Cost of ER therapy = Rs. 75 per private hospital visit and Rs.50 per public hospital visit. Cost of hospitalizations per day = Rs.115.	Intervention costs - used unit cost of personnel and resource cost of materials. Cost of ER therapy - based on personnel time and resource utilized. ER visit - weighted average based on length of visit. Per day cost (stays in hospital) - estimated	Intervention cost was calculated by estimating the unit cost of personnel and resource cost of materials - The four training sessions = Rs. 28 per patient, cost of the public transport system for 4 sessions = Rs.12 per patient, and indirect cost (e.g. lost time at work) = Rs.30 per patient per session.	***Mean per patient during year after baseline***. Direct costs: Int = Rs.4224; Con = Rs.5052. Indirect costs: Int = Rs.879; Con = Rs.1704. Total = Rs. 5263; Con = Rs. 6756	Health status; peak expiratory flow rate (PEFR); no. of hospitalizations, ER visits.	Daily diary for four individual months (before baseline interview, 4th, 8th and 12th month. Mini peak flow meter used to measure daily PEFR.	Mean PEFR: Int. = 332; Con. = 290. Hospital days: Int. = 5.8; Con. = 12.5. Percent hospitalized: Int. = 27.1% Con. = 36.8%. ER visits: Int. = 11.6; Con. = 21.8. Percent ER visits: Int. = 42.9%; Con. = 50%	Not stated

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		from information on hospitals total budgetary allocation, number of beds, and occupancy rate. Indirect costs - multiplied number of productive days lost by wages earned (minimum wage paid for a daily worker in all patients including those without employment)						
Gordois et al, 2007, Australia	Healthcare utilization and service delivery time. Costs used in model. Albuterol (salbutamol) mean daily dose: Mild	Direct costs of asthma program and treatment. Australian national 2006 price data.	Mean time of pharmacist delivering program (47 minutes per visit). Hourly fee = $A70. Cost of	Annual review 5 years: Total costs (Int = $A2136 and Con = $A1514)	Assessment of Quality of Life instrument. QALYs	Patient self-report - purpose designed questionnaires	Annual review 5 years (Int = 3.443, Con = 3.312)	Not stated

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	($A9.66), Moderate ($A9.66), Severe ($A22.60). GP Visits: Mild ($A34.44), Moderate ($A34.44), Severe ($A67.26). Hospital admissions: Mild ($A24.70), Moderate ($89.33), Severe ($89.33). ED visits: Mild ($A 0.39), Moderate ($A0.39), Severe ($A3.74)	Asthma medication changes - analysed by using pooled WHO defined daily dose data. Hourly fee of pharmacist taken from the Medical Benefits Schedule (MBS) reimbursement rate of $A134.10 for accredited pharmacists performing a 'domiciliary medication management review'.	spirometers and consumables, software, promotional material and training resources.					
Greineder et al, 1999, United States	Albuterol - Mild asthma ($A 9.66), Moderate asthma ($A 9.66), Severe asthma ($A22.60) GP visits - Mild	Costs outside of health plan use - extracted from data related to	Not stated	Total outside plan use: Before (Int. = $A 78,070; Con = $A 63,450) After (Int = $A	Emergency ward (EW), hospitalization	Mostly done over the telephone, and additional visits. Counted manually from	EW use: Con.: Before = 44 visits and After = 27 visits; Int. Before = 45 visits and After = 12 visits.	Not stated

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	asthma ($A 34.44), Moderate asthma ($A 34.44), Severe asthma ($A 67.26) Hospital admission - Mild asthma ($A24.70), Moderate asthma ($A 89.33), Severe asthma ($A 89.33) ED visits - Mild asthma (0.39), Moderate asthma (0.39), Severe asthma (3.74)	asthma related diagnoses from the claims computer		13,672; Con = $A 45,862)		a printout of the data from claims computer	Hospitalization use: Con. Before = 28 admissions and After = 16 admissions. Int. Before = 25 admissions and After = 4 admissions.	
Higgins et al, 1998, United States	Inhaled Beta 2 agonist (Albuterol 17gm, $2.91), Inhaled anti-inflammatory agent (Triamcinolone 20gm, $6.97), Hospitalization ($2552.16 for 2.1 days - average length of stay), ED ($244.05 - including professional fee),	Pharmaceutical costs - military pharmacy price listing. Average costs for treating paediatric asthma - Managed Care Department	Not stated	Annual costs per patient: Hospitalizations (Before = $4563.20, After = $214.40). ER visits (Before = $330.90, After = $82.00). Clinic visits (Before = $605.60, After = $408.10). Chest radiographs	Hospital admissions, ED visits, Outpatient clinic visits (Paediatric, Family Practice, Primary Care), visits with the same provider (continuity measure), number of chest radiographs ordered, number of prescriptions for inhaled anti-inflammatory agents and beta 2 agonists	From health records, and log book which noted the class attendance from the parents/patients.	Monthly mean results: Hospital admissions (Before = 0.149, After = 0.007, p = 0.164). ED visits (Before = 0.113, After = 0.028, p = 0.147). Clinic visits (Before = 0.463, After = 0.312, p = 0.083). Visits with same provider (Before = 0.181, After = 0.201, p = 0.610).	None

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	clinic visits ($109), posterior/anterior and lateral chest radiographs ($31.11)			(Before = $60.85, After = $5.23). Inhaled anti-inflammatory drugs (Before = $7.86, After = $16.47). Beta 2 agonists (Before = $8.94, After = $5.86). Total cost per patient year before class = $5,577.35. Total cost per patient year after class = $4845.29			Chest radiographs (Before = 0.163, After = 0.014, p = 0.040). Prescriptions of inhaled anti-inflammatory drugs (Before = 0.094, After = 0.197, p = 0.007). Prescriptions of beta 2 agonists (Before = 0.256, After = 0.168, p = 0.345)	
Johnson et al, 2003, United States	All costs included for hospital inpatient, emergency department and outpatient visits.	The number of inpatient admissions or emergency department visits or outpatient visits divided by the average membership for the 12	Not stated	Savings from: Inpatient services = $US 100,000; Emergency department = $US 13,940; Outpatient = $US 2,400. roi: 131%	Inpatient days, Emergency department, and Outpatient departmental/physician visits	Medical service utilization of IP, ED and MD services were evaluated by service codes and CPT (Physicians' Current Procedural Terminology)	***Percentage change from baseline to program:*** Inpatient: Participants in program = -50%; non-participants referred to program = 5.6%; non-participants identified through medical claims = 25.2%. Emergency	Not stated

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		months in the study				code, running through the program period Nov 1998 - April 1999. Membership and medical claims data were used to estimate utilization rates before and after program implementation. Utilization rates were calculated for the post-program period by dividing the number of IP admissions, ED/MD visits by the average membership for the 12 months in the study.	department: Participants in program = -28.2%; non-participants referred to program = -8.8%; non-participants identified through medical claims = 10.1%. Outpatient: Participants in program = -6.2%; non-participants referred to program = -10.3%; non-participants identified through medical claims = -2.5%	

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Kamps et al, 2004, Netherlands	All costs relating to outpatient management; both within and outside of healthcare sector. Within healthcare sector: prescription costs, outpatient visits to nurse (€28.90) or paediatrician (€111.70), GP due to respiratory symptoms (€17 per visit), Emergency department, and hospitalizations. Outside costs: travel costs (€0.12 per km), productivity loss (€8 per hour independent of paid or unpaid labour)	Nurse and paediatrician visits based on hourly wage with the time of the sessions (initial visits lasted 45 minutes or 30 minutes respectively; following this 15 minutes was assumed for follow-up visits as this is the standard time for outpatient visits) used in the calculations. Cost of prednisone based on a 5 day course of 2 $mg.kg^{-1}.day^{-1}$, cost of	Not stated	***Median Healthcare costs Per patient*** Within health sector (Int = €307.40; Con = €330.80). Outside healthcare sector (Int = €35.50; Con = €25.50). Overall costs (Int = €342.60; Con = €357.20)	Healthcare utilization	1, 3, 6 and 12 months for follow up visits by either the asthma nurse or paediatrician with continuity of the same healthcare provider. Depending on each patient, more follow up visits were planned. Each patient kept a diary two weeks prior to each follow up visits recording their symptoms, use of salbutamol medication, time off school, any additional GP visits due to respiratory problems. Data	1 excluded from the study due to being diagnosed with tracheomalacia, therefore new total of patients in study is 73. Fluticasone propionate (median daily dose): Int. =200; Con. = 200. Salbutamol (median daily use): Int. =0.2; Con. = 0.1. Prednisolone (median): Int. = 0; Con. =0. Antibiotics (median): Int. = 0; Con. = 0. Additional outpatient visits (median): Int. = 2; Con. =0. Extra visits to GP (median): Int = 0; Con = 0. Hospitalisations (median): Int. = 0; Con. = 0. Emergency department visits (median): Int. = 0; Con. = 0	98.6% completed

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		antibiotics based on a 7 day course, and medications were obtained from Dutch Drug Compendium (2000). The costs of the GP visits, travel costs, loss of productivity, were obtained from the Dutch Manual for Costing in Economic Evaluations.				collected by patient was checked by the healthcare provider at follow up visits.		
Karnick et al, 2007, Netherlands	Hospitalizations ($5,865), hospital days, ED visits ($132), medications and clinic visits ($19).	Telephone or face to face interviews. Costs taken from the Illinois Department	Sum of: Salary of health educator and case manager, start-up and operating costs. Average cost of conducting the	Total healthcare costs. IDHFS reimbursement / child / year. Group 1: $ 4,115.06; Group 2: $4,295.34;	Healthcare utilization, medication use, symptoms, school days missed	Summed up individual monthly follow up values of the health resource utilization. If a	Percentage change from baseline and FU: Hospitalizations (Group 1 = - 76%, Group 2 = - 81%, Group 3 = - 86%),	77.8% completed 9 month follow up

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		of Healthcare and Family Services (IDHFS)	program with those lost to follow-up were also integrated into each group's program costs.	Group 3: $5,166.26		follow up was missed, the information was captured during the next follow up telephone call (to minimize bias this recall was limited to less than 3 months). In place of a missing data point, used the participant's average value.	Hospital days (Group 1 = - 55%, Group 2 = - 66%, Group 3 = - 86%). ED visits (Group 1 = - 52%, Group 2 = - 65%, Group 3 = - 74%). Clinic Visits (Group 1 = - 45%, Group 2 = - 49%, Group 3 = - 79%)	
Kattan et al, 2005, United States	Scheduled medical visits ($35.89), unscheduled clinic visit ($49.34), emergency department visit ($390), inpatient hospital stay ($1131), anti-inflammatory medications: inhaled steroid inhalers ($46.00), cromolyn inhalers	Taken from various sources: Medicaid reimbursement survey, extrapolated from Sullivan et al 2002; hospital cost and utilization project, kids'	Intervention component costs: Skin test = $50, Equipment = $422, Salary = $784, Average travel costs = $100, Pest management services = $113.	Direct medical costs per child 2 years. Int = $4704; Con = $3662	Ambulatory visits, scheduled clinic visits, hospitalizations, pharmaceutical use, length of stay	Symptom free days per child per year. Telephone interviews (every 2 months) to collect medication data, service use and asthma symptoms	Average annual use: Scheduled medical visits: Int. =1.44; Con. = 1.51 p=0.62. Unscheduled clinic visits: Int. = 1.06; Con. = 1.20 p=0.03. Emergency department visits: Int. = 0.77; Con. = 0.87; p=0.30. Inpatient hospital days: Int. = 0.62; Con. = 0.73 p =	Dropout rates mentioned were equal in both arms of the study. 85% complete 2 year service use data

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	($70.16); beta-agonist inhalers ($20.49)	inpatient database; drugs for asthma paper/letter.					0.39. No. of inhaled steroid inhalers: Int. = 4.84; Con. = 5.35 p =0.30. No. of cromolyn inhalers: Int. = 2.64; Con = 2.60 p=0.86. No. of beta-agonist inhalers: Int. = 5.95; Con. = 6.81 p <0.001	
Kauppinen et al, 1998, Finland	Lung clinic visits (FIM 773), Inpatient day (FIM 1200), Emergency clinic visit (FIM 1200), Public health centre visits (FIM 178); Nurses/physiotherapist valued at gross salary including social security contributions (FIM 100/hr), Average return of transportation costs to hospital visit (FIM 48) and health centre visit	The average unit resource cost	Not stated	Mean direct costs (Int = FIM 1269; Con = FIM 595). Mean indirect costs (Int = FIM 1489; Con = FIM 1727) Mean Total costs (Int = FIM 2757; Con = FIM 2351)	HRQL measured: St. Georges Respiratory Questionnaire and Generic 15D. Forced vital capacity (FVC) and forced expiratory volume (FEV). Peak expiratory flow (PEF). Airway responsiveness.	The HRQL questionnaires were completed by patients in hospital when they had visits. Clinical measurements taken at baseline and 12 months. FVC and FEV were measured by a flow volume spirometer, Medikro 101. PEF was measured by	SGRQ: Intervention: Baseline = 26.4, 1year = 16.5. Control: Baseline = 27.9, 1 year =20.5 p = 0.16. 15 D: Intervention: Baseline = 0.89, 1 year = 0.93. Control: Baseline = 0.89, 1 year = 0.91. p = 0.47.	3 patients dropped out from IG; they did not show up for their follow up visits. In control; 1 patient died in a traffic accident and 1 patient moved away.

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	(FIM 24). Average daily gross wage (FIM 711 /day)					Wright's peak-flow meter during the visit in clinic - the Finnish normal spirometric and Nunn's PEF values were used and adjusted for age, gender and height. Airway responsiveness measured by the dosage of histamine required to cause a 15% fall in FEV.		
Kauppinen et al, 1999, Finland	Nurses and physiotherapist (£13 per hour). Drugs - valued at retail price. Working time lost; average daily gross wage (£89 per day).	Cost of nurses and physiotherapist time calculated from gross salary. Extra drugs used valued at retail prices.	Average 3 year extra costs without the regular asthma drugs = £247	Mean total costs. Int = £464 and Con. = £476	Clinical and Quality of Life measurements. Peak expiratory flow (PEF), Forced expiratory volume (FEV)and HRQL	Baseline, 12 and 36 months clinical measurements were taken after 12 hours of using the latest bronchodilator drug. Lung function was	HRQL scores: 15D: Baseline - Int. = 0.89, Con. = 0.89. 3 years - Int. = 0.92; Con. = 0.92, Difference: $p < 0.01$ SGRQ: Baseline - Int. = 27.0, Con = 27.7. 3 years - Int. = 15.5, Con. = 16.8	Intervention group: 72 patients left (3 patients did not attend the control visits during the 1st year, 3 moved away, 2

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						measured by using a two flow volume spirometer. PEF was measured using a Wright's PEF meter. Airway responsiveness measured by using a proactive dose a histamine. HRQL measured by using the St George's Respiratory Questionnaire (SGRQ) and generic 15D - the patients completed the questionnaires during their visits.	Difference: p < 0.001	unwilling to attend due to being symptomless). Control group: 78 patients left (2 dropped out in the 1st year, 1 died in a traffic accident, 1 moved away, 2 others failed to attend at 3 years)
Kauppinen et al, 2001, Finland	Asthma medication; Outpatient visits; Inpatient visits;	Data collected on bought and reimbursed	Average total 5 year costs without drug costs = £220	Mean total costs over 5 year. Int = £1906, Con = £2287	Lung functions, airway hyperreponsiveness and quality of life	Baseline, 12, 36, and 60 months measurements	15 D: Baseline - Int. = 0.89, Con. = 0.89. 5 years - Int. = 0.93, Con. = 0.93. SGRQ:	Intervention group: 64 patients remained (5

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	Emergency visits; Patient education	drugs from the Finnish Social Insurance Institution available for the first year. Extra drugs - average retail prices. Costs of patient education visits to outpatient clinics, inpatient or emergency visits used all-inclusive unit costs in South Karelia Central Hospital				taken at least 12 hours after medication taken. PEF measured with a Wright's Peak Flow, airway responsiveness measured with a dose of histamine. HRQL: SGRQ - shortened version AQ20 and 15D	Baseline - Int. = 27.0, Con. = 27.7. 5 years - Int. = 15.0 Con. = 13.6	patients missed the control visits after baseline, 4 patients moved away, 7 patients were unwilling to attend). Control group: 70 patients remained (1 patient died in a traffic accident after baseline, 1 died of a coronary heart disease, 4 moved away, 6 failed to make contact).

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Lara et al, 2013, Puerto Rico	Mean and SE estimates for paediatric asthma hospital stay charges and general paediatric ED visit charges, stratified by age group and gender	Used two US National databases: Agency for Healthcare Research and Quality - the Healthcare Cost and Utilization Project Kid's inpatient database and the Medical Expenditure Panel Survey database. Identified study participants for pre- and post-intervention health care utilization. Developed a mathematical model to generate hypothetical values of ED	Not stated	Mean costs: ED visits - Pre = $1996, Post = $818. Hospitalizations - Pre =$11,187, Post = $6452. Total expenditures - Pre = $13,183, Post = $7270	Improved symptom control. Hospitalizations and ED visits	Survey data collected face to face by trained Spanish native-speaker interviewers at baseline (in clinic) and 12 month follow up (at home). Parent - reported.	Mean total 8-item symptom score in the past month: Baseline = 21.12, 12 month follow up = 13.03, p = 0.000. Hospitalizations in past 12 months: Baseline = 35.9%, 12 month follow up = 13.7% p <0.001. ED visit: Baseline = 82.1%, 12 month follow up = 45.3%, p < 0.001. Any controller medication in past month: Baseline = 17.2%, 12 month follow up = 35.2%, p < 0.001. Appropriate daily controller medication use in past month: Baseline = 13.8%, 12 month follow up = 30.3%, p < 0.001. Any rescue medication use in past month:	117 patients (81%) follow up rate

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		visits and hospitalization expenditures pre and post intervention. Monte Carlo simulation with 10,000 iterations.					Baseline = 70.3%, 12 month follow up = 16.6%, p < 0.001. Rescue medication in past 2 week: Baseline = 62.2%, 12 month follow up = 24.7%, p< 0.001. Have a regular provider for asthma past 12 month: Baseline = 65.2%, 12 month follow up = 93.4%, p<0.001. Talked to a health care provider about asthma in past 12 month: Baseline = 74.3%, 12 month follow up = 99.1%, p < 0.001. Had a nebulizer: Baseline = 64.1%, 12 month follow up = 87.2%, p< 0.001. Had a spacer: Baseline = 12.6%, 12 month follow up = 74.4%, p < 0.001. Had a peak flowmeter: Baseline = 0.7%, 12	

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							month follow up = 43%, $p < 0.001$. Taught to respond to early symptoms of an attack: Baseline = 37.2%, 12 month follow up = 88.8%, $p < 0.001$. Taught what to do in case of attack: Baseline = 49.0%, 12 month follow up = 88.8%, $p < 0.001$. Taught how to use inhaler: Baseline = 26.9%, 12 month follow up = 87.1%, $p< 0.001$. Taught how to use a spacer: Baseline = 17.9%, 12 month follow up = 79.1%, $p < 0.001$. Taught how to use a peak flowmeter: Baseline = 5.5%, 12 month follow up = 47.8%, $p< 0.001$. Given an asthma action plan in past 12 month: Baseline = 3.5%, 12 month	

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							follow up = 53.4%, p < 0.001	
Levenson et al, 1997, United States	ER visits ($362.20), 4 day hospital admission ($6, 663.30), 1 day intensive care unit admission ($10,311.95)	Exact cost per patient not available - lacked complete records. Approximate cost of inpatient care per year per patient calculated based on itemized charges for representative patients at North-western Memorial Hospital during January 1994 to July 1995	Not stated	Mean before intervention per person per year ($22,999) and Mean after intervention per person per year ($=1,107) p<0.02	Hospitalizations, Emergency Room visits, Intensive Care Unit	Not stated	Mean cases per patient: Hospitalizations (Before = 6.25, After = 2.38), ICU (Before = 0.5, After = 0), ER (Before = 6.38,After = 1.25)	100%
Lindberg et al, 2002, Sweden	Not stated	Average patient costs used. Questionnaires completed	Not stated	12 months prior to answering questionnaire (Swedish Crowns per	HRQL - Patient questionnaires	Spirometry, Peak flow meters, PEF diaries, reversibility	Use a PEF instrument: ANP = 84%, Non-ANP = 50% p < 0.001. Daily asthma	For ANP response rate for questionnaires = 82%.

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		by patients at each of their visits (e.g. inpatient & outpatient visits) were used to find out the direct health care costs. Different centres costs obtained from country councils were used to estimate the direct health care costs. Indirect costs (i.e. sick days) calculated from patient questionnaires.		patient). Total Int = SEK 2879, Total Con = SEK 3509		tests. HRQL-ED-5D and another asthma specific questionnaire issued at 3 months for those older than 6 years old to all practices. Patients completed questionnaires (for children, the parents completed the questionnaires) about quality of life, symptoms, self-management, and health status - they dropped these in boxes at their GP visits or at their ANP visits in the	medication: ANP = 95%, Non-ANP = 90%. Instruction on how to use asthma inhaler medication: ANP = 98%, Non-ANP = 96%. Written plan of action: ANP = 66%, Non-ANP = 45% p < 0.001. Received information about asthma prevention: ANP = 89%, Non-ANP = 75% p < 0.001. Adequate knowledge about the disease: ANP = 91%, Non-ANP = 81% p < 0.01. Knowing which Doctor is responsible for your treatment: ANP = 92%, Non-ANP = 94%. Automatic appointments for an asthma check-up: ANP = 94%, Non-ANP = 80% p < 0.001. EQ-5D	For non-ANP response rate for questionnaires = 53%

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						primary health care centre.	showed no significant difference between ANP and non-ANP group.	
Lucas et al, 2001, United States	Cost per visit/day. Hospital days ($1640); ED visits ($383); Urgent care visits ($75); Scheduled visits ($65)	Collected at each time point: baseline, 3, 6, 12 and 24 months by a third party vendor to protect participant confidentiality	Not stated	Total savings = $175,317. ROI = 254%	Daily functioning, quality of life, healthcare resource utilization including productivity	Follow up at baseline, 3, 6, 12, and 24 months after educational and behavioural program if participants attended at least 5 out of the 8 sessions. Patient paper and pencil surveys through self-reported mailed surveys (at 12 and 24 months), telephone surveys (at 3 and 6 months). SF-36 completed	No. of hospitalizations: Baseline = 16, 1 year = 5, 2 years = 6. No. of days in hospital: Baseline = 64, 1 year = 15, 2 years = 24. No. of ED visits: Baseline = 38, 1 year = 21, 2 years = 6. No. of urgent care visits: Baseline = 151, 1 year = 108, 2 years = 71. No. of scheduled visits: Baseline = 254, 1 year = 279, 2 years = 208.	Not stated

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McCowan et al, 1997, United Kingdom	Primary care: Patient-initiated consultation (£9.61) GP or nurse review of asthma (£6.66). Hospital care: Average hospital admission (£408.59), Hospital outpatient attendance (£27.00), Accident and emergency attendance (£29.00). Prescription costs per child per year: Step 1 - bronchodilator only (£7.60), Step 2 - bronchodilator and cromoglycate-like drugs (£102.24), Step 3 - inhaled corticosteroids low dose, < 400 µg daily (£84.69), Step 4 - inhaled	NHS scale of fees and allowances; prescription costs from the BNF, Hospital costs from Tayside Health Board Sources	Not stated	Overall costs. Pre visit (Year 1): Int = £68,500, Con = £57,780. Post visit (Year 2): Int = £62, 300. Con = £53, 910. Follow up (Year 3): Int = £45, 700. Con = £45, 280. Follow up (Year 4): Int = £43, 550, Con = £44, 960	Primary care consultations for asthma/respiratory problems, exacerbations of asthma, anti-asthma prescriptions (classified by BTS steps), hospital admissions, outpatient attendances, A&E attendances.	Medical events checked by patient medical records	***Primary care consultations (no. of children):*** Patient-initiated for asthma (YEAR 1: Int = 182, Con = 203 YEAR 2: Int = 198, Con = 163. YEAR 3: Int = 236, Con = 252. YEAR 4: Int = 213, Con = 250). ***Patient-initiated for other respiratory problems*** (YEAR 1: Int = 706, Con = 711; YEAR 2: Int = 564, Con = 537; YEAR 3: Int = 325, Con = 291; YEAR 4: Int = 269, Con = 225). ***Practice reviews of asthma*** (YEAR 1: Int = 184, Con = 187; YEAR 2: Int = 355, Con = 158; YEAR 3: Int = 170, Con = 174; YEAR 4: Int = 166, Con = 171). ***Maintenance prescribing (no. of***	75.8% records inspected

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	corticosteroids high dose > 400 µg daily (£161.78).						***children):*** Bronchodilators only (YEAR 1: Int = 391, Con = 395; YEAR 2: Int = 398, Con = 317; YEAR 3: Int = 314, Con = 313; YEAR 4: Int = 282, Con = 307). Cromoglycate-like drugs (YEAR 1: Int = 80, Con = 82; YEAR 2: Int = 95, Con = 64; YEAR 3: Int = 52, Con = 42; YEAR 4: Int = 32, Con = 27). ***Inhaled corticosteroids*** (YEAR 1: Int = 79, Con = 78; YEAR 2: Int = 125, Con = 133; YEAR 3: Int = 169, Con = 164; YEAR 4: Int = 172, Con = 199). ***Acute prescribing (no. of children):*** Exacerbations of asthma (YEAR 1: Int = 336, Con = 352; YEAR 2: Int =	

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							286, Con = 227; YEAR 3: Int = 102, Con = 132; YEAR 4: Int = 107, Con = 114). ***Courses of oral corticosteroids*** (YEAR 1: Int = 7, Con = 4; YEAR 2: Int = 22, Con = 16; YEAR 3: Int = 35, Con = 28; YEAR 4: Int = 30, Con = 31). ***Episodes of emergency nebulizations*** (YEAR 1: Int = 38, Con = 31; YEAR 2: Int = 42, Con = 40; YEAR 3: Int = 29, Con = 32; YEAR 4: Int = 18, Con = 32). ***Hospital contacts for asthma (no. of children):*** Admissions (YEAR 1: Int = 33, Con = 18; YEAR 2: Int = 24, Con = 25; YEAR 3: Int = 11, Con = 12; YEAR 4: Int = 9, Con = 14).	

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							Accident & Emergency (YEAR 1: Int = 9, Con = 8; YEAR 2: Int = 4, Con = 4; YEAR 3: Int = 6, Con = 8; YEAR 4: Int = 5; Con = 6). Outpatients (YEAR 1: Int = 67, Con = 64; YEAR 2: Int = 62, Con = 56; YEAR 3: Int = 37; Con = 33; YEAR 4: Int = 40; Con = 36).	
McLean et al, 2003, British Columbia	Medical visits ($26.00). Emergency visits ($120.00). Hospitalizations ($558.00/day). Prescription drugs (per year cost). Pharmacist fees (per year costs). Days off school/work ($117.00/day)	Patients reported the number of ER visits, number of days in hospital and number of days off from school or work. They reported them to the pharmacist. Valued using prices / costs	Not stated	Total major costs (direct & indirect) per month. Usual care = $351, Enhanced care = $150	Recorded PEFR, quality of life on 5 point scale, medical and emergency room visits, hospital visits, days off from school or work. Completed in a monthly diary	Calendar/diary (monthly) - recorded their PEFR twice daily in diary, quality of life survey including 15 questions on a 5 point scale.	***Clinical outcomes:*** Asthma symptoms = 50% reduction. Peak flow rate = 11% increase. Beta-agonist use = 50% reduction. Inhaled steroid use = not significant. ***Quality of Life Outcomes:*** Quality of life scores = 19% improvement. Knowledge levels = More than doubled. ***Economic***	EC: 88 patients dropped out, 27 had insufficient data. Therefore total of 119 out of 191 completed (62.3%). UC: 95 patients dropped out, 14 had insufficient

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		taken from Victoria and British Columbia (BC) Ministries of Health 1998, BC Pharmacare 1998, Ottawa Statistics 1998, Krahn et al 1996 journal paper.					***outcomes:*** Physician visits = 75% reduction. Emergency room visits = 75% reduction. Hospitalizations = Not significant. Days off of work or school = 61% reduction. Overall health costs = 57% reduction.	data. Therefore total of 105 out of 214 completed (49.1%). Reasons for dropouts: patients not keeping appointments, patients changing pharmacies, avoiding completing the forms, not co-operating in data collection, or patients died during the study from unrelated asthma causes
Meer et al, 2011, the	Health care costs: face-to-face contacts,	Patients reported use of healthcare	Intervention costs: software support ($7917 per year),	Total health care costs: (Int = $2555, Con =	QALY and VAS	Patients completed EQ-5D and VAS at	EQ-5D difference: Baseline = 0.026, p = 0.31; 3 months =	EQ-5D outcomes missing:

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Netherlands	telephone contacts, home contacts, GP, chest physician, specialists, physiotherapists, psychologists, complementary care, other paramedical professionals, ER visits, hospital admissions, asthma & non-asthma medications. Productivity costs: absence from work.	resources in a quarterly cost questionnaire (3, 6, 9, 12 months). Dutch standard prices used for unit costs. Hours of absenteeism converted to costs by multiplying them with age & gender of average hourly wage. Prices of drugs derived from pharmacy records. Missing cost questionnaires and pharmacy record were imputed using	electronic spirometer ($19.22 per device), development educational aids ($26 per hr), education sessions ($26 per hr), data review and patient communication ($26 per hour) travel costs for session ($6 per session), travel costs for sessions incl. travel time ($20 per session), time costs for monitoring ($0.50 per log in - 3 minutes per log in), internet log in costs ($0.0016 per log in), mobile phone costs ($0.20 per message) Internet and text messaging costs	$2518 p = 0.94). Total societal costs: (Int = $6289, Con = $5647, p = 0.63)		baseline, 3 and 12 months. Missing data was replaced by 5 imputed values based from switching regression with regression variables (randomisation group, age, sex, asthma control) at baseline and available utility measures at all time points.	0.037, p = 0.099; 12 months = 0.006, p = 0.80; QALY = 0.024, p =0.25. VAS difference: baseline = - 0.013, p =0.43; 3 months = 0.012, p = 0.54; 12 months = 0.013, p = 0.37; QALYs = 0.007, p = 0.57	baseline = 6.5%, 3 months = 10%, 12 months = 8.5%. VAS missing: baseline = 7%, 3 months = 10%, 12 months = 9%. Cost questionnaires missing: 3 months = 10%, 6 months = 14%, 9 months = 19%, 12 month = 9%. Pharmacy data missing = 9%

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		multiple imputation.						
Mogasale et al, 2013, Australia	GP consultation ($30.20), ED visit for age < 50 yrs ($301), ED visit for age > 49 yrs ($346), Hospitalization for age < 50 yrs ($1, 655), Hospitalization for age > 49 yrs ($2, 509), Hourly cost of nurse ($24.46), One way travel cost per GP visit ($3.70), hourly wage of a patient ($17.44)	The RCT conducted in Australia in 1999 was used for costing asthma clinics. Calculated the nurse time per person per year, the hourly wage of nurses estimated from a 2005 salary survey, a GP consultation charge calculated from the Australian Medical Benefit Scheme guidelines, the	Not stated	Median costs without time & travel: Scenario 1 = $263 million, scenario 2 = $263 million, scenario 3 = $189 million	Acute exacerbation and GP visits; Acute exacerbation and ED visits; Acute exacerbation and hospitalizations; disability weights	The effectiveness based on a Cochrane review for optimal management. GP visits, Emergency departments and no. of hospitalizations were estimated from nationwide telephone interviews conducted from December 2003 to January 2004. Disability weight derived from Australian Burden of Disease Study. Telephone	Health benefit- all DALY: Scenario 2 = 11,000 and Scenario 3 - 11,000	Not stated

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		emergency department visits and hospitalizatio n costs were taken from the Australian hospital statistics for public hospitals.				surveys recorded symptoms.		
Neri et al, 1996, Italy	Relevant gross salaries included: 1 min of chest physician ($0.402); psychologist ($0.304); Respiratory therapist ($0.266); Respiratory technician ($0.195). Videotapes ($1.90) per patient. Room and video recorder rental ($1.00) per patient per lesson. Hospital	Drug costs = the unit cost of drug X total number of assumed doses. Indirect costs estimated according to monthly gross salary indicated in national statistics.	Medical examination ($44 - 30 minutes), Spirometry ($39.30 - 15 minutes), PEF monitoring ($77.50 - 30 minutes), Lessons 1-4,6 ($37.10 - 4x5x60 minutes), Lesson 5 ($6.30 - 4 x 60 minutes), Booklet ($9.20), Follow-up medical examination ($264 - 6 x 30 minutes),	***Cost by episode prevented (by unit of effect).*** Asthma attacks: Complete Program (CP) = $193.80, Reduced Program (RP) = $669.84. Urgent medical examinations: CP = $758.70, RP = $669.84. Admission days: CP = $110.20, RP = $94.01. Working days	Spirometry, PEF	Outcomes recorded daily by patient in a custom-designed diary for 1 year. Questionnaires and counter-checked by medical records	***Complete Program:*** Year before (mean) - no. of asthma attacks = 8.40; no. of urgent medical examinations = 1.66; no. of admission days = 6.59, no. of working days lost = 9.4. Year after (mean) - no. of asthma attacks = 4.72, no. of urgent medical examinations = 0.72, no. of admission days = 0.12, no. of working days lost = 2.1.	CP = 7 dropouts (17.5%); RP = 8 dropouts (20%)

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	admissions (general per diem cost of Italian hospital) ($244.50). Salary per day of work lost ($75.00), estimated based on monthly gross salary ($1587.20)		Spirometry ($235.80 - 6 x 15 minutes)	lost: CP = $97.70, RP = $126.40. ***Total morbidity costs before and after.*** Before (CP = $2641.80, RP = $2837.30). After (CP = $747.10, RP = $1139.50)			***Reduced Program:*** Year before (mean) - no. of asthma attacks = 7.84, no. of urgent medical examinations = 1.87, no. of admission days = 7.24, no. of working days lost = 10.4. Year after: no. of asthma attacks = 7.91, no. of urgent medical examinations = 2.18, no. of admission days = 0.12, no. of working days lost = 5.1	
Ng et al, 2006, Hong Kong	Average cost of public ward services (HK$1702 / day). Hospitalization costs in standard program (HK$6213 / patient). Hospitalization costs in intensified program (HK	Telephone interview using structured questionnaire to get incidence of health care utilization	Not stated	HK $969 net savings per patient	No. of ER visits, no. of GP visits due to acute asthma attack, no. of nocturnal symptoms, no. of episodes of asthma attacks, no. of hospitalizations, compliance on medication prescribed, compliance on environmental control	Phone interview 3 months after discharge.	No. of ER visits: 0 visits: Int. = 39, Con. = 19; 1 visit: Int. = 8, Con. = 10, 2 visits: Int. = 8, Con. = 7, 3 visits: Con. = 3, 4 visits: Con. = 6. p = 0.004. No. of patient hospitalizations: 0 episodes: Int. = 52, Con. = 32; 1	Not stated

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	$5003 / patient). Extra nursing hour (HK$241 / patient).				measures, parents' satisfaction		episode: Int. = 3, Con. = 13 p = 0.0037. No. of unscheduled GP visits: 0 visit: Int. = 39, Con. = 30; 1 visit: Int. = 1, Con. = 10; 2 visits: Int. = 15, Con. = 2, 3 visits: Con. = 1, 4 visits: Con. = 2. No. of nocturnal symptoms (mean): Int. = 2.13, Con. = 1.84 p = 0.332. Episodes of asthma attack (mean): Int. = 2.04, Con. = 2.36 p = 0.281. Days off school (mean): Int. = 1.58, Con. = 1.67 p = 0.72	
Polisena et al, 2007, Canada	Emergency department physician consultant ($80.75; 3 hours per visit). Primary care physician visit ($29.95). Respiratory	Volume use multiplied by unit price for each item or service provided. Unit prices for all items from,	Unit cost of asthma action plan (2 information sessions with asthma educator and written materials). Time spent with nurse x nurses' hourly	Inpatient care: Int. = $937, Con. = $832. Emergency visits: Int. = $320, Con. = $286. Family physician services: Int. =	Demographics, medication use, health service use, receipt of asthma education, action plans.	Personal interview to parents and older children between November 2000 and March 2003	***Family physician visits:*** Int. = 91, Con. = 334. p<0.01, ***Paediatrician visits:*** Int. = 57, Con. = 192. ***Respiratory specialist visits:*** Int. = 173, Con. = 329 p	Not stated

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	specialist visit ($57.10; 1.5 hours). Paediatrician visit ($53.15; 1 hour). Family practice visit; ($54.10; 1 hour). In-patient physician assessment ($125 for first day & $23 for remaining days). Emergency department visit ($141.21). Asthma in-patient case cost ($836.90; 1 to < 5 yrs); $860.60 (> 4 to <12 yrs old); $803.40 (>11 to < 19 yrs old). Dispensing fee - public plan ($6.54). Dispensing fee - private plan ($11.99). Asthma prescription ($4.64 - $204.47). Asthma educator ($26). Asthma	provincial physician fee schedule, provincial drug formulary, inpatient case costing database, statistics Canada wage database and self-reported database. Inpatient costs based on the Ontario Case Costing Initiative (OCCI) using ICD10 code J45 for asthma. Inpatient admission: OCCI x average length of stay (LOS). Physician	wage. Add price of written materials.	$142, $188. Respiratory specialist services: Int. = $239, Con. = $133. Paediatrician services: Int. = $97, Con. = $92. Asthma medication costs: Int. = $505, Con. = $374. Dispensing fees: Int. = £272, Con. = $238. Nebulizers: Int. = $35, Con. = $38. Spacers: Int. = $13, Con. = $13. Peak flow meter: Int. = $12, Con. = $5. Asthma education: Int. = $27, Con. = $6. Parent's productivity loss: Int. =			<0.01. ***Hospital admissions:*** Int. = 51, Con. = 169. ***Emergency department visits:*** Int. = 111, Con. = 351.	

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	education brochures ($5). Asthma action plan ($0.25). Productivity time loss - hourly wage ($0-31.76). Spacer ($19.99). Nebulizer ($129.99). Peak flow meter ($43). Homemaker time loss - hourly wage ($9.13)	cost for inpatient care: 1 full consultation fee per day of remaining LOS. Asthma medication: 1 monthly supply. Annual medication costs per child: Cost of each prescription x 8. Daily wage: (Annual income / 239 total working days per year) / 8 hours. NB 239 total working days [subtracted 104 weekend days, 12 statutory holidays, 10		$4,350. Con. = $3,940				

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		vacation days]. Students, homemakers, social assistance, disabled (Ontario's homemaker's 2001 salary in CENSUS used and adjusted for inflation to 2003) - total time loss with each child x hourly wage.						
Rhee et al, 2012, United States	Hospitalizations, ED visits, asthma specialist visits, primary care provider (PCP) visits, scheduled visits, and school clinic visits	Not stated	Peer leader payments for attending training sessions, payments for subjects for completing study questionnaires, transportation. Plus all community care program costs	Study costs (Average per person): Peer-led program = $173. Adult-led program = $162. Net cost saving per participant in study: 3 months = $5.8, 9 months = $5.0.	Hospitalizations, ED visits, asthma specialist visits, primary care provider (PCP) visits for worsening asthma, scheduled visits, school clinic visits.	Healthcare utilization data collected at baseline, 3 months, 6 months, and 9 months post the intervention. Parents completed a demographic	***Days of hospitalization (mean):*** 3 months: Int. = 0, Con. = 0.09. p =0.29 6 months: Int. = 0.02, Con. = 0.11. p = 0.49. 9 months: Int. = 0.02, Con. = 0. p=0.33. ***No. of ED visits (mean):*** 3 months: Int. = 0.05, Con. =	Not stated

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			(payment for educators, rental fee, camp activities, food, printing materials)	Net cost saving per participant in the community: 3 months = $51.8, 9 months = $51.		form that included sociodemographic information. All study participants reported their healthcare service utilization.	0.02. p=0.62 6 months: Int. = 0.05, Con. = 0.09 p = 0.58. 9 months: Int. = 0.07, Con. = 0 p = 0.16. ***No. of specialist visits (mean):*** 3 months: Int. = 0.14, Con. = 0.11 p = 0.87. 6 months: Int. = 0.15, Con. = 0.13. p = 0.65. 9 months: Int. = 0.12, Con. = 0.20 p = 0.63. ***No. of acute PCP visits (mean):*** 3 months: Int. = 0.07, Con. = 0.28 p = 0.01. 6 months: Int. = 0.17, Con. = 0.15 p = 0.61. 9 months: Int. = 0.07, Con. = 0.27 p = 0.04. ***No. of routine PCP visits (mean):*** 3 months; Int. = 0.10, Con. = 0.25. p = 0.11. 6 months: Int. = 0.24, Con. = 0.15. p = 0.24. 9 months: Int.	

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							= 0.26, Con. = 0.32 p = 0.43. ***No. of school clinic visits (mean):*** 3 months: Int. = 0.76, Con. = 0.19 p = 0.23. 6 months: Int. = 0.67, Con. = 0.15, p = 0.29. 9 months: Int. = 0.74, Con. = 0.10, p = 0.09.	
Rossiter et al, 2000, United States	Emergency visit, inpatient visit, outpatient visit, physician office, drugs	Claims files from the Virginia Department of Medical Assistance Services. Asthma drugs - National Drug Compendium (NDC) codes of the Food and Drug Administration	Not stated	Program saved $839 per physician trained for Medicaid. Cost of asthma drugs rose by approximately $180. Net savings = $659. Incremental cost for VHOP training in asthma & communication skills was $235 per physician.	Claims for ER visits and claims for guideline-recommended drugs	Measured from available claims data quarterly	***Mean Emergency visit by quarters:*** Pre-intervention = Q1-96 (Int = 180.6, Con = 128.4, p < 0.001). Q2-96 (Int = 222.9, Con = 171.9, p < 0.001). Post Intervention: Q3-96 (Int = 140.7, Con = 135.4, p < 0.001). Q4-96 (Int = 83.6, Con = 65.2, p < 0.001). Q1-97 (Int = 132.8, Con = 100.5, p < 0.001). Q2-97 (Int = 225.2, Con = 147.6, p < 0.001). Q3-97 (Int = 147.7, Con = 102.3).	495 completed surveys (adults and children in both intervention and comparison groups)

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							Inhaled Albuterol Metered Dose Inhaler: Q1-96 (Int = 23.6, Con = 21.5, $p < 0.001$). Q2-96 (Int = 22.5, Con = 20.7, $p < 0.001$). Q3-96 (Int = 25.6, Con = 21.7, $p < 0.001$). Q4 - 96 (Int = 26.6, Con = 22.6, $p < 0.001$). Q1-97 (Int = 32.5, Con = 23.8, $p < 0.001$). Q2-97 (Int = 34.3, Con = 23.8, $p < 0.001$). Q3-97 (Int = 31.8, Con = 23.7, $p < 0.001$). Inhaled Albuterol Nebulizer: Q1-96 (Int = 72.1, Con = 117.7, $p < 0.001$). Q2-96 (Int = 69.6, Con = 116.1, $p = 0.126$). Q3-96 (Int = 68.7, Con = 112.8, $p = 0.015$). Q4-96 (Int = 79.9, Con = 122.7, $p = 0.188$). Q1-97 (Int = 92.5, Con =	

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							126.3, p = 0.827). Q2-97 (Int = 98.0, Con = 122.4, p < 0.001). Q3-97 (Int = 104.24, Con = 124.3, p = 0.602). Inhaled Steroid Metered Dose Inhaler: Q1-96 (Int = 16.2, Con = 10.4, p < 0.001) Q2-96 (Int = 12.5, Con = 10, p = 0.101). Q3-96 (Int = 13.0, Con = 11.5, p = 0.1). Q4-96 (Int = 13.2, Con = 10.6, p < 0.001). Q1-97 (Int = 11.9, Con = 10.9, p = 0.107). Q2-97 (Int = 11.3, Con = 12, p = 0.866). Q3-97 (Int = 11.4, Con = 11, p = 0.014). Inhaled Cromolyn Metered Dose Inhaler: Q1-96 (Int = 22.7, Con = 14.6, p < 0.001). Q2-96 (Int = 17.8, Con = 16.2, p = 0.584). Q3-96 (Int =	

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							17.1, Con = 15.0, p = 0.156). Q4-96 (Int = 15.9, Con = 15.3, p = 0.546). Q1-97 (Int = 15.3, Con = 14.2, p = -0.081). Q2-97 (Int = 14.0, Con = 17.1, p = 0.057). Q3-97 (Int = 16.8, Con = 14.5, p = 0.313). Inhaled Cromolyn Nebulization Inhaler: Q1-96 (Int = 166.8, Con = 139.7, p = 0.418). Q2-96 (Int = 161.60, Con = 145.8, p = 0.055). Q3-96 (Int = 170.0, Con = 147.3, p = 0.704). Q4-96 (Int = 160.7, Con = 142.2, p = 0.429). Q1-97 (Int = 181.5, Con = 147.8, p = 0.086). Q2-97 (Int = 171.1, Con = 148.4, p = 0.053). Q3-97 (Int = 169.4, Con = 148.4, p = 0.851)	

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Runge et al, 2006, Germany	Direct costs: GP consultation (€34.20 for first visit; €23.60 for subsequent visits in a quarter). Specialist consultation fee (€43.40 for first visits; €34.00 for subsequent visits in a quarter) Hospital day (€346.70). Emergency department visit (€26.00). Ambulance transport in case of emergency (€461.78). Emergency physician answering an emergency call (€512.78). GP answering an emergency call (€32.80). Traditional patient education	Documented by physicians based on electronic patient records for control group. Patient questionnaire (quality of life; KINDL questionnaire and a disease-specific asthma module consisting of 6 further items). Further questionnaires mailed to GPs, patients and caregivers in case of patient education. Physicians'	Patient education costs - taken from existing reimbursement contracts between paymasters and providers.	Cost savings: Paymaster perspective (Con = €1.55; Standardized patient management program (SPMP) = €300.78; SPMP & IEP = €461.45). Societal perspective (Con = €57.50, SPMP = €333.20, SPMP & IEP = €467.05	Quality of life, lung function, use of rescue medication, number of days absent from school due to asthma	Health service utilization data collected at baseline, 6 months and 12 months. Documented by physicians based on electronic patient records for control group.	***Baseline (mean)***: Physician consultations (con = 3.5; SPMP = 3.4; SPMP&IEP = 5.2, p =0.11). Hospital days (Con = 0.3, SPMP = 0.1, SPMP&IEP = 0.1, p = 0.16). Emergencies (Con = 0.4, SPMP = 0.6, SPMP & IEP = 0.4, p =0.99). Working days lost for caregivers (Con = 0.51, SPMP = 0.65, SPMP & IEP = 0.25, p = 0.23). Daily use of rescue medication (Con = 0.20, SPMP = 0.23, SPMP & IEP = 0.26, p = 0.16). Days absent from school (Con = 2.0, SPMP = 3.4, SPMP & IEP = 4.0, p = 0.78). ***Visit 1 (mean)***: Physician consultations (con =	Complete medical resource use data: Con = 48 (56%), SPMP = 86 (68%), SPMP & IEP = 44 (30%).

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	(€541.14). IEP, additional fee (€43.99). Medication (varies by medication). Nonmedical costs - public transport per scheduled or unscheduled visits (€3.10). Internet fees within 6 months (€14.40). Indirect costs - productivity loss per day of absence from work (€94.70)	prescription records - daily asthma medication costs. Transportation costs - public inner-city transport tariffs assuming a round trip ticket. Caregiver's loss of workdays due to child's asthma - average daily gross earning using human-capital approach based on national statistics.					3.3; SPMP = 2.3; SPMP&IEP = 2.7, p =0.49). Hospital days (Con = 0, SPMP = 0.3, SPMP&IEP = 0.2, p = 0.43). Emergencies (Con = 0.2, SPMP = 0.3, SPMP & IEP = 0, p =0.04). Working days lost for caregivers (Con = 1.07, SPMP = 0.56, SPMP & IEP = 0.14, p = 0.77). Daily use of rescue medication (Con = 0.12, SPMP = 0.21, SPMP & IEP = 0.10, p = 0.10). Days absent from school (Con = 1.3, SPMP = 1.7, SPMP & IEP = 1.3, p = 0.01). ***Visit 2 (mean):*** Physician consultations (SPMP = 1.9; SPMP&IEP = 2.3, p =0.63). Hospital	

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							days (SPMP = 0, SPMP&IEP = 0, p = 0.22). Emergencies (SPMP = 0.2, SPMP & IEP = 0.1, p =0.68). Working days lost for caregivers (SPMP = 0.17, SPMP & IEP = 0.25, p = 0.93). Daily use of rescue medication (SPMP = 0.21, SPMP & IEP = 0.06, p = 0.25). Days absent from school (SPMP = 1.0, SPMP & IEP = 1.0, p = 0.14).	
Ryan et al, 2012, United Kingdom	GP consultation, general practice nurse consultation, out of hours attendances, emergency department attendances, asthma admissions	Researcher extracted data on adverse events (admissions and unscheduled consultations) and use of healthcare resources over 6 month	Not stated	Mean total healthcare costs (Int = £315, Con = £245, p = 0.006).	***Primary outcome measures:*** Asthma Control Questionnaire (ACQ) - change in asthma control between baseline and 6 months. Knowledge, attitude, and self-efficacy asthma questionnaire (KASE-AQ) - change in self-efficacy between intervention and control groups at 6 months.	Blinded researcher collected primary outcome data at final trial visit. Postal questionnaires at 3 months. Practice asthma nurse recorded duration of	Mean change: Primary outcomes: ACQ - (Int = 0.75, Con = 0.73). KASE-AQ self-efficacy scale (Int = -4.4, Con = -2.4). KASE-AQ attitude scale (Int = -1.7, Con = -1.8). Secondary outcomes: mini-AQLQ (Int = -0.75, Con = -0.65). mPEI	Postal questionnaires returned at 3 months (Int = 67%; Con = 69%). Questionnaires returned at 6 months (Int = 81%, Con = 77%)

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		trial period from the primary records			***Secondary outcome measures:*** Mini-asthma quality of life questionnaire. Adverse occurrences obtained from practice records (admissions for asthma exacerbations, prescribed courses of oral steroids and unscheduled consultations). Prescriptions of asthma drugs. Modified patient enablement instrument (mPEI). Engagement with process.	each review and noted whether the patient was controlled or needed a further appointment. Researcher extracted data on adverse events.	(Int = -0.96, Con = 0.22)	
Schermer et al, 2002, the Netherlands	Direct health care cost: Budesonide, Short-acting & Long-acting bronchodilators, Theophylline, Prednisone, Antibiotics, Other asthma medication, influenza vaccinations, physiotherapy, allergen avoidance	Units consumed by patient multiplied by the cost per unit of resource use. Bronchodilators and other prescribed non-steroid medication, over-the-counter	Cost per unit multiplied by no. of units, and then summed for total cost. Cost components included prestudy training and instruction of family physicians, educational & self-management aids, peak flow meters, education	Mean per 2 years: Int = €1,084, Con = €1,097	No. of successfully treated weeks; QALYs	Utilities assessed at baseline, and half-yearly at pulmonary function laboratory. Asthma quality of life questionnaire completed by patients - looked from the minimal	QALYs (Int = 0.039, Con = 0.024). No. of successfully treated weeks (Int = 81, Con = 75). Proportion of patients with MCID for AQLQ total score (Int = 39, Con = 29)	Int (13 withdrawn - 3 lost to follow up; 10 other reason). Con (9 withdrawn - 2 lost to follow up; 7 other reason)

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	measures. Other resources: family physician consultations, chest physician's consultations, diagnostic procedures, ER visits, hospital admissions. Productivity cost: limited activity days	medication and limited activity days were extracted from diary cards. Out-of-pocket patient's costs assessed using an ad hoc retrospective questionnaire. Family physician reported healthcare utilization. Unit resource use: sum charged by family physicians for privately insured patients; drug and diagnostic indexes were	sessions, family physician time, and patient time.			clinically important difference between baseline and final visits (defined as within subject 0.5 improvement). Patients also marked a reference health state and their perceived health state on a rating scale. No. of successfully treated weeks - recorded scores for shortness of breath in diaries.		

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		taken from Dutch College of Health Insurance. Human Capital approach used for limited activity days - average gross hourly wage based on 8 hour workdays and used regardless of employment status or income of individuals. Resources valued in Dutch guilders & converted to euros.						
Shelledy et al, 2009,	Clinic visits, ED visits, hospitalizations,	Collected by blinded research	Not stated	Mean values at 6 months: Hospitalizations	SF-36, St Georges Respiratory Questionnaire (SGRQ)	Blinded research associate,	Mean values for HRQL: SGRQ (AMP-RN = -6.0,	Not stated

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United States	in-patient hospital days, ICU admission	associate through hospital medical records. Patients were asked about their healthcare utilization outside the county hospital system for double checking data collection.		(Asthma Management Programs provided by nurses (AMP-RN) = $0, Asthma Management Programs provided by respiratory therapists (AMP-RT) = $202, Con = $1,065). ED costs (AMP-RN = $218, AMP-RT = $73, Con = $313). Total hospitalization costs: (AMP-RN = $0, AMP-RT = $9,292, Con = $62,835)	for Health Related Quality of Life (HRQL). Borg dyspnoea score and severity of asthma symptoms. Patient satisfaction survey (PS), asthma episode self-management simulation (AESM), environmental assessment	investigator or co-investigator collected the demographics. Patients completed the Short Form 36 (SF-36), SGRQ, PS, AESM and environmental assessment. This was repeated at 6 months.	AMP-RT = -11.0, Con = -2.5). SF-36 physical component (AMP-RN = 9.4, AMP-RT = 16.9, Con = -3.1). SF-36 mental component (AMP-RN = 8.5, AMP-RT = 15.0, Con = 1.9). Environmental assessment (AMP-RN = 69, AMP-RT = 75, Con = 68). AESM (AMP-RN = 24, AMP-RT = 37, Con = 22). Patient satisfaction (AMP-RN = 83, AMP-RT = 97, Con = 55)	
Shelledy et al, 2005, United States	Hospitalizations, non-ICU hospital days, ICU days, ED visits, doctor's visits, school days missed	Collected 12 months before and 12 months after Asthma Disease Management	Not stated	Mean values compared before and after ADMP intervention: Hospitalization (Before =	ICU days, non-ICU days, ED visits, office visits, school days missed	Collected 12 months before and 12 months after ADMP intervention. Hospital medical	Mean values for outcomes: Hospitalizations (Before = 1.78, After = 0.33). ICU days (Before = 3.67, After = 0.28). Non-	100%

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		Program (ADMP) intervention. Hospital medical records - Hospitalizations, non-ICU hospital days, ICU days, ED visits. Parents and children interviewed - doctor's visits, school days missed. All data collected by co-investigator.		$7,866.67, After = $805.56). ICU (Before = $3,486.11, After = $347.22). Non-ICU (Before = $4,930.56, After = $458.33). ED (Before = $1,477.78, After = $213.89). Office visit (Before = $319.44, After = $102.78)		records - Hospitalizations, non-ICU hospital days, ICU days, ED visits. Parents and children interviewed - doctor's visits, school days missed. All data collected by co-investigator.	ICU hospital days (Before = 6.22, After = 0.61). No. of ED visits (Before = 4.22, After = 0.61). Doctor's office visits (Before = 6.39, After = 2.17). School days missed (Before = 19.0, After = 6.69).	
Smith et al, 2012, United Kingdom	Primary care, secondary care, out of hours, medication	Primary care data and medications retrieved from computerised records using NHS MIQUEST or practice	Estimated using researcher records. Set-up (£414.24) + Training (£1211.17) + Follow up (£62.00). Average cost per patient was £51.69	Mean change annual levels per patient: Total cost (Int = £60.23, Con = £149.14)	Primary outcome: no. of patients experiencing a moderate-severe exacerbation (death, hospitalization, A&E attendance, out-of-hours medical contact, or course of prednisolone). Secondary outcomes: outpatient attendances,	Primary care data and medications retrieved from computerised records using NHS MIQUEST or practice specific	Moderate-severe asthma exacerbation (Int = 53.6%, Con = 46.5% p = 0.105). Hospitalizations (Int = 3.3%, Con = 6.4% p =0.051). A&E attendance (Int = 6.4%, Con =	Int = 93%, Con = 94.7% complete data

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		specific software. Secondary care and out of hours data retrieved manually from letters/reports in individual records.			primary care contacts, did not attends (DNAs), prescription data, asthma severity, smoking history, comorbidities	software. Secondary care and out of hours data retrieved manually from letters/reports in individual records.	8.2% p = 0.284). Out of hours (Int = 5.7%, Con = 7.1% p = 0.350). Oral prednisolone course (Int = 54.1%, Con = 46.9% p = 0.112). Ambulance call for asthma exacerbation (Int = 2.8%, Con = 2.6% p = 0.954). Nebulised short-acting beta agonist (Int = 7.9%, Con = 13.9% p = 0.061). Secondary care outpatient consultations (Int = 17.7%, Con = 15.6% p = 0.283). DNA of primary care (Int = 17.9%, 23.1% p = 0.396).	
Steuten et al, 2007, the Netherlands	No. of planned consultations with GP, RNS, pulmonologist. No. of non-routine consultations due to an exacerbation. Amount and type	Clinical parameters and direct and indirect costs came from clinical trial - data was collected	Not stated	Base case (Int = €2,973, Con = €3,302). Subgroup analyses: RNS had higher costs = + €757, Pulmonologist	QALY	Quality of life taken from clinical trial data. Written EQ-5D questionnaire	Base case: (Int = 3.4, Con = 2.7). Subgroup analyses: RNS = Int had higher QALYs of +1.2, Pulmonologist = +0.2, GP = +0.1	Quality of life and cost questionnaires (range 55-96%). Clinical data (range 80-100%)

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	of maintenance and emergency medication used. No. & duration of hospital admissions. No. of sick leave days	3 months before implementation of DMP, and then ever 3-6 months after until 1 year. Clinical data taken from medical patient record. Costs based on actual resource use from a written questionnaire and verified by administrative data from care providers. Medication costs: taken from Dutch Pharmacotherapeutic Compass. Consultation		= - €3,687, GP = +€23.				

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		s with GPs, medical specialists, emergency stay, and hospital inpatient stay: taken from Dutch guidelines for economic evaluations. Consultations with RNS - no tariff available so bottom up approach used. Overhead costs included (employment of a medical & project coordinator, continuing education of the RNS, the costs of an administrativ						

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		e support office, maintenance costs of the electronic patient record system that the RNS use, telephone and travel costs of the RNS, and salary costs of the unit leader). Productivity losses - used age-dependent friction costs method.						
Suh et al, 2000, United States	Hospitalization, Emergency Room, Physician visits, Asthma medication	Claims data	Not stated (not even collected)	***Mean asthma treatment costs in $ (Int)***: Hospitalization (Before = 4183, After = 3734, p = 0.4851). Emergency room (Before =	Hospitalization length of stay, emergency room visits, physician office visits, no. of prescriptions	Claims data	***Frequency of medical service use per patient (Int):*** No. of hospitalizations (Before = 0.047, After = 0.043, p = 0.5989). No. of emergency room	Not stated

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				215, After = 217, p = 0.0075). Physician visits (Before = 153, After = 99, p = 0.0001). Asthma medication (Before = 220, After = 239, p = 0.4605). ***Mean asthma treatment costs in $ (Con):*** Hospitalization (Before = 3373, After = 3491, p = 0.7861). Emergency room (Before = 169, After = 167, p = 0.4837). Physician visits (Before = 98, After = 84, p = 0.0001). Asthma medication (Before = 96,			visits (Before = 0.115, After = 0.083, p = 0.0017). No. of physician office visits (Before = 3.059, After = 2.227, p = 0.0001). No. of prescriptions (Before = 5.794, After = 5.456, p = 0.0001). ***Frequency of medical service use per patient (Con):*** No. of hospitalizations (Before = 0.026, After = 0.025, p = 0.8605). No. of emergency room visits (Before = 0.064, After = 0.060, p = 0.5636). No. of physician office visits (Before = 2.091, After = 1.859, p = 0.0001). No. of prescriptions (Before = 1.601, After = 1.893, p = 0.0002).	

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				After = 122, p = 0.0001).				
Sullivan et al, 2005, United States	Hospital days ($630.10), emergency department visits ($188.72), physician visits ($40.04)	Medical and pharmacy claims database. Physician costs: calculated as weighted average of the cost of the first visit and subsequent follow up visits. Unit costs: based on US average wholesale prices and reduced by 15% to approximate actual acquisition costs. Cost calculations based on standard recommende	Fixed and variable costs for program implementation and maintenance summed. Included personnel, materials and training costs. Wage rages for personnel: national average wage rates for physicians, nurses, and support personnel.	Annual medical costs per patient: PLE = $591, PACI = $1591, Usual care = $385	Primary outcome: Symptom free days (coughing, wheezing, limitation in activity, night wakening)	Caregivers reported symptom free days in the 2 weeks before the follow up interviews.	Symptom free days: PLE = gained 6.5 days per year compared to usual care. PACI = gained 13.3 days per year compared to usual care. Usual care = gained 14.8 per year.	Not stated

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		d daily dose of drug for children. Costs of day absence from school: estimated using human capital approach for daily wage rate of caregiver.						
Sullivan et al 2002, United States	Scheduled medical visit ($33.50), Unscheduled medical visit ($33.50), ED visit ($325.00), Hospital day (non-ICU) ($840.00), Hospital day (ICU) ($1050.00), Inpatient physician visit ($34.00), Personnel (includes training) ($90.50), Extermination visit ($80.00),	Self-reported: inpatient hospital days (including ICU days), ED visits, unscheduled clinic visits. Costs of resources: mean Medicaid reimbursement level for the specific service.	Summed fixed and variable costs for program development, implementation, and maintenance and included personnel, materials, and training costs. Wage rates: used salary and benefits records from centres. Facility rental, supplies, and intervention-related materials	Int = $2589.30, Con = $2344.65	Symptom free days	Derived from NCICAS clinical trial and Medicaid Statistical Information System database of inpatient, outpatient, and prescription drug claims maintained by the Health Care Financing Administration.	Int = 565.10, Con = 538.51	Not stated

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	Skin test ($60.00), Asthma control devices (peak flowmeter, mattress cover, pillow covers, Aerochamber) ($86.06), Other expenses ($20.50)		and aids valued at actual cost.					
Tagaya et al, 2005, Japan	GP consultations, ER visits, pharmaceuticals.	Not stated	Not stated	Direct costs: Before (Int ~975 Yen, Con = ~875 Yen) During trial (Int = ~650 Yen, Con = ~1000 Yen)	PEF; frequency of asthma exacerbations defined as episodes which required admission to hospital, ER visit, intravenous administration of bronchodilators	Patient dairy - compared peak flows measurements at week 4, 8, 12, 18, 24.	***PEF*** (Int = 9.3% increase at 3 months, then remaining at high levels until 6 months). ***No. of visits to GP:*** Before (Int ~0.8, Con = 0.98) After (Int ~0.7 $p < 0.01$, Con ~1.0). ***Patients with exacerbations:*** Before (Int ~24%, Con ~28%) After (Int ~ 18 $p < 0.05$, Con ~28%).	100%
Tai et al, 2011, United States	ER visits ($195 million for school aged asthmatic children) Hospital costs ($324 million for school	Tertiary databases for prediction of medical costs. ER visit ($195	***8 public data sources used to calculate costs of implementing SBHC:*** ***1.*** American Lung	SBHC savings: ER reduction = $12.3 million. Hospital reduction = $247.5 million.	Reduction in ER use, reduction in hospital use.	Cincinnati study, 2005	Reduction in ER use: 6.3% in SBHC. Reduction in hospital use: 76.4%.	not stated

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	aged asthma children)	million for school aged asthmatic children for 2006) and hospital costs ($324 million for school aged asthma children) estimated from the 2006 Medical Expenditure Panel Survey data. Parents' work loss = calculated from US average per capita hourly wage rate, 2006: $22.40/h wage x 8 hr/workday = $179.20/day x 12.8 million school days	Association, 2006: Trends in Asthma Morbidity & Mortality. **2.** Bureau of Labour Statistics (BLS) 2006: Consumer Expenditure Survey. **3**. Centre for Disease Control and Prevention (CDC): National Health Interview Survey, 2003-2005 (NHIS). **4.** Centre for Disease Control and Prevention (CDC): National Surveillance for Asthma, 1980-2004. **5.** Medical Expenditure Panel Survey (MEPS), 2006. **6.** National Centre for Education Statistics (NCES), 2006: Digest of Education	Outpatient care reduction = $1.432 billion. Reduction in parents' work loss = $22.938 billion. Reduction in premature school aged asthma deaths = $192.60 million				

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		absent = $22,937,600,000. Future earnings due to premature death: Mean adjusted to 2006 dollars = $1,405,684 x asthma deaths/year for school aged children (137)	Statistics. **7.** National Centre for Education Statistics (NCES), 2004: Schools and Staffing Survey (SASS: 2003-2004). **8.** Salary Wizard (Salary.com), 2010. School nurse staffing: 0.75hr/week x 5.64 million prevalence = 4,231,095 child-hours/40 hr/week = 205,777 full time equivalent					
Taitel et al, 1995, United States	***Direct costs:*** Physician visits, hospital admissions, emergency department visits, asthma medication, self-administered antigen injections, laboratory fees. ***Indirect costs:***	Health maintenance organizations	Not stated	***Pre-intervention:*** Physician visits = $19,984, hospital admissions = $18,488, emergency department visits = $5,199, medication = $25,555,	Reduction in physician visits, hospitalizations, emergency department visits, medication	Health maintenance organizations	Average benefit per cost category: Physician visits = -83.67, hospital admissions = 332.35, emergency department visits = 30.96, medication = -104.89, antigen injections = 46.31, laboratory fees = -9.52, travel = 24.10,	47/76 completed baseline data = 62%

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	travel to health care facilities, lost income because of asthma, miscellaneous expenses (air-conditioning, cleaning devices)			antigen injections = $4,051, laboratory fees = $1,820, travel = $4,354, income lost = $11, 593, miscellaneous = $16,211. ***Post-intervention:*** Physician visits = $24,000, Hospital admissions = $1,538, Emergency department visits = $3,496, Medication = $30,485, Antigen injections = $1,550, laboratory fees = $2,315, travel = $3,101, income lost = $4, 589, miscellaneous = $9,165.			income lost = 142.94, miscellaneous = 123.61.	

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Tinkelman et al, 2004, United States	Physician visits, hospitalizations, emergency department visit, anti-inflammatory medications	UB-92 claims - hospital and facilities charges reported by Colorado Medicaid	Not stated	***Per member per month:*** Baseline (Int = $351.97, Con = $361.79). Intervention year (Int = $179.17, Con = $250.76)	Reduction in night-time symptoms, reduction in emergency department visits, reduction in anti-inflammatory medications	Not stated	Intervention group: Inflammatory medications: (Baseline = 72.6%, 6 months = 85.2%). Night-time symptoms = reduction of 75% at 6 months compared to baseline. Reduction in emergency department visits (Baseline = 253, Intervention period = 36)	258/388 completed intervention = 90%
Tschopp et al, 2002, Switzerland	Hospitalizations, length of hospital stay, lost work-days, emergency consultations	Patients completed questionnaire. Average cost of day's hospital stay or lost work day based on Federal Statistics Office averages. Patients seen at 3, 6, 9, and 12 months	Not stated	Indirect costs = CHF 202,510. Direct costs = CHF 131,200. Cost savings = CHF 5,056.	Quality of life	Patient completed questionnaire to capture quality of life.	Overall QoL: Before = 4.5, After = 5.2, $p < 0.001$. Hospitalizations (Before = 35%, After = 8%). Emergency consultations (Before = 88%, After = 53%). Lost workdays (Before = 39%, After = 14%)	66/76 completed = 87%

First author, Year, Country of Population	*Resource use (unit cost)*	*Method of estimating & valuing resources*	*Method of estimating intervention cost component*	*Cost results (Int. & Con.)*	*Types of outcomes measured*	*Method of estimating & valuing outcomes*	*Outcome results*	*Response rates*
		after baseline with physiotherapist for data collection.						
Tschopp et al, 2005, Switzerland	Hospital days (533€), Emergency visits (47€), Outpatient visits (26€), work absenteeism	Emergency visits, hospitalizations and work absenteeism: data obtained from GP with further confirmation from insurance companies if necessary. Mean daily cost of hospitalisation: obtained from Federal office of statistics. Cost of emergency visits: estimated from data of 2 local	Summed brochure development and printing (66,352 €), teaching session and extra-costs (12,667 €) and coordinating nurse salary (29,400 €).	Hospital days (Before = 232€, After = 68€). Emergency visits (Before = 314€, After = 128€). Outpatient visits (Before = 339€, After = 375€). Anti-asthmatic medications (Before = 42799€, After = 51143€).	Quality of life - Asthma Quality of Life Questionnaire(AQLQ)	Patients completed questionnaire before and at 12 months after intervention on quality of life and severity of asthma.	Hospitalizations = Before = 35%, After = 8%, $p < 0.001$. Emergency visits: Before = 88%, After = 53%, $p < 0.001$. Work absenteeism = Before = 39%, after = 14%, $p < 0.002$	66/76 completed = 87%

First author, Year, Country of Population	*Resource use (unit cost)*	*Method of estimating & valuing resources*	*Method of estimating intervention cost component*	*Cost results (Int. & Con.)*	*Types of outcomes measured*	*Method of estimating & valuing outcomes*	*Outcome results*	*Response rates*
		hospitals. Prescriptions : pharmacists collected these.						
Turcotte et al, 2014, United States	Hospitalization ($4922), emergency department ($834), Doctor Visit ($100)	Massachusetts Department of Public Health: data obtained for hospitalization, emergency department visits. Local paediatricians' offices: data obtained for doctor visit. Total cost reductions in utilization calculated by: decreased number of occurrences in urgent care x per utilization cost.	Not stated	Net savings from intervention: 4 week = $38,522, 6 month = $394,332, 12 month = $821,304	Decreased no. of occurrences in urgent care	Home health assessment workers (HHAW) conducted health questionnaire with caregiver. Children's Health Survey for Asthma (CHSA) conducted at week 4. General outdoor allergens and safety survey: administered by environmental assessor.	Decrease in occurrence: Hospitalization = 8, Emergency department = 29, Doctor visit = 76	Not stated

First author, Year, Country of Population	*Resource use (unit cost)*	*Method of estimating & valuing resources*	*Method of estimating intervention cost component*	*Cost results (Int. & Con.)*	*Types of outcomes measured*	*Method of estimating & valuing outcomes*	*Outcome results*	*Response rates*
Westley et al, 1997, United States	Hospital ($1088.00), ER visit ($176.00), Sick office visit ($68.25)	Costs based on fee for service charges made to previous members who might continue to seek medical care at Kaiser Health Plan clinics	Not stated	Total savings: Sick office visits = $9,487. ER visits = $26,048. Hospitalizations = $109,932.	Hospitalizations, emergency room visits, sick office visits	Not stated	Sick office visits (Before = 308, After = 169, p = 0.0001), ER visits (Before = 266, After = 118, p = 0.0001), Hospitalizations (Before = 34, After = 11)	Not stated
Willems et al, 2007, the Netherlands	GP visit (€20.20), GP telephone visit (€10.10), assistant visit (€20.20), assistant telephone visit (€10.10), nurse practitioner visit (€20.20), day admission (€229.00), emergency room (€139.00), lung specialist outpatient visit (€100.00), paediatric lung specialist outpatient visit (€100.00), asthma	Hospital care: obtained from hospital billing system of the university hospital Maastricht. Other resource use: obtained from prospective cost diary at 1, 4, 8, 12 months follow up; data from	Micro-costing calculation: asthma monitor (€476), price of modem (€1428); 5 year depreciation with 4.5% interest = €434 annual cost per patient. Annual cost of insurance for equipment = €16 per patient. Computer equipment that nurse uses (personal computer, software, monitor,	Total costs for adults (Int = €2,973, Con = €1948). Total costs for children (Int = €1,206, Con = €597)	EQ-5D and SF-6D to obtain utility values. Also captured Asthma Quality of Life Questionnaire (AQLQ) or Paediatric Asthma Quality of Life Questionnaire (PAQLQ)	Patient questionnaires at baseline, 4, 8, and 12 months	***Mean EQ-5D utility for adults (18 yrs and over):*** Baseline (Int = 0.89, Con = 0.78). Month 4 (Int = 0.91, Con = 0.80). Month 8 (Int = 0.86, Con - 0.78). Month 12 (Int =0.90, Con = 0.79). ***Mean EQ-5D utility for children (7-18 years):*** Baseline (Int = 0.92, Con = 0.96), Month 4 (Int = 0.98, Con = 0.99). Month 8 (Int = 0.98, Con = 0.98). Month 12 (Int = 0.98, Con = 0.97).	5 from intervention lost to follow up and 2 from control lost to follow up.

First author, Year, Country of Population	*Resource use (unit cost)*	*Method of estimating & valuing resources*	*Method of estimating intervention cost component*	*Cost results (Int. & Con.)*	*Types of outcomes measured*	*Method of estimating & valuing outcomes*	*Outcome results*	*Response rates*
	nurse practitioner outpatient visit (€62.72), other medical specialists outpatient visit (€100.00), speech therapist (€25.00), homoeopath (€52.50), company medical officer (€51.61), medication (drug costs), pharmacist fee (€6.45), professional home care (€26.70 per hour), over the counter medication (out of pocket costs) informal care (€8.30 per hour), loss of productivity at volunteer/household work (€8.30 per hour), loss of productivity at paid work (friction costs)	each time point of cost diary was multiplied by 3 to capture the entire 1 year follow up period. Unit prices: obtained from Dutch manual for cost research. Productivity loss for volunteers or household activities: given a price of €8.30 per hour of absence. Productivity losses from paid work: calculated by using friction cost method. School absenteeism (included	printer) = €1,150; 5 year depreciation with 4.5% interest = €5 per patient per year. Other fixed costs: Development and production of instruction material = €4 and €7 per patient per year. Administrative tasks of nurse practitioner = €7 per patient per year. Nurse practitioner: salary (€44,700 per year) and 1540 workable hours per year = €29 per hour. Overhead costs calculated over all direct material and personnel costs				***Mean SF-6D utility for adults (18 yrs and over):*** Baseline (Int = 0.75, Con = 0.69). Month 4 (Int = 0.71, Con = 075). Month 8 (Int = 0.74, Con = 0.71). Month 12 (Int = 0.75, Con = 0.74)	

First author, Year, Country of Population	*Resource use (unit cost)*	*Method of estimating & valuing resources*	*Method of estimating intervention cost component*	*Cost results (Int. & Con.)*	*Types of outcomes measured*	*Method of estimating & valuing outcomes*	*Outcome results*	*Response rates*
		government costs and parental contribution which varied on school type and class): obtained from cost diaries and calculated by multiplying hours of school absenteeism by unit price						
Wood et al, 2011, United States	ED and hospitalizations	Researchers reviewed patient's charts for no. of physician office visits, hospitalizations, and ED visits and documented these on a billing request form. Billing	Not stated	Significant reductions in costs.	No. of ED and hospital visits	Researchers reviewed patient's charts for no. of physician office visits, hospitalizations, and ED visits	Significant reductions in number and length of stay for physician, hospital, and ED visits.	Not stated

First author, Year, Country of Population	*Resource use (unit cost)*	*Method of estimating & valuing resources*	*Method of estimating intervention cost component*	*Cost results (Int. & Con.)*	*Types of outcomes measured*	*Method of estimating & valuing outcomes*	*Outcome results*	*Response rates*
		agency corresponded the cost charges to the visit dates for diagnostic testing, room charges, respiratory care, medicines, physician care, and ED care.						
Woods et al, 2012, United States	ED visit and hospitalizations	Hospital administrative data.	Summed: 1.0 full time equivalent (FTE) nurse, 1.0 FTE sub-contracted community health worker (CHW), 0.25 FTE program coordinator, 0.1 program director, 0.1 FTE evaluator, IPM materials, and IPM exterminator services (including $194, 246 personnel,	Costs of ED visits and hospitalizations for CAI per patient: Baseline = $2956, 1 year = $1335, 2 years = $750. Costs comparison with population (Dorchester, N=559): Baseline = $2093, 1 year = $1340, 2 years = $1322	ED visits, hospitalizations, missed school or parent/guardian missed work days, limited physical activity	Parental report collected outcome data at 6 monthly intervals on ED visits, hospitalizations, limitation of physical activity, missed school or parent/guardian missed work days because of asthma	ED visits (Baseline = 1.0, 6 month = 0.3, 12 months = 0.3, $p < 0.0001$). Hospitalizations: Baseline = 0.5, 6 months = 0.1, 12 months = 0.1, $p < 0.0001$ .Days of limitation of physical activity: Baseline = 2.7, 6 months = 1.2, 12 months = 1.2, $p < 0.0001$. Missed school days: Baseline = 5.1, 6	Not stated

First author, Year, Country of Population	*Resource use (unit cost)*	*Method of estimating & valuing resources*	*Method of estimating intervention cost component*	*Cost results (Int. & Con.)*	*Types of outcomes measured*	*Method of estimating & valuing outcomes*	*Outcome results*	*Response rates*
			$58,712 materials, and $5000 exterminator services).				months = 3.1, 12 months = 2.4, p < 0.0001. Missed work days: Baseline = 2.1, 6 months = 1.1, 12 months = 1.1, p < 0.0001	
Xu et al, 2010, Australia	Emergency department presentation ($255.76), Hospital admission ($1479), GP visit ($32.10), Corticosteroid course ($13.91)	ED visit, hospital admission: Commonwealth Department of Health and Ageing. GP visit and corticosteroid: Australian Government Department of Health and Ageing.	Nurse salary for fortnightly calls ($35.31 per hour), IVR installation of automated call service ($2181.82), IVR charge per call for mobile ($2.00) and landline ($1.32)	In 6 month trial period: lower healthcare costs of A$225 for Nurse support compared to control, and A$451 for IVR group compared to control	Healthcare resource utilizations (GP visits, hospital ED visits, hospital admissions)	Unplanned health service use, time off work/school, oral steroid use: recorded by IVR system and specialist nurse. Patient questionnaires: Paediatric Asthma Quality of Life Questionnaire (PAQLQ), and Quality of Life Inventory (PedsQL)	No significant difference between the 3 groups for ED visits, oral steroid use, hospital admission, school days lost, work days lost, quality of life data	Control = 1 lost to follow up. IVR = 63% responded to calls; 67% completed end of study questionnaires. Nurse group = 56% successful calls, 53% successful emails and 63% responded to end of study questionnaire

Appendix VI: Estimating the loss associated with an asthma-related crisis event (ESQUARE) - Study documents

Appendix VI a Participant information sheet

Trust's logo

University of East Anglia

Version Number: 4.1

Date (dd/mm/yyyy): 23/02/2016

Chief investigator: Christina-Jane Crossman-Barnes

All participants should be given a copy of the participant information sheet to keep. If you agree to take part in this study, then please sign the consent form at the end of the booklet. A copy of the signed consent form will be yours to keep.

Part 1

Study Title

Estimating the loss in quality of life associated with an asthma-related crisis event.

Invitation

We would like to invite you to take part in our research study. Our study focuses on people with asthma (asthma alone, asthma with COPD, or asthma with a respiratory condition) who have had an asthma-related flare up and been admitted to hospital or had an accident and emergency (A&E) attendance. Before you decide we would like you to understand why the research is being done and what it will involve for you. One of our team will go through the information sheet with you and answer any questions that you may have.

Part 1 of the information sheet will tell you the purpose of this study and what will happen to you if you take part.

Part 2 of the information sheet will give you more detailed information about the conduct of the study.

Do not hesitate to ask us anything if you feel that it is unclear.

What is the purpose of the study?

There are many people across the world who have asthma. It is important to find ways to improve their quality of life. The main aim of this study is to estimate the quality of life of people with asthma. This will inform other studies which seek to work out the benefits of different asthma health care services.

Why have I been invited?

You have been invited to participate in this study because the asthma nurse or a member of the respiratory team has noticed that you fit the criteria for this study. This is because you have had an asthma-related flare up, been admitted to hospital or had an A&E attendance and are aged 18 years old or above. We aim to recruit 100 patients into this study.

Do I have to take part?

No, the treatment you receive will not be affected by your decision. It is up to you whether you take part. We will describe the study and go through this information sheet. If you agree to take part, we will then ask you to sign a consent form. You are free to withdraw at any time, without giving a reason.

What will happen to me if I take part?

If you agree to take part in this study, you will be involved in the research for approximately 8 weeks. We will ask you to complete some questions about your asthma and your quality of life from when you are in hospital and every day following that until approximately 8 weeks after you have been discharged. We will ask you to complete some of these questions on paper-based questionnaires, and some with the researcher. At your follow-up appointment (approximately 4 weeks after discharge) extra questions about your time off work/education and quality of life will be asked, and this should last approximately 30 minutes. Your self-completed peak flow diary, which is to be completed as part of your usual care from your A&E attendance or hospital admission until your follow-up appointment, will also be important for this study. We will take a copy of your self-completed peak flow diary at your follow-up appointment.

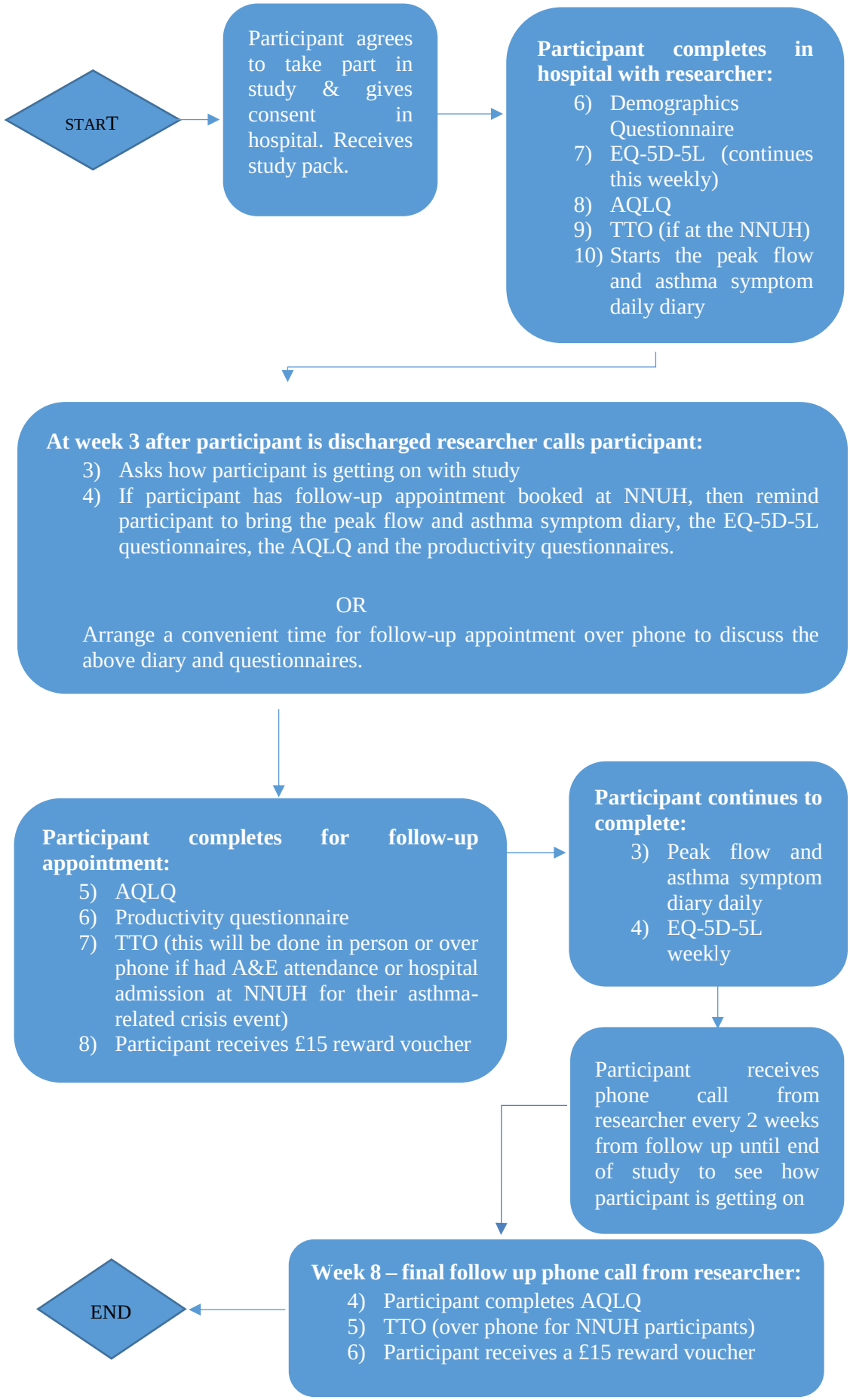
Expenses and payments

You will not have to do any additional travel, however you may need extra parking time when going to your follow-up appointment. As a thank you for taking part in this study and for allowing extra time, we would like to give you some reward vouchers. A £15 Love2shop voucher will be given to you at your follow-up appointment and if you continue to take part in the study, you will receive another £15 Love2shop voucher at the end of the study.

What will I have to do?

You will be involved in the research for approximately 8 weeks. This will be from when you have consented at the hospital until 8 weeks later. Your first interaction with the researcher will be face to face before you are discharged from hospital. We will talk you through the research study, making sure that you are aware of what will be involved, and answer any questions that you may have. Should you choose to take part, we will ask you to provide some information about yourself, (age, gender, ethnicity, etc.) and to confirm your address and contact telephone number. We will ask you to complete some questions about your asthma and quality of life daily for approximately 8 weeks. At approximately 4 weeks, before your follow-up appointment, we will also ask you to complete another questionnaire about your time off work/education. We will contact you 3 weeks after your discharge to either remind you to bring these completed questionnaires to your follow up appointment with your peak flow and symptom diary and allow extra time at the appointment, or to review these over the phone at a convenient time for you. We will also be able to help you complete these questionnaires if you so wish. We will contact you after your follow-up appointment at two weekly intervals until the end of the study in week 8. Up to three attempts will be made to contact you; we will only leave a message once if there is no

response. You will also have the option to post these questionnaires back to us in a pre-paid freepost envelope that will be provided in the first pack of questionnaires. Below is a diagram to show what will happen during the study.


START
Participant agrees to take part in study & gives consent in hospital. Receives study pack.
Participant completes in hospital with researcher:
6) Demographics Questionnaire
7) EQ-5D-5L (continues this weekly)
8) AQLQ
9) TTO (if at the NNUH)
10) Starts the peak flow and asthma symptom daily diary
At week 3 after participant is discharged researcher calls participant:
3) Asks how participant is getting on with study
4) If participant has follow-up appointment booked at NNUH, then remind participant to bring the peak flow and asthma symptom diary, the EQ-5D-5L questionnaires, the AQLQ and the productivity questionnaires.
OR
Arrange a convenient time for follow-up appointment over phone to discuss the above diary and questionnaires.
Participant completes for follow-up appointment:
5) AQLQ
6) Productivity questionnaire
7) TTO (this will be done in person or over phone if had A&E attendance or hospital admission at NNUH for their asthma-related crisis event)
8) Participant receives £15 reward voucher
Participant continues to complete:
3) Peak flow and asthma symptom diary daily
4) EQ-5D-5L weekly
Participant receives phone call from researcher every 2 weeks from follow up until end of study to see how participant is getting on
Week 8 – final follow up phone call from researcher:
4) Participant completes AQLQ
5) TTO (over phone for NNUH participants)
6) Participant receives a £15 reward voucher
END

What are the possible disadvantages and risks of taking part?

The only disadvantage of taking part in this study is the time it will take you to participate. This will involve approximately 20 minutes before discharge, approximately 10 minutes daily for 8 weeks and approximately 30 minutes extra will be needed at your follow up appointment (approximately week 4 and week 8). This study will not affect the care given now or in the future.

What are the possible benefits of taking part?

This research study aims to inform future research about the costs and health benefits for health care services for asthma patients.

What happens when the research study stops?

When the research study stops you will be informed of the study's results through a one page summary that will be posted or emailed to you. This will be predicted to arrive in 2017.

What if there is a problem?

Any complaint about the way you have been dealt with during the study or any possible harm you might suffer will be investigated. The detailed information on this is given in Part 2.

Will my taking part in the study be kept confidential?

Yes. We will follow ethical and legal practice and all information about you will be handled in confidence. All study results will be reported in an anonymous format. The details are included in Part 2.

This completes part 1.

If the information in Part 1 has interested you and you are considering participation, please read the additional information in Part 2 before making any decisions.

Part 2

What will happen if I don't want to carry on with the study?

If you wish to withdraw from the study that will be fine. However, we will use the data collected up to your withdrawal. If you do not wish for us to use this data, please let the researcher know.

What if there is a problem?

If you have a concern about any aspect of this study, you should ask to speak to the researchers who will do their best to answer your questions.

Christina-Jane Crossman-Barnes, PhD student

Email: C.Crossman-Barnes@uea.ac.uk

Phone: 07763775509

Dr Garry Barton, Academic Supervisor

Email: G.Barton@uea.ac.uk

Phone: 01603 591 936

If you remain unhappy and wish to complain formally, you can do this by following the NHS Complaints Procedure. Details can be found on the following website: www.england.nhs.uk/contact-us/complaint/. Otherwise, you can contact the Patient Advice and Liaison Service (PALS) for a more informal and confidential chat about your concerns. Details for PALS are 01603 289036 or pals@nnuh.nhs.uk.

In the event that something does go wrong and you are harmed during the research and this is due to someone's negligence, then you may have grounds for a legal action for compensation against the University of East Anglia, but you may have to pay your legal costs. The normal National Health Service complaints mechanisms will still be available to you.

Will my taking part in this study be kept confidential?

All information which is collected about you during the course of the research will be kept strictly confidential in accordance with the data protection act. The data will be collected through paper based questionnaires which will be locked in a filing cabinet in a secure room on site at the University of East Anglia. The information will be stored securely in a password protected Microsoft Excel document and coded to ensure your details will remain anonymous. Only members of the research team will have access to your data. With your consent we will use your data that has been collected for this study in other ethically approved asthma studies. The researchers from both studies will know your identity but otherwise it will remain anonymous. At the end of the study the anonymised research data will be kept for 10 years. Once the time period has passed, your data will be disposed of securely.

Involvement of the General Practitioner/Family Doctor (GP)

Your GP will be written a letter in order to be notified of your participation in the study. They will be given a copy of the participant information sheet with the letter. If you do wish to withdraw from the study, your GP will also be notified.

What will happen to the results of the research study?

This study will form part of a PhD thesis for the chief investigator, Christina-Jane Crossman-Barnes. The results will be used to estimate the difference between your quality of life at 8 weeks, your follow-up appointment and your A&E attendance or hospital admission. The different quality of life measures will also be compared. The loss of productivity questionnaire will help us to better estimate the costs involved with asthma, after an A&E attendance or hospital admission. The results may be published in scientific journals, but all the data will be anonymised so that none of the participants are identified. The results of the research study will be summarised and posted or emailed to each participant involved in the study. This is predicted to arrive in 2017.

Who is organising and funding the research?

The University of East Anglia will be sponsoring the research. The research will be funded by the Collaborations for Leadership in Applied Health Research and Care East of England (CLAHRC EoE).

Who has reviewed the study?

All research in the NHS is looked at by an independent group of people, called a Research Ethics Committee, to protect your interests.

Further information and contact details.

If you have any further questions and would like to know more information about this study, please do not hesitate to contact the researchers:

Christina-Jane Crossman-Barnes, PhD student

Email: C.Crossman-Barnes@uea.ac.uk

Phone: 07763775509 (study research phone number)

Dr Garry Barton, Academic Supervisor

Email: G.Barton@uea.ac.uk

Phone: 01603 591 936

If you wish to agree to take part in this study please complete the consent form.

PLEASE TURN THE PAGE TO COMPLETE AND SIGN THE CONSENT FORM

Appendix VI b Consent form

University of East Anglia

Trust's logo

Centre Number:

Study Number:

Patient ID Number for this trial:

CONSENT FORM

Title of Project: ***Estimating the loss in quality of life associated with an asthma-related crisis event.***

Name of Researcher: ***Miss Christina-Jane Crossman-Barnes***

Please initial the boxes

1. I confirm that I have read and understand the information sheet dated 23rd February 2016 (version 4.1) for the above study. I have had the opportunity to consider the information, ask questions and have these answered satisfactorily. ☐

2. I understand that my participation is voluntary and that I am free to withdraw at any time without giving any reason, without my medical care or legal rights being affected as your data will be kept securely and anonymously. ☐

3. I understand that relevant sections of my medical notes and data collected during the study, may be looked at by individuals from University of East Anglia, from regulatory authorities or from the NHS trust, where it is relevant to my taking part in this research. I understand that my data may be examined as part of monitoring this study and assessing the PhD qualification. I give permission for these individuals to have access to my records. ☐

4. I agree that my data will be used in other ethically approved asthma studies. ☐

5. I give permission for my contact details to be used by the researchers to contact me by phone or mail as part of the research process. ☐

6. I agree to my GP being informed of my participation in the study. ☐

7. I agree to take part in the above study. ☐

PLEASE SIGN BELOW

Name of Patient:

Date (dd/mm/yyyy):

Signature:

Name of researcher/person taking consent:

Date (dd/mm/yyyy):

Signature:

When completed a copy of the consent form should be given to:

- The participant
- The researcher for site file
- Original should be kept in medical notes

Appendix VI c GP letter

Version Number: 1.1

Date (dd/mm/yyyy): 23/02/2016

Norwich Medical School

Faculty of Medicine and Health Sciences

University of East Anglia

Norwich

Norfolk

NR4 7TJ

Miss C Crossman-Barnes

Email: C.Crossman-Barnes@uea.ac.uk

GP Surgery's Address

Date:

Dear Dr

RE:

Study Title: ***Estimating the loss in quality of life associated with an asthma-related crisis event.***

Patient's name:

Patient's D.O.B:

I am writing to inform you that your patient, (PATIENT'S NAME), has agreed to take part in the study entitled above at (HOSPITAL NAME). This study is part of a PhD project and is sponsored by the University of East Anglia and funded by Collaborations

for Leadership in Applied Health Research and Care East of England (CLAHRC EoE). It is a cohort study which will estimate the loss of utility associated with an asthma-related crisis event (in this case an asthma-related accident and emergency attendance or hospital admission) through economic evaluation methods.

Your patient's consent was obtained when they had an asthma-related accident and emergency (A&E) attendance or hospital admission, and they will be involved in the study for approximately eight weeks. They will be asked to self-complete quality of life questionnaires (EQ-5D-5L and AQLQ), peak flow and symptom questions during their hospital stay and for approximately eight weeks after discharge. They will also be asked to complete a loss of productivity questionnaire at approximately four weeks time. We will follow-up their responses by either reviewing this at their routine follow-up appointment, or over the phone. Your patient will also have the option of posting their responses back to us. If your patient was admitted to the Norfolk and Norwich University Hospital, they will also be asked time trade-off questions (a way of valuing their state of health) during their A&E attendance or hospital admission and at their follow-up appointment. After we have reviewed your patient's responses at approximately eight weeks after discharge, their involvement in the study will end.

I have enclosed a copy of the participant information sheet (Version 4.1, Dated 23rd February 2016) for your reference, however if you have any questions please don't hesitate to contact me on my details written above.

Yours sincerely,

Christina-Jane Crossman-Barnes

PhD student researcher

Appendix VI d Demographics questionnaire

University of East Anglia

Demographics

Centre number:

Version 4.1

Please can you answer these questions about yourself. This will help us with our research.

Before you start please can you fill in your:

Patient ID number:

Date (dd/mm/yyyy):

Please can you complete these questions.

1) What is your age? _____

2) What gender are you?

   Male ☐ Female ☐

3) What is your smoking status?

   Never smoked ☐ Non-smoker ☐ Ex-Smoker ☐ Smoker ☐

   If you have ticked 'non-smoker' or 'ex-smoker', how long ago did you stop smoking? _____

4) What is your ethnic group?

   White

   English/Welsh/Scottish/Northern Irish/British ☐

   Irish ☐

   Gypsy or Irish Traveller ☐

   Any other white background, please describe: _____

   _____

   Mixed/Multiple Ethnic groups

   White and Black Caribbean ☐

   White and Black African ☐

   White and Asian ☐

   Any other mixed/multiple ethnic background, please describe:

   _____

   Asian/Asian British

   Indian ☐

   Pakistani ☐

   Bangladeshi ☐

   Chinese ☐

   Any other Asian Background, please describe: _____

Black/African/Caribbean/Black British

African ☐

Caribbean ☐

Any other Black/African/Caribbean background, please describe:

_____

Other Ethnic group

Arab ☐

Any other ethnic group, please describe: _____

_____

5) What is the highest level of education that you have completed?

School ☐ College/Sixth Form ☐ University degree ☐

6) What is your employment status?

Full-time ☐ Part-time ☐ Unemployed ☐

Student ☐ Retired ☐ Stay at home parents ☐

7) When did your asthma-related event peak (e.g. on route to hospital, after 2 hours in hospital)?

_____

8) What was your route of entry to the hospital (e.g. did you call for the ambulance, did your GP refer you)?

_____

_____

9) In the last year, relating to your asthma and excluding your current A&E attendance or hospital admission:

How many hospital accident and emergency attendances did you have that did not result in a hospital admission? _____

How many hospital admissions did you have? _____

10) Before your current asthma A&E attendance or hospital admission, what medications (including your dosage e.g. in micrograms) have you been prescribed for your asthma (e.g. budesonide, salbutamol, terbutaline, formoterol, salmeterol, montelukast etc)?

NAME OF MEDICATION	DOSAGE	QUANTITY	FREQUENCY OF USE

END OF QUESTIONS

Thank you for completing the questionnaire.

We are very grateful for your help.

Appendix VI e EuroQol 5 Dimension 5 Level questionnaire

Health Questionnaire

Patient ID number:

Date (dd/mm/yyyy):

English version for the UK

Under each heading, please tick the ONE box that best describes your health TODAY.

MOBILITY

I have no problems in walking about ❑

I have slight problems in walking about ❑

I have moderate problems in walking about ❑

I have severe problems in walking about ❑

I am unable to walk about ❑

SELF-CARE

I have no problems washing or dressing myself ❑

I have slight problems washing or dressing myself ❑

I have moderate problems washing or dressing myself ❑

I have severe problems washing or dressing myself ❑

I am unable to wash or dress myself ❑

USUAL ACTIVITIES *(e.g. work, study, housework, family or leisure activities)*

I have no problems doing my usual activities ❑

I have slight problems doing my usual activities ❑

I have moderate problems doing my usual activities ❑

I have severe problems doing my usual activities ❑

I am unable to do my usual activities ❑

PAIN / DISCOMFORT

I have no pain or discomfort ❑

I have slight pain or discomfort ❑

I have moderate pain or discomfort ❑

I have severe pain or discomfort ❑

I have extreme pain or discomfort ❑

ANXIETY / DEPRESSION

I am not anxious or depressed ❑

I am slightly anxious or depressed ❑

I am moderately anxious or depressed ❑

I am severely anxious or depressed ❑

I am extremely anxious or depressed ❑

We would like to know how good or bad your health is TODAY.

This scale is numbered from 0 to 100.

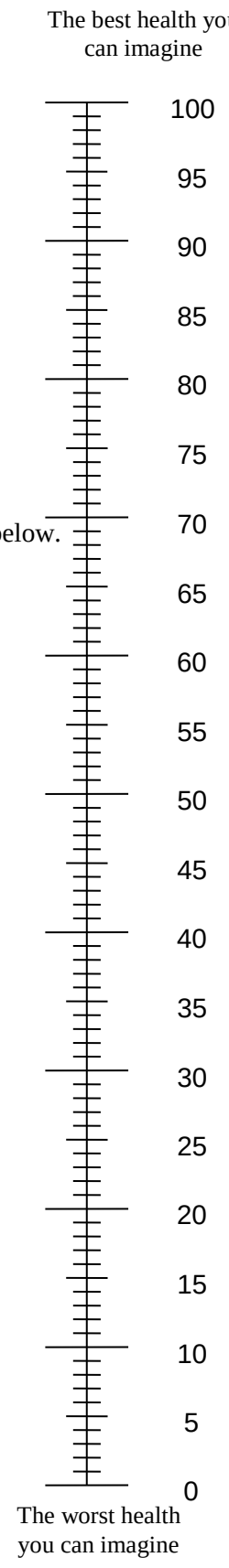
100 means the best health you can imagine.

0 means the worst health you can imagine.

Mark an X on the scale to indicate how your health is TODAY.

Now, please write the number you marked on the scale in the box below.

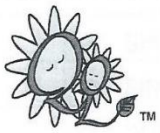
YOUR HEALTH TODAY = ☐



Appendix VI f Asthma Quality of Life Questionnaire

ASTHMA QUALITY OF LIFE QUESTIONNAIRE (AQLQ)

SELF-ADMINISTERED ENGLISH VERSION FOR THE UK



For further information:

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Translation by MAPI RESEARCH INSTITUTE
Senior Translator: Prof. Elizabeth Juniper

AUGUST 1999

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ASTHMA QUALITY OF LIFE QUESTIONNAIRE
(ENGLISH VERSION FOR THE UK)
SELF-ADMINISTERED

PATIENT ID: _____

DATE: _____

ACTIVITIES

We should like you to think of ways in which asthma limits your life. We are particularly interested in activities that you still do, but which are limited by your asthma. You may be limited because you do these activities less often, or less well, or because they are less enjoyable. These should be activities which you do frequently and which are important in your day-to-day life. These should also be activities that you intend to do regularly throughout the study.

Please think of all the activities which you have done during the last 2 weeks, in which you were limited as a result of your asthma.

Here is a list of activities in which some people with asthma are limited. We hope that this will help you to identify the 5 most important activities in which you have been limited **by your asthma during the last 2 weeks.**

1. BICYCLING	15. SHOPPING
2. WASHING CAR	16. SINGING
3. DANCING	17. DOING REGULAR SOCIAL ACTIVITIES
4. DOING HOME MAINTENANCE	18. HAVING SEXUAL INTERCOURSE
5. DOING YOUR HOUSEWORK	19. SLEEPING
6. GARDENING	20. TALKING
7. HURRYING	21. RUNNING UPSTAIRS OR UPHILL
8. JOGGING OR EXERCISING OR RUNNING	22. VACUUMING
9. LAUGHING	23. VISITING FRIENDS OR RELATIVES
10. MOPPING OR SCRUBBING THE FLOOR	24. GOING FOR A WALK
11. MOWING THE LAWN	25. WALKING UPSTAIRS OR UPHILL
12. PLAYING WITH PETS	26. WOODWORK OR CARPENTRY
13. PLAYING WITH CHILDREN OR GRANDCHILDREN	27. CARRYING OUT YOUR ACTIVITIES AT WORK
14. PLAYING SPORTS	

Write your 5 activities on the next page.

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ASTHMA QUALITY OF LIFE QUESTIONNAIRE
(ENGLISH VERSION FOR THE UK)
SELF-ADMINISTERED

PATIENT ID: _____

DATE: _____

Please write your 5 most important activities on the lines below and then tell us how much you have been limited **by your asthma** in each activity **during the last 2 weeks** by checking the box with the appropriate rating.

HOW **LIMITED** HAVE YOU BEEN DURING THE LAST 2 WEEKS IN THESE ACTIVITIES?

	Totally Limited	Extremely Limited	Very Limited	Moderate Limitation	Some Limitation	A Little Limitation	Not at all Limited	Activity Not Done
	1	2	3	4	5	6	7	
1._____	☐	☐	☐	☐	☐	☐	☐	☐
2._____	☐	☐	☐	☐	☐	☐	☐	☐
3._____	☐	☐	☐	☐	☐	☐	☐	☐
4._____	☐	☐	☐	☐	☐	☐	☐	☐
5._____	☐	☐	☐	☐	☐	☐	☐	☐

HOW MUCH **DISCOMFORT OR DISTRESS** HAVE YOU FELT OVER THE LAST 2 WEEKS?

	A Very Great Deal	A Great Deal	A Good Deal	Moderate Amount	Some	Very Little	None
	1	2	3	4	5	6	7
6. How much discomfort or distress have you felt over the last 2 weeks as a result of CHEST TIGHTNESS?	☐	☐	☐	☐	☐	☐	☐

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ASTHMA QUALITY OF LIFE QUESTIONNAIRE
(ENGLISH VERSION FOR THE UK)
SELF-ADMINISTERED

PATIENT ID: _____

DATE: _____

IN GENERAL, **HOW MUCH OF THE TIME** DURING THE LAST 2 WEEKS DID YOU:

	All of the Time	Most of the Time	A Good Bit of the Time	Some of the Time	A Little of the Time	Hardly Any of the Time	None of the Time
	1	2	3	4	5	6	7
7. Feel CONCERNED ABOUT HAVING ASTHMA?	☐	☐	☐	☐	☐	☐	☐
8. Feel SHORT OF BREATH as a result of your asthma?	☐	☐	☐	☐	☐	☐	☐
9. Experience asthma symptoms as a RESULT OF BEING EXPOSED TO CIGARETTE SMOKE?	☐	☐	☐	☐	☐	☐	☐
10. Experience a WHEEZE in your chest?	☐	☐	☐	☐	☐	☐	☐
11. Feel you had to AVOID A SITUATION OR ENVIRONMENT BECAUSE OF CIGARETTE SMOKE?	☐	☐	☐	☐	☐	☐	☐

HOW MUCH **DISCOMFORT OR DISTRESS** HAVE YOU FELT OVER THE LAST 2 WEEKS?

	A Very Great Deal	A Great Deal	A Good Deal	Moderate Amount	Some	Very Little	None
	1	2	3	4	5	6	7
12. How much discomfort or distress have you felt over the last 2 weeks as a result of COUGHING?	☐	☐	☐	☐	☐	☐	☐

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ASTHMA QUALITY OF LIFE QUESTIONNAIRE
(ENGLISH VERSION FOR THE UK)
SELF-ADMINISTERED

PATIENT ID: _____

DATE: _____

IN GENERAL, **HOW MUCH OF THE TIME** DURING THE LAST 2 WEEKS DID YOU:

	All of the Time	Most of the Time	A Good Bit of the Time	Some of the Time	A Little of the Time	Hardly Any of the Time	None of the Time
	1	2	3	4	5	6	7
13. Feel FRUSTRATED as a result of your asthma?	☐	☐	☐	☐	☐	☐	☐
14. Experience a feeling of CHEST HEAVINESS?	☐	☐	☐	☐	☐	☐	☐
15. Feel CONCERNED ABOUT THE NEED TO USE MEDICATION for your asthma?	☐	☐	☐	☐	☐	☐	☐
16. Feel the need to CLEAR YOUR THROAT?	☐	☐	☐	☐	☐	☐	☐
17. Experience asthma symptoms as a RESULT OF BEING EXPOSED TO DUST?	☐	☐	☐	☐	☐	☐	☐
18. Experience DIFFICULTY BREATHING OUT as a result of your asthma?	☐	☐	☐	☐	☐	☐	☐
19. Feel you had to AVOID A SITUATION OR ENVIRONMENT BECAUSE OF DUST?	☐	☐	☐	☐	☐	☐	☐
20. WAKE UP IN THE MORNING WITH ASTHMA SYMPTOMS?	☐	☐	☐	☐	☐	☐	☐
21. Feel AFRAID OF NOT HAVING YOUR ASTHMA MEDICATION AVAILABLE?	☐	☐	☐	☐	☐	☐	☐
22. Feel bothered by HEAVY BREATHING?	☐	☐	☐	☐	☐	☐	☐

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ASTHMA QUALITY OF LIFE QUESTIONNAIRE
(ENGLISH VERSION FOR THE UK)
SELF-ADMINISTERED

PATIENT ID: _____

DATE: _____

IN GENERAL, **HOW MUCH OF THE TIME** DURING THE LAST 2 WEEKS DID YOU:

	All of the Time	Most of the Time	A Good Bit of the Time	Some of the Time	A Little of the Time	Hardly Any of the Time	None of the Time
	1	2	3	4	5	6	7
23. Experience asthma symptoms as a RESULT OF THE WEATHER OR AIR POLLUTION OUTSIDE?	☐	☐	☐	☐	☐	☐	☐
24. Were you WOKEN AT NIGHT by your asthma?	☐	☐	☐	☐	☐	☐	☐
25. AVOID OR LIMIT GOING OUTSIDE BECAUSE OF THE WEATHER OR AIR POLLUTION?	☐	☐	☐	☐	☐	☐	☐
26. Experience asthma symptoms as a RESULT OF BEING EXPOSED TO STRONG SMELLS OR PERFUME?	☐	☐	☐	☐	☐	☐	☐
27. Feel AFRAID OF GETTING OUT OF BREATH?	☐	☐	☐	☐	☐	☐	☐
28. Feel you had to AVOID A SITUATION OR ENVIRONMENT BECAUSE OF STRONG SMELLS OR PERFUME?	☐	☐	☐	☐	☐	☐	☐
29. Has your asthma INTERFERED WITH GETTING A GOOD NIGHT'S SLEEP?	☐	☐	☐	☐	☐	☐	☐
30. Have a feeling of FIGHTING FOR AIR?	☐	☐	☐	☐	☐	☐	☐

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ASTHMA QUALITY OF LIFE QUESTIONNAIRE
(ENGLISH VERSION FOR THE UK)
SELF-ADMINISTERED

PATIENT ID: _____

DATE: _____

HOW LIMITED HAVE YOU BEEN DURING THE LAST 2 WEEKS?

	Severely Limited Most Not Done	Very Limited	Moderately Limited Several Not Done	Slightly Limited	Very Slightly Limited Very Few Not Done	Hardly Limited At All	Not Limited Have Done All Activities
	1	2	3	4	5	6	7
31. Think of the OVERALL RANGE OF ACTIVITIES that you would have liked to have done during the last 2 weeks. How much has your range of activities been limited by your asthma?	☐	☐	☐	☐	☐	☐	☐

	Totally Limited	Extremely Limited	Very Limited	Moderate Limitation	Some Limitation	A Little Limitation	Not at all Limited
	1	2	3	4	5	6	7
32. Overall, among ALL THE ACTIVITIES that you have done during the last 2 weeks, how limited have you been by your asthma?	☐	☐	☐	☐	☐	☐	☐

DOMAIN CODE:

Symptoms: 6, 8, 10, 12, 14, 16, 18, 20, 22, 24, 29, 30
Activity Limitation: 1, 2, 3, 4, 5, 11, 19, 25, 28, 31, 32
Emotional Function: 7, 13, 15, 21, 27
Environmental Stimuli: 9, 17, 23, 26

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University of East Anglia

Peak flow and symptom score

Centre number:

Version 1.0

Please can you answer these questions about your peak flow, symptoms and activities. It is important that you answer these questions every day as this will help us with our research.

Before you start please can you fill in your:

Patient ID number:

Date (dd/mm/yyyy):

Please complete the following table, and bring this with you to your hospital follow-up appointment.

For the peak expiratory flow readings, please enter the morning and evening scores that you see on your peak flow after blowing.

For the sleeping, usual asthma symptoms and usual activities questions, please enter a number between 0 and 3:

0 – absent symptoms (no sign/symptoms evident)

1 – mild symptoms (sign/symptoms clearly present, but minimal awareness and easily tolerated)

2 – moderate symptoms (definite awareness of sign/symptoms that is bothersome but tolerable)

3 – severe symptoms (sign/symptoms that is hard to tolerate; causes interference with activities of daily living)

For the EQ-5D check question, this is a reminder to complete your EQ-5D questionnaire and tick the box when complete.

Reminder:

The week of your follow-up appointment, please complete and bring with you your Asthma quality of life questionnaire AND the productivity questionnaire.

	Day 1	Day 2	Day 3	Day 4	Day 5	Day 6	Day 7	Day 8	Day 9	Day 10	Day 11	Day 12
Peak Expiratory Flow reading (AM): Please record AM reading here												
Peak Expiratory Flow reading (PM): Please record PM reading here												
Sleeping: Have you had difficulty sleeping because of your asthma?												
Usual asthma symptoms: Have you had your usual asthma symptoms during the day (cough, wheeze, breathlessness, chest tightness)?												
Usual activities: Has your asthma interfered with your usual activities (e.g. housework, child care, work, school etc.)?												
EQ-5D check: Have you completed your EQ-5D today?												

0 – absent symptoms (no sign/symptoms evident); **1 – mild symptoms** (sign/symptoms clearly present, but minimal awareness and easily tolerated); **2 – moderate symptoms** (definite awareness of sign/symptoms that is bothersome but tolerable); **3 – severe symptoms** (sign/symptoms that is hard to tolerate; causes interference with activities of daily living)

	Day 13	Day 14	Day 15	Day 16	Day 17	Day 18	Day 19	Day 20	Day 21	Day 22	Day 23	Day 24
Peak Expiratory Flow reading (AM): Please record AM reading here												
Peak Expiratory Flow reading (PM): Please record PM reading here												
Sleeping: Have you had difficulty sleeping because of your asthma?												
Usual asthma symptoms: Have you had your usual asthma symptoms during the day (cough, wheeze, breathlessness, chest tightness)?												
Usual activities: Has your asthma interfered with your usual activities (e.g. housework, child care, work, school etc.)?												
EQ-5D check: Have you completed your EQ-5D today?												

0 – absent symptoms (no sign/symptoms evident); **1 – mild symptoms** (sign/symptoms clearly present, but minimal awareness and easily tolerated); **2 – moderate symptoms** (definite awareness of sign/symptoms that is bothersome but tolerable); **3 – severe symptoms** (sign/symptoms that is hard to tolerate; causes interference with activities of daily living)

	Day 25	**Day 26**	**Day 27**	**Day 28**	**Day 29**	**Day 30**	**Day 31**	**Day 32**	**Day 33**	**Day 34**	**Day 35**	**Day 36**
Peak Expiratory Flow reading (AM): Please record AM reading here												
Peak Expiratory Flow reading (PM): Please record PM reading here												
Sleeping: Have you had difficulty sleeping because of your asthma?												
Usual asthma symptoms: Have you had your usual asthma symptoms during the day (cough, wheeze, breathlessness, chest tightness)?												
Usual activities: Has your asthma interfered with your usual activities (e.g. housework, child care, work, school etc.)?												
EQ-5D check: Have you completed your EQ-5D today?												

0 – absent symptoms (no sign/symptoms evident); **1 – mild symptoms** (sign/symptoms clearly present, but minimal awareness and easily tolerated); **2 – moderate symptoms** (definite awareness of sign/symptoms that is bothersome but tolerable); **3 – severe symptoms** (sign/symptoms that is hard to tolerate; causes interference with activities of daily living)

	Day 37	Day 38	Day 39	Day 40	Day 41	Day 42	Day 43	Day 44	Day 45	Day 46	Day 47	Day 48
Peak Expiratory Flow reading (AM): Please record AM reading here												
Peak Expiratory Flow reading (PM): Please record PM reading here												
Sleeping: Have you had difficulty sleeping because of your asthma?												
Usual asthma symptoms: Have you had your usual asthma symptoms during the day (cough, wheeze, breathlessness, chest tightness)?												
Usual activities: Has your asthma interfered with your usual activities (e.g. housework, child care, work, school etc.)?												
EQ-5D check: Have you completed your EQ-5D today?												

0 – absent symptoms (no sign/symptoms evident); **1 – mild symptoms** (sign/symptoms clearly present, but minimal awareness and easily tolerated); **2 – moderate symptoms** (definite awareness of sign/symptoms that is bothersome but tolerable); **3 – severe symptoms** (sign/symptoms that is hard to tolerate; causes interference with activities of daily living)

Thank you for completing these questions. We are very grateful for your help.

University of East Anglia

Productivity Questionnaire

Centre number:

Version 4.1

Please can you answer these questions about yourself, your ability to work, and/or attend classes and do activities. When you answer these questions we would like you to think about how you are affected by having your asthma-related A&E attendance or hospital admission compared to when you did not have your asthma event. This will help us with our research.

Before you start please can you fill in your:

Patient ID number:

Today's date (dd/mm/yyyy):

PLEASE TURN THE PAGE TO START THE QUESTIONNAIRE.

PART 1

1) What was the date of your recent asthma-related A&E attendance or hospital admission?

_____ (Day/Month/Year)

2) How long were you in hospital for? _____

3) Compared to your asthma state when you were in hospital approximately 4 weeks ago, how would you rate your asthma now?

Very good ☐

Good ☐

Moderate ☐

Poor ☐

Very Poor ☐

4) Do you think you have completely recovered from when you were in hospital approximately 4 weeks ago?

Yes ☐ No ☐

5) If you are in employment (paid work), have you returned to work yet?

Yes ☐ No ☐

Do not work (unemployed/student/retired/stay at home parents) ☐

Tick and circle

IF YES, GO TO PART 2

IF YOU ARE A STUDENT, GO TO PART 3. OTHERWISE CONTINUE TO PART 4.

PART 2

1) What was the date that you returned to work after having your asthma-related A&E attendance or hospital admission?

_____ (Day/Month/Year)

2) **On average**, how many **hours per week** did you work in the four weeks before your asthma-related A&E attendance or hospital admission?

_____ Hours per week

3) Since your asthma-related A&E attendance or hospital admission, **on average**, how many **hours or minutes per week** have you missed from work because of your asthma? *Include hours you missed on sick days, times you went in late, left early, because of your asthma. Do not include time you missed to participate in this study.*

_____ Hours per week OR _____ Minutes per week

4) Since your asthma-related A&E attendance or hospital admission, **on average per week**, how much did your asthma affect your productivity <u>while you were working?</u>

Think about days you were limited in the amount or kind of work you could do, days you accomplished less than you would like, or days you could not do your work as carefully as usual. If your asthma affected your work only a little, choose a low number. Choose a high number if your asthma affected your work a great deal.

Consider only how much your asthma affected productivity <u>while you were working</u>. Circle a number.

Your asthma had no effect on my work	0 1 2 3 4 5 6 7 8 9 10	Your asthma completely prevented me from working

GO TO PART 4

PART 3

1) Do you currently attend classes in an academic setting (school, sixth-form college, university, etc.)?

YES ☐ NO ☐ **IF NO, GO TO PART 4**

2) During term time, before your asthma-related A&E attendance or hospital admission, **on average** how many **hours per week** did you usually attend classes?

_____ Hours per week

3) Since your asthma-related A&E attendance or hospital admission, **on average**, how many **hours or minutes per week** have you missed class because of your asthma? *Do not include time you missed to participate in this study.*

_____ Hours per week OR _____ Minutes per week

4) Since your asthma-related A&E attendance or hospital admission, **on average per week**, how much did your asthma affect your productivity <u>while in school or attending classes</u> in an academic setting?

Think about days your attention span was limited, you had trouble with comprehension or days in which you could not take tests as effectively as usual. If your asthma affected your productivity at school or in class only a little, choose a low number. Choose a high number if your asthma affected your productivity at school or in class a great deal.

Consider only how much your asthma affected productivity <u>while in school or attending classes.</u> Circle a number.

Your asthma had no effect on my class work		Your asthma completely

prevented me from doing my class work

0 1 2 3 4 5 6 7 8 9 10

GO TO PART 4

PART 4

1) Since your asthma-related A&E attendance or hospital admission, **on average per week**, how much did your asthma affect your ability to do your regular daily activities, other than work at a job or attending classes?

   By regular activities, we mean the usual activities you do, such as work around the house, shopping, child care, exercising, studying, etc. Think about times you were limited in the amount or kind of activities you could do and times you accomplished less than you would like. If your asthma affected your activities only a little, choose a low number. Choose a high number if your asthma affected your activities a great deal.

Consider only how much your asthma affected your ability to do your regular daily activities, other than work at a job or attending classes. Circle a number.

Your asthma had no effect on my daily activities	0	1	2	3	4	5	6	7	8	9	10	Your asthma completely prevented me from doing my daily activities

GO TO PART 5

PART 5

1) Since your last asthma-related A&E attendance or hospital admission have you bought any extra products (e.g. prescriptions, allergy-free bedding, cleaning products, food items) or used a service (e.g. a visit to a complementary therapist) to that which you would normally buy/use e.g. in the four weeks prior to your asthma-related A&E Attendance or hospital admission?

YES ☐ NO ☐ **IF NO, GO TO PART 6**

2) If YES, list the name of the product and the cost in the table below including any new medicines and dosage in micrograms prescribed (e.g. budesonide, salbutamol, terbutaline, formoterol, salmeterol, montelukast etc).

NAME OF EXTRA PRODUCT	HOW MANY?	DOSAGE & FREQUENCY OF USE	COST PER PRODUCT

PART 6

Please provide us with any comments that you may have.

COMMENTS

END OF QUESTIONNAIRE

Thank you for completing the questionnaire.

We are very grateful for your help.

Appendix VI i Ethics letters

NHS
Health Research Authority

East of England - Cambridge South Research Ethics Committee
The Old Chapel
Royal Standard Place
Nottingham
NG1 6FS

Telephone: 020 7104 8144

04 February 2016

Miss Christina-Jane Crossman-Barnes
PhD Student
University of East Anglia
Norwich Medical School
University of East Anglia
Norwich
NR4 7TJ

Dear Miss Crossman-Barnes

Study Title:	**Estimating the loss in quality of life associated with an asthma related crisis event**
REC reference:	**16/EE/0023**
IRAS project ID:	**181141**

The Research Ethics Committee reviewed the above application at the meeting held on 28 January 2016. Thank you to you and Garry Barton for attending to discuss the application.

Provisional opinion

The Committee is unable to give an ethical opinion on the basis of the information and documentation received so far. Before confirming its opinion, the Committee requests that you provide the further information set out below.

Authority to consider your response and to confirm the Committee's final opinion has been delegated to the Chair.

Further information or clarification required

1. You are required to confirm whether a secondary site will be involved in the study, as indicated in the IRAS form but not listed at Part C.

2. You are required to confirm what action will be taken should a participant have a second asthma attack during the study.

3. The Committee requires that you re-visit the protocol and consider an alternative option to approaching patients in the A&E Department. They require that you seek advice from an A&E clinician regarding the practicalities, chance of uptake from clinicians and, most importantly, the ethics around approaching patients for non-essential research in this circumstance. The Committee suggests it may be possible to approach patients following admission to hospital. If you propose the continue with the original approach please provide further justification and evidence that you have considered the ethics of the approach in A&E and are able to mitigate against causing undue stress or upset.

4. You are required to exclude patients who require assistance of a carer to complete questionnaires.

5. You are required to confirm the telephone contact number given in the participant information sheet is not a personal number.

6. The following changes to the participant information sheet are required:
   a) The flow chart should be removed and replaced with the version used within the protocol.
   b) The other conditions forming part of the study, such as COPD, should be mentioned.
   c) The name of the Chief Investigator and Trust's logo must be added.

7. As advisory points only, the Committee suggest the demographics questionnaire could include an option at question 6 to indicate if patients are stay at home parents. It would also benefit from asking how long ago 'non-smokers' and 'ex-smokers' stopped smoking.

If you would find it helpful to discuss any of the matters raised above or seek further clarification from a member of the Committee, you are welcome to contact Ellen Swainston at nrescommittee.eastofengland-cambridgesouth@nhs.net

When submitting a response to the Committee, the requested information should be electronically submitted from IRAS. A step-by-step guide on submitting your response to the REC provisional opinion is available on the HRA website using the following link: http://www.hra.nhs.uk/nhs-research-ethics-committee-rec-submitting-response-provisional-opinion/

Please submit revised documentation where appropriate underlining or otherwise highlighting the changes which have been made and giving revised version numbers and dates. You do not have to make any changes to the REC application form unless you have been specifically requested to do so by the REC.

The Committee will confirm the final ethical opinion within a maximum of 60 days from the date of initial receipt of the application, excluding the time taken by you to respond fully to the above points. A response should be submitted by no later than 05 March 2016.

Summary of the discussion at the meeting

Social or scientific value; scientific design and conduct of the study

appropriate for you to approach a potential participant and it would be different for every patient. Given this was quite a significant condition you would wait for the nurse or clinical team to let you know whether a patient was stable enough. Members asked what was the earliest point in treatment that a patient may be approached or have the study mentioned by their care team. *You confirmed that patients would receive the care they needed first in order that they could be stabilised before the study was mentioned.* Members sought to clarify that this meant patients would need to be in a stable condition and only then would they be approached about the study. *You confirmed this was the case.* Given the clinicians would be the 'gatekeepers', the Committee commented that there may be some patients they never see. *You agreed you would not see those patients who clinicians deemed to be in an unstable condition, distressed or lacking capacity.*

The Committee continued to have reservations about the recruitment of individuals whilst in A&E, given they will be going through a stressful experience and care will be critical. *You responded that you had incorporated criteria that patients would only be approached outside of the critical first hour to reduce the risk of distress.* The Committee noted this, adding it was important patients were not approached if there was any possibility of exacerbating stress or upset.

The Committee noted that the application stated that the productivity questionnaire could be completed by a carer if needed, and sought to clarify in what situation a patient's carer would be involved. *You explained that if the carer was present they may be involved in questionnaire completion and the study team would have regular communication with them to keep them involved.* The Committee stated it was uncommon to have carers complete quality of life questionnaires for the patient because answers would normally be based on personal experience. *You clarified that if the patient was able to converse then the document could be completed by the carer whilst talking to the patient. You would take into account that answers may not be as thorough as if the patient was physically completing it, but it should be satisfactory. You added you were not using proxy questionnaires, only those intended for completion by the participants themselves.*

Following your departure, the Committee commented that it would not be appropriate for the carer to facilitate consent, and sought confirmation this would not occur. In addition, it was agreed that the need for a carer to be involved indicated the patient remained vulnerable and was not sufficiently recovered, and the data given in this way may not be as accurate as desired anyway. For these reasons the Committee were in agreement that patients requiring carer assistance should not be included in the study.

Favourable risk benefit ratio; anticipated benefit/risks for research participants (present and future)

The Committee commented that they could not clearly see the benefits of this study to patients in order to weigh up the risk/benefit ratio. They asked you what the potential benefits of the study were. *You responded that the benefits were the potential to help future asthma patients by enhancing other asthma quality of life studies and analysing which treatments are more cost effective.* The Committee noted that you were not looking at costs associated with A&E admission. *You confirmed this, adding you wanted to estimate the cost of hospital admissions and translate that against the quality of life score also.* Members asked whether cost effectiveness was the main factor being measured, given it could likely be predicted that quality of life would decrease following an asthma attack. *You informed that you needed to demonstrate the extent to which that occurred,*

as there wasn't currently firm data. This would help you to demonstrate value for money against each treatment, which was something NICE were interested in.

Informed consent process and the adequacy and completeness of participant information

The Committee noted the telephone contact number given in the participant information sheet and wished to query whether this was a personal number. They were in agreement it would not be appropriate for the researcher or the patient to use a personal number. It was also commented that the flow chart in the protocol was much clearer than the version used in the participant information sheet and should be added in place of this version. Members stated also that the participant information sheet should refer to the other groups involved in the study, such as those with COPD. They commented the participant information sheet needed the name of the Chief Investigator and the Trust's logo adding to the front.

Suitability of the applicant and supporting staff

The Committee asked whether the Chief Investigator felt there was enough time, within the framework of her PhD, to conduct the study with 100 patients. *You believed there was adequate time. You added that if recruitment was slow you would consider other sites and had spoken with clinicians already regarding numbers and how the process would work.*

Suitability of supporting information

Members noted the 5 questionnaires and diary did not always seem to align with a situation relating to a sudden asthma attack and this may affect the relevance of some of the data gathered for the study. In addition, members agreed that the demographics questionnaire would benefit from an option at question 6 to indicate 'stay at home parents', who did not fall neatly into the other categories. It should also ask how long ago 'non-smokers' and 'ex-smokers' stopped smoking, as smoking status could fluctuate.

Documents reviewed

The documents reviewed at the meeting were:

Document	*Version*	*Date*
Evidence of Sponsor insurance or indemnity (non NHS Sponsors only) [Insurance and indemnity letter]		
GP/consultant information sheets or letters [GP letter]	1.0	23 November 2015
IRAS Checklist XML [Checklist_22122015]		22 December 2015
Non-validated questionnaire [Peak flow and symptoms diary]	1.0	20 November 2015
Non-validated questionnaire [Demographics]	4.0	23 November 2015
Non-validated questionnaire [Time trade off]	1.0	01 October 2015
Non-validated questionnaire [Productivity questionnaire]	4.0	20 November 2015
Other [Andrew Wilson's CV]		
Other [Tracey Sach's CV]		

Other [Letter response to Proportionate review ethical issues]	1.0	22 December 2015
Participant consent form [Consent form]	3.0	23 November 2015
Participant information sheet (PIS) [Participant Information Sheet]	4.0	23 November 2015
REC Application Form [REC_Form_26112015]		26 November 2015
Research protocol or project proposal [Protocol. Estimating the loss in quality of life associated with an asthma-related hospital admission]	5.0	23 November 2015
Summary CV for Chief Investigator (CI) [C.Crossman-Barnes' CV]		
Summary CV for student [C.Crossman-Barnes' CV]		
Summary CV for supervisor (student research) [Garry Barton's CV]		
Validated questionnaire [EQ-5D-5L]		
Validated questionnaire [Asthma Quality of Life Questionnaire]		

Membership of the Committee

The members of the Committee who were present at the meeting are listed on the attached sheet

Statement of compliance

The Committee is constituted in accordance with the Governance Arrangements for Research Ethics Committees and complies fully with the Standard Operating Procedures for Research Ethics Committees in the UK.

16/EE/0023	**Please quote this number on all correspondence**

Yours sincerely

pp. L. Gelling

Dr Leslie Gelling
Chair

Email: nrescommittee.eastofengland-cambridgesouth@nhs.net

Enclosures: *List of names and professions of members who were present at the meeting and those who submitted written comments.*

Copy to: *Mrs Susan Steel*
Ms Laura Harper

East of England - Cambridge South Research Ethics Committee

Attendance at Committee meeting on 28 January 2016

Committee Members:

Name	*Profession*	*Present*	*Notes*
Dr Richard Aldridge		Yes	
Mrs Martha Byrne	Director, Clinical & Pharmacoviligance QA	Yes	
Dr Ian Dumbelton	Retired General Medical Practitioner (Alternate Vice-Chair)	Yes	
Dr Leslie Gelling	(Chair) Reader in Research Ethics	Yes	
Mr Colin Green	Drugs & Therapeutics Pharmaceutical Advisor	Yes	
Mrs Alison Hall	Programme Lead - Humanities	Yes	
Dr Linda Harvey	Head of Scientific Support	Yes	
Mr John Kirkpatrick	Statistician	No	
Miss Angela Palmer	Retired Patent Litigator	Yes	
Mrs Nikki Phillimore	Antibiotic/infection management pharmacist	Yes	
Dr Michael Sheldon	Retired Clinical Psychologist	Yes	
Miss Carol Smee		Yes	
Mr Phil Tempest	Compliance Manager	No	
Dr Frank Wells	(Vice-Chair) Retired Pharmaceutical Physician	Yes	
Dr Kate Williams	Senior Research Associate	Yes	
Dr Rashid Zaman	Consultant Psychiatrist and Director of Bedfordshire Centre for Mental Health Research	No	

Also in attendance:

Name	*Position (or reason for attending)*
Helen Poole	REC Manager

NHS
Health Research Authority

East of England - Cambridge South Research Ethics Committee
The Old Chapel
Royal Standard Place
Nottingham
NG1 6FS

29 March 2016

Miss Christina-Jane Crossman-Barnes
PhD Student
University of East Anglia
Norwich Medical School
University of East Anglia
Norwich
NR4 7TJ

Dear Miss Crossman-Barnes

Study title:	**Estimating the loss in quality of life associated with an asthma related crisis event**
REC reference:	**16/EE/0023**
IRAS project ID:	**181141**

Thank you for your letter of 21 March 2016, responding to the Committee's request for further information on the above research and submitting revised documentation.

The further information has been considered on behalf of the Committee by the Chair.

We plan to publish your research summary wording for the above study on the HRA website, together with your contact details. Publication will be no earlier than three months from the date of this opinion letter. Should you wish to provide a substitute contact point, require further information, or wish to make a request to postpone publication, please contact the REC Manager, Ellen Swainston, nrescommittee.eastofengland-cambridgesouth@nhs.net.

Confirmation of ethical opinion

On behalf of the Committee, I am pleased to confirm a favourable ethical opinion for the above research on the basis described in the application form, protocol and supporting documentation as revised, subject to the conditions specified below.

Conditions of the favourable opinion

The REC favourable opinion is subject to the following conditions being met prior to the start of the study.

Management permission must be obtained from each host organisation prior to the start of the study at the site concerned.

Management permission should be sought from all NHS organisations involved in the study in accordance with NHS research governance arrangements. Each NHS organisation must confirm through the signing of agreements and/or other documents that it has given permission for the research to proceed (except where explicitly specified otherwise).

Guidance on applying for NHS permission for research is available in the Integrated Research Application System, www.hra.nhs.uk or at http://www.rdforum.nhs.uk.

Where a NHS organisation's role in the study is limited to identifying and referring potential participants to research sites ("participant identification centre"), guidance should be sought from the R&D office on the information it requires to give permission for this activity.

For non-NHS sites, site management permission should be obtained in accordance with the procedures of the relevant host organisation.

Sponsors are not required to notify the Committee of management permissions from host organisations

Registration of Clinical Trials

All clinical trials (defined as the first four categories on the IRAS filter page) must be registered on a publically accessible database within 6 weeks of recruitment of the first participant (for medical device studies, within the timeline determined by the current registration and publication trees).

There is no requirement to separately notify the REC but you should do so at the earliest opportunity e.g. when submitting an amendment. We will audit the registration details as part of the annual progress reporting process.

To ensure transparency in research, we strongly recommend that all research is registered but for non-clinical trials this is not currently mandatory.

If a sponsor wishes to contest the need for registration they should contact Catherine Blewett (catherineblewett@nhs.net), the HRA does not, however, expect exceptions to be made. Guidance on where to register is provided within IRAS.

It is the responsibility of the sponsor to ensure that all the conditions are complied with before the start of the study or its initiation at a particular site (as applicable).

Ethical review of research sites

NHS sites

The favourable opinion applies to all NHS sites taking part in the study, subject to management permission being obtained from the NHS/HSC R&D office prior to the start of the study (see "Conditions of the favourable opinion" below).

Non-NHS sites

Approved documents

The final list of documents reviewed and approved by the Committee is as follows:

Document	*Version*	*Date*
Evidence of Sponsor insurance or indemnity (non NHS Sponsors only) [Insurance and indemnity letter]		
GP/consultant information sheets or letters [GP letter - tracked version]	1.1	23 February 2016
GP/consultant information sheets or letters [GP letter - cleaned]	1.1	23 February 2016
IRAS Checklist XML [Checklist_22122015]		22 December 2015
IRAS Checklist XML [Checklist_21032016]		21 March 2016
Non-validated questionnaire [Peak flow and symptoms diary]	1.0	20 November 2015
Non-validated questionnaire [Time trade off]	1.0	01 October 2015
Non-validated questionnaire [Productivity questionnaire - tracked version]	4.1	23 February 2016
Non-validated questionnaire [Productivity questionnaire - cleaned versio]	4.1	23 February 2016
Non-validated questionnaire [Demographics - tracked version]	4.1	23 February 2016
Non-validated questionnaire [Demographics cleaned version]	4.1	23 February 2016
Other [Andrew Wilson's CV]		
Other [Tracey Sach's CV]		
Other [Letter response to Proportionate review ethical issues]	1.0	22 December 2015
Other [Response to provisional approval]	1.0	21 March 2016
Participant consent form [Consent form tracked version]	3.1	23 February 2016
Participant consent form [Consent form cleaned version]	3.1	23 February 2016
Participant information sheet (PIS) [Participant Information Sheet - tracked version]	4.1	23 February 2016
Participant information sheet (PIS) [Participant Information Sheet - cleaned version]	4.1	23 February 2016
REC Application Form [REC_Form_26112015]		26 November 2015
Research protocol or project proposal [Protocol. Estimating the loss in quality of life associated with an asthma-related hospital admission]	5.1	23 February 2016
Response to Request for Further Information		21 March 2016
Summary CV for Chief Investigator (CI) [C.Crossman-Barnes' CV]		
Summary CV for student [C.Crossman-Barnes' CV]		
Summary CV for supervisor (student research) [Garry Barton's CV]		
Validated questionnaire [EQ-5D-5L]		
Validated questionnaire [Asthma Quality of Life Questionnaire]		

Statement of compliance

The Committee is constituted in accordance with the Governance Arrangements for Research Ethics Committees and complies fully with the Standard Operating Procedures for Research Ethics Committees in the UK.

After ethical review

Reporting requirements

The attached document *"After ethical review – guidance for researchers"* gives detailed guidance on reporting requirements for studies with a favourable opinion, including:

- Notifying substantial amendments
- Adding new sites and investigators
- Notification of serious breaches of the protocol
- Progress and safety reports
- Notifying the end of the study

The HRA website also provides guidance on these topics, which is updated in the light of changes in reporting requirements or procedures.

User Feedback

The Health Research Authority is continually striving to provide a high quality service to all applicants and sponsors. You are invited to give your view of the service you have received and the application procedure. If you wish to make your views known please use the feedback form available on the HRA website:
http://www.hra.nhs.uk/about-the-hra/governance/quality-assurance/

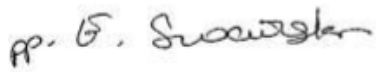
HRA Training

We are pleased to welcome researchers and R&D staff at our training days – see details at http://www.hra.nhs.uk/hra-training/

16/EE/0023	**Please quote this number on all correspondence**

With the Committee's best wishes for the success of this project.

Yours sincerely



Dr Les Gelling
Chair

Email:nrescommittee.eastofengland-cambridgesouth@nhs.net

Enclosures: "After ethical review – guidance for researchers"

Copy to: *Mrs Susan Steel*
Ms Laura Harper

Appendix VII: STATA code for post-viva revisions

STATA version 12

```
*Chapter 2

*Comparison of Qhes scores between Yong & Shafie 8 studies (post 2008) and Campbell policy 14 studies (< 2008)
ttest  Y_8== campbell_policy
*Comparison of Qhes scores between all Yong & Shafie 49 studies and Campbell policy 14 studies (note, Y&S all years included)
ttest  y_49== campbell_policy
*Comparion of the additional 15 studies in my Sys Rev and Campbell policy 14 studies
ttest  c_15== campbell_policy
*Comparison of all Yong and Shafie and all additional 15 studies found in my Sys Rev
ttest  y_49== c_15

*Chapter 3

*Post-hoc power calculation
sampsi 0 0.5, sd1(2) alpha(0.05) power(.80) onesample


*Chapter 4

*exploring ceiling effect of eq5d5l at baseline*
tab asthma_peak if eq5d5l0==1

tab asthma_peak, gen(asthma_peak)
rename asthma_peak1 before
rename asthma_peak2 hospital
rename asthma_peak3 route
```

```
regress eq5d5l0 before route

tab asthma_peak if tto0==1
regress tto0 before route


*missing data table for all variables (nb demographic variables all observed, not missing)
misstable summ eq5d5l0 eq5d5l1 eq5d5l2 eq5d5l3 eq5d5l4 eq5d5l5 eq5d5l6 eq5d5l7 eq5d5l8 tto0 tto4 tto8 aql5d0 aql5d4 aql5d8 age gender ethnicity employment_status smoking_status  highest_education
*missing data patterns
misstable patterns eq5d5l0 eq5d5l1 eq5d5l2 eq5d5l3 eq5d5l4 eq5d5l5 eq5d5l6 eq5d5l7 eq5d5l8 tto0 tto4 tto8 aql5d0 aql5d4 aql5d8 age gender ethnicity employment_status smoking_status  highest_education, freq

*predictors of missingness using logistic regression (Odds ratios and CI)
gen r_eq5d5l1=(eq5d5l1!=.)
xi: logistic r_eq5d5l1  age
xi: logistic r_eq5d5l1 i.gender
xi: logistic r_eq5d5l1 i.smoking_status
xi: logistic r_eq5d5l1 i.ethnicity
xi: logistic r_eq5d5l1 i.employment_status
xi: logistic r_eq5d5l1 i.highest_education
xi: logistic r_eq5d5l1 age i.gender i.smoking_status i.ethnicity i.employment_status i.highest_education

gen r_eq5d5l2=(eq5d5l2!=.)
xi: logistic r_eq5d5l2  age
xi: logistic r_eq5d5l2 i.gender
xi: logistic r_eq5d5l2 i.smoking_status
xi: logistic r_eq5d5l2 i.ethnicity
xi: logistic r_eq5d5l2 i.employment_status
```

xi: logistic r_eq5d5l2 i.highest_education

xi: logistic r_eq5d5l2 age i.gender i.smoking_status i.ethnicity i.employment_status i.highest_education

gen r_eq5d5l3=(eq5d5l3!=.)

xi: logistic r_eq5d5l3 age

xi: logistic r_eq5d5l3 i.gender

xi: logistic r_eq5d5l3 i.smoking_status

xi: logistic r_eq5d5l3 i.ethnicity

xi: logistic r_eq5d5l3 i.employment_status

xi: logistic r_eq5d5l3 i.highest_education

xi: logistic r_eq5d5l3 age i.gender i.smoking_status i.ethnicity i.employment_status i.highest_education

gen r_eq5d5l4=(eq5d5l4!=.)

xi: logistic r_eq5d5l4 age

xi: logistic r_eq5d5l4 i.gender

xi: logistic r_eq5d5l4 i.smoking_status

xi: logistic r_eq5d5l4 i.ethnicity

xi: logistic r_eq5d5l4 i.employment_status

xi: logistic r_eq5d5l4 i.highest_education

xi: logistic r_eq5d5l4 age i.gender i.smoking_status i.ethnicity i.employment_status i.highest_education

gen r_eq5d5l5=(eq5d5l5!=.)

xi: logistic r_eq5d5l5 age

xi: logistic r_eq5d5l5 i.gender

xi: logistic r_eq5d5l5 i.smoking_status

xi: logistic r_eq5d5l5 i.ethnicity

xi: logistic r_eq5d5l5 i.employment_status

xi: logistic r_eq5d5l5 i.highest_education

xi: logistic r_eq5d5l5 age i.gender i.smoking_status i.ethnicity i.employment_status i.highest_education

gen r_eq5d5l6=(eq5d5l6!=.)

xi: logistic r_eq5d5l6 age

xi: logistic r_eq5d5l6 i.gender

xi: logistic r_eq5d5l6 i.smoking_status

xi: logistic r_eq5d5l6 i.ethnicity

xi: logistic r_eq5d5l6 i.employment_status

xi: logistic r_eq5d5l6 i.highest_education

xi: logistic r_eq5d5l6 age i.gender i.smoking_status i.ethnicity i.employment_status i.highest_education

gen r_eq5d5l7=(eq5d5l7!=.)

xi: logistic r_eq5d5l7 age

xi: logistic r_eq5d5l7 i.gender

xi: logistic r_eq5d5l7 i.smoking_status

xi: logistic r_eq5d5l7 i.ethnicity

xi: logistic r_eq5d5l7 i.employment_status

xi: logistic r_eq5d5l7 i.highest_education

xi: logistic r_eq5d5l7 age i.gender i.smoking_status i.ethnicity i.employment_status i.highest_education

gen r_eq5d5l8=(eq5d5l8!=.)

xi: logistic r_eq5d5l8 age

xi: logistic r_eq5d5l8 i.gender

xi: logistic r_eq5d5l8 i.smoking_status

xi: logistic r_eq5d5l8 i.ethnicity

xi: logistic r_eq5d5l8 i.employment_status

xi: logistic r_eq5d5l8 i.highest_education

xi: logistic r_eq5d5l8 age i.gender i.smoking_status i.ethnicity i.employment_status i.highest_education

```
gen r_tto4=(tto4!=.)
xi: logistic r_tto4 age
xi: logistic r_tto4 i.gender
xi: logistic r_tto4 i.smoking_status
xi: logistic r_tto4 i.ethnicity
xi: logistic r_tto4 i.employment_status
xi: logistic r_tto4 i.highest_education
xi: logistic r_tto4 age i.gender i.smoking_status i.ethnicity i.employment_status i.highest_education

gen r_tto8=(tto8!=.)
xi: logistic r_tto8  age
xi: logistic r_tto8 i.gender
xi: logistic r_tto8 i.smoking_status
xi: logistic r_tto8 i.ethnicity
xi: logistic r_tto8 i.employment_status
xi: logistic r_tto8 i.highest_education
xi: logistic r_tto8 age i.gender i.smoking_status i.ethnicity i.employment_status i.highest_education

gen r_aql5d4=(aql5d4!=.)
xi: logistic r_aql5d4  age
xi: logistic r_aql5d4 i.gender
xi: logistic r_aql5d4 i.smoking_status
xi: logistic r_aql5d4 i.ethnicity
xi: logistic r_aql5d4 i.employment_status
xi: logistic r_aql5d4 i.highest_education
xi: logistic r_aql5d4 age i.gender i.smoking_status i.ethnicity i.employment_status i.highest_education

gen r_aql5d8=(aql5d8!=.)
```

```
xi: logistic r_aql5d8  age
xi: logistic r_aql5d8 i.gender
xi: logistic r_aql5d8 i.smoking_status
xi: logistic r_aql5d8 i.ethnicity
xi: logistic r_aql5d8 i.employment_status
xi: logistic r_aql5d8 i.highest_education
xi: logistic r_aql5d8 age i.gender i.smoking_status i.ethnicity i.employment_status i.highest_education


/*exploring removing 'healthy' baseline participants*/
/*testing the difference between variables using Wilcoxon signed-rank test*/
signrank eq5d5l0=eq5d5l8
signrank vas0=vas8
signrank aqlq_baseline_overall=aqlq_week8_overall
signrank aql5d0=aql5d8
signrank tto0=tto8

signrank eq5d5l4=eq5d5l8
signrank vas4=vas8
signrank aqlq_week4_overall=aqlq_week8_overall
signrank aql5d4=aql5d8
signrank tto4=tto8

signrank eq5d5l0=eq5d5l4
signrank vas0=vas4
signrank aqlq_baseline_overall=aqlq_week4_overall
signrank aql5d0=aql5d4
signrank tto0=tto4

/*Hierarchical model*/
```

```
/* change orientation of data into long data set where each time point for eq5d5l is on a new line for the same id*/
reshape long eq5d5l, i(id) j(time)

xtmixed eq5d5l time || id: time, covariance(unstructured) variance
xtmixed eq5d5l time age || id: time, covariance(unstructured) variance


/* renaming variables*/
tab gender, gen(gender)
rename gender1 female
rename gender2 male

xtmixed eq5d5l time female, || id: time, covariance(unstructured) variance
xtmixed eq5d5l time age female, || id: time, covariance(unstructured) variance

tab smoking_status, gen(smoking)
rename smoking1 exsmoker
rename smoking2 never
rename smoking3 nonsmoker
rename smoking4 smoker

xtmixed eq5d5l time exsmoker never nonsmoker, || id: time, covariance(unstructured) variance
xtmixed eq5d5l time age exsmoker never nonsmoker, || id: time, covariance(unstructured) variance
xtmixed eq5d5l time age female exsmoker never nonsmoker, || id: time, covariance(unstructured) variance

tab ethnicity, gen(ethnicity)
rename ethnicity1 mixed
rename ethnicity2 white
```

rename ethnicity3 wother

xtmixed eq5d5l time mixed white, || id: time, covariance(unstructured) variance

xtmixed eq5d5l time age mixed white, || id: time, covariance(unstructured) variance

xtmixed eq5d5l time age female mixed white, || id: time, covariance(unstructured) variance

xtmixed eq5d5l time age female exsmoker never nonsmoker mixed white, || id: time, covariance(unstructured) variance

tab highest_education, gen(education)

rename education1 college

rename education2 degree

rename education3 school

xtmixed eq5d5l time college degree, || id: time, covariance(unstructured) variance

xtmixed eq5d5l time age college degree, || id: time, covariance(unstructured) variance

xtmixed eq5d5l time age female college degree, || id: time, covariance(unstructured) variance

xtmixed eq5d5l time age female exsmoker never nonsmoker college degree, || id: time, covariance(unstructured) variance

xtmixed eq5d5l time age female exsmoker never nonsmoker mixed white college degree, || id: time, covariance(unstructured) variance

tab employment_status, gen(employment)

rename employment1 fulltime

rename employment2 parttime

rename employment3 retired

rename employment4 home

rename employment5 student

rename employment6 unemployed

xtmixed eq5d5l time fulltime parttime retired home student, || id: time, covariance(unstructured) variance

xtmixed eq5d5l time age fulltime parttime retired home student, || id: time, covariance(unstructured) variance

xtmixed eq5d5l time age female fulltime parttime retired home student, || id: time, covariance(unstructured) variance

xtmixed eq5d5l time age female exsmoker never nonsmoker fulltime parttime retired home student, || id: time, covariance(unstructured) variance

xtmixed eq5d5l time age female exsmoker never nonsmoker mixed white fulltime parttime retired home student, || id: time, covariance(unstructured) variance

xtmixed eq5d5l time age female exsmoker never nonsmoker mixed white college degree fulltime parttime retired home student, || id: time, covariance(unstructured) variance

graph to show the first 10 IDs and connection between eq5d5l and the 8 time points

twoway connected eq5d5l time if id<10, connect(ascending)

generating a quadratic time variable

gen time2 = time*time

model including time2

xtmixed eq5d5l time time2 || id: time, covariance(unstructured) variance

xtmixed eq5d5l time time2 age female exsmoker never nonsmoker mixed white college degree fulltime parttime retired home student, || id: time, covariance(unstructured) variance

clear

insert data set

for aql5d

rename categorical variables as above

reshape long aql5d, i(id) j(time)

xtmixed aql5d time || id: time, covariance(unstructured) variance

xtmixed aql5d time age || id: time, covariance(unstructured) variance

tab gender, gen(gender)
rename gender1 female
rename gender2 male

xtmixed aql5d time age female, || id: time, covariance(unstructured) variance

tab smoking_status, gen(smoking)
rename smoking1 exsmoker
rename smoking2 never
rename smoking3 nonsmoker
rename smoking4 smoker

xtmixed aql5d time age female exsmoker never nonsmoker, || id: time, covariance(unstructured) variance

tab ethnicity, gen(ethnicity)
rename ethnicity1 mixed
rename ethnicity2 white
rename ethnicity3 wother

xtmixed aql5d time age female exsmoker never nonsmoker mixed white, || id: time, covariance(unstructured) variance

tab highest_education, gen(education)
rename education1 college
rename education2 degree
rename education3 school

xtmixed aql5d time age female exsmoker never nonsmoker mixed white college degree, || id: time, covariance(unstructured) variance

```
tab employment_status, gen(employment)
rename employment1 fulltime
rename employment2 parttime
rename employment3 retired
rename employment4 home
rename employment5 student
rename employment6 unemployed

xtmixed aql5d time age female exsmoker never nonsmoker mixed white college degree fulltime parttime retired home student, || id: time, covariance(unstructured) variance

*graph to show the first 10 IDs and connection between aql5d and the 8 time points*
twoway connected aql5d time if id<10, connect(ascending)

*generating a quadratic time variable*
gen time2 = time*time

*model including time2*
xtmixed aql5d time time2 || id: time, covariance(unstructured) variance
xtmixed aql5d time time2 age female exsmoker never nonsmoker mixed white college degree fulltime parttime retired home student, || id: time, covariance(unstructured) variance
xtmixed aql5d time time2 age female exsmoker never nonsmoker mixed white, || id: time, covariance(unstructured) variance



clear
*insert data set*
*for tto*
*rename categorical variables as above*
```

```
reshape long tto, i(id) j(time)
xtmixed tto time || id: time, covariance(unstructured) variance
xtmixed tto time age || id: time, covariance(unstructured) variance

tab gender, gen(gender)
rename gender1 female
rename gender2 male

xtmixed tto time age female, || id: time, covariance(unstructured) variance

tab smoking_status, gen(smoking)
rename smoking1 exsmoker
rename smoking2 never
rename smoking3 nonsmoker
rename smoking4 smoker

xtmixed tto time age female exsmoker never nonsmoker, || id: time, covariance(unstructured) variance

tab ethnicity, gen(ethnicity)
rename ethnicity1 mixed
rename ethnicity2 white
rename ethnicity3 wother

xtmixed tto time age female exsmoker never nonsmoker mixed white, || id: time, covariance(unstructured) variance

tab highest_education, gen(education)
rename education1 college
rename education2 degree
rename education3 school
```

```
xtmixed tto time age female exsmoker never nonsmoker mixed white college degree, || id: time, covariance(unstructured) variance

tab employment_status, gen(employment)
rename employment1 fulltime
rename employment2 parttime
rename employment3 retired
rename employment4 home
rename employment5 student
rename employment6 unemployed

xtmixed tto time age female exsmoker never nonsmoker mixed white college degree fulltime parttime retired home student, || id: time, covariance(unstructured) variance

*graph to show the first 10 IDs and connection between aql5d and the 8 time points*
twoway connected tto time if id<10, connect(ascending)

*generating a quadratic time variable*
gen time2 = time*time

*model including time2*
xtmixed tto time time2 || id: time, covariance(unstructured) variance
xtmixed tto time time2 age female exsmoker never nonsmoker mixed white college degree fulltime parttime retired home student, || id: time, covariance(unstructured) variance


*General: graphing data and relationships

*Histograms for utility data
hist eq5d5l0, normal
```

```
hist eq5d5l1, normal
hist eq5d5l2, normal
hist eq5d5l3, normal
hist eq5d5l4, normal
hist eq5d5l5, normal
hist eq5d5l6, normal
hist eq5d5l7, normal
hist eq5d5l8, normal
hist aql5d0, normal
hist aql5d4, normal
hist aql5d8, normal
hist tto0, normal
hist tto4, normal
hist tto8, normal

*Testing skewness in utility data
sktest eq5d5l0
sktest eq5d5l1
sktest eq5d5l2
sktest eq5d5l3
sktest eq5d5l4
sktest eq5d5l5
sktest eq5d5l6
sktest eq5d5l7
sktest eq5d5l8
sktest aql5d0
sktest aql5d4
sktest aql5d8
sktest tto0
sktest tto4
sktest tto8
```

*Using Q plots to compare normality against utility data

qnorm eq5d5l0

qnorm eq5d5l1

qnorm eq5d5l2

qnorm eq5d5l3

qnorm eq5d5l4

qnorm eq5d5l5

qnorm eq5d5l6

qnorm eq5d5l7

qnorm eq5d5l8

qnorm aql5d0

qnorm aql5d4

qnorm aql5d8

qnorm tto0

qnorm tto4

qnorm tto8

STATA version 15

Power calculation

*estimate correlation between AQLQ baseline and AQLQ week 8

correlate aqlq_baseline_overall aqlq_week8_overall

*estimate power required for a sample size of 65 as observed in table 32 of thesis using correlation estimated above

power pairedmeans 0 0.5, n(65) sd (1.5)

Multi-level modelling - eq5d5l

*Growth curve modelling

reshape long eq5d5l, i(id) j(week)

graph box eq5d5l, over(week)

gen week2=week^2

```
order week2, after(week)

*generate dummy variables
tab gender, gen(gender)
rename gender1 female
rename gender2 male
tab smoking_status, gen(smoking)
rename smoking1 exsmoker
rename smoking2 never
rename smoking3 nonsmoker
rename smoking4 smoker
tab ethnicity, gen(ethnicity)
rename ethnicity1 mixed
rename ethnicity2 white
rename ethnicity3 wother
tab highest_education, gen(education)
rename education1 college
rename education2 degree
rename education3 school
tab employment_status, gen(employment)
rename employment1 fulltime
rename employment2 parttime
rename employment3 retired
rename employment4 home
rename employment5 student
rename employment6 unemployed
sum age, meanonly
gen agecentered = age -r(mean)

*regression model with factors predictive of missingness added to aid in identifying missing values
```

```
regress eq5d5l agecentered exsmoker never nonsmoker fulltime parttime retired home student

*generating new variable to identify missing eq5d5l data points
gen include_eq5d5l=0
replace include_eq5d5l=1 if e(sample)==1

*Null model (random intercept)
xtset id week
mixed eq5d5l ||id: if include_eq5d5l==1
est store null
predict predri1, fitted
twoway (scatter eq5d5l week, mcolor(black) msymbol(smx))(lfitci predri1 week, clpattern(solid)ytitle("eq5d5l") xtitle("week"))
qnorm predri1

*Random intercept, fixed slope
mixed eq5d5l week ||id: if include_eq5d5l==1
est store r_intercept
predict predri2, fitted
twoway (scatter eq5d5l week, mcolor(black) msymbol(smx))(lfitci predri2 week, clpattern(solid)ytitle("eq5d5l") xtitle("week"))
qnorm predri2
lrtest null r_intercept

*Random slope model - relaxing assumption slope is constant over all individuals
mixed eq5d5l week ||id: week if include_eq5d5l==1, cov(unstruc)
est store r_slope
predict predri3, fitted
twoway (scatter eq5d5l week, mcolor(black) msymbol(smx))(lfitci predri3 week, clpattern(solid)ytitle("eq5d5l") xtitle("week"))
qnorm predri3
```

lrtest r_intercept r_slope

*random polynomial model - non-linear over time

*can explore quadratic model with week^2 as fixed and random effect

mixed eq5d5l week week2 ||id: week if include_eq5d5l==1, cov(unstruc)

est store r_nlin

predict predri4,fitted

twoway (scatter eq5d5l week, mcolor(black) msymbol(smx))(lfitci predri4 week, clpattern(solid)ytitle("eq5d5l") xtitle("week"))

qnorm predri4

lrtest r_slope r_nlin

*adding to the polynomial model (which includes the factors predictive of missingness) one covariate at a time.

mixed eq5d5l week week2 agecentered exsmoker never nonsmoker fulltime parttime retired home student||id: week, cov(unstruc)

mixed eq5d5l week week2 agecentered exsmoker never nonsmoker fulltime parttime retired home student female||id: week, cov(unstruc)

mixed eq5d5l week week2 agecentered exsmoker never nonsmoker fulltime parttime retired home student mixed white||id: week, cov(unstruc)

mixed eq5d5l week week2 agecentered exsmoker never nonsmoker fulltime parttime retired home student college degree||id: week, cov(unstruc)

*best eq5d5l polynomial model with added covariates

mixed eq5d5l week week2 agecentered exsmoker never nonsmoker fulltime parttime retired home student||id: week, cov(unstruc)

*bootstrap preferred eq5d5l model

bootstrap _b[_cons] _b[week] _b[week2] _b[agecentered] _b[exsmoker] _b[never] _b[nonsmoker] _b[fulltime] _b[parttime] _b[retired] _b[home] _b[student], reps(500)

seed(1): mixed eq5d5l week week2 agecentered exsmoker never nonsmoker fulltime parttime retired home student||id: week, cov(unstruc)

*estimate of AUC disutility

bootstrap((4*_b[week]+40*_b[week2])*8/52), reps(500) seed(1): mixed eq5d5l week week2 agecentered exsmoker never nonsmoker fulltime parttime retired home student||id: week, cov(unstruc)

*generate dummy variable for baseline utility which is either 1 or <1

gen baseeq5d5lutility = 0

replace baseeq5d5lutility = 1 if eq5d5l0<1

*exploring the impact of baseline utility on disutility estimate

mixed eq5d5l week week2 agecentered exsmoker never nonsmoker fulltime parttime retired home student baseeq5d5lutility ||id: week, cov(unstruc)

bootstrap((4*_b[week]+40*_b[week2])*8/52), reps(500) seed(1): mixed eq5d5l week week2 agecentered exsmoker never nonsmoker fulltime parttime retired home student baseeq5d5lutility||id: week, cov(unstruc)

*Multiple Imputation - eq5d5l

mi set wide

mi register imputed eq5d5l1 eq5d5l2 eq5d5l3 eq5d5l4 eq5d5l5 eq5d5l6 eq5d5l7 eq5d5l8 agecentered exsmoker never nonsmoker fulltime parttime retired home student

mi misstable patterns, frequency

*impute missing values

mi impute chained (pmm, knn(30)) eq5d5l1 eq5d5l2 eq5d5l3 eq5d5l4 eq5d5l5 eq5d5l6 eq5d5l7 eq5d5l8 agecentered exsmoker never nonsmoker fulltime parttime retired home student, add(30) rseed(285019)

mi reshape long eq5d5l, i(id) j(week)

gen week2 = week^2

order week2, after(week)

```
sort week id
by week: summ
_1_eq5d5l_2_eq5d5l_3_eq5d5l_4_eq5d5l_5_eq5d5l_6_eq5d5l_7_eq5d5l_8_eq5d5l
sort id week

*generate dummy variables
tab gender, gen(gender)
rename gender1 female
rename gender2 male
tab smoking_status, gen(smoking)
rename smoking1 exsmoker
rename smoking2 never
rename smoking3 nonsmoker
rename smoking4 smoker
tab ethnicity, gen(ethnicity)
rename ethnicity1 mixed
rename ethnicity2 white
rename ethnicity3 wother
tab highest_education, gen(education)
rename education1 college
rename education2 degree
rename education3 school
tab employment_status, gen(employment)
rename employment1 fulltime
rename employment2 parttime
rename employment3 retired
rename employment4 home
rename employment5 student
rename employment6 unemployed
sum age, meanonly
```

gen agecentered = age -r(mean)

mi estimate: mixed eq5d5l week week2 agecentered exsmoker never nonsmoker fulltime parttime retired home student mixed white college degree female||id: week, cov(unstruc)
mi estimate (dis_u: (4*_b[week]+40*_b[week2])*8/52): mixed eq5d5l week week2 agecentered exsmoker never nonsmoker fulltime parttime retired home student mixed white college degree female||id: week, cov(unstruc)

Multi-level modelling - aql5d

*Growth curve modelling

reshape long aql5d, i(id) j(week)

graph box aql5d, over(week)

gen week2=week^2

order week2, after(week)

*generate dummy variables

tab gender, gen(gender)

rename gender1 female

rename gender2 male

tab smoking_status, gen(smoking)

rename smoking1 exsmoker

rename smoking2 never

rename smoking3 nonsmoker

rename smoking4 smoker

tab ethnicity, gen(ethnicity)

rename ethnicity1 mixed

rename ethnicity2 white

rename ethnicity3 wother

tab highest_education, gen(education)

rename education1 college

rename education2 degree

```
rename education3 school
tab employment_status, gen(employment)
rename employment1 fulltime
rename employment2 parttime
rename employment3 retired
rename employment4 home
rename employment5 student
rename employment6 unemployed
sum age, meanonly
gen agecentered = age -r(mean)

*regression model with factors predictive of missingness added to aid in identifying missing values
regress aql5d agecentered exsmoker never nonsmoker fulltime parttime retired home student

*generating new variable to identify missing eq5d5l data points
gen include_aql5d=0
replace include_aql5d=1 if e(sample)==1

*Null model (random intercept)
xtset id week
mixed aql5d ||id: if include_aql5d==1
est store null
predict predri1, fitted
twoway (scatter aql5d week, mcolor(black) msymbol(smx))(lfitci predri1 week, clpattern(solid)ytitle("aql5d") xtitle("week"))
qnorm predri1

*Random intercept, fixed slope
mixed aql5d week ||id: if include_aql5d==1
est store r_intercept
```

```
predict predri2, fitted
twoway (scatter aql5d week, mcolor(black) msymbol(smx))(lfitci predri2 week, clpattern(solid)ytitle("aql5d") xtitle("week"))
qnorm predri2
lrtest null r_intercept

*Random slope model - relaxing assumption slope is constant over all individuals
mixed aql5d week ||id: week if include_aql5d==1, cov(unstruc)
est store r_slope
predict predri3, fitted
twoway (scatter aql5d week, mcolor(black) msymbol(smx))(lfitci predri3 week, clpattern(solid)ytitle("aql5d") xtitle("week"))
qnorm predri3
lrtest r_intercept r_slope

*random polynomial model - non-linear over time
*can explore quadratic model with week^2 as fixed and random effect
mixed aql5d week week2 ||id: week if include_aql5d==1, cov(unstruc)
est store r_nlin
predict predri4,fitted
twoway (scatter aql5d week, mcolor(black) msymbol(smx))(lfitci predri4 week, clpattern(solid)ytitle("aql5d") xtitle("week"))
qnorm predri4
lrtest r_slope r_nlin

*adding to the random slope model (which includes the factors predictive of missingness) one covariate at a time.
mixed aql5d week agecentered exsmoker never nonsmoker fulltime parttime retired home student||id: week, cov(unstruc)
mixed aql5d week agecentered exsmoker never nonsmoker fulltime parttime retired home student female||id: week, cov(unstruc)
```

mixed aql5d week agecentered exsmoker never nonsmoker fulltime parttime retired home student mixed white||id: week, cov(unstruc)

mixed aql5d week agecentered exsmoker never nonsmoker fulltime parttime retired home student college degree||id: week, cov(unstruc)

*best aql5d random slope model with added covariates

mixed aql5d week agecentered exsmoker never nonsmoker fulltime parttime retired home student||id: week, cov(unstruc)

*bootstrap preferred aql5d model

bootstrap _b[_cons] _b[week] _b[agecentered] _b[exsmoker] _b[never] _b[nonsmoker] _b[fulltime] _b[parttime] _b[retired] _b[home] _b[student], reps(500) seed(20619): mixed aql5d week agecentered exsmoker never nonsmoker fulltime parttime retired home student||id: week, cov(unstruc)

*estimate of AUC disutility

bootstrap((4*_b[week])*8/52), reps(500) seed(20076): mixed aql5d week agecentered exsmoker never nonsmoker fulltime parttime retired home student||id: week, cov(unstruc)

*generate dummy variable for baseline utility which is either 1 or <1

gen baseaql5dutility = 0

replace baseaql5dutility = 1 if aql5d0<1

*exploring the impact of baseline utility on disutility estimate

mixed aql5d week agecentered exsmoker never nonsmoker fulltime parttime retired home student baseaql5dutility ||id: week, cov(unstruc)

bootstrap((4*_b[week])*8/52), reps(500) seed(20096): mixed aql5d week agecentered exsmoker never nonsmoker fulltime parttime retired home student baseaql5dutility||id: week, cov(unstruc)

*Multiple Imputation - aql5d

```
mi set wide
mi register imputed aql5d0 aql5d4 aql5d8 agecentered exsmoker never nonsmoker fulltime parttime retired home student
mi misstable patterns, frequency

*impute missing values
mi impute chained (pmm, knn(5)) aql5d0 aql5d4 aql5d8 agecentered exsmoker never nonsmoker fulltime parttime retired home student, add(30) rseed(20830)
mi reshape long aql5d, i(id) j(week)


sort week id
by week: summ _0_aql5d_4_aql5d_8_aql5d
sort id week

*generate dummy variables
tab gender, gen(gender)
rename gender1 female
rename gender2 male
tab smoking_status, gen(smoking)
rename smoking1 exsmoker
rename smoking2 never
rename smoking3 nonsmoker
rename smoking4 smoker
tab ethnicity, gen(ethnicity)
rename ethnicity1 mixed
rename ethnicity2 white
rename ethnicity3 wother
tab highest_education, gen(education)
rename education1 college
rename education2 degree
```

```
rename education3 school
tab employment_status, gen(employment)
rename employment1 fulltime
rename employment2 parttime
rename employment3 retired
rename employment4 home
rename employment5 student
rename employment6 unemployed
sum age, meanonly
gen agecentered = age -r(mean)

mi estimate: mixed aql5d week exsmoker never nonsmoker female mixed white fulltime parttime retired home student agecentered college degree||id: week, cov(unstruc)
mi estimate (dis_u:(4*_b[week])*8/52): mixed aql5d week exsmoker never nonsmoker female mixed white fulltime parttime retired home student agecentered college degree||id: week, cov(unstruc)


Multi-level modelling - tto
*Growth curve modelling
reshape long tto, i(id) j(week)
graph box tto, over(week)
gen week2=week^2
order week2, after(week)

*generate dummy variables
tab gender, gen(gender)
rename gender1 female
rename gender2 male
tab smoking_status, gen(smoking)
rename smoking1 exsmoker
rename smoking2 never
```

```
rename smoking3 nonsmoker
rename smoking4 smoker
tab ethnicity, gen(ethnicity)
rename ethnicity1 mixed
rename ethnicity2 white
rename ethnicity3 wother
tab highest_education, gen(education)
rename education1 college
rename education2 degree
rename education3 school
tab employment_status, gen(employment)
rename employment1 fulltime
rename employment2 parttime
rename employment3 retired
rename employment4 home
rename employment5 student
rename employment6 unemployed
sum age, meanonly
gen agecentered = age -r(mean)

*regression model with factors predictive of missingness added to aid in identifying missing values
regress tto agecentered exsmoker never nonsmoker fulltime parttime retired home student

*generating new variable to identify missing eq5d5l data points
gen include_tto=0
replace include_tto=1 if e(sample)==1



*Null model (random intercept)
xtset id week
```

```
mixed tto ||id: if include_tto==1
est store null
predict predri1, fitted
twoway (scatter tto week, mcolor(black) msymbol(smx))(lfitci predri1 week, clpattern(solid)ytitle("tto") xtitle("week"))
qnorm predri1

*Random intercept, fixed slope
mixed tto week ||id: if include_tto==1
est store r_intercept
predict predri2, fitted
twoway (scatter tto week, mcolor(black) msymbol(smx))(lfitci predri2 week, clpattern(solid)ytitle("tto") xtitle("week"))
qnorm predri2
lrtest null r_intercept

*Random slope model - relaxing assumption slope is constant over all individuals
mixed tto week ||id: week if include_tto==1, cov(unstruc)
est store r_slope
predict predri3, fitted
twoway (scatter tto week, mcolor(black) msymbol(smx))(lfitci predri3 week, clpattern(solid)ytitle("tto") xtitle("week"))
qnorm predri3
lrtest r_intercept r_slope

*random polynomial model - non-linear over time
*can explore quadratic model with week^2 as fixed and random effect
mixed tto week week2 ||id: week if include_tto==1, cov(unstruc)
est store r_nlin
predict predri4,fitted
twoway (scatter tto week, mcolor(black) msymbol(smx))(lfitci predri4 week, clpattern(solid)ytitle("tto") xtitle("week"))
```

```
qnorm predri4
lrtest r_slope r_nlin

*adding to the polynomial slope model (which includes the factors predictive of missingness) one covariate at a time.
mixed tto week week2 agecentered exsmoker never nonsmoker fulltime parttime retired home student||id: week, cov(unstruc)
mixed tto week week2 agecentered exsmoker never nonsmoker fulltime parttime retired home student female||id: week, cov(unstruc)
mixed tto week week2 agecentered exsmoker never nonsmoker fulltime parttime retired home student mixed white||id: week, cov(unstruc)
mixed tto week week2 agecentered exsmoker never nonsmoker fulltime parttime retired home student college degree||id: week, cov(unstruc)

*best tto polynomial slope model with added covariates
mixed tto week week2 agecentered exsmoker never nonsmoker fulltime parttime retired home student||id: week, cov(unstruc)

*bootstrap preferred tto model
bootstrap _b[_cons] _b[week] _b[week2] _b[agecentered] _b[exsmoker] _b[never] _b[nonsmoker] _b[fulltime] _b[parttime] _b[retired] _b[home] _b[student], reps(500) seed(210698): mixed tto week week2 agecentered exsmoker never nonsmoker fulltime parttime retired home student ||id: week, cov(unstruc)

*estimate of AUC disutility
bootstrap((4*_b[week]+40*_b[week2])*8/52), reps(500) seed(210699): mixed tto week week2 agecentered exsmoker never nonsmoker fulltime parttime retired home student ||id: week, cov(unstruc)

*generate dummy variable for baseline utility which is either 1 or <1
gen basettoutility = 0
replace basettoutility = 1 if tto0<1
```

*exploring the impact of baseline utility on disutility estimate

mixed tto week week2 agecentered exsmoker never nonsmoker fulltime parttime retired home student basettoutility ||id: week, cov(unstruc)

bootstrap((4*_b[week]+40*_b[week2])*8/52), reps(500) seed(20096): mixed tto week week2 agecentered exsmoker never nonsmoker fulltime parttime retired home student basettoutility||id: week, cov(unstruc)

*Multiple Imputation - tto

mi set wide

mi register imputed tto0 tto4 tto8 agecentered exsmoker never nonsmoker fulltime parttime retired home student

mi misstable patterns, frequency

*impute missing values

mi impute chained (pmm, knn(5)) tto0 tto4 tto8 agecentered exsmoker never nonsmoker fulltime parttime retired home student, add(30) rseed(1)

mi reshape long tto, i(id) j(week)

gen week2 = week^2

order week2, after(week)

sort week id

by week: summ _0_tto_4_tto_8_tto

sort id week

*generate dummy variables

tab gender, gen(gender)

rename gender1 female

rename gender2 male

tab smoking_status, gen(smoking)

rename smoking1 exsmoker

rename smoking2 never

```
rename smoking3 nonsmoker
rename smoking4 smoker
tab ethnicity, gen(ethnicity)
rename ethnicity1 mixed
rename ethnicity2 white
rename ethnicity3 wother
tab highest_education, gen(education)
rename education1 college
rename education2 degree
rename education3 school
tab employment_status, gen(employment)
rename employment1 fulltime
rename employment2 parttime
rename employment3 retired
rename employment4 home
rename employment5 student
rename employment6 unemployed
sum age, meanonly
gen agecentered = age -r(mean)

mi estimate: mixed tto week week2 fulltime parttime retired home student mixed white agecentered female exsmoker never nonsmoker college degree||id: week, cov(unstruc)
mi estimate (dis_u: (4*_b[week]+40*_b[week2])*8/52): mixed tto week week2 fulltime parttime retired home student mixed white agecentered female exsmoker never nonsmoker college degree||id: week, cov(unstruc)
```

Appendix VIII: Scatter plots and Q-Q plots which support the step-wise multi level model build

Figure 44: A scatter plot to show the EQ-5D-5L against weekly time points with the predicted intercept from the null model

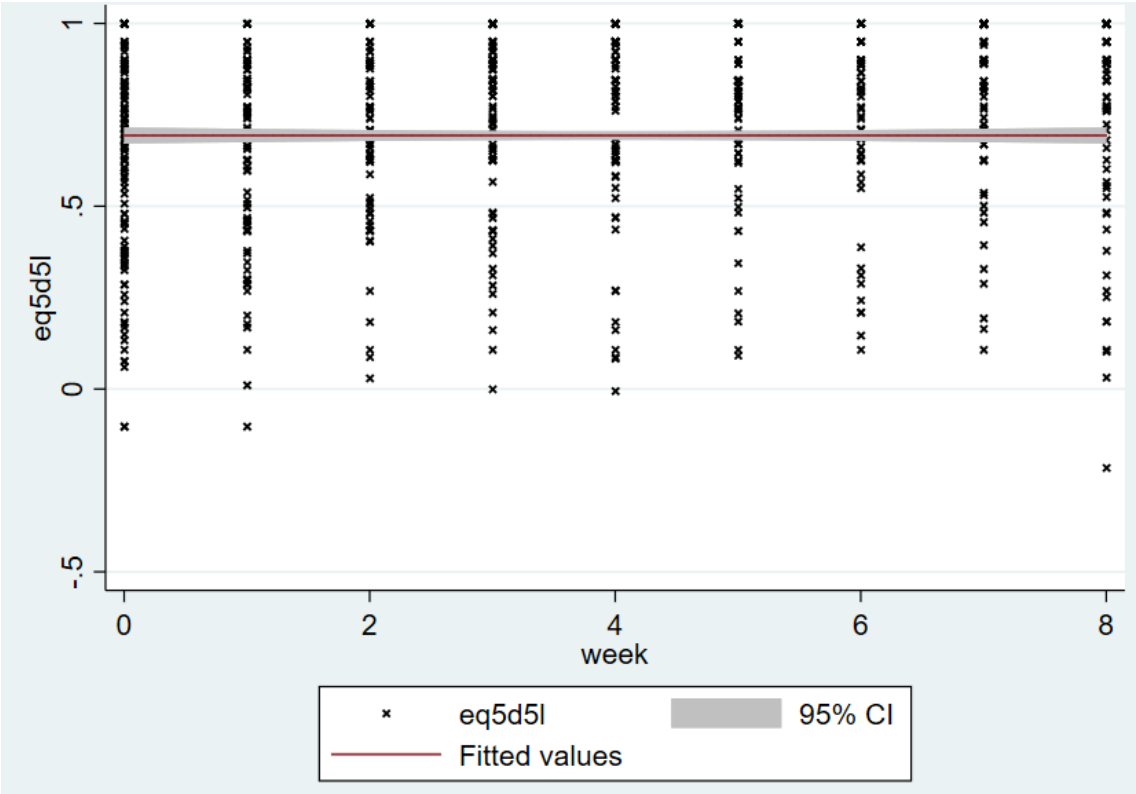


Figure 45: A Q-Q plot based on the predicted null model for EQ-5D-5L

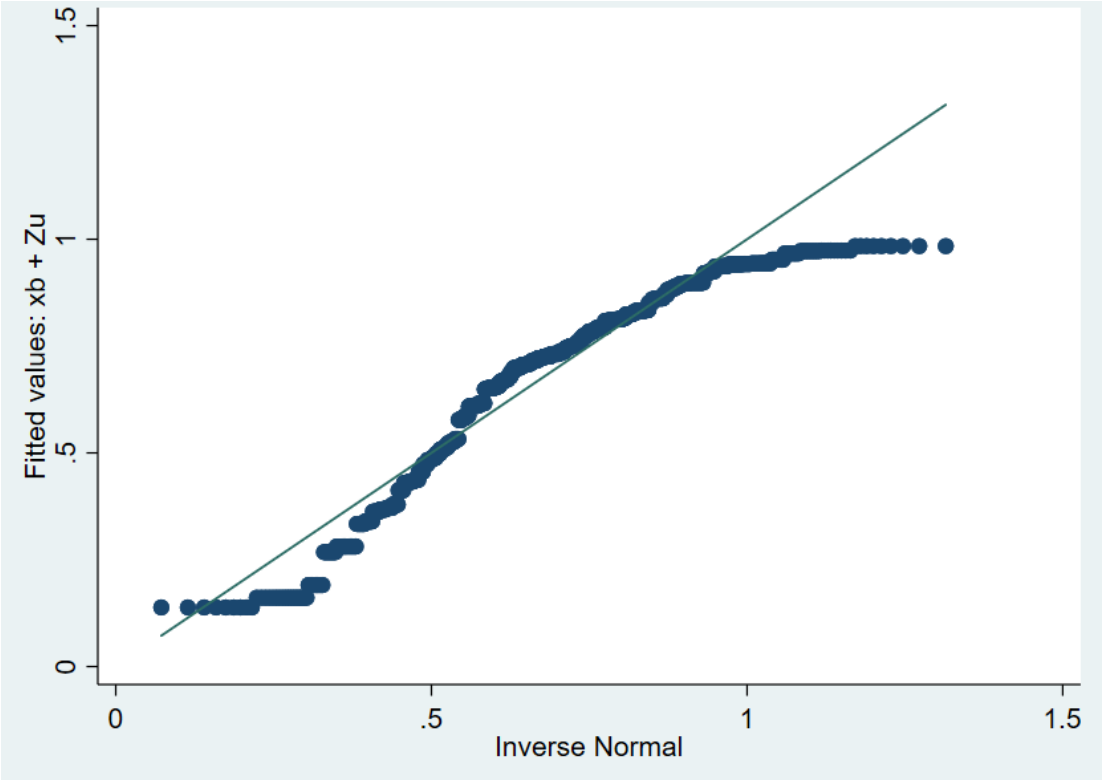


Figure 46: A scatter plot to show the EQ-5D-5L against weekly time points with the predicted random intercepts model

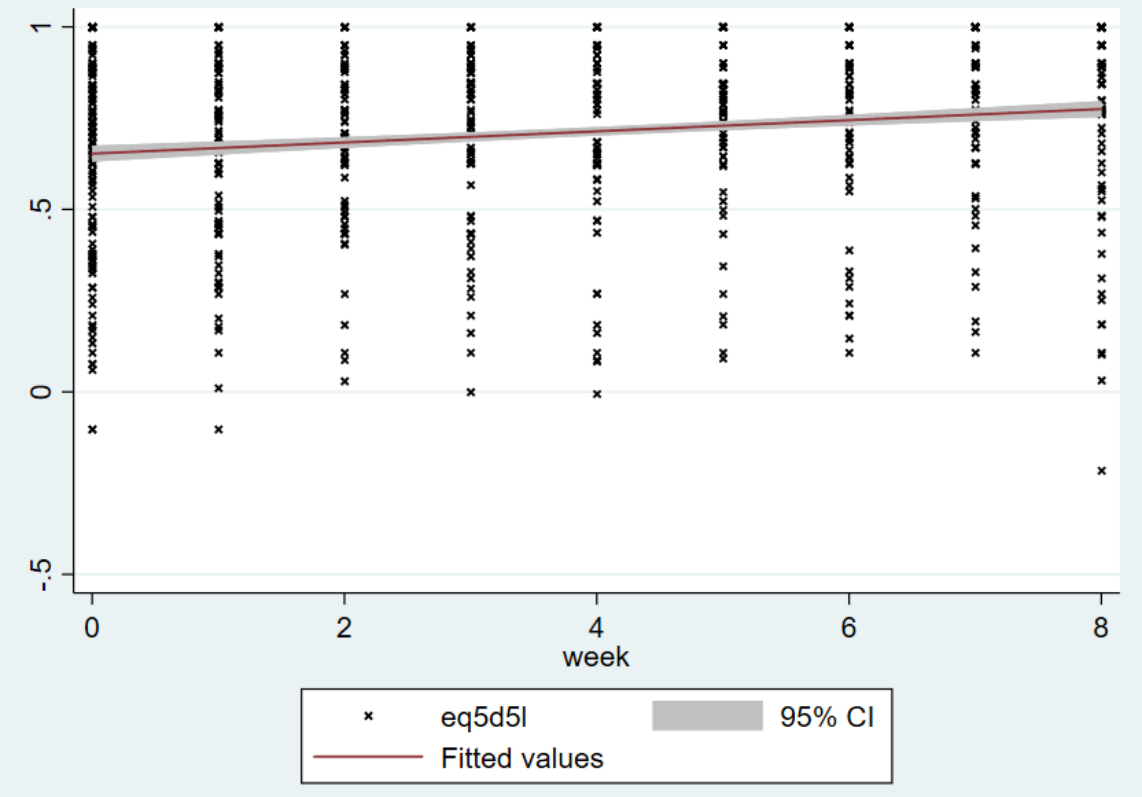


Figure 47: A Q-Q plot based on the predicted random intercept, fixed slope model for the EQ-5D-5L

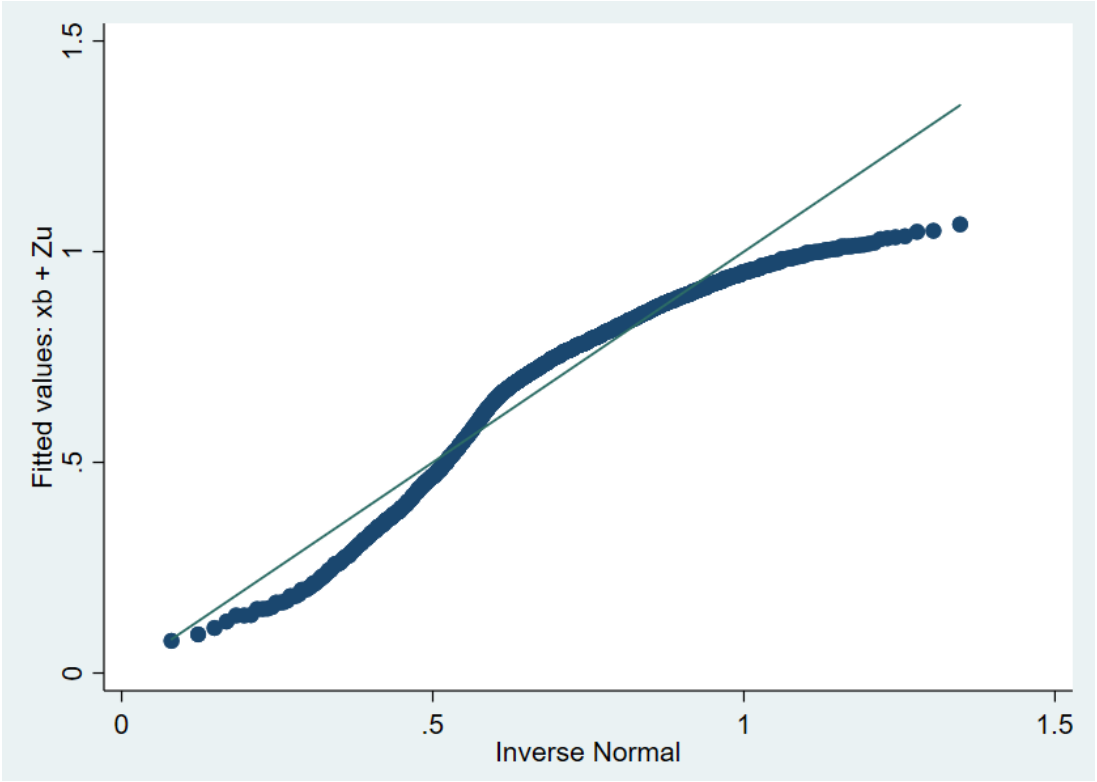


Figure 48: A scatter plot to show the EQ-5D-5L against weekly time points with the predicted random slope model

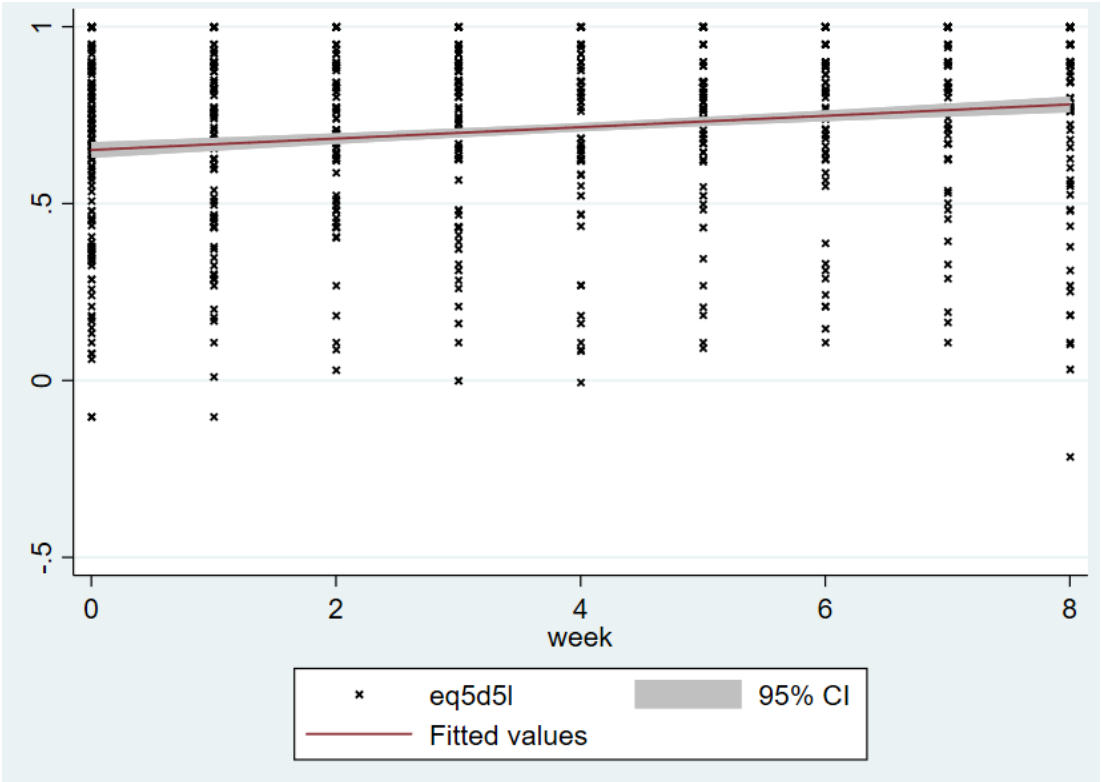


Figure 49: A Q-Q plot based on the predicted random slope model for the EQ-5D-5L

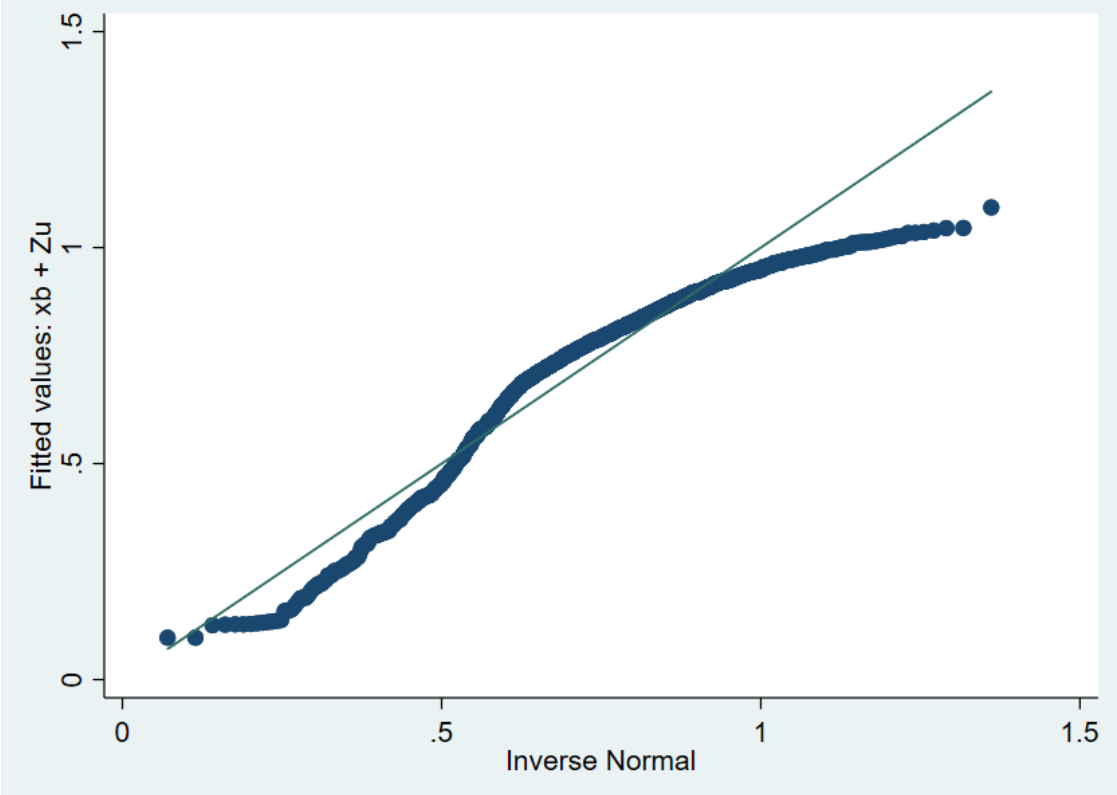


Figure 51: A scatter plot to show the EQ-5D-5L against weekly time points with the predicted random polynomial model

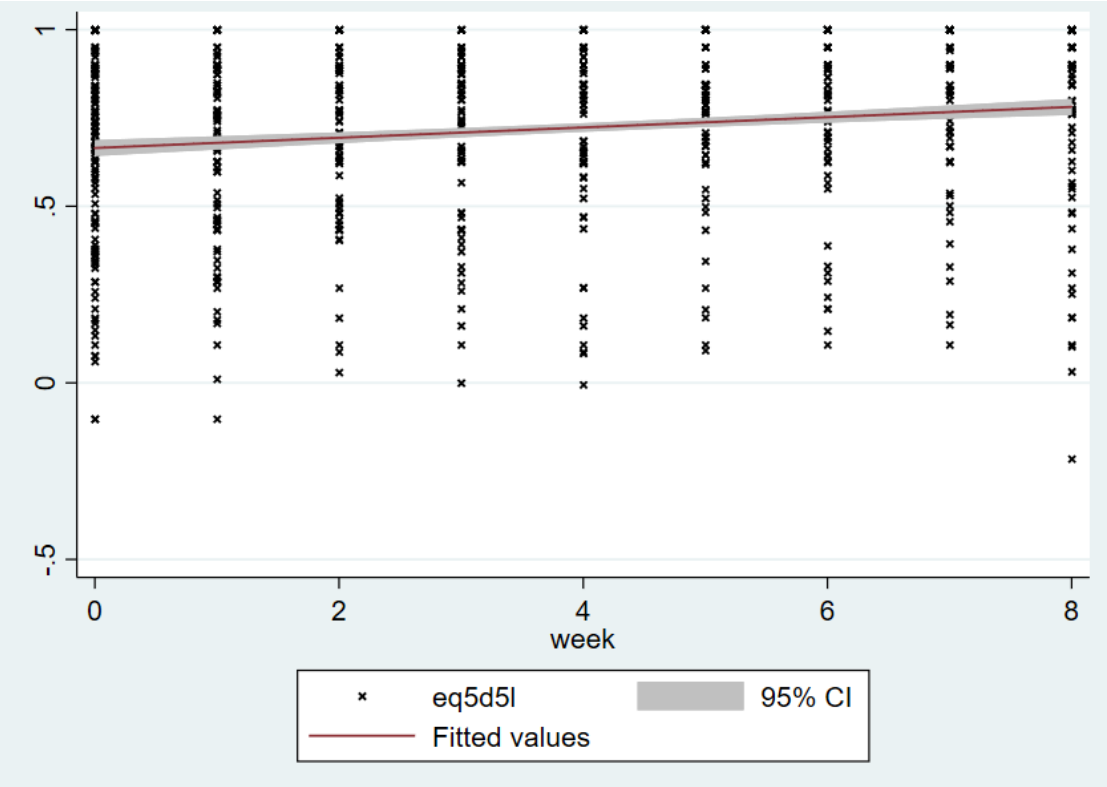


Figure 50: A Q-Q plot based on the predicted random polynomial model for the EQ-5D-5L

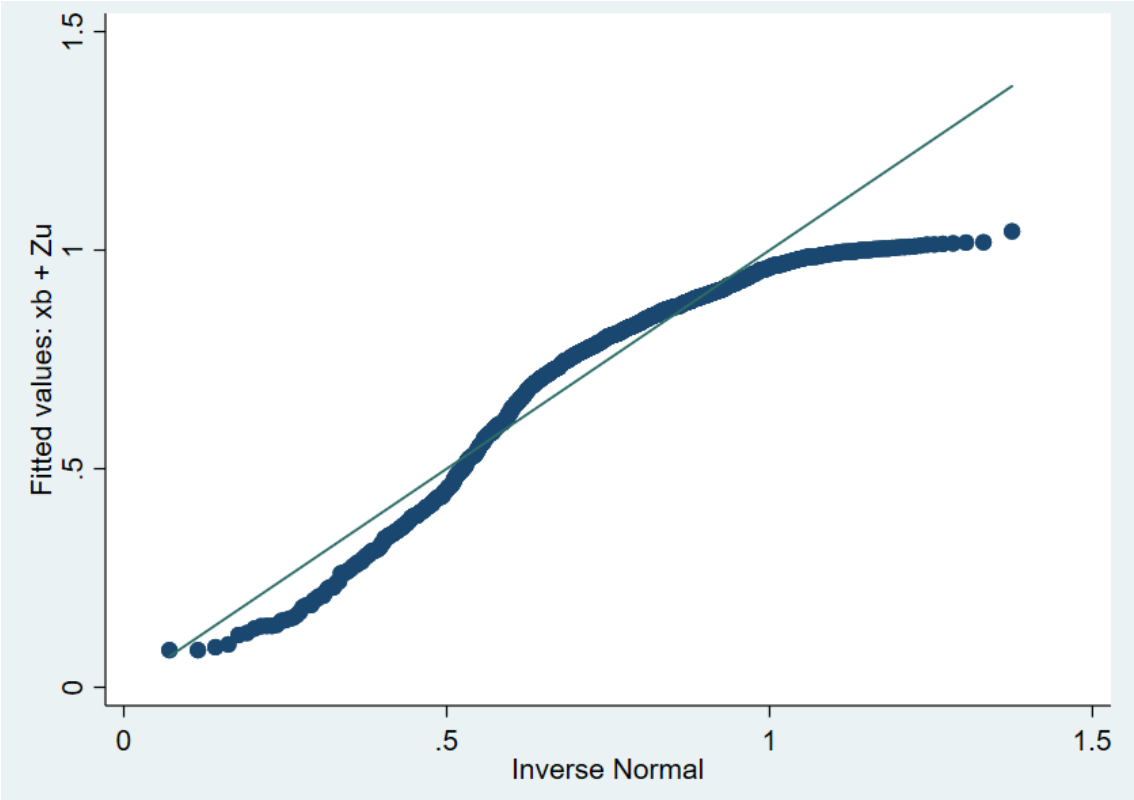


Figure 52: A scatter plot to show the AQL-5D against monthly time points with the predicted null model

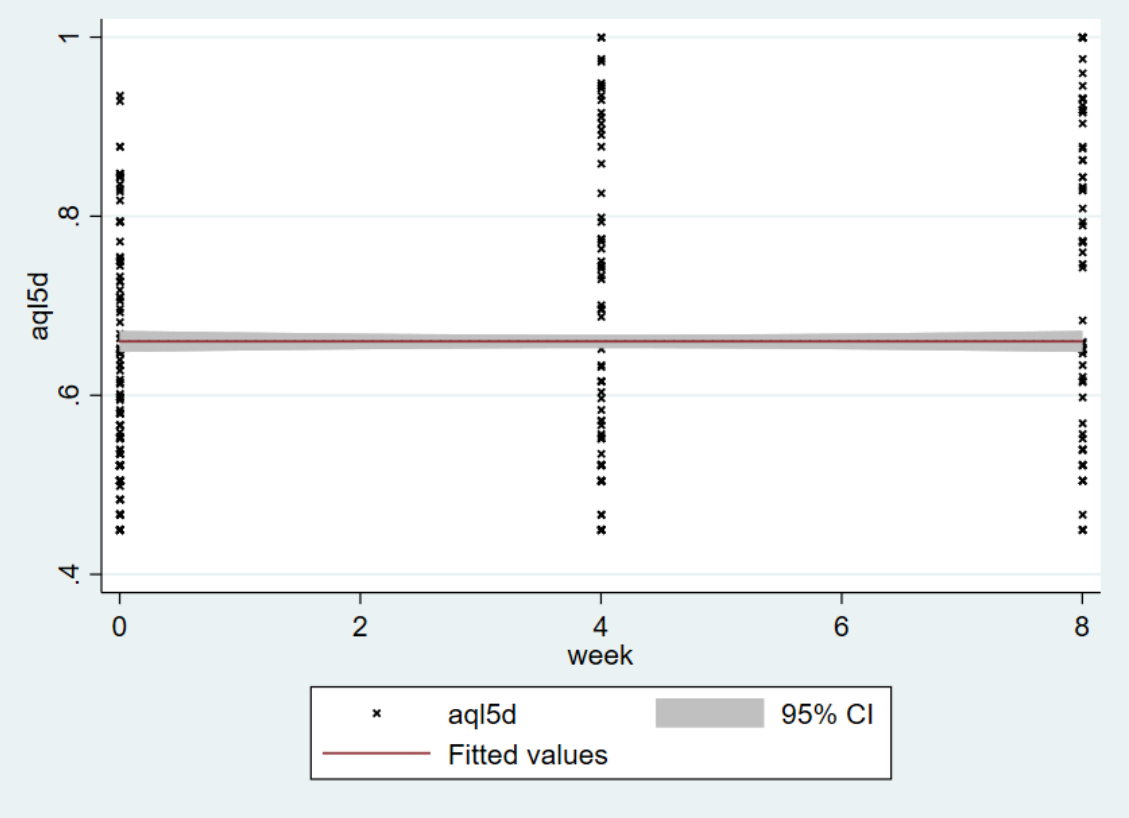


Figure 53: A Q-Q plot based on the predicted null model for the AQL-5D

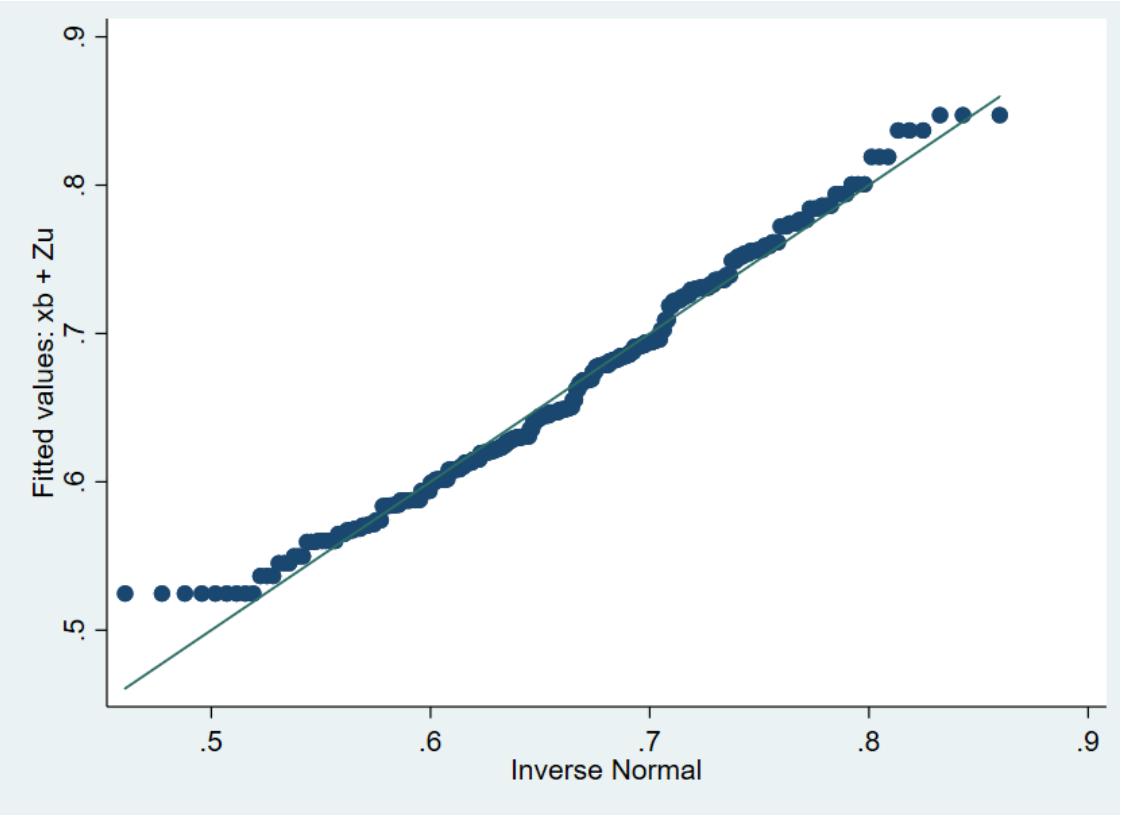


Figure 54: A scatter plot to show the AQL-5D against monthly time points with the predicted random intercepts model

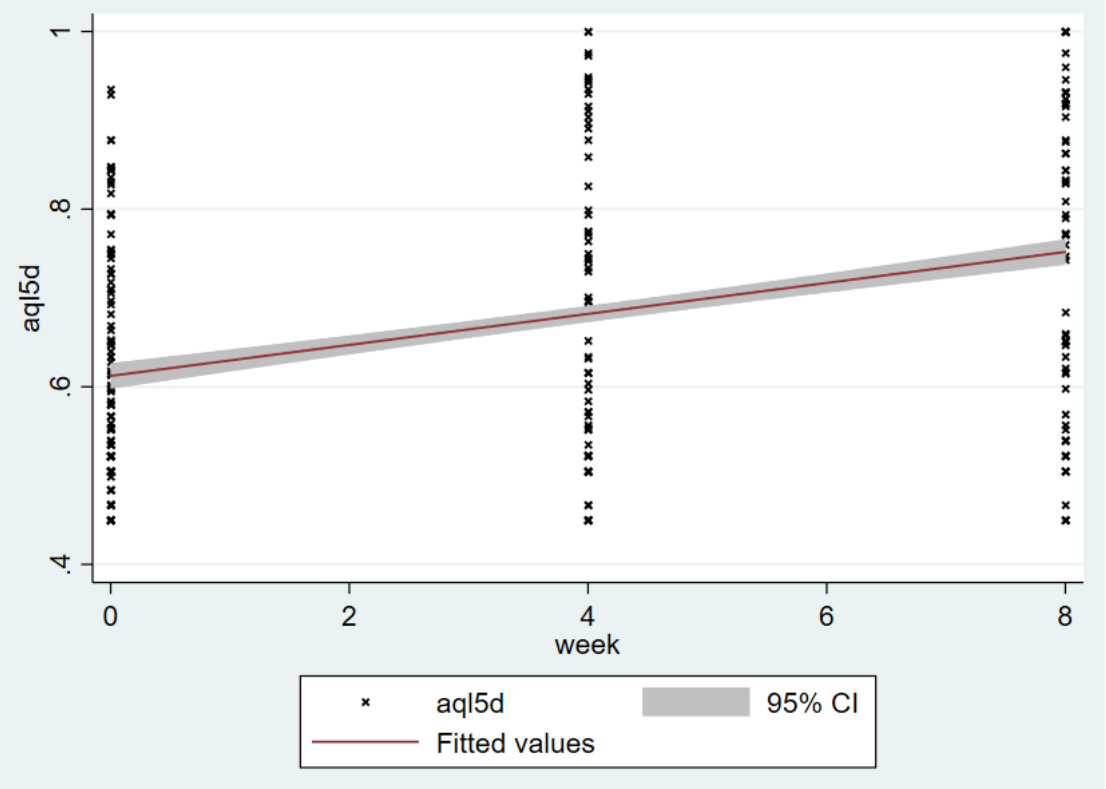


Figure 55: A Q-Q plot based on the predicted random intercept, fixed slope model for the AQL-5D

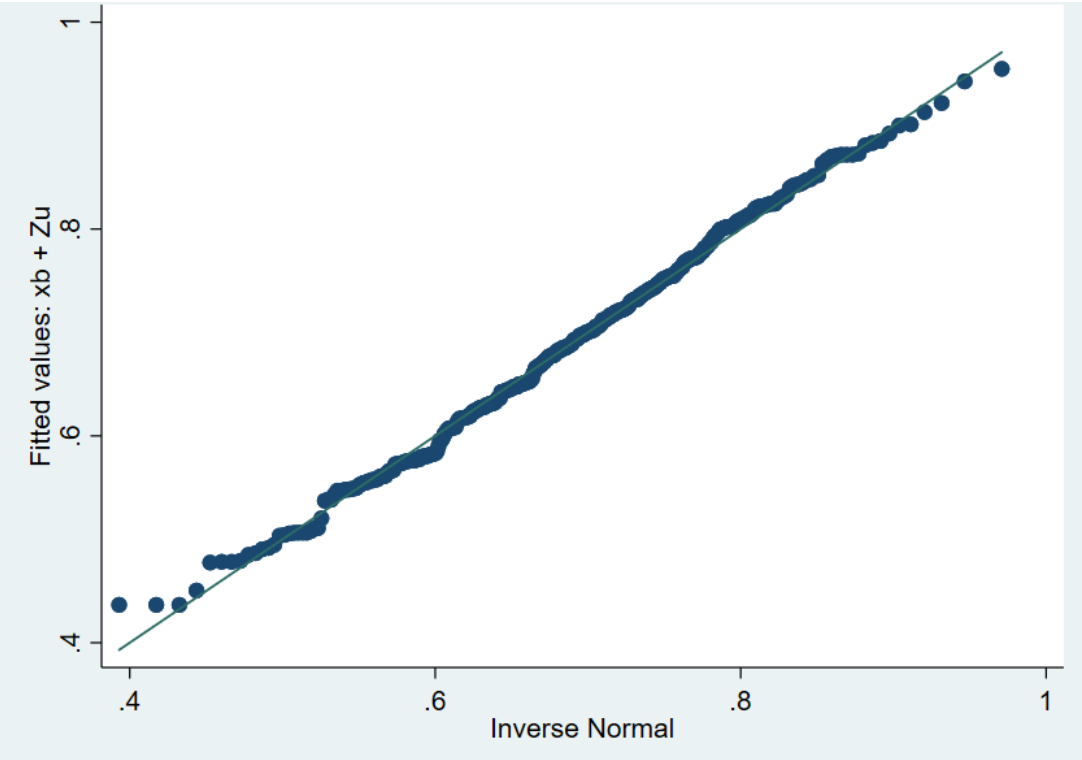


Figure 56: A scatter plot to show the AQL-5D against monthly time points with the predicted random slope model

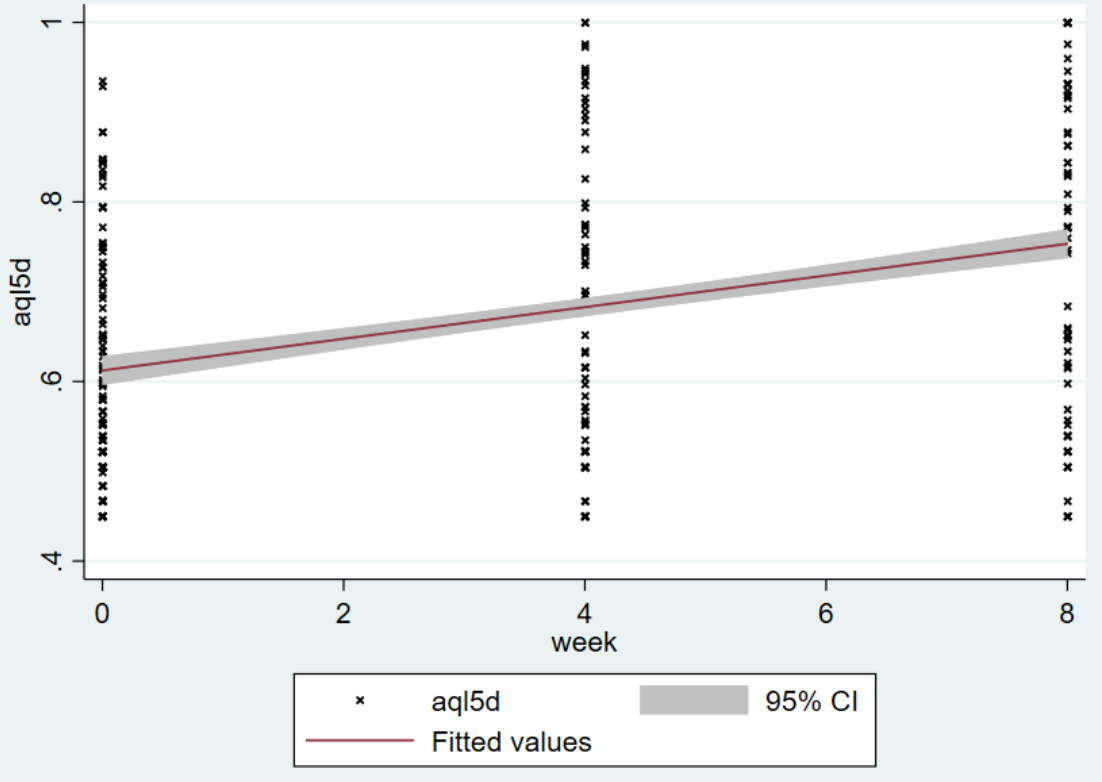


Figure 57: A Q-Q plot based on the predicted random slope model for the AQL-5D

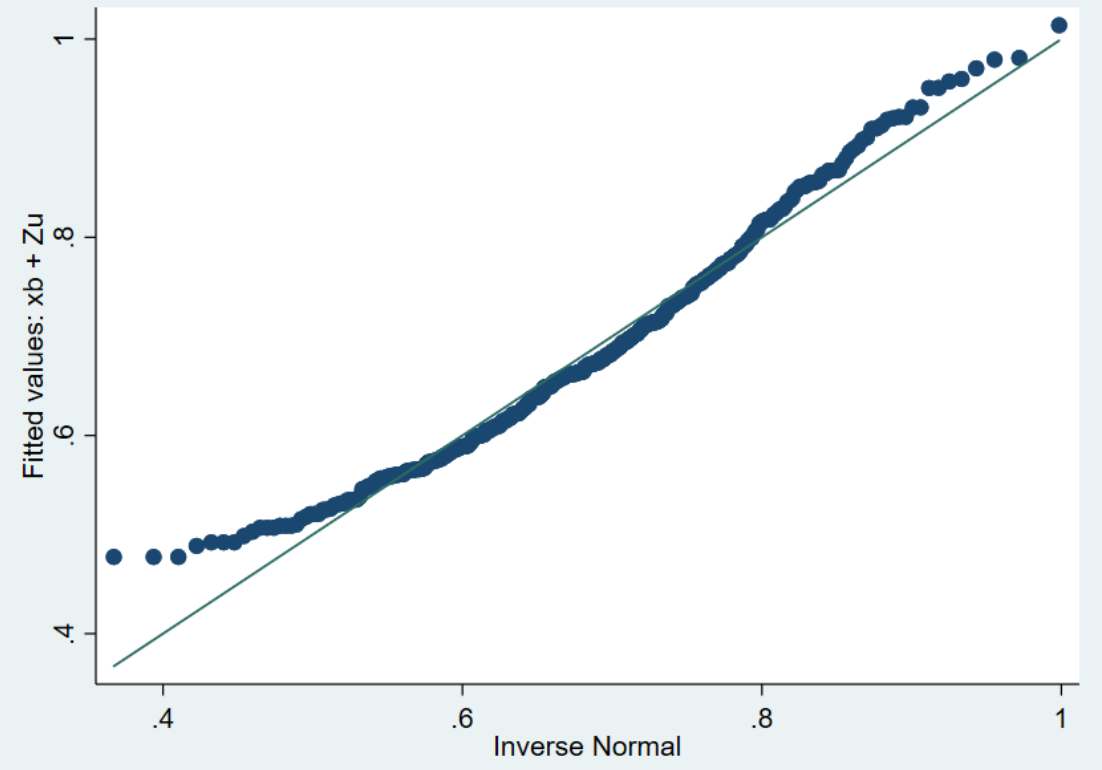


Figure 58: A scatter plot to show the AQL-5D against monthly time points with the predicted random polynomial model

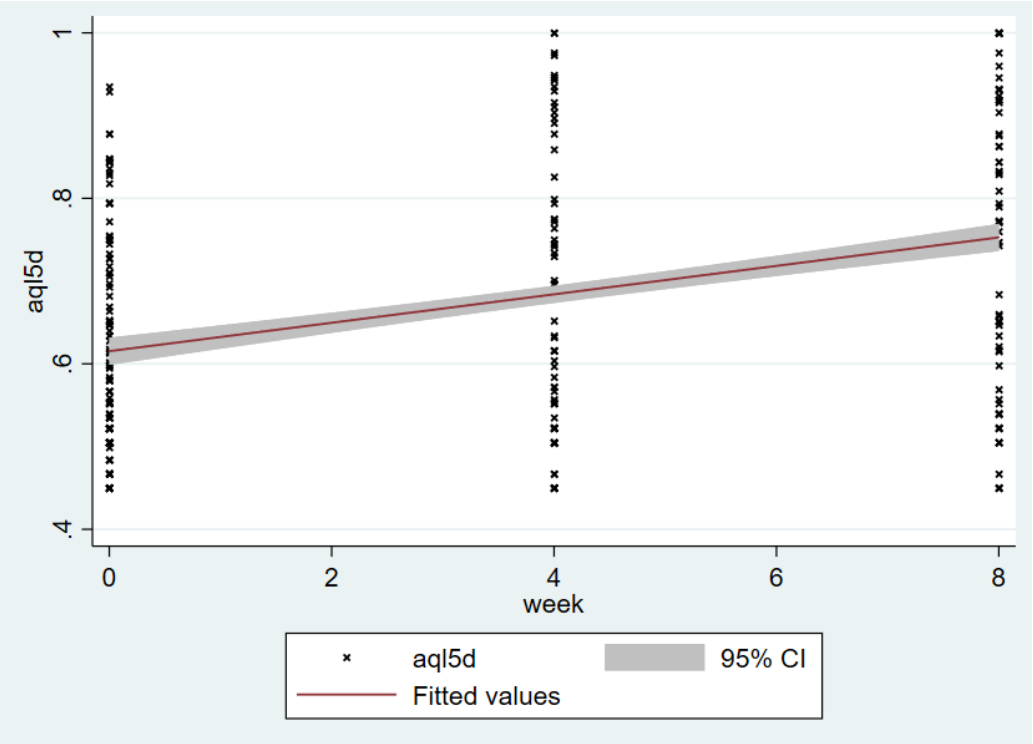


Figure 59: A Q-Q plot based on the predicted random polynomial model for the AQL-5D

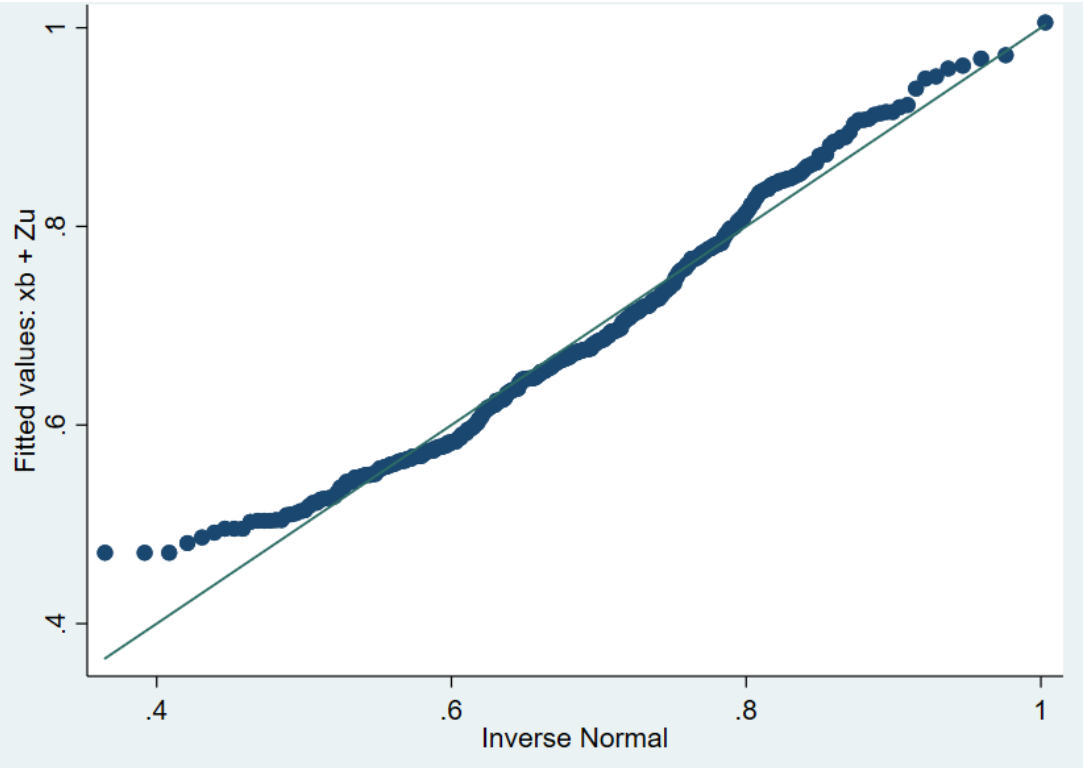


Figure 60: A scatter plot to show the TTO against monthly time points with the predicted null model

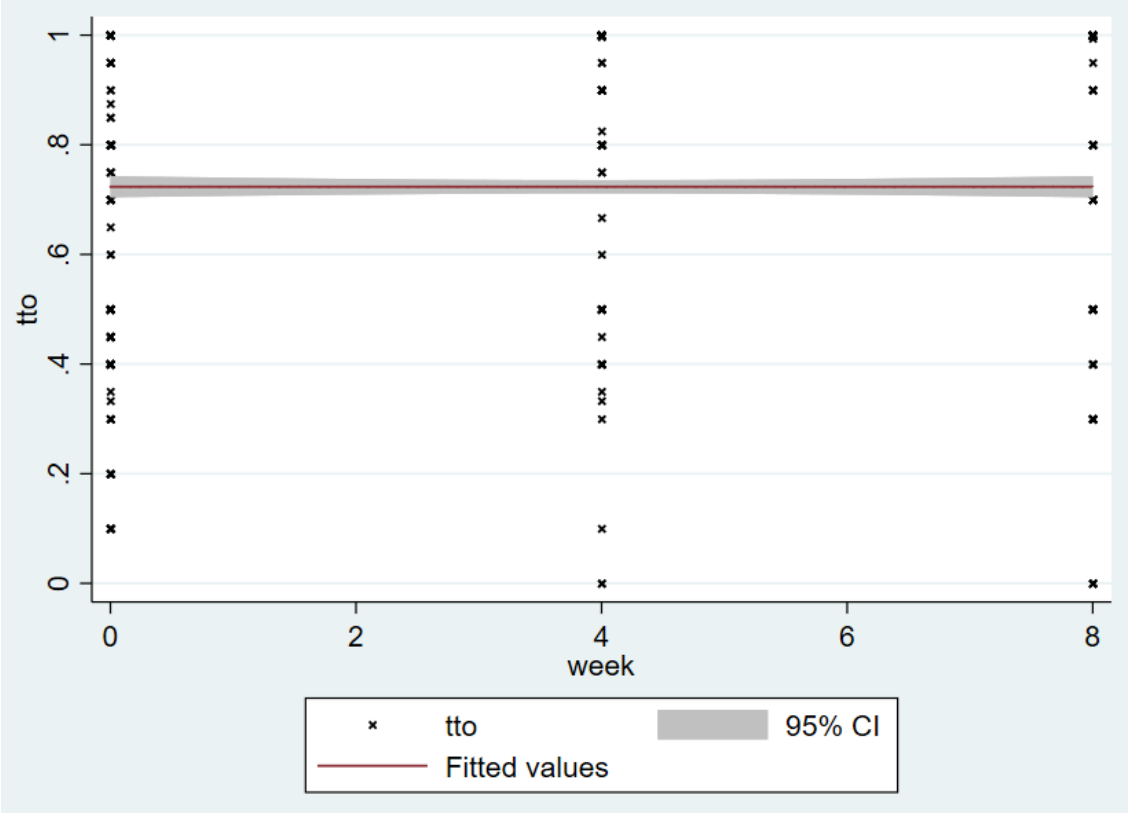


Figure 61: A Q-Q plot based on the predicted null model for the TTO

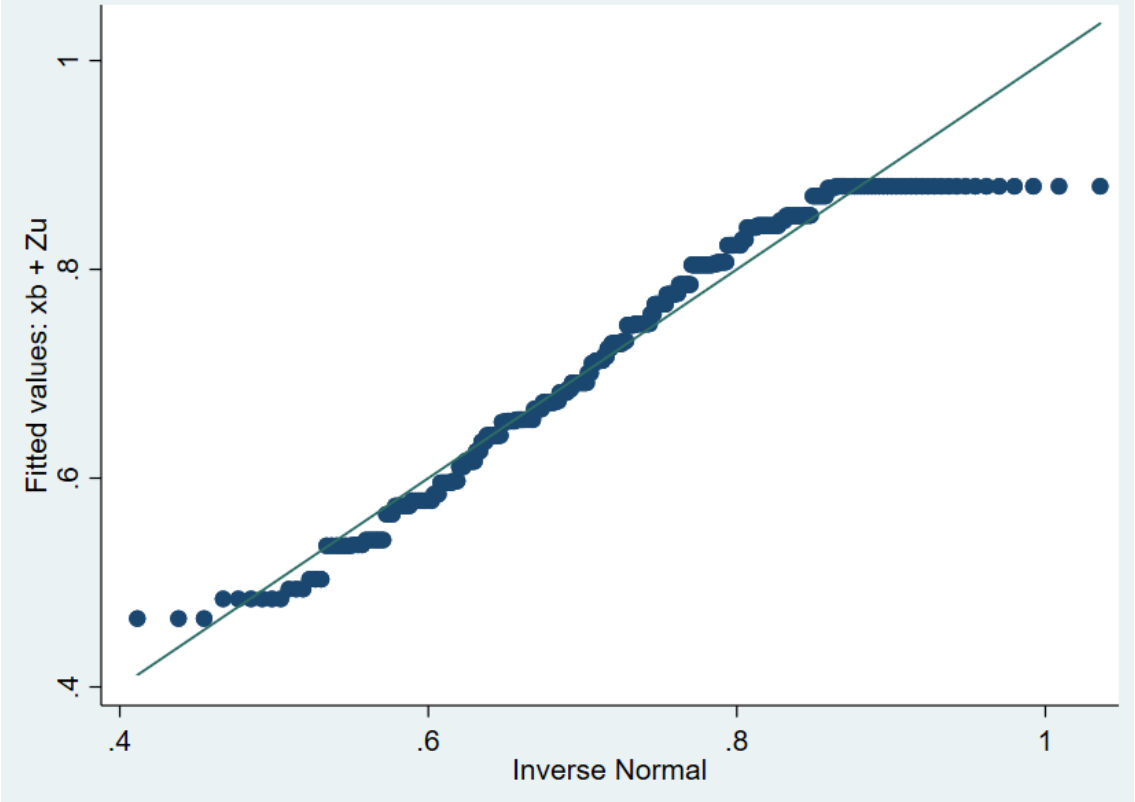


Figure 62: A scatter plot to show the TTO against monthly time points with the predicted random intercepts model

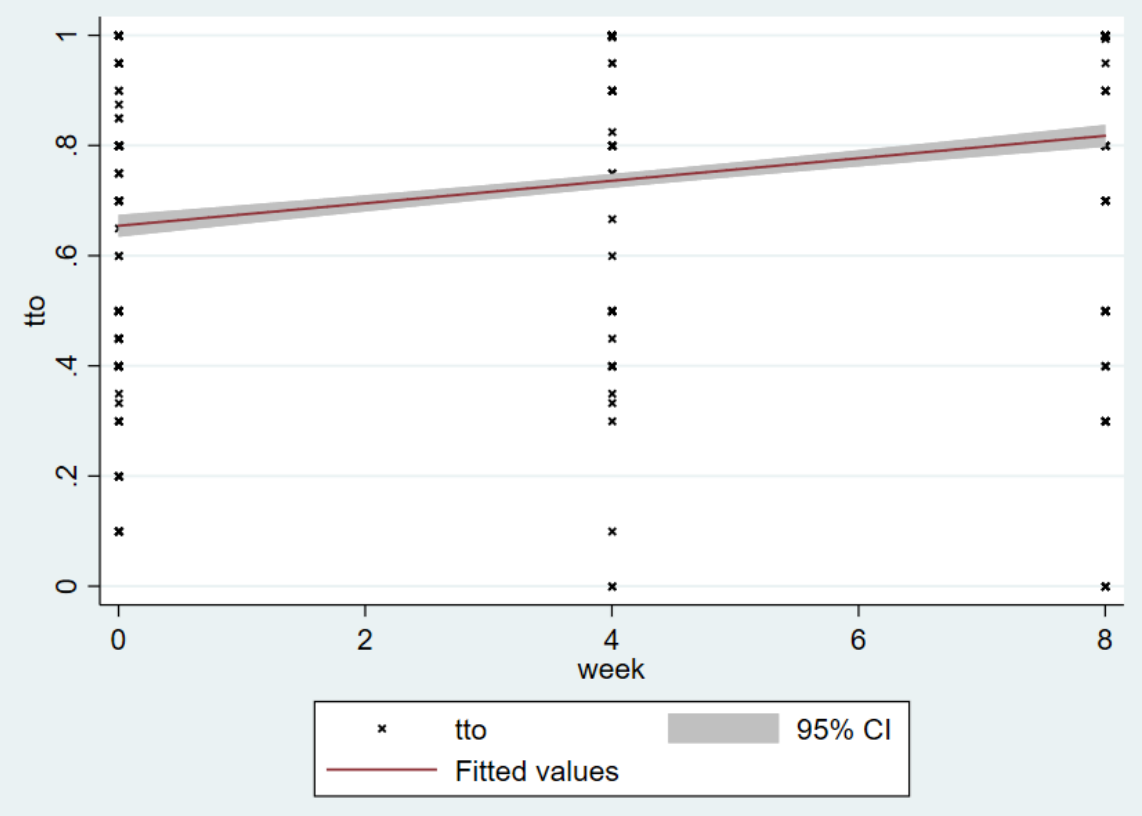


Figure 63: A Q-Q plot based on the predicted random intercept, fixed slope model for the TTO

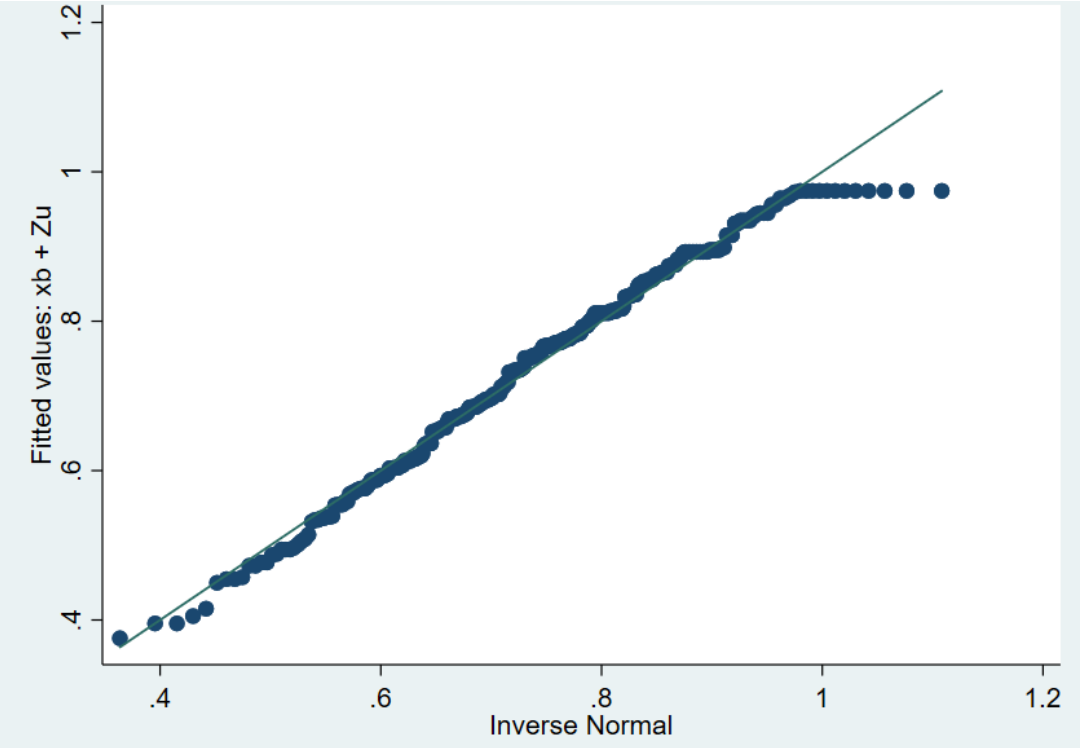


Figure 64: A scatter plot to show the TTO against monthly time points with the predicted random slope model

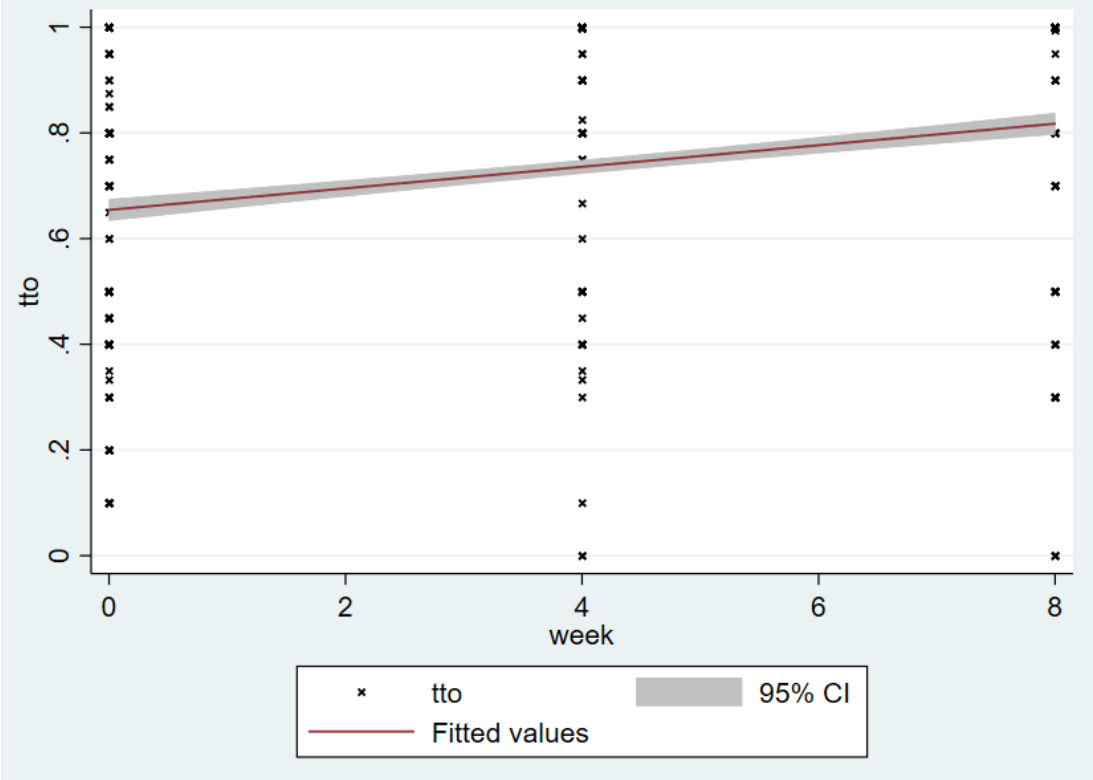


Figure 65: A Q-Q plot based on the predicted random slope model for the TTO

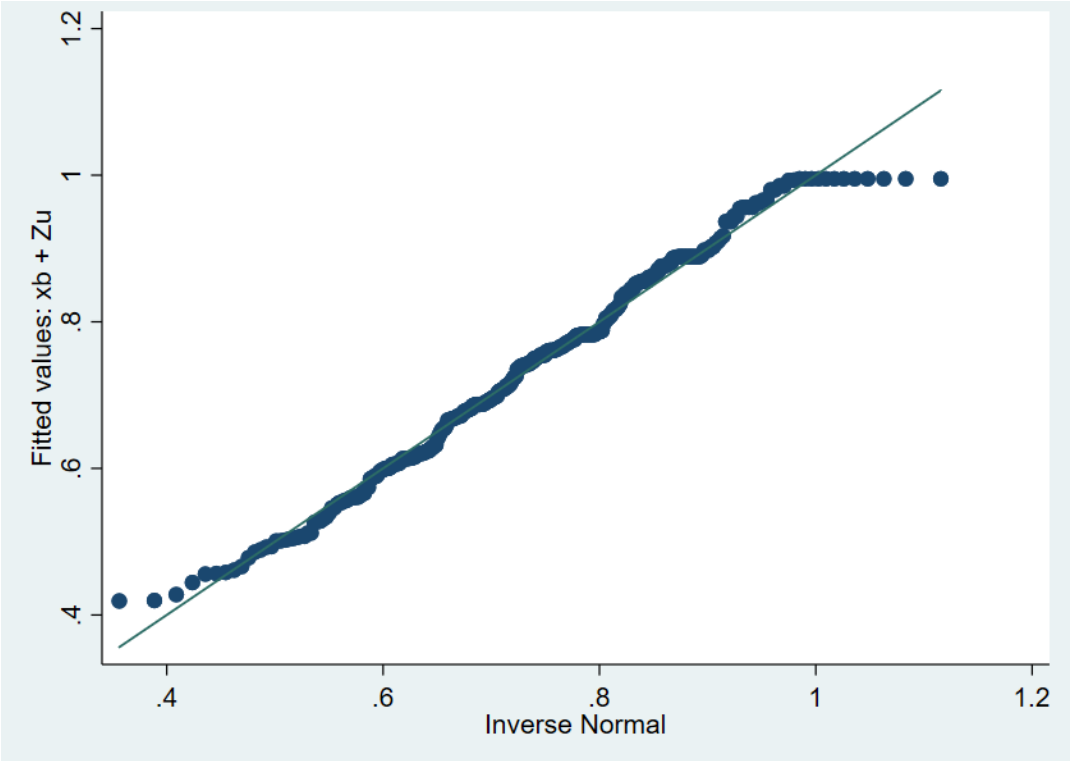


Figure 66: A scatter plot to show the TTO against monthly time points with the predicted random polynomial model

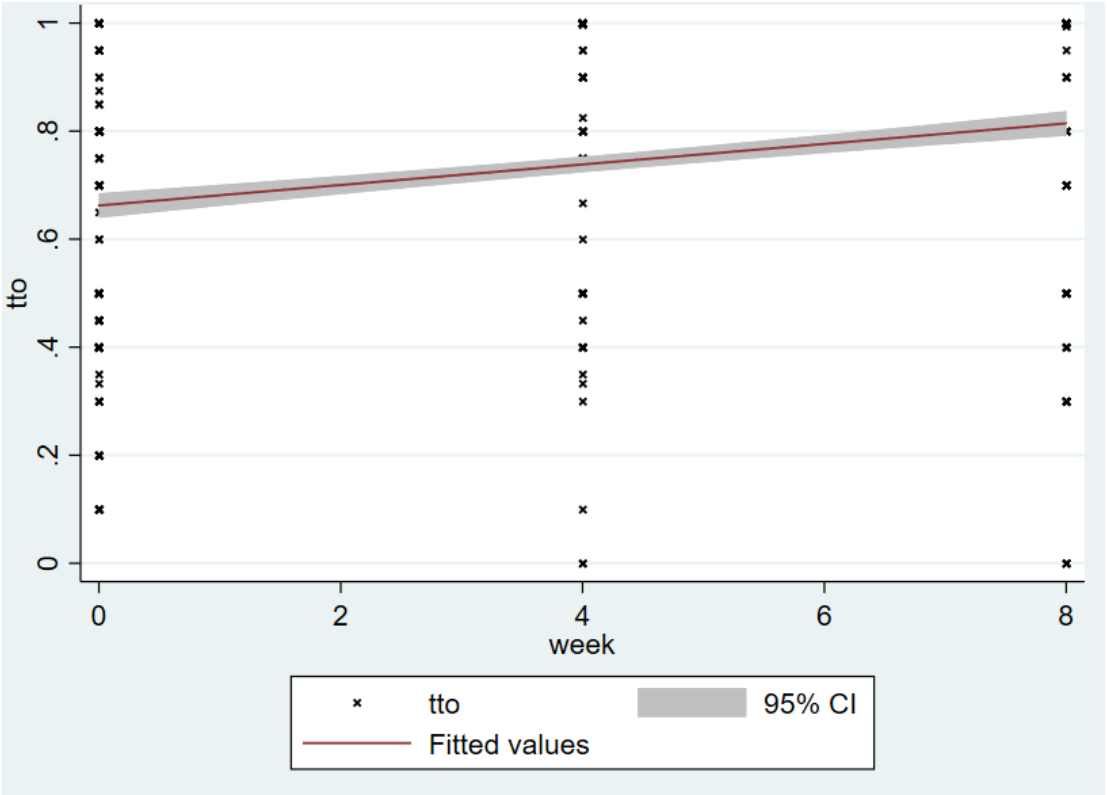


Figure 67: A Q-Q plot based on the predicted random polynomial model for the TTO