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Near Fatal Asthma in Children and Young People



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III. Declaration

I declare that the content of this thesis is my own work and that all contributions and collaborations have been explicitly acknowledged in the text. No material presented in thesis has been submitted to any other university or for any other degree.

Deepa Varghese

4th October 2024

Abstract

Introduction

Asthma is a common respiratory condition affecting 1 in 11 children in the UK¹. There are approximately 1200 deaths from asthma every year in the UK across all ages. Within Europe, the UK has the highest rate of asthma mortality in children 0 – 19 years old^{2,3}. In the UK the diagnosis and management of asthma has been standardised, with specific management for acute asthma attacks depending on the severity of symptoms. Acute asthma attacks are categorised by national guidelines into severity: mild, moderate, severe and life threatening⁴. Life threatening asthma is a broad category that is not further subcategorised to differentiate near fatal asthma (NFA). The lack of a clearly defined category of near fatal asthma attack may have an impact on its clinical recognition and the possibility of intervention to prevent future fatal asthma attack.

The definition of near fatal asthma has evolved over time but remains poorly defined beyond the most severe form of survivable acute asthma. Unlike severe asthma, near fatal asthma does not describe chronic symptoms. Factors associated with more acute severe progression of asthma attacks remain poorly elucidated. The terms severe asthma, life threatening asthma and near fatal asthma are often used interchangeably and without precision. Terminology such as 'life threatening attack' or 'status asthmaticus' had previously described severe asthma attacks but these terms also lack clear

definition in terms of comparative severity. In contrast, near fatal asthma indicates a pre terminal attack which would most probably result in asthma death without intervention. Understanding these attacks could be key to reducing and ideally preventing asthma deaths. The management of children with near fatal asthma is neither standardised or well described. In part through the lack of a distinct category, the frequency of these attacks in children and young people in the UK is not known.

In this thesis, I will ascertain the frequency of NFA (as defined by an e-Delphi consensus) and characterise NFA attacks in detail through an observational surveillance project. Through a systematic review, the influence of environmental risk factors, specifically outdoor air pollution will be examined in the context of near fatal asthma attacks.

Objectives

1. To conduct a systematic review on ambient outdoor air pollution and its association with severe asthma attacks in children. As a secondary outcome review the multiplicity of associated asthma risk factors that may contribute to near fatal asthma.
2. Through an observational surveillance study, measure the annual frequency of NFA attacks in children and young people in the UK and Republic of Ireland, and to describe key characteristics and potential risk factors.
3. Using the data set identified in the surveillance study, assess the effect of environmental and infective factors on NFA attacks in children

and young people, to include air pollution, weather, pollen levels and prevalent respiratory viruses.

4. Assess if the method of surveillance was adequate to draw conclusions from the data and consider if the use of an alternative research methodology to identify near fatal attacks such as disease registries could strengthen analysis.

Methods

To identify relevant literature observing any association between outdoor air pollution and near fatal and fatal asthma in children and young people, a systematic review was completed following Cochrane methodology.

To determine the frequency of near fatal asthma in children and young people in the UK, I conducted an observational surveillance study. Data were collected on near fatal asthma attacks in children aged 5 – 15 years over 18 months (1st October 2022 – 1st April 2024). Detailed questionnaires were sent to clinicians who are part of the British Paediatric Surveillance Unit and receive monthly e-reporting cards. An eDelphi consensus definition of near fatal asthma was included on the monthly reporting cards. Any clinicians who reported a case of near fatal asthma completed a questionnaire. Data were submitted to and analysed within a safe haven (Health Informatics Centre (HIC) Dundee). Data linkage was carried out within the safe haven. Cases were described in detail. Patient demographics and presentations were compared to current literature on near fatal asthma in children.

Within the safe haven, data on air pollution, respiratory viral infections in the UK, weather, social deprivation and seasonal pollen data were observed throughout the study period using publicly available data sources.

Results

Only four studies met the inclusion criteria of the systematic review for near fatal and fatal asthma attacks in children associated with outdoor air pollution. The heterogeneity of these studies limited synthesis of the data. A key finding of the review was the lack of definition of asthma severity in studies attempting to associate outdoor air pollution with asthma attacks in children. A significant number of studies (n = 217) could not be included in the review as the severity of the asthma attack was not specified by the paper.

Observational surveillance study results: Fifty one near fatal cases were reported during the study period (1st October 2022 – 1st April 2024). Two cases had two attacks within the study period (n = 49 patients, 51 cases of NFA). Cases were more frequently observed in males (n=30) compared to females (n=19). The median age of a NFA case was 10.7 years. Of the 51 cases 19.7% (n = 10) of cases did not require invasive ventilation or experience cardiorespiratory arrest. The median duration of admission was 5.5 days (IQR 3 – 10 days). Eight cases (18.2%) were not known to have asthma prior to near fatal attack. Fewer than 5 cases did not make a full recovery from the attack and were discharged with neurological or other sequelae. 1 in 5 cases did not have a change in medication on discharge and

25% were known to be discharged home without an asthma action plan.

Follow up varied from asthma nurse only (n= 1) to respiratory paediatrician (n= 28). One third of patients were from the lowest deprivation quintile in England.

Air pollution data based on postcode was available for 44 of the 49 patients. Annual mean modelled background Particulate Matter (PM) levels for PM₁₀, PM_{2.5} and Nitrogen dioxide (NO₂) were obtained for patient postcode from the Department of Environment, Food and Rural Affairs (DEFRA). The median PM₁₀ concentration was 12.2µg/m³ (IQR 10.8 – 14.7) with 11 patients (11/44, 25%) exceeding the World Health Organization (WHO) recommended limit for annual PM₁₀ exposure (15µg/m³). Forty two patients (42/44 cases, 95%) exceeded the WHO recommendation for PM_{2.5} annual exposure level (5µg/m³). Twenty seven patients (27/44, 61.4%) exceeded the WHO recommended annual exposure for NO₂ (10µg/m³).

Conclusion

Near fatal asthma is rare in children and young people (51 cases in the UK and Ireland in 18 months). The results of this study present baseline characteristics for this population (age, gender, ethnicity) and reaffirm previous studies observing an increase in cases in patients from lower social deprivation quintiles. Follow up care is not standardised throughout the UK and Ireland and must be addressed to prevent further near fatal asthma attacks in this population. Outdoor air pollution exceeding WHO recommended guidelines was commonly observed particularly for PM_{2.5} and

outdoor air pollution exposure should be considered in collateral history for near fatal asthma. Results from the systematic review support the need for further studies on clearly defined near fatal asthma and outdoor air pollution. Estimating the frequency of cases through clinician surveillance presented challenges such as clinician engagement, incomplete data and survey fatigue and future studies must consider if clinician surveillance is the most effective method to gain insight into near fatal asthma attacks. Identification of near fatal asthma, recognition of outdoor air pollution as a potential risk factor for attacks and clear management pathways are required to ensure standardised care of children with near fatal asthma in the UK and Ireland.

Lay summary

Asthma affects 1 in 11 children in the UK. Asthma attacks vary in severity, but the most severe form of asthma attack is called a 'Near Fatal Asthma' attack. It is the most severe form of survivable asthma attack. Children who experience near fatal asthma have an increased risk of further severe asthma attacks and death from asthma. The UK has one of the highest rates of death from asthma in Europe in children and young people. Near fatal asthma attacks are not well understood and at present, there is no standardised management for near fatal asthma.

The first and second chapters of this thesis provide a detailed background on asthma and near fatal asthma and how data has previously been collected about these conditions in the UK and in Europe. The third chapter of the thesis explores if previous studies have found a link between outdoor air pollution and near fatal asthma in children and young people through a structured search of existing studies on this topic.

The fourth chapter describes how I set up a project to look in detail at cases of near fatal asthma in children and young people in the UK and Ireland over 18 months. I used an organisation – the British Paediatric Surveillance Unit (BPSU) to help access surveillance data on children presenting to hospital with near fatal asthma. Surveillance data are data routinely collected by clinicians who manage children with near fatal asthma in hospitals and healthcare settings across the UK and Ireland. By using surveillance data, researchers are able to say how often near fatal asthma attacks occurred

over the 18 month study period. The study group created a questionnaire for doctors to answer online to provide detailed information about each near fatal asthma attack. The clinical information about each attack was entered and stored in an online safe haven (a secure data storage system for health and personal data).

Results

The review of existing studies on outdoor air pollution and fatal and near fatal attacks showed a small number of papers (4 papers identified in our search) addressed near fatal and fatal attacks in children linked to outdoor air pollution. A large number of papers (217 papers) were excluded from our analysis because they did not include any information on how severe the asthma attacks were. This is an important finding for future researchers investigating outdoor air pollution and asthma.

Paediatric doctors in the UK and Ireland reported 51 cases of near fatal asthma in the 18 month surveillance study. Using the data entered into the safe haven we have been able to describe the near fatal attacks in detail. Near fatal asthma attacks were more common in males in our study and in children from areas of deprivation in England. Eight cases were not known to have asthma before the near fatal attack. Four children did not recover fully from the near fatal asthma attack and were discharged from hospital with long term medical problems. We found that 95% of the children in the study were exposed to background levels of air pollution (PM_{2.5}) above the recommended level from the World Health Organization (WHO). Twenty

eight of the 51 cases were followed up by a respiratory paediatrician. Eleven patients did not have any changes to their medication when discharged home after the near fatal asthma attack.

The findings from the study show that near fatal asthma in children and young people is rare in the UK and Ireland. This study adds to what we already know about children with near fatal asthma but uniquely, has allowed researchers to use a clear definition to identify near fatal asthma attacks. The study provides new, detailed information on this patient group in the UK and demonstrates the varied presentation and management of children with NFA in different hospitals and regions throughout the UK and Ireland. The work from the systematic review and the study emphasises the importance of addressing outdoor air pollution in children with near fatal asthma and reiterates the impact of social deprivation has on the occurrence of near fatal asthma.

Future work in this area should continue to highlight the importance of recognising this group of patients by clearly defining attacks and creating guidance on how they should be treated both in hospital, on discharge from hospital and when followed up by clinicians to reduce the risk of repeated near fatal attacks and hopefully to prevent future fatal asthma attacks in children with near fatal asthma.

Abbreviations

AUKCAR	Asthma UK Centre for Applied Research
AURN	Automatic Rural Urban Network
BPSU	British Paediatric Surveillance Unit
BTS	British Thoracic Society
CAG	Confidential Advisory Group
CO	Carbon Monoxide
CYP	Children and Young People
DEFRA	Department of Environment, Food and Rural Affairs
DPIA	Data Protection Impact Assessment
ED	Emergency Department
EHR	Electronic Health Record
GDPR	General Data Protection Regulation
GINA	Global Initiative for Asthma
GP	General Practitioner
ICD	International Statistical Classification of Diseases and Related Health Problems
IMD	Index of Multiple Deprivation
LSOA	Lower layer Super Output Area
MSOA	Middle layer Super Output Area
NFA	Near Fatal Asthma
NHS	National Health Service
NO ₂	Nitrogen Dioxide
NPRANG	National Paediatric Respiratory and Allergy Nurses Group
O ₃	Ozone
PAC	Privacy Advisory Committee
PBPP	Public Benefit and Privacy Panel
PCCS	Paediatric Critical Care Society
PERUKI	Paediatric Emergency Research in the UK and Ireland

PICANet	Paediatric Intensive Care Audit Network
PM	Particulate Matter
PPI	Patient and Public Involvement
RCPCH	Royal College of Paediatrics and Child Health
REC	Research Ethics Committee
ROI	Republic of Ireland
SIGN	Scottish Intercollegiate Guidelines Network
SO ₂	Sulphur Dioxide
TRE	Trusted Research Environment
UK	United Kingdom
UKHSA	UK Health Security Agency
WHO	World Health Organization

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Contributions to Science

Poster Presentations

Asthma UK Centre for Applied Research, Annual Scientific Meeting 2022

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Publications

Near Fatal and Fatal Asthma in children and young people associated with outdoor air pollution: A systematic review. Deepa Varghese, Kathryn Ferris, Bohee Lee, Jonathan Grigg, Hilary Pinnock, Steve Cunningham. European Respiratory Journal 2023 62: PA1624; DOI: 10.1183/13993003.congress-2023.

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Outdoor air pollution and near-fatal/fatal asthma attacks in children: A systematic review. Deepa Varghese, Kathryn Ferris, Bohee Lee, Jonathan Grigg, Hilary Pinnock, Steve Cunningham. *Pediatric Pulmonology*. 13 March 2024. <https://doi.org/10.1002/ppul.26932>

1 Chapter 1: Overview of thesis

1.1 Summary of thesis

Asthma is a respiratory condition which affects over 262 million people globally⁵. A wealth of evidence exists on the management of asthma and its associated risk factors in children and young people. Despite this, asthma deaths continue to rise in children and young people in the UK and the burden of asthma care in the UK is increasing⁶⁻⁸. It is not yet clear why the UK has one of the highest rates of death from asthma⁹ in children and young people in Europe.

In 2014 the UK National Review of Asthma Deaths highlighted 28 paediatric asthma deaths. The report brought several key messages about asthma care and management into focus. Thirteen of the 28 children were felt to have inadequate care from clinicians prior to their fatal attack and in 27 of 28 children and young people (CYP) the risk of fatal attack was reportedly not recognised by health care professionals¹⁰.

Children admitted to intensive care with near fatal asthma have an increased risk of a further severe attack and fatal asthma¹¹ and are highlighted by Global Initiative for Asthma (GINA) guidelines as at increased risk of asthma related death¹². There is no consensus within UK or guidelines globally on how to manage near fatal asthma either acutely or in the longer-term. Near fatal asthma has been poorly defined. At present the International Classification of Diseases (ICD) 10th or 11th revision does not include a definition for near-fatal asthma^{13,14} and several terms including status asthmaticus and critical asthma syndrome are used interchangeably without

clear physiological or clinical parameters. Attacks that require admission to intensive care have also been used as a threshold for near fatal asthma definition in children but admission criteria to intensive care is not standardised nationally nor internationally. Similarly invasive ventilation is used as a definition threshold but the indications for this are not standardised, and this may not be an indication of clinical severity e.g., it could reflect airway stabilisation for transfer to another centre. These deficiencies mean that for children near fatal asthma attack frequency is not known and clinical care is not standardised across the UK and Ireland.

I have chosen to conduct surveillance of near fatal asthma attacks in children and young people using a definition proposed by an e-delphi consensus process. This is the first surveillance project in the UK and Ireland to use a definition for near fatal asthma based on an e-delphi consensus to determine the frequency of near fatal asthma cases in children and young people.

This thesis is introduced by an overview of asthma and a detailed review of current literature on near fatal asthma attacks. Using a systematic review, I explored if outdoor air pollution had an impact on near fatal and fatal asthma and highlighted the significance of clear terminology and pitfalls of coding when researching near fatal asthma. I used an observational surveillance study to determine the frequency of attacks in UK and Ireland over 18 months. Using information gathered from detailed clinical questionnaires I have described the characteristics of the near fatal attacks. Using data linkage, I examined correlations between NFA attacks and ambient outdoor air pollution, meteorological and airborne aero allergens.

Finally, I have summarised my findings on near fatal asthma by highlighting similarities and differences between existing literature and knowledge of near fatal asthma and those captured in this surveillance study. I have used the relevant findings from this project to suggest how care of patients with near fatal asthma could be improved by highlighting clear definitions and targeted follow up.

This project has identified the challenges of using routinely collected data in surveillance in the UK with regards to General Data Protection Regulation (GDPR) and clinician engagement in the study. I have reflected on the methodology used and proposed how future research could benefit from the work completed as part of this project.

1.2 Thesis Objectives

1. To conduct a systematic review on ambient outdoor air pollution and its association with severe asthma attacks in children. As a secondary outcome review the multiplicity of associated asthma risk factors that may contribute to near fatal asthma.
2. Through an observational surveillance study, measure the annual frequency of NFA attacks in children and young people in the UK and Republic of Ireland, and to describe key characteristics and potential risk factors.
3. Using the data set identified in the surveillance study, assess the effect of environmental and infective factors on NFA attacks in children and young people, to include air pollution, weather, pollen levels and prevalent respiratory viruses.

4. Assess if the method of surveillance was adequate to draw conclusions from the data and consider if the use of an alternative research methodology to identify near fatal attacks such as disease registries could strengthen analysis.

1.3 Background to this thesis: Narrative Cases

Asthma deaths in children and young people are devastating for the families and health care professionals involved in their care. As demonstrated by the National Review of Asthma Deaths (2014), 45% of the deaths may have been avoidable if national guidelines were implemented correctly¹⁰. National guidelines in the UK recognise that (undefined) near fatal asthma is a risk factor for a future severe attack^{4,12}. Without a clear definition of near fatal asthma, its recognition may be compromised and the risk of subsequent fatal asthma not recognised. The two narrative cases below bring into focus the clinical impact of the work this thesis aims to address.

Narrative Case 1

Box 1 below contains extracts from a coroner's report for a child in the UK who presented with a near fatal asthma attack. This example highlights the importance of recognising near fatal asthma.

Box 1 Case Report 1

Case 1
William Gray – age 7. Quotes from Section 4, Coroners Report 8 th December 2023 ¹⁵

William's care and treatment was sub-optimal; his asthma was poorly controlled in the absence of appropriate assessment and reviews. William required chest compressions and intramuscular adrenaline in accordance with the Joint Royal Colleges Ambulances Liaison Committee (JRCALC) Guidelines with oxygen for a life-threatening asthma attack on 27 October 2020 that saved his life. William was conveyed to Southend Hospital where he was discharged home four hours later with no assessment of his recent symptomatology and no change to his medications.... William was lost to follow-up at Southend Hospital following a consultant appointment on 14 November 2020. As a consequence of multiple failures, William suffered an inevitable life-threatening asthma attack.

William had experienced a near fatal asthma attack in October 2020. He did not receive follow up care or an escalation in preventative medications. He was not reviewed by an asthma specialist and unfortunately suffered a fatal asthma attack 12 months later.

Narrative Case 2

The identification of asthma triggers and risk factors are important in the management of acute attacks. As will be demonstrated by the results of my systematic review and the case below, it can be difficult to identify if outdoor air pollution is a risk factor for near fatal asthma. Case 2 highlights a

landmark case from the UK which demonstrates the difficulty in identifying if outdoor air pollution is associated with near fatal asthma symptoms.

Box 2 Case Report 2

Case 2
Ella Adoo Kissi Debrah – age 9. Quotes from Section 4, Coroners Report, 20 th April 2020
<i>Ella died at the age of 9. She had severe, hypersecretory asthma causing episodes of respiratory and cardiac arrest and requiring frequent emergency hospital admissions. On 15 February 2013 she had a further asthmatic episode at home and was taken to hospital where she suffered a cardiac arrest from which she could not be resuscitated... Air pollution was a significant contributory factor to both the induction and exacerbations of her asthma. During the course of her illness between 2010 and 2013 she was exposed to levels of nitrogen dioxide and particulate matter in excess of World Health Organization Guidelines. The principal source of her exposure was traffic emissions...During this period there was a recognized failure to reduce the level of nitrogen dioxide to within the limits set by EU and domestic law which possibly contributed to her death.</i>

Ella had multiple episodes of near fatal asthma attacks which were related by the Coroner to exposure to high levels of outdoor air pollution. It was challenging for health care professionals to link outdoor air pollution as the trigger for her chronic and acute symptoms.

These narrative cases highlight key aspects that will be explored in this thesis. Both children experienced a near fatal asthma attack prior to their fatal asthma attack. The Coroners reports demonstrate the lack of recognition of near fatal asthma and the interchangeable terms used to describe near fatal attacks (critical asthma syndrome, life threatening asthma, status asthmaticus). The reports show a lack of recognition of risk factors for near fatal asthma, of near fatal asthma management pathways and of standardised follow up care.

These examples are poignant and acutely highlight the need for recognition of near fatal asthma in children and implementation of standardised acute and follow-up care. The recommendations of this thesis include suggestions for the management of children with near fatal asthma to avoid future fatal asthma attacks in children and young people.

1.4 Patient and Public Involvement

In collaboration with the Asthma UK Centre for Applied Research (AUKCAR) a discussion group regarding the study methodology and data acquisition process was facilitated by our Patient and Public Involvement (PPI) colleagues. This included parents and young people with asthma. Parents of children with asthma shared reflections on their own experience of being in hospital with a child experiencing an acute asthma attack and how this study would appropriately allow data to be gathered on near fatal asthma attacks. The PPI input was vital to the successful commencement of this study.

1.5 Thesis chapter overview

Chapter 2 will discuss asthma and give an overview of the pathophysiology associated with asthma attacks. I will summarise the current evidence on near fatal asthma in children and young people. I will review the risk factors associated with asthma and near fatal asthma including gender, ethnicity, social deprivation, and environmental exposures. This chapter will outline surveillance studies in the UK and the data considerations required when undertaking a surveillance study.

Chapter 3 will further explore the theme of outdoor air pollution and near fatal asthma as highlighted by the case of Ella Kissi Debrah (Box 2) through a systematic review of the evidence on near fatal and fatal asthma in children and young people and outdoor air pollution. I will focus on whether outdoor air pollution, is a risk factor for near fatal asthma and fatal asthma in children and young people. The review will highlight the challenges in identification of near fatal asthma specifically related to the coding of severity of asthma attacks within reported literature and the difficulties in applying temporal spatial geographical data to an acute individual attack.

Chapter 4 (Methodology) will explore the methodology of the surveillance study I have used to determine the frequency of near fatal asthma. I will discuss in detail the permissions and ethical approvals required for this study and the challenges that were highlighted in the access and storage of routine data. I will also discuss the data linkage and relevant approvals that were required for this project and how I planned to use data linkage to identify any

common themes within my data and compare this to what is already known about near fatal asthma in children and young people.

Chapter 5 will report the results of the surveillance study by firstly providing an overview of the identified cases and subsequently a description of the cases highlighting common features. I will compare any features identified in the background chapters on near fatal asthma in children and young people.

Chapter 6 will discuss the challenges of data collection and the active surveillance period. I will explain in detail how I addressed issues of survey fatigue, incomplete data and overcame barriers encountered during the use of the reporting system managed by the BPSU.

Chapter 7 will discuss the context of my results and the success (and limitations) of my methodology to determine the frequency of near fatal asthma in children and young people.

2 Chapter 2: Introduction

Asthma is a chronic respiratory illness hallmarked by airway bronchospasm¹⁶. Historically, the typical asthma patient would present with 'allergic' asthma driven by a Type 2 inflammatory response (see Figure 1). As the evidence base around asthma has developed, it is now clear that asthma is a heterogenous condition presenting with varying observable characteristics or phenotypes¹². The term 'asthma' is now regarded as an umbrella term to describe wheeze, shortness of breath, chest tightness and cough¹⁷. These can originate from different endotypes, some of which are not yet well described¹⁷. The successful treatment of asthma depends on the underlying physiological pathway which is driving the symptomatology. This chapter will explore briefly the pathophysiology of asthma, discuss near fatal asthma in depth and review how data on fatal asthma has impacted my research and formulated the question on near fatal/fatal asthma and air pollution addressed in chapter 3.

INFLAMMATORY PATHWAY	TYPE 1	TYPE 2	TYPE 3
Primary immune cells	 Macrophage  Th1  ILC1  NK	 Th2  ILC2  Mast cell  Basophil  Eosinophil	 Neutrophil  Th17  ILC3
Key cytokines	IFNγ TNF IL-6 IL-12 IL-18 IL-2	IL-4 IL-5 IL-13 IL-31	IL-17 IL-6 IL-22 IL-23
Function	- Antitumor activity - Cellular immunity: antiviral/antibacterial - Suppression of type 2	- Humoral immunity: antiparasitic helminths - Neutralizes toxins - Regulates wound repair and regeneration - Suppression of type 1	- Regulation of intestinal epithelial barrier - Responses to extracellular bacteria and fungi
Examples of consequence of dysregulation and associated disease	- Ankylosing spondylitis - Atherosclerosis - Autoimmune gastritis - Diabetes mellitus - Hashimoto thyroiditis - Inflammatory bowel disease - Multiple sclerosis - Rheumatoid arthritis - Sarcoidosis	- Allergy - Anaphylaxis - Type 2 asthma - Atopic dermatitis - Chronic obstructive pulmonary disease with type 2 inflammation - Chronic rhinosinusitis with nasal polyps	- Ankylosing spondylitis - Multiple sclerosis - Psoriasis - Rheumatoid arthritis - Uveitis

Figure 1 Overview of types 1, 2, and 3 inflammation.

This diagram represents immune concepts that do not occur in complete isolation. IFN γ interferon- γ , IL interleukin, ILC innate lymphoid cell, NK natural killer, Th1/2 T helper type 1/2 cell, TNF tumor necrosis factor ¹⁸ Reprinted with Permission

2.1 Asthma

There are three key components in the pathophysiology that result in the symptoms of asthma:

1. Airway hyperresponsiveness causing bronchoconstriction
2. Inflammation
3. Airway remodelling

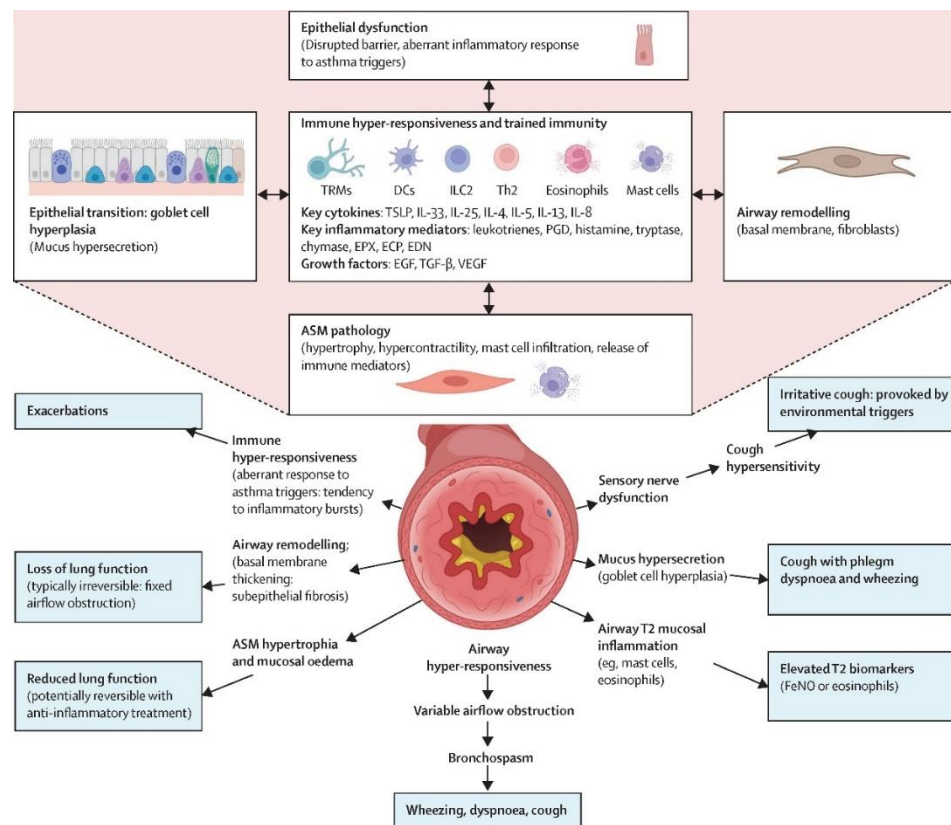


Figure 2 Key pathophysiological mechanisms of asthma and resulting disease components and clinical features¹⁶ Reprinted with permission

As demonstrated in figure 2, these processes are not sequential or mutually exclusive which increases the difficulty for clinicians to target asthma treatment. The acute and chronic symptoms of asthma are a culmination of these underlying structural and immunological processes.

2.1.1 Pathophysiology

To explore airway hyperresponsiveness and inflammation, it is helpful to consider the underlying potential inflammatory pathways. A comprehensive review by Papi et al (2018) categorised the cellular mechanisms of asthma into 5 groups; eosinophilic asthma, non eosinophilic asthma, non-allergic eosinophilic asthma, mixed granulocytic asthma and, Type1 and Type 17

neutrophilic inflammation¹⁹. The most recognised of this group is eosinophilic asthma (also known as T2-type asthma²⁰ Type 2 high²¹ or T2 high²²). Non eosinophilic asthma is also known as non T2 type²⁰ or type 2- low asthma²¹ or non T2²²) and includes Type 1 and Type 17 neutrophilic inflammation as identified by Papi et al, (2018). Holgate et al, (2015) suggest that T2 type asthma is more typical in children whilst Non-T2 type asthma predominates in adults²⁰.

Eosinophilic asthma

Changes in the architecture of the respiratory epithelium result in the disruption of airway epithelial cells and loss of tight junction proteins leading to increasing epithelial permeability and sensitivity to allergens²¹. Disruption of this epithelium results in release of thymic stromal lymphopoietin (TSLP), IL-25, and IL-33²², stimulation of these result in production of IL5 and IL13 with activated dendritic cells producing IL4. These cytokines stimulated by eosinophils, predominate in Th2 asthma. This pathway, when triggered by allergens has been labelled as Th2 (eosinophilic) asthma and is suggested to be associated with over 80% of asthma linked to atopy²⁰.

Non eosinophilic asthma

Although separated into two categories by Papi et al.(2018) this can also be reviewed as a broader group of 'non eosinophilic' asthma. More commonly associated in adults, non eosinophilic asthma phenotypically presents in those who are non-atopic, smokers, obese and elderly²². Non-allergic eosinophilic asthma as suggested by Papi et al.(2018) is triggered by

oxidative stress, microbes and air pollutants and results in IL33 and TSLP cascading to ILC2 and IL5 production. Non eosinophilic asthma in adults has also been associated with near fatal and fatal asthma and has been associated with a rapid onset of near fatal/fatal attacks which is more commonly associated with a predominance of airway neutrophils. The inflammatory pathway of non-eosinophilic asthma in children is poorly understood¹⁷ but in contrast to adults, evidence from a small study of paediatric patients suggest that a higher proportion of airway neutrophils is associated with improved lung function and better controlled asthma (based on Asthma Control Scores)²³.

Histology

To examine the mechanism of airway obstruction in asthma and airway remodelling in further detail, it is helpful to first identify the histological differences in asthmatic airways compared to those without asthma. As demonstrated in Figure 3 an asthmatic airway is comprised of abnormal airway epithelium due to the increased presence of goblet cells, Type 2 helper cells (TH2 cells), macrophages and dendritic cells as well as an increase in airway smooth muscle mass²⁴. During an acute attack, increased mucus production, airway wall oedema and constriction of smooth muscle results in a narrowed airway lumen.

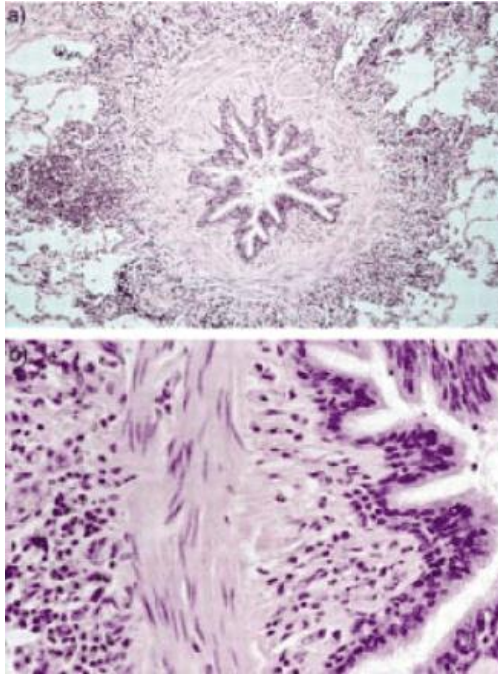


Figure 3 Histopathological changes in acute asthma. Photomicrographs showing a bronchiole from a subject who died during an asthma attack. a) Luminal occlusion caused by muscle constriction, thickening of the airway wall, increased smooth muscle mass and a marked inflammatory process in the airway wall, mainly characterized by eosinophils. b) Detail from a). The distribution of the inflammatory process is more obvious: there is a greater density of eosinophils in the area outside the smooth muscle ("outer" region) than in that inside it ("inner" region). (Haematoxylin and eosin staining²⁴ Reprinted with permission

In asthma, airway obstruction caused by the processes illustrated in Figure 3 are variable and is evidenced by spirometry which, in a stable asthmatic patient can be within the normal predicted range based on age, gender, height and ethnicity. Evidence of airway obstruction both acute and chronic results in a decreased Forced Expiratory Volume measured in 1 second (FEV1) and reduced FEV1/Forced Vital Capacity (FVC) ratio. Variable obstruction can be further tested using bronchodilator reversibility where an improvement in FEV1 of 12% is considered significant and suggestive of reversible bronchospasm⁴. The mechanism of persistent airway obstruction and long term airway remodelling in children with asthma has not been

clearly demonstrated. As argued by Bush (2019), airway remodelling in asthma cannot be attributed solely to recurrent eosinophilic inflammation¹⁷.

2.1.2 Risk factors for developing asthma in children

Gender

In early childhood, several studies have shown that males have an increased risk of wheeze and asthma²⁵. This appears to change during adolescence, where females have an increased risk after puberty and into adult years^{26,27}.

Genetics

Asthma has a genetic susceptibility but is a complex multi loci condition where the interplay of genetics and environmental factors remain unclear. Several studies have identified genes associated with childhood asthma related to 17q12 locus^{28–30}. Variants in ORMDL3/GSDMB gene locus and CDHR3³¹ identified in European and American populations in children have also been associated with asthma²⁸. Similar findings have been noted in worldwide, primarily in other white populations²⁹. Although these genetic variants have been observed in these populations they have not been found to be causal^{16,32}. The heterogeneity of asthma has not however been explained by current genetic studies, although CDHR3 has been associated with severe asthma attacks in children³³ (severe defined as hospital admission for acute attack).

Obesity

Obesity in childhood has been associated with childhood asthma^{34–36}. The underlying causation is not known but has been suggested in non eosinophilic asthma through impaired Th2 pathways^{35,37}. Obesity in

childhood has also been associated with increased severity of asthma attacks, including a significantly greater requirement for mechanical ventilation to manage acute asthma attacks. (OR 1.59, 95% CI 1.28-1.99)³⁸.

Environmental

Tobacco smoke: Exposure to tobacco smoke both antenatally and in childhood are associated with an increased risk of developing asthma³⁹.

Tobacco smoking causes activation of the inflammatory pathways associated with asthma (see 2.1.1) whilst increasing the severity of airway remodelling⁴⁰.

Air pollution

Outdoor and indoor air pollution are both known to trigger asthma attacks.

Outdoor air pollution exposure in the antenatal period and in childhood have been shown to reduce lung function in non-asthmatic children (specifically FEV1)^{41–43}. Outdoor air pollution exposure is associated with both eosinophilic and non-eosinophilic pathways which lead to the development of asthma symptoms⁴⁴. As demonstrated in the figure below from Pfeffer et al (2021), exposure to outdoor air pollutants causes impairment from in-utero lung development. As exposure is increased and the child develops, air pollution exposure can lead to an asthma attack.

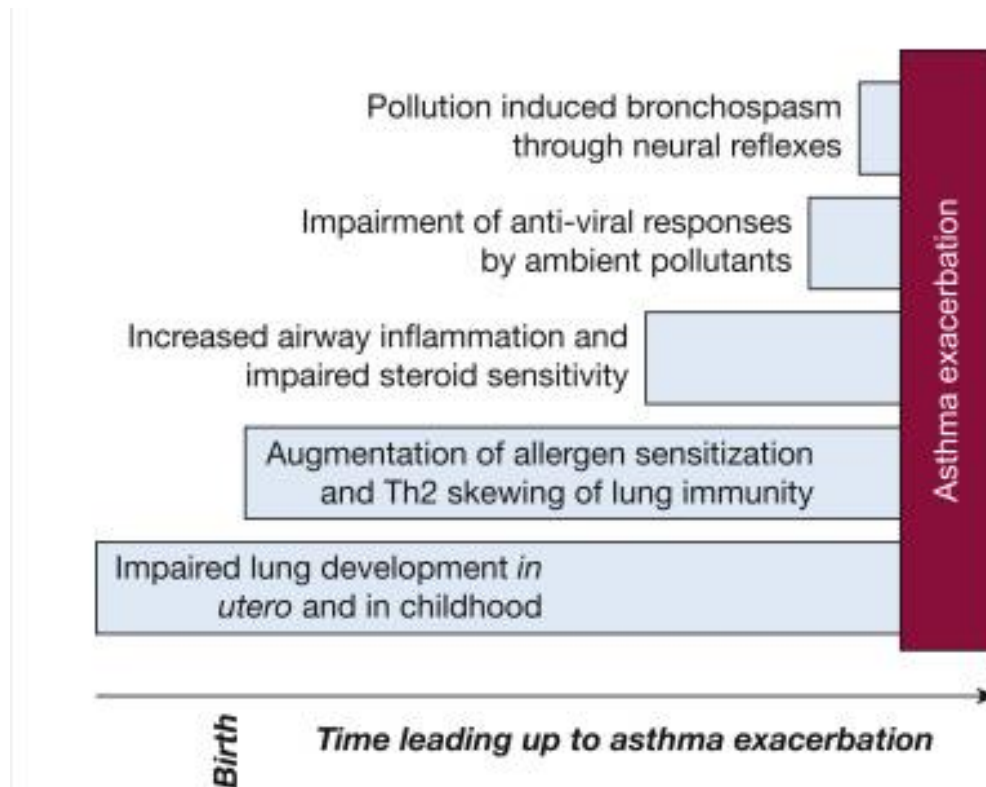


Figure 4 Air pollution exposure contributing to asthma attack⁴⁴ Reprinted with permission.

Outdoor air pollutants consist of a combination of natural and industrial or chemical waste products consisting of particles and gaseous products which can negatively impact health⁴⁵. Outdoor pollutants, specifically particulate matter (PM) are observed to cause oxidative stress in the lungs, promoting inflammatory responses, airway hyperresponsiveness and airway remodelling within the lungs with early exposure^{46,47}. As explored in the article Near-fatal and fatal asthma and air pollution: are we missing an opportunity to ask key questions? (Appendix 2), the World Health Organization recognises, PM, Carbon Monoxide (CO), Ozone (O₃) Nitrogen dioxide (NO₂), Sulphur Dioxide (SO₂) as the major air pollutants negatively contributing to respiratory and cardiovascular health outcomes⁴⁸. A systemic review and meta-analysis combining 41 studies conducted by Khreis et

al,(2017) examined if traffic related air pollution (TRAP) exposure impacted the risk of development of childhood asthma and found an increased risk in asthma development relating to higher levels of black carbon (BC), NO₂, PM_{2.5} and PM₁₀ (random-effects risk estimates (95% CI) were 1.08(1.03, 1.14) per black carbon, 1.05 (1.02, 1.07) per 4µg/m³ nitrogen dioxide, 1.48 (0.89, 2.45) per 30µg/m³ nitrogen oxides (NO_x), 1.03 (1.01, 1.05) per 1µg/m³ PM_{< 2.5µm} in diameter, and 1.05 (1.02, 1.08) per 2µg/m³ PM₁₀⁴⁹. Early life (< 5 years of age) exposure to PM_{2.5} and NO₂ has also been associated with an increase in asthma incidence (NO₂ per increase 6.1µg/m³, 1.25 [95% CI, 1.03-1.52] and PM_{2.5} per 3.4µg/m³increase 1.31 [95% CI, 1.04-1.66]). A cohort study from Dutch PIAMA (Prevention and Incidence of Asthma and Mite Allergy) birth cohort also observed a higher incidence of asthma persisting into adolescence and adulthood in children exposed to higher levels of NO₂ and PM₁₀ at their birth address indicating birth exposure may have long term implications on respiratory health (PM₁₀ 1.09 (1.01–1.18), NO₂ 1.20 (1.10–1.32) per interquartile range increase)⁵⁰.

Indoor allergens: There is evidence that early sensitisation in childhood to indoor allergens such as house dust mite, cockroach and domestic animal dander and mould can increase the risk of developing wheeze in adolescence^{20,21,51}. This is primarily based on studies in high income countries. Further impact of indoor air pollutants has not been addressed within this thesis.

As discussed in the article Near-fatal and fatal asthma and air pollution: are we missing an opportunity to ask key questions? (Appendix 2) when

considering the impact of outdoor air pollution and asthma, the duration of exposure in relation to the development of asthma symptoms or acute attack should be considered. Ambient air pollution assumes a background level of exposure, children may be subjected to periods of increased exposure for example walking to school beside a busy road⁵². Air pollution exposure based on modelled ambient data should be interpreted with context. Using modelled air pollution data involves computational simulations to estimate pollutant concentrations across different spatial and temporal scales. These models, such as dispersion models or chemical transport models, integrate inputs like emissions inventories, meteorological data, and topographical features to predict air quality. Background ambient air pollution refers to the baseline level of air pollutants present in the environment, typically influenced by natural sources and long-range transport of pollutants rather than direct local emissions and may not reflect short peaks and troughs of acute exposure. . Consideration of whether short exposures to high levels have an impact on acute attacks may require the use of personal air pollution monitoring devices to capture short periods of higher air pollution exposure.

Viral exposures

There is a strong association between human rhinovirus (HRV) infection and asthma triggers in children. The causal relationship between asthma and early age rhinovirus infection is at present unclear and a larger topic which will not be discussed in this thesis. Similarly Respiratory Syncytial Virus (RSV) infection in early infancy may result in asthma in later years but evidence regarding this is conflicting^{20,51,53}.

Ethnicity and Social deprivation

Individuals living in socially deprived environments face a combination of factors that exacerbate asthma risk, including poor housing conditions, exposure to air pollutants, and limited access to healthcare. As explored by Cruz et al 2010, the relationship between poverty and asthma is complex and multifactorial⁵⁴. In the United States of America there is an observed correlation with ethnic minorities, socioeconomic deprivation and increased prevalence of asthma^{55,56}.

2.2 Acute asthma attacks

In the UK, an estimated 1 in 11 people are currently receiving treatment for asthma². An asthma attack is an acute episode of bronchospasm usually due to exposure to a specific trigger. Asthma attacks vary in severity from mild to fatal.

2.2.1 Physiology in acute asthma

In an asthmatic airway, the reduced lumen diameter associated with bronchospasm and inflammation results in reduction of airflow in small airways. Decreased airflow in smaller airways at bronchiole level causes airway collapse and air trapping which results in hyperinflation. Hyperinflation can reduce pulmonary blood flow and compress adjacent lung areas. As changes in airflow throughout the lung are not uniform, ventilation perfusion mismatch can occur⁵⁸. During an acute asthma attack hypoxia can occur and when accompanied by hyperventilation can result in an initial low PaCO₂. As obstruction becomes more severe, gas exchange is further impaired and

results in high PaCO₂ or hypercapnia. Metabolic changes occur acutely during asthma, initially resulting in a respiratory alkalosis in the presence of hyperventilation and finally with hypoventilation and respiratory failure by a decrease in pH and hypercapnia.

2.2.2 Acute asthma triggers

An acute asthma attack is initiated by the exposure of an asthmatic patient to a trigger. A trigger can be a singular or repeated exposure. In children, viral infections are the most common cause of asthma attack²⁰. Other common triggers are listed below (table 1).

Table 2.1 Common triggers of asthma attacks⁵⁹

Environmental exposure	Personal exposure
Weather – cold or humidity conditions, extreme weather conditions including thunderstorms, sandstorms, wildfires	Indoor allergens – house dust mite, cockroach, or animal dander
Airborne allergens – pollen, fungal spores	Exercise
Outdoor air pollutions	Tobacco smoke, vaping/e-cigarettes
Occupational exposure	Bacterial chest infection
	Viral infections

House dust mite, animal dander, tobacco smoke or air pollution be chronic exposures but may also be associated with acute attacks. Children with asthma should be made aware of their own personal triggers and these should be highlighted on personal asthma action plans.

Outdoor air pollution

Outdoor air pollution is a significant environmental risk factor for asthma attacks in children. As discussed previously, exposure to pollutants such as particulate matter (PM_{2.5} and PM₁₀), nitrogen dioxide (NO₂), and ozone (O₃) can trigger or worsen asthma symptoms by inducing airway inflammation and oxidative stress⁴⁶. Children, due to their developing respiratory systems and higher breathing rates relative to their body size, are particularly vulnerable to these pollutants⁶⁰. A systematic review by Orellano et al (2017) has shown a correlation between elevated levels of outdoor air pollution (NO₂, SO₂ and PM_{2.5}) and increased rates of asthma attacks, emergency attendances, and hospital admissions among paediatric patients⁶¹.

Airborne allergens – fungal and pollen spores

Airborne aeroallergens, such as pollen, mould spores, dust mites, and animal dander, are significant environmental triggers for asthma attacks in children⁶². These allergens can induce airway inflammation and bronchoconstriction, leading to acute asthma attacks, particularly in sensitized individuals⁶³. Studies have shown that exposure to high levels of airborne allergens correlates with an increased frequency and severity of asthma symptoms, including hospital admissions and emergency room visits^{64,65}. Seasonal variations in allergen levels, such as increased pollen counts during spring and autumn can further exacerbate these risks⁶⁶.

Viral triggers

Viral infections are a leading cause of asthma exacerbations in children.

Respiratory viruses such as rhinovirus⁶⁷, respiratory syncytial virus (RSV), and influenza⁶⁸ are commonly implicated in triggering acute asthma attacks by inducing airway inflammation and bronchoconstriction. Rhinovirus, in particular, is frequently associated with severe asthma exacerbations in children⁶⁹, especially after a return to school after a seasonal break^{70,71}.

Weather

Weather conditions play a significant role in triggering asthma exacerbations in children, with various meteorological factors such as temperature, humidity and extreme weather events such as thunderstorms influencing asthma symptoms. Cold air is a well-known trigger, causing bronchoconstriction and increased airway resistance, which can lead to asthma attacks. Similarly, high humidity levels and temperature changes have been observed to increase emergency presentations with asthma attacks in children⁷².

Weather phenomena such as thunderstorms can influence air pollution levels and aero allergens (pollen) leading to higher particulate matter concentrations that can trigger asthma attacks in children⁷³.

Tobacco smoke and vaping

Tobacco smoke is known to contain harmful chemicals, including nicotine and particulate matter, which contribute to airway inflammation and increased asthma severity. Second hand smoke has been associated with increased hospitalisation for children with asthma exacerbations⁷⁴. E-cigarettes, while often marketed as a safer alternative, still introduce harmful substances

volatile organic compounds, heavy metals, and ultrafine particles⁷⁵. These components can cause airway inflammation and increase bronchial hyperreactivity, contributing to acute asthma attack.

2.2.3 Acute asthma treatment

Asthma management in the acute attack has a step wise approach depending on the clinical signs at presentation (see Figure 5 British Thoracic Society (BTS) Guidelines Management of Acute Asthma). Control of chronic background asthma symptoms are also escalated using a stepwise approach however emphasis on the underlying endotype of asthma is crucial to ensure escalating treatment pathways are resulting in control of symptoms. Regular review by asthma specialist services in the community (asthma nurse or General Practitioner (GP)) are recommended by both GINA and BTS guidelines and both highlight the importance of personalised asthma action plans.

Management of acute asthma in children in hospital					
Age 2–5 years			Age >5 years		
ASSESS AND RECORD ASTHMA SEVERITY			ASSESS AND RECORD ASTHMA SEVERITY		
Moderate asthma - SpO₂ ≥92% - No clinical features of severe asthma NB: If a patient has signs and symptoms across categories, always treat according to their most severe features	Acute severe asthma - SpO₂ <92% - Too breathless to talk or eat - Heart rate >140/min - Respiratory rate >40/min - Use of accessory neck muscles	Life-threatening asthma - SpO₂ <92% plus any of: - Silent chest - Poor respiratory effort - Agitation - Confusion - Cyanosis	Moderate asthma - SpO₂ ≥92% - PEF >50% best or predicted - No clinical features of severe asthma NB: If a patient has signs and symptoms across categories, always treat according to their most severe features	Acute severe asthma - SpO₂ <92% - PEF 33–50% best or predicted - Heart rate >125/min - Respiratory rate >30/min - Use of accessory neck muscles	Life-threatening asthma - SpO₂ <92% plus any of: - PEF <33% best or predicted - Silent chest - Poor respiratory effort - Confusion - Cyanosis
First-line treatments			First-line treatments		
Oxygen via face mask/nasal prongs to achieve SpO ₂ 94–98%			Oxygen via face mask/nasal prongs to achieve SpO ₂ 94–98%		
- β₂ bronchodilator: - via spacer ± facemask* - Consider oral prednisolone 20 mg	- β₂ bronchodilator - via nebuliser (preferably oxygen-driven), salbutamol 2.5 mg - or, if nebuliser not available, via spacer* - Oral prednisolone 20 mg or IV hydrocortisone 4 mg/kg if vomiting - Repeat β₂ bronchodilator up to every 20–30 minutes according to response - If poor response add 0.25 mg nebulised ipratropium bromide to every nebulised β₂ bronchodilator every 20 minutes for 1–2 hours	- β₂ bronchodilator with ipratropium - via nebuliser (preferably oxygen-driven), salbutamol 2.5 mg and ipratropium 0.25 mg - Repeat bronchodilators every 20–30 minutes - Oral prednisolone 20 mg or IV hydrocortisone 4 mg/kg if vomiting - Consider adding 150 mg magnesium sulphate to each β₂ bronchodilator/ipratropium nebuliser in first hour	- β₂ bronchodilator: - via spacer* - Oral prednisolone 30–40 mg	- β₂ bronchodilator - via nebuliser (preferably oxygen-driven), salbutamol 5 mg - or, if nebuliser not available, via spacer* - Oral prednisolone 30–40 mg or IV hydrocortisone 4 mg/kg if vomiting - Repeat β₂ bronchodilator up to every 20–30 minutes according to response - If poor response add 0.25 mg nebulised ipratropium bromide to every nebulised β₂ bronchodilator every 20 minutes for 1–2 hours	- β₂ bronchodilator with ipratropium - via nebuliser (preferably oxygen-driven), salbutamol 5 mg and ipratropium 0.25 mg - Repeat bronchodilators every 20–30 minutes - Oral prednisolone 30–40 mg or IV hydrocortisone 4 mg/kg if vomiting - Consider adding 150 mg magnesium sulphate to each β₂ bronchodilator/ipratropium nebuliser in first hour
Reassess within 1 hour			Reassess within 1 hour		
ASSESS RESPONSE TO TREATMENT			ASSESS RESPONSE TO TREATMENT		
Record respiratory rate, heart rate and oxygen saturation every 1–4 hours			Record respiratory rate, heart rate, oxygen saturation and PEF/FEV every 1–4 hours		
Second-line treatments			Second-line treatments		
RESPONDING - Continue bronchodilators 1–4 hours as necessary - Discharge when stable on 4-hourly treatment - Continue prednisolone 20 mg daily until recovery (minimum 3–5 days) At discharge - Ensure stable on 4-hourly inhaled treatment - Review the need for regular treatment and the use of inhaled steroids - Review inhaler technique - Provide a written asthma action plan for treating future attacks - Arrange GP follow up within 48 hours - Arrange hospital asthma clinic follow up in 4–6 weeks	NOT RESPONDING - Continue 20–30 minute nebulisers - Consider chest X-ray and blood gases - Discuss with senior clinician, paediatrician or PICU - Consider admission to HDU/PICU - Consider risks and benefits of: - Bolus IV infusion of magnesium sulphate 40 mg/kg (max 2 g) over 20 minutes - Bolus IV salbutamol 15 micrograms/kg if not already given - Continuous IV salbutamol infusion 1–5 micrograms/kg/min (200 micrograms/ml solution) - IV aminophylline 5 mg/kg loading dose over 20 minutes (omit in those receiving oral theophyllines) followed by continuous infusion 1 mg/kg/hour Assess response before initiating each new treatment		RESPONDING - Continue bronchodilators 1–4 hours as necessary - Discharge when stable on 4-hourly treatment - Continue prednisolone 30–40 mg daily until recovery (minimum 3–5 days) At discharge - Ensure stable on 4-hourly inhaled treatment - Review the need for regular treatment and the use of inhaled steroids - Review inhaler technique - Provide a written asthma action plan for treating future attacks - Arrange GP follow up within 48 hours - Arrange hospital asthma clinic follow up in 4–6 weeks	NOT RESPONDING - Continue 20–30 minute nebulisers - Consider chest X-ray and blood gases - Discuss with senior clinician, paediatrician or PICU - Consider admission to HDU/PICU - Consider risks and benefits of: - Bolus IV infusion of magnesium sulphate 40 mg/kg (max 2 g) over 20 minutes - Bolus IV salbutamol 15 micrograms/kg if not already given - Continuous IV salbutamol infusion 1–5 micrograms/kg/min (200 micrograms/ml solution) - IV aminophylline 5 mg/kg loading dose over 20 minutes (omit in those receiving oral theophyllines) followed by continuous infusion 1 mg/kg/hour Assess response before initiating each new treatment	

* β₂ bronchodilator via spacer given one puff at a time, inhaled separately using tidal breathing; according to response, give another puff every 60 seconds up to a maximum of 10 puffs

Figure 5 British Thoracic Society Guidelines Management of Acute Asthma Reprinted with permission

2.3 Near Fatal Asthma

A near fatal asthma attack is the most severe form of survivable asthma attack. Described in children in 1988, Newcombe et al.(1988) observed a cohort of patients who presented with respiratory failure were at high risk of repeated similar presentations and ‘catastrophic’ outcomes⁷⁶. Newcombe and colleagues state in their conclusion that *‘better understanding might allow such patients to be treated more effectively and even identified before their first episode of respiratory failure’*⁷⁶. Over 30 years later the evidence base on near fatal asthma is growing but it is still not clear how frequently near fatal asthma attacks occur, how best to manage them and if there are risk factors associated with the attacks. Understanding and characterising near fatal asthma is necessary to gain knowledge of why these attacks occur if there are associated risk factors and if interventions can be put in place to prevent them. This section will explore the current evidence base on near fatal asthma, highlight gaps in the literature and explore the challenges that near fatal asthma presents to clinicians and researchers.

2.3.1 Definition

To investigate near fatal asthma, a clear definition of the described attack needs to be used and have distinct clinical features to ensure clinicians use terminology consistently. Within asthma, the severity of an attack is determined by the clinical presentation and physiological observations such as pulse arterial oxygen saturation (SpO₂) (degree of hypoxia) or peak expiratory flow rate (PEFR).

2.3.1.1 *Current definitions for acute asthma severity* *Life threatening asthma*

The BTS guidelines used in the UK identify the most severe form of acute asthma attack as a 'life threatening attack' (See Figure 5 British Thoracic Guidelines Management of Acute Asthma). This is defined by SpO₂ <92% and one of the following: silent chest, poor respiratory effort, agitation, confusion and cyanosis. Although clear features of life threatening asthma are established by this definition, a patient with these features who responds well to initial management and improves quickly would be considered the same severity as a patient who has a respiratory arrest or requires invasive ventilation to manage the asthma attack.

Status Asthmaticus

Status asthmaticus is used by ICD10 as a classification for acute asthma severity. It is referenced in the BTS Guidelines regarding as an indication for ketamine and non invasive ventilation to treat acute asthma but is not defined. Status asthmaticus has been defined as acute severe asthma that does not respond to initial therapy⁷⁷. No specific clinical parameters or treatment parameters are set for this definition.

Critical Asthma Syndrome

Kenyon et al (2018) suggested the term Critical Asthma Syndrome as an umbrella term to describe any child or adult who is high risk for fatal asthma⁷⁷. Critical asthma syndrome includes near fatal asthma, brittle asthma, acute severe asthma, refractory asthma and status asthmaticus. As highlighted by Kenyon et al, (2018) Critical Asthma Syndrome differs from severe asthma and does not include chronic asthma symptoms. As near fatal

asthma is included under the umbrella of critical asthma syndrome, the definition of near fatal asthma is important to differentiate from the other terminology within this group.

2.3.2 Physiological parameters

In near fatal asthma, a patient is likely to be exhausted with evidence of poor gas exchange or respiratory failure (hypercapnia and hypoxia). As discussed in Chapter 2.2.1 hypoxia and hypercapnia are biochemical evidence of respiratory failure in asthma. In a clinical setting, these can be used to indicate the severity of asthma in combination with clinical signs. In near fatal asthma, a patient will be exhausted and at risk of cardiac or respiratory arrest. The patient will experience hypoxia and hypercapnia but the extent of the hypoxaemia and hypercapnia is not yet clearly demarcated. In the UK, the British Thoracic Society guidelines reference $\text{SpO}_2 < 92\%$ (Figure 5) in life threatening asthma in children and adults but there is no limit suggested for near fatal asthma. Globally, one observational study in Japan, has used a SpO_2 threshold of $< 90\%$ in near fatal asthma in adults (> 16 years old) where 27% of included patients presented with $\text{SpO}_2 < 84\%$.

Hypercapnia as a marker of respiratory failure has been used as a defining feature of near fatal asthma, but this is not included in UK guidelines and existing literature presents a range of values when describing near fatal asthma. A systematic review by Alvarez et al (2005) used PaCO_2 45mmHg (kPa 5.9) as a threshold for inclusion⁷⁸ in their review based on American Thoracic Guidelines for Chronic Obstructive Pulmonary Disease (COPD). A PaCO_2 at this value has been recognised as a possible threshold by other

sources in adults^{79,80} but higher thresholds of 50 mmHg (6.6kPa) have also been suggested^{81–83}. The previous lack of clear consensus on PaCO₂ threshold highlights the difficulty in using this as a marker of near fatal asthma but also suggests this should not be a sole category for diagnosis.

An additional consideration in using hypoxaemia and hypercapnia as a definition for near fatal asthma are the abnormal responses to hypoxaemia and hypercapnia observed in some patients with near fatal asthma. In both fatal and near fatal attacks, it has been suggested that patients may have abnormal physiological response to hypoxaemia, therefore presenting later than expected with severe hypercapnia. Some patients do not perceive this physiological state until severe obstruction⁸⁴. Small studies have hypothesised a blunted response to hypoxaemia occurs in adults who have previously experienced a near fatal asthma attack^{85,86} although the validity of this has been debated suggesting there may be a component of anxiety related to previous near fatal attack⁸⁷. This effect has not reproduced in studies with children.

Acidaemia has been noted in other sources to have an association with increased risk of mortality (pH <7.3)⁸⁸. Similarly, to hypercapnia and hypoxaemia, no defined parameters have been set for criteria to define a near fatal asthma attack. A small observational study of children admitted to intensive care for asthma in the Netherlands noted a mean PaCO₂(kPa) of 5.5 and pH 7.37 (lower than values suggested by adult data)⁸⁹. This suggests a lower threshold for admission and highlights the difficulty of using intensive care admission as a definition for near fatal asthma.

2.3.3 Clinical parameters for near fatal asthma

The most common clinical parameter used to identify a near fatal asthma attack in existing research is the level of care provided for the attack. This is most commonly defined by the need for an admission to intensive care^{90–93}. Whilst it is acknowledged that an intensive care admission suggests a severely unwell patient, using this as a definition for a near fatal asthma attack does not clearly demarcate the clinical or physiological characteristics of this patient group as intensive care admission criteria is not universally standardised. Intensive care admission thresholds may differ depending on hospital acuity, geographical location, resources available or clinician experience. Admission may be based on medication use, for example Belessis et al (2004) use intravenous salbutamol requiring intensive care⁹³. In low income countries, using intensive care as a definition for near fatal asthma may not reflect available resources or transfer services to intensive care facilities.

Although intensive care as a definition is not translatable to all hospitals, this cohort of patients does provide insight into the demographics, common treatments and centre specific burden of care required in severe asthma attacks. A large observational study in the United States and Canada observed 1 in 10 children admitted to intensive care with an episode of acute asthma were likely to have a readmission in the next year and 28 – 40% of these would have a readmission to intensive care⁹⁴. This increased risk of readmission has also been observed in Australia⁹³ and in the United States⁹⁵.

Another clinical parameter for near fatal asthma similar to admission to intensive care is the use mechanical ventilation as part of near fatal asthma management. This has been used as a parameter in both adults and children^{96,97}. Previous large surveillance studies using hospital mortality and intubation and mechanical ventilation as a marker of life-threatening asthma noted higher risk of death with intubation and mechanical ventilation ^{97,98}. Respiratory arrest due to acute asthma has also been used to define near fatal asthma in adults⁹⁹.

2.3.4 Near fatal asthma phenotypes

Two distinct phenotypes of attack have been described in near fatal asthma. These have been predominantly observed in adults, but are also recognised in children⁹⁶. Near fatal asthma attacks are most commonly differentiated by the speed of deterioration - slow or rapid onset. Slow deterioration may take several days to eventuate in near fatal asthma attack. Whilst slow onset is considered to have more dominant and persistent airway inflammation, rapid onset attacks occur over a shorter period (1-6 hours) and are hypothesised to have a significant component of severe, acute airway obstruction¹⁰⁰. These two phenotypes have also been labelled as type 1 or type 2 attacks – type 1 which is slow onset with slow response to treatment and type 2 is a rapid deterioration and a rapid response to treatment. Type 1 in adults has an observed clinical picture of mucus plugging, slow response to treatment and histological evidence of eosinophilic airway inflammation¹⁰¹ and is more commonly triggered by viral infection¹⁰⁰. Type 2 has been attributed to

triggers including respiratory allergens, exercise and psychological stress¹⁰², is associated with greater severity of near fatal crisis¹⁰³ and histologically associated with neutrophilic airway infiltration. In adults, whilst type 1 slow deterioration is more commonly observed^{103,104}, rapid onset was seen in 20% of patients with near fatal asthma by Plaza et al (2009). A gender discrepancy has also been observed, where rapid onset is more commonly observed in males and slow onset observed in females^{100,105}. However, the time frame used to define rapid onset of symptoms in adults differs between studies. Plaza et al (2009) found 80% of subject had slow onset but used a rapid onset criteria of <2 hours, whereas those studies using a longer rapid onset time (3 or 6 hours) found fewer patients met rapid onset criteria^{104,106}. A previous surveillance of children with near fatal asthma chose to use 60 mins to define a type 2 rapid onset NFA⁹⁶. Again, this lack of consensus in defining near fatal attacks highlights the difficulty in clearly characterising near fatal asthma attacks and any subgroups.

2.3.5 Inflammatory markers

There is a small body of evidence suggesting there is a correlation in inflammatory markers and near fatal asthma. As described by Arsenault et al¹⁰⁷, the role of 6 inflammatory markers (serum levels of cytokines: Granulocyte-macrophage colony-stimulating factor (GM-CSF), Platelet-derived growth factor-AA (PDGF-AA), Platelet-derived growth factor-AB/BB (PDGF-AB/BB) and Regulated upon Activation, Normal T Cell Expressed and Presumably Secreted (RANTES), Interleukin-20 (IL-20), and Tumour

necrosis factor-Related Apoptosis Inducing Ligand (TRAIL) were up regulated in an intensive care admission compared to no intensive care admission for acute asthma attack.

2.3.6 Near fatal asthma in adults

In adults, near fatal attacks have been associated with poor medication adherence, stable lung function when well and mild -moderate symptom reporting^{102,108}. Adult studies observing near fatal asthma have described common features in adults such as delayed health seeking behaviour, poor adherence to therapy, psychological factors such as anxiety, allergen exposure and previous mechanical ventilation for asthma as common features in near fatal asthma. Ethnicity although reported to effect hospital readmission¹⁰⁹ has not been linked to increased risk of ICU admissions⁹¹ but has noted to have an impact on increased asthma presentation⁹². In contrast to children, adult presentations are more commonly categorised by the phenotypes discussed in 2.3.4.

2.3.7 Near fatal asthma in children

Near fatal asthma has been described in children within the context of intensive care admission for an acute asthma attack^{90–92,95,110,111}. As highlighted in Chapter 2.23 this definition delivers a heterogenous group which is defined by the subjective and variable decision to treat asthma in intensive care and therefore is not standardised. Within intensive care, use of mechanical ventilation is a less subjective level of care and one surveillance study in children used mechanical ventilation as a definition for near fatal asthma⁹⁶.

Age

The age of children included across reported studies varies. Children <1 year of age are generally excluded due to limited number of children with a diagnosis of asthma at this age. The diagnosis of asthma is generally considered more difficult in children under 5 years of age given the frequency of the phenotypically similar yet self resolving viral induced wheeze in this age group. Children with viral induced wheeze develop wheeze related to a viral infection but unlikely to have interval symptoms. Children <6 years however can be diagnosed with asthma and as such the age parameter for near fatal asthma is challenging to define. In an observational study of 141 children admitted to intensive care with asthma in Australia, the majority of patients were aged 1 – 4 years(62%)⁹³.

Previous history of asthma

In children, a near fatal asthma attack can be the initial presentation of asthma. This has been demonstrated by several studies where the first presentation in children with asthma was the near fatal event (17%⁹³, 13%⁹⁵ and 10%⁹³)

Gender

Gender differences in children have been observed in the frequency of near fatal asthma in children in the context of intensive care defined near fatal asthma however these are not consistent across differing study populations. Males were more commonly admitted in two studies in Australia^{90,93} (66% and 57%). Male and female cases of near fatal asthma were observed to be

similar in one previous surveillance study in Germany⁹⁶, America⁹¹ and an earlier study in different region of South Australia.

2.3.8 Near fatal asthma management

The management of near fatal asthma has been primarily described in the context of intensive care admissions in patients requiring mechanical ventilation. The management follows BTS guideline as highlighted by Figure 5. The overall aim of treatment aims to facilitate bronchodilation and effective gas exchange. In the context of a near fatal asthma attack, respiratory failure has occurred or is imminent. This escalation of severity of symptoms may result in invasive ventilation to support the airway in a collapsed or unconscious patient.

Acute management

Oxygen therapy delivered invasively or non-invasively to achieve oxygen saturations of 90- 94%^{100,112,113}. Bronchodilator therapy using B2 agonists can be given intravenously, by nebuliser or by metered dose inhaler(MDI) (if patient is conscious and has ability to coordinate use of MDI). The role of adrenaline (1:1000 given intramuscularly) in near fatal asthma has been suggested as an effective emergency bronchodilator¹¹³ however is not currently included in UK⁴ or GINA¹² guidelines. Nebulised adrenaline is not shown to have superior benefit and is not recommended in BTS guidelines. Anticholinergic nebulisers can also be administered to reduce bronchospasm. Theophylline can be administered in the context of respiratory failure but has significant cardiac side effects and a narrow

therapeutic index¹¹³. Corticosteroids are advised in near fatal asthma given either orally or intravenously. Non-invasive ventilation when administered by an experienced clinician in an intensive care setting has been shown to be safe⁴ however may not be tolerated by patients and should be used with caution. In patients who have required invasive ventilation, controlled hypoventilation with permissive hypercapnia is advised to avoid complications of air trapping and barotrauma¹¹². The use of Extracorporeal Membrane Oxygenation (ECMO) is indicated in children in the UK for treatment of severe asthma¹¹⁴ and has been associated with favourable outcomes¹¹⁵.

Management on discharge from intensive care

On discharge from intensive care, it is recommended patients are referred to or reviewed by a respiratory specialist. Medications should be reviewed, GINA guidelines recommend an inhaled corticosteroid (ICS) -formoterol inhaler in children 12 and older to reduce the risk of future severe attack¹². Asthma education, personalised asthma management plans and regular review from asthma services are emphasised in UK and global guidelines^{4,12}.

2.3.9 Near Fatal Asthma Risk Factors

As expected, literature on near fatal asthma risk factors highlight several of the risk factors to the summarised guidelines above. Research to date has not yet determined if specific risk factors are associated with a near fatal asthma attack. Risk factors for asthma mortality include previous intensive

care admission and length of hospital stay^{88,98,116}. Table 2 highlights risk factors identified for severe or fatal asthma attack by UK and GINA guidelines. As discussed in sections 2.36 and 2.37 in near fatal asthma, the definition of intensive care is subjective and many of the risk factors stated for near fatal asthma are based on readmission to intensive care. Studies supporting these risk factors are from high income countries therefore may not be applicable to global populations.

Table 2.2 Risk factors identified for severe or fatal asthma attack

BTS Guidelines ⁴	GINA Guidelines ¹²
Pre school • Age of presentation • Male (prepubertal) • Atopy • Abnormal Lung function	• Uncontrolled asthma • Medications: ICS not prescribed; poor adherence; incorrect inhaler technique; high SABA use (with increased mortality if >1x200-dose canister/month)
School age children • High: previous attacks/persistent symptoms • Moderate: suboptimal drug regime/comorbid atopic allergic disease/low-income family/vitamin D Deficiency • Slight: Younger age/tobacco smoke/obesity/low parental education	• Comorbidities: obesity; chronic rhinosinusitis; gastro-oesophageal reflux disease; confirmed food allergy; anxiety; depression; pregnancy • Exposures: smoking; allergen exposure if sensitized; air pollution
Adults (future attacks) • High: Previous history of asthma attacks • Moderate: Poor control • Slight: Older age/female/reduced lung function/obesity/smoking/depression	• Setting: major socioeconomic problems • Lung function: low FEV1

Gender

As discussed in section 2.3.7, some studies have observed male children are more likely to present with near fatal asthma. This has not been evidenced in older children or adults despite asthma incidence increasing in post pubertal females (Section 2.1.2).

Ethnicity

Although asthma presentations in America are more common in non-white children¹¹⁷, current evidence suggests there is not an increased frequency in near fatal asthma (defined by intensive care admission) in children^{91,118}. This may be reflective of health care access and socioeconomic disparities in USA. There is however evidence from a large observational which has shown an increased risk of readmission in ethnic minority groups to intensive care with asthma in children in USA¹¹⁹.

Social Deprivation

In the UK, an observation study noted an increase in admissions to paediatric intensive care from children from areas of higher deprivation¹²⁰. This study evaluated the socioeconomic status of children admitted to PICU (0 - 14 years) with a primary diagnosis of asthma from 1st April 2006 to 31st March 2013. English Index of Multiple Deprivation (EIMD) (2010) was used to evidence socio economic status. EIMD quintile 1 (EIMD1) represented the least deprived and EIMD5 the most deprived neighbourhood.

Environmental exposures

In line with risk factors for asthma, concurrent allergies, smoking environments were considered as risk factors by Bosch et al¹¹¹.

Weather

Seasonal trends for severe asthma admissions were noted in children with a previous UK surveillance study of asthma admissions noted a peak in mortality in spring and summer months despite increase in admissions in September ¹¹⁶.

Outdoor Air pollution

There is a growing concern that outdoor air pollution may contribute to both the increase in asthma prevalence and is it well recognised as trigger for asthma attack. It is not clear if high levels of outdoor air pollution are associated with near fatal asthma attacks. This is explored in chapter 3 (systematic review).

Previous near fatal attack

A previous admission with near fatal asthma (defined by ICU admission) is consistently observed as a risk factor for repeated or subsequent readmissions with asthma to intensive care. This has been observed in both adults and children. Observations by Plaza et al (2017) have proposed a cluster analysis suggested three clusters of near fatal asthma phenotype in adults⁸⁰. These three groups identify increased medication use short acting beta 2 agonist¹¹², history of previous hospital¹²¹ or ICU admissions and mechanical ventilation^{112,121} as common themes in admission to intensive care with asthma. Less severe asthma attacks managed in the emergency department are not observed increase near fatal asthma presentation¹²¹. In a 10 year observational study in children age 2 -18 years, Carroll et al (2010) observed a readmission rate of 11% to intensive care in children with a previous near fatal asthma attack (defined by intensive care admission) with an increased risk (OR 2.26 CI (1.05 – 4.88)) in children who were overweight

(weight for age >95% 1977 National Centre for Health Statistics growth chart) and had public health insurance 3.58 (1.50–8.53)¹²². These results are from a single centre in the USA and should be interpreted with context. They are based on a single centre admission criteria to intensive care and where health care resource utilisation may depend on individual health care insurance. In children, the time frame for readmission appears to range between 12 months and 18 months after initial admission to intensive care suggesting in children there may be a high risk period for readmission^{122, 123}. Although readmission to intensive care may be a useful indicator for a repeated severe attack the use of intensive care as a definition for near fatal asthma must be considered with an awareness that admission criteria may differ between hospitals.

2.4 Identifying cases by asthma coding

The National Respiratory Audit Programme (NRAP) and the National Review of Asthma Deaths (NRAD) report required patients with asthma to be identified from medical records using ICD codes. The ICD codes were introduced by the World Health Organization to create a common language for recording, monitoring and reporting diseased world wide¹²⁴. For respiratory illnesses, ICD 10 codes J00 – J99 are used to classify ‘disorders of the respiratory system’. Within this, codes are sub categorised to include the most common respiratory illnesses. For example, asthma is coded within the subsection ‘J45 – J46’ (see Box 3). Whilst these codes are globally recognised and used by electronic health care records, the system relies on the clinician who is reviewing a patient applying the correct code to the

condition. ICD 10 codes are purposefully broad to allow global translation but reduces the granularity of disease description.

In addition to ICD codes, electronic health care databases may have unique medical codes to enable data categorisation within their internal organisational system or database. For example, within the NHS in the UK, different GP practices may choose to use differing IT systems depending on cost or licensing agreement, each of these will use specific medical codes for data entry. Two different GP practices using two different systems may have differing codes for asthma. This can also apply to hospital medical record storage or electronic health records. At a local level, these specific medical codes are created primarily for categorisation and storage of medical data therefore research access and data extraction does not always reflect research objectives¹²⁵.

J45 Asthma

Excl.:

acute severe asthma ([J46](#))
 chronic asthmatic (obstructive) bronchitis ([J44.-](#))
 chronic obstructive asthma ([J44.-](#))
 eosinophilic asthma ([J82](#))
 lung diseases due to external agents ([J60-J70](#))
 status asthmaticus ([J46](#))

2.5.2 J45.0 Predominantly allergic asthma

Allergic:

- Bronchitis NOS
- Rhinitis with asthma

Atopic asthma

Extrinsic allergic asthma

Hay fever with asthma

J45.1 Nonallergic asthma

Idiosyncratic asthma

Intrinsic nonallergic asthma

J45.8 Mixed asthma

Combination of conditions listed in J45.0 and J45.1

J45.9 Asthma, unspecified

Asthmatic bronchitis NOS

Late-onset asthma

J45 Status asthmatics

Incl.:

Acute severe asthma

*NOS – not otherwise specified

In the NHS, Read codes have been historically used in primary care to categorise different medical conditions and symptoms^{126,127} and used to monitor disease epidemiology, resources allocation and targets for disease management. However, as iterations of an illness present, more codes are

created. In addition, these codes may not be translated to codes used within primary health care systems and as a result, a wealth of codes for a specific illness can exist. A systematic review by MacRae et al (2022) found over 200 Read codes exist for asthma¹²⁵ in a search of UK databases. This plethora of codes creates a layer of complexity for clinicians selecting the correct code when seeing a patient. Overlapping codes can lead to inaccuracies within the data and some databases may only supply the most commonly used medical codes. A patient with a rare condition may not have a corresponding code. Their disease data is then not recorded or reflected in the local dataset.

Currently in the UK there is no read code to represent near fatal or fatal asthma¹²⁸. A patient who is admitted to hospital with a mild asthma attack requiring minimal treatment can be coded in the same way as a patient with a severe or near fatal or fatal asthma attack. Without a specific and defined medical code, electronic health records cannot be used to find near fatal asthma cases in the UK without clinician review of each case. The NRAD report and NRAP dataset demonstrate there is a willingness from clinicians to engage in data entry for asthma however both of these initiatives relied on data coding which unfortunately can be inaccurate¹²⁹.

2.5 UK Health Care Data

Another key aspect of obtaining data from health records in the UK, is the structure of medical records and electronic health records. In the UK, healthcare is primarily delivered by the National Health Service (NHS). The NHS is divided into national sections (Scotland, England, Wales, and

Northern Ireland) and then further sub divided into NHS trusts in England and Wales, and in Scotland and Northern Ireland, Health Boards. Each NHS trust is allocated governmental monetary resources to allow service provision, planning and delivery relevant to the service need and population in each geographical region. This is relevant for accessing health care data as each NHS trust can currently choose how medical records and patient data is stored depending on cost, usability or population demographic¹³⁰. Plans are in proposal for all trusts in England and Wales to have EHR by March 2025¹³¹. Each local health care authority may rely on scanning paper notes or electronic medical note systems. As a result, patients who are transferred between different hospitals or within hospital departments may have differing mediums to documentation of medical notes. Within any one hospital there may be different health record systems for emergency, ward and critical care areas. For example, patient notes on a ward may be paper based notes but may become electronic if transferred to critical care. Figure 6 below highlights the different methods of documentation that could be used in a child or young person presenting with near fatal asthma.

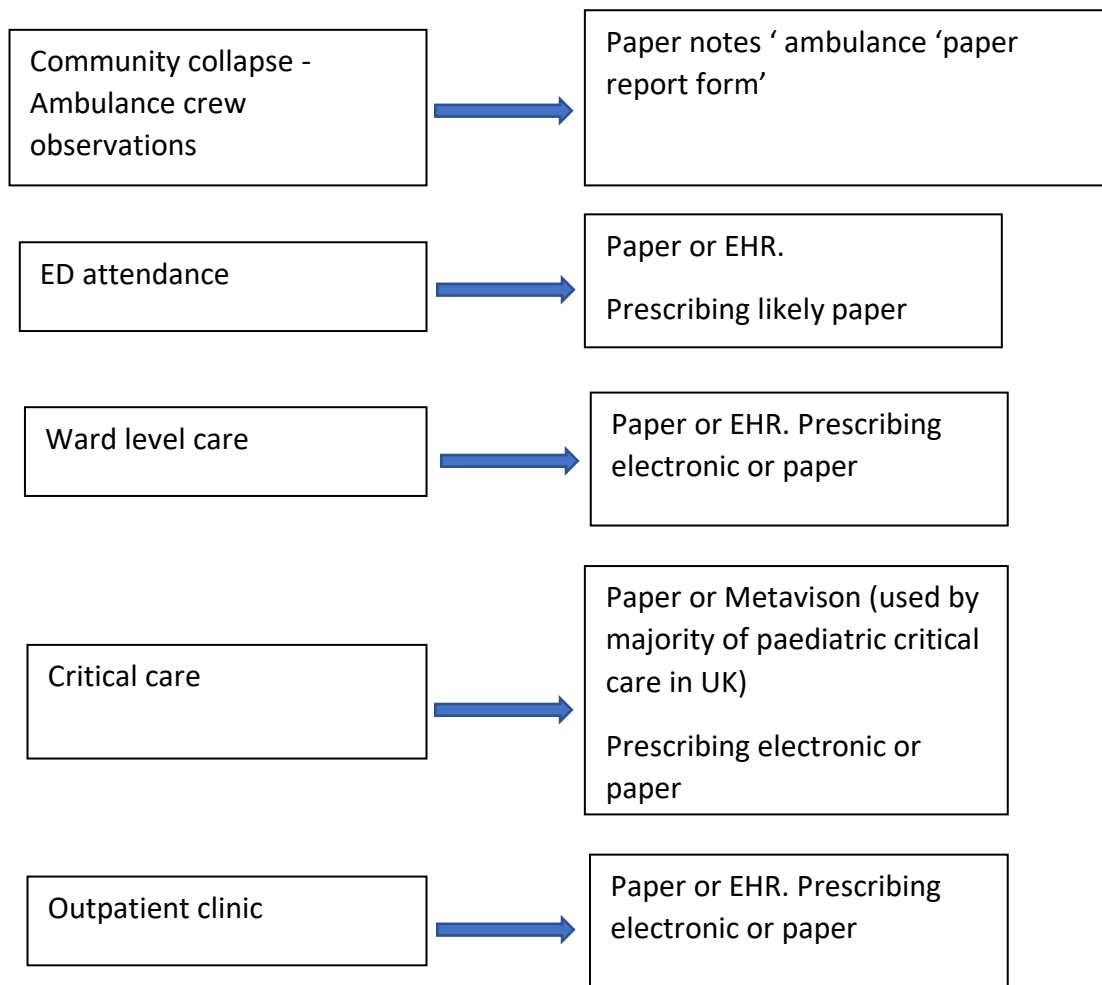


Figure 6 Types of Documentation

A wealth of information is therefore stored and available in the UK however is not available in a standardised and unified platform¹³² and there is a lack of overarching policy across the UK but also within each individual nation. For example, Scotland has population of 5 million has 14 health Boards each with an independent IT policy. Primary health care electronic health records are less fragmented but often do not align with hospital records therefore a patient presenting to the GP with extensive notes regarding near fatal asthma cannot be visualised by the receiving hospital team.

It is important to recognise that surveillance data therefore may be incomplete, not standardised across health care trusts and depending on the method of recording, may contain erroneous measurements. This is in contrast to data obtained in a research or trial environment which will use a standardised protocol or methodology for all participants to avoid reporting bias.

2.5.1 Surveillance Data

Surveillance data in health care describes any data which is routinely and continuously collected by health information systems in a population. It facilitates measurement and analysis of outcomes related to health at a specific time point or over a period of time. Surveillance data can be used to determine disease prevalence, estimate service use or monitor how specific conditions are treated¹³³ and the disease outcome. Surveillance data can be gathered from existing electronic health records or targeted - gathered by health care professionals to answer a specific research question.

Surveillance data can be active or passive. Active surveillance involves researchers contacting data sources (such as clinicians) and engaging them to report data. Passive surveillance depends on data reporting sources engaging with a reporting system unprompted¹³⁴. Data collection methods in disease surveillance can vary depending on disease demographics, data collection resources and relevant population. Examples of data collection methods are listed below¹³⁴:

1. Use of vital statistics e.g., number of weekly deaths
2. Syndromic Surveillance – used for early detection of epidemics

3. Disease notification
4. Health care provider networks
5. Disease registries
6. Laboratory surveillance
7. Sentinel surveillance – data routinely collected from limited number of sentinel sites
8. Population health surveys
9. Healthcare information systems

2.5.2 Limitations of surveillance data

Although surveillance data may be rich in detail and provide large data sets, inconsistencies in the data should be recognised, specifically when using disease notification as a method of data collection. As discussed in their chapter on Public Health Surveillance, Gilbert and Cliff 2016 describe a 'succession of events' is required for disease notification to occur. A patient must seek healthcare, the clinician must recognise the condition under surveillance and then the clinician must report the case¹³⁴. Reporting bias may exist by either erroneous case reporting or lack of case reporting. However, the use of surveillance data allows a real-time 'snapshot' of the frequency of a condition, it can be used to obtain detailed, relevant clinical information at a population level.

2.5.3 Considerations for data linkage within surveillance data

Once a report has been confirmed within a surveillance study, data linkage may be applied to provide context on the report. For example, if a child was noted to have a rhinovirus infection during a near fatal attack, it is interesting to consider if within the population, high levels of rhinovirus infection were

noted by laboratory reports within a similar time period. Data linkage must in the context of public health data dissemination must remain anonymised unless consent has been given to allow publication of personal and special category data. To respect the confidential nature of data linkage, within the UK, geographical data release boundaries can be applied to allow appropriate pseudonymisation of public health data.

2.5.4 Geographical considerations

In the UK, nationwide information on exposures such as weather, air pollution and viral data are publicly available but released within geographical boundaries. It is important to understand the different population and geographical boundaries that were applied to each division.

2.5.4.1 *Postcodes*

An individual postcode corresponds to a specific geographical location. Information gained regarding air pollution and weather corresponding to postcode data (modelled data in the absences of personal monitoring device) will provide an accurate measure of potential exposure. Postcodes are comprised of sections to allow geographical location to be determined:

- 1. Postcode area** (i.e., EH) 124 in the UK
- 2. Postcode district** (i.e., EH16) 2979 in the UK

Subdivided to -

Postcode sector (i.e., EH16 4) 11323 in the UK

Unit Postcode (i.e., EH16 4TJ) 1.8 million in UK

Postcode areas will differ in size and population. Area postcodes also vary in number of districts (Shetland – 3 districts, Northern Ireland 84¹³⁵). Due to this huge variation, it was recognised that area postcode would not provide granularity on environmental exposures related to the near fatal asthma attack. It was important for this study that area and district postcode data were included in the patient demographics. Large postcode areas would not be reflective of weather exposures and outdoor air pollution exposure.

2.5.4.2 *Output areas*

Within the NHS, postcode areas and districts are not used to map statistical data. The NHS use two levels of geographical hierarchy called Output Areas. Output areas were created in 2001 and reflect data gathered during national census and are based on number of households in a geographical area.

Lower Layer Super Output Area (LSOA) Usually 4 -5 output areas, 400 –

1200 households. Population 1000 - 3000

Middle Layer Super Output Areas

Comprised of 4 -5 LSOA's, approx. 2000 – 6000 households, population 5000 – 15000¹³⁶

Social deprivation indices are Wales, Northern Ireland and England are measured over Super Output Areas and in Scotland over data zones.

2.5.4.3 *Local authorities*

Local authorities are divided depending on resources. Upper tier local authorities or counties exist in England and also are further subdivided into districts/boroughs/city councils or lower tier local authorities. Wales and

Scotland do not have upper tier local authorities and are only divided into lower tier local authorities.

2.5.5 Deprivation indices

Deprivation describes a lack in resources. Indices of deprivation have been used throughout England since 1970¹³⁷. Deprivation indices are used to identify areas of need and subsequently allocate resources and funding¹³⁸. It is useful to note that deprivation indices are applicable to a geographical area and not an individual or household. There are concerns that area based measures may under-represent rural deprivation¹³⁹. Health inequalities are evident correlating to deprivation indices with a reduction in life expectancy and increase in disability in areas of higher deprivation¹⁴⁰. Relating to paediatric asthma, Mukherjee et al (2022) noted children from areas with high deprivation represented the majority of asthma admissions to intensive care¹²⁰.

Deprivation indices differ throughout the UK and Ireland.

Scottish – Index of Multiple Deprivation¹⁴¹

Rank from 1st to 6976th (least deprived)

7 Domains: income, employment, education, health, access to services, crime, housing

Measured over data zones. Approx. 700 – 800 people per data zone.

England – English Indices of Deprivation¹³⁷

Rank from 1st to 32844th (least deprived)

Measured over lower-layer super output areas in England with an average population 1500. 7 Domains: income, employment, education, health, crime, barriers to housing and services and living environment.

Wales - Welsh Multiple Index of Deprivation¹⁴².

Rank 1st to 1909th (least deprived)

Measured over lower layer super output areas. Lower layer super output is a statistical geography which represents a small area with population approx. 1600 people

8 Domains: income, employment, education, health, access to services, housing, community safety, physical environment

Northern Ireland – Northern Ireland Multiple Deprivation Measure¹⁴³

Rank 1st to 890th (least deprived)

Measured over Super Output Areas. Average population 2100 people.

7 Domains: income, employment, education, health and disability, access to services, living environment, crime.

2.5.6 UK Meteorological data

UK meteorological data is measured through satellite observation, ground level observations (or weather stations) and predicted by computerised modelling. Weather stations or land observation stations are located throughout the UK and are approximately 40 km apart¹⁴⁴. Combination of observed and measured data can allow predicted forecasts but also accurate measurement of meteorological patterns in a specific geographical area for

example a postcode. Potential sources of UK weather data are monitored by differing geographical constrictions. Table 3 highlights the different weather sources available in the UK. Figure 7 demonstrates the position of land observation stations in the UK.



Figure 7 UK Land Observation Stations
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Table 2.3 Possible Sources for UK Meteorological Data

Met Office Historic Monthly Data	Temp min and max Air frost Rainfall Sunshine	UK	Data up to 2003 publicly accessible, thereafter unclear if detailed data available NB can apply for task that will take up to 30 mins for free Freely available – monthly averages, specific stations
CEDA Archive MIDAS hourly weather observations	Air temp Relative humidity Mean wind speed Atmospheric Pressure	Large repository	Needs application Unclear what format is provided Could apply on behalf of HIC, freely available data
Met Office HADUK GRID overview 1kmx1km GRID observations	Air temp Relative humidity Mean wind speed Atmospheric Pressure	Online available 2021	Estimated with only certain weather stations around the UK. Unclear GRID and observations need to be worked out, possible to put into R HIC may have access to this
Google weather Used underground weather	Temp min and max Humidity Wind speed	Multiple UK Stations (need to check locations) Put in postcode – can get retrospective data easily and quickly No permissions required	Need to check validity - unclear source -> seems to be from airport stations

2.6 British Paediatric Surveillance Unit Study

The British Paediatric Surveillance Unit is a well-established reporting system in the UK used by paediatricians to gather information on rare paediatric conditions. The BPSU is also recognised by the International Network of Paediatric Surveillance Units (INoPSU). The British Paediatric Surveillance Unit has undertaken over 120 projects in the UK and Republic of Ireland since its origin in 1985. Rare conditions have been defined by the BPSU a frequency of <360 cases per year. Notification is undertaken by registered members of the BPSU who are consultant paediatricians and are members of the Royal College of Paediatrics (UK) or the Royal College of Physicians of Ireland, Faculty of Paediatrics. Each month, a list of predefined rare paediatric conditions will be circulated to the BPSU clinician mailing list. A clinician will respond 'yes' or 'no' depending on whether or not they have encountered a case. If the respondent answers yes, a questionnaire is sent from the research team to the clinician to gain observational information from the medical notes regarding that specific condition. Clinical information regarding the patient's presentation and management is collected retrospectively by the clinician who reported the case from the patient notes and returns to the researcher for analysis. Patient consent to data acquisition is not required in as BPSU studies are observational only, no intervention or change in management is required. The BPSU also recognises in rare conditions, a small number of withdrawals may impact overall observational descriptive data. Study opt out is available for any patients who wish their data to not be collected as part of routine healthcare data¹⁴⁵.

In 2020 the BPSU reported an 88% return rate on questionnaires from 4277 clinicians signed up to the BPSU¹⁴⁶. This suggests a wide coverage of paediatric clinicians throughout the UK and Ireland (estimated 3977 whole time equivalent paediatric consultants in the UK in 2019)¹⁴⁷. This method of collection information on rare paediatric conditions enabled research on conditions such as Paediatric Multisystem Inflammatory Syndrome¹⁴⁸, Herpes Simplex Virus in infants under 90 days of age¹⁴⁹ and button battery ingestion¹⁵⁰.

2.6.1 Epidemiology

British Paediatric Surveillance Unit studies are conducted over a defined time period. In that time, any new cases of the condition are reported. Existing case numbers are not included in surveillance. As surveillance is nationwide, there is no designated study population for the time period, population data is dynamic as people leave or enter the defined population – people may move countries, enter the country, death or birth may occur. Incidence calculated the number of new cases in a defined population. In a BPSU study, if a lower and upper age limit is defined, the population throughout the study period will not reflect the true changing and dynamic nature of even if an estimate from a census is given, this will only reflect the population number at a specific time point, not throughout the study. Prevalence explains the number of cases of a disease or illness existing in a population at a specific time point. A BPSU study with a defined age range will inform the case frequency of a disease/illness during the specified surveillance period.

2.7 General Data Protection Regulation

Patient consent is not required for all types of surveillance data. To ensure a study enables clinicians to access and provide researchers with the relevant surveillance data, key principles of General Data Protection Regulation (GDPR) were explored for this study. An understanding of GDPR facilitated insight for ethical approval and key aspects of the study to be approved by national ethics and permissions committees throughout the UK.

2.7.1 Personal data

Data can be categorised into personal data and further subdivided into special categories of personal data. Personal data can be directly identifiable or indirectly identifiable. Directly identifiable data includes a person's name with an age, address or phone number whereas indirectly identifiable could identify the individual in combination with relevant data from another source for example an internet search.

2.7.2 Special categories of personal data

Special categories of personal data are deemed as sensitive and therefore require additional permissions when obtained for research. In the UK special category data are listed below¹⁵¹:

- personal data revealing racial or ethnic origin;
- personal data revealing political opinions;
- personal data revealing religious or philosophical beliefs;
- personal data revealing trade union membership;
- genetic data;
- biometric data (where used for identification purposes);
- data concerning health;

- data concerning a person's sex life; and
- data concerning a person's sexual orientation.

There are circumstances which legally allow access to special categories of personal data by an external body¹⁵²:

- 1) Consent
- 2) Necessary for employment
- 3) Necessary to protect vital interests
- 4) Processing by not for profit bodies or associations
- 5) Personal data manifestly made public
- 6) Establishment, defence or exercise of legal claims
- 7) Substantial public interest
- 8) Public health
- 9) Archive, statistical or research purposes

2.8 Previous fatal and near fatal asthma data collection in children and young people

2.8.1 Fatal Asthma

In 2019 asthma was related to 455000 deaths globally¹⁵³. The UK has one of the highest death rates from asthma in Europe¹⁵⁴. In 2021, Office of National Statistics (ONS) published data from England and Wales showing in children <19 years old 12 deaths were coded as 'asthma' or 'status asthmaticus'. As discussed in the previous section, acute asthma management is standardised in national and global guidelines, despite this asthma deaths continue to rise¹⁵⁵. It has been suggested that learning from near fatal asthma attacks can provide further information on fatal asthma¹⁵⁶.

In the UK, previous asthma surveillance has been collected and analysed using electronic health records (EHR). Using medical codes for asthma and conditions related to asthma, electronic health records can be interrogated for asthma related health care events. These can range from general practitioner (GP) attendances to hospital admissions and cases of fatal asthma. In this section I will highlight two significant national surveillance datasets on asthma.

2.8.1.1 *National Review of Asthma Deaths*

In 2014, the Healthcare Quality Improvement Partnership (HQIP) commissioned the Royal College of Physicians (RCP) to provide a detailed report on asthma deaths in the UK. This was the National Review of Asthma Deaths (NRAD). Using data from the Office of National Statistics (ONS), Northern Ireland Statistics and Research Agency (NISRA) and National Records of Scotland (NRS), deaths from asthma identified on medical certificates (coded using International Statistical Classification of Diseases and Related Health Problems 10th revision (ICD-10) were examined by an expert panel of respiratory clinicians and allied health professionals. Over 3000 cases of asthma were identified by ICD10 code on death certificates during the 11 month review period (February 2012 to January 2013). After cases with multiple comorbidities due to age were excluded, 900 cases were identified for review by the NRAD panel. Clinicians directly involved with the care of each case were asked to submit medical records, detailed care summary and prescription histories to the NRAD clinical lead for review. With panel support, the clinical lead excluded cases that had incomplete data requests, were incorrectly coded or were not asthma related deaths. In total,

there were 195 deaths were examined for the report by the expert panel in the UK, 28 of these were in children¹⁰.

Each case was scrutinised by the NRAD panel. Patient medical history, GP consultations, hospital presentations and clinical features of the fatal attack were examined by the panel. Environmental exposures such as weather and allergens were reviewed at the time of each event as well as exposure to household tobacco smoke. Air pollution levels in the relevant postcode 6 days before and on the day of the event were also taken into account.

The report concluded that almost 45% of the patients fatal asthma attacks could have been prevented¹⁵⁷. The standard of care for children and young people included in the report was felt to be inadequate in 13 of 28 cases, and doctors and nurses failed to recognise and act on risk factors for fatal asthma¹⁰.

This detailed report allowed key insights into the care and background of patients who died of an asthma attack. Near fatal asthma patients may also provide a key insight into fatal asthma attacks. Recognised by Newcombe et al (1988), near fatal asthma patients have an increased risk of fatal asthma⁷⁶. This pattern has been recognised by many clinicians and researchers and consistently reported in literature¹⁵⁵. While it is recognised that patients with near fatal asthma may be a separate entity to patients with fatal asthma¹²¹, it is useful to consider if this group has similar features compared to those identified in the NRAD report. Of the 28 children examined by the NRAD report, 18 died between March and September. Previous evidence based on

a review of asthma deaths in children in the South East of England¹⁵⁹ and in a review of asthma deaths in Danish children (age 1 – 19 years)¹⁶⁰ follows this seasonal pattern.

Air pollution data was not available for the full duration of the study period in the NRAD report therefore exposure time around each attack could not be examined. In the UK, a landmark case has attributed high levels of air pollution were significant in the death of a child with asthma¹⁶¹, this questions if near fatal and fatal asthma are associated with high levels of outdoor air pollution in children.

The NRAD report highlights the vital need to address the care of asthma in the UK. This report has provided a key opportunity to find those most at risk of fatal asthma and intervene. The NRAD methodology however also demonstrates the difficulties in applying broad ICD 10 codes to large datasets to identify patients with specific disease outcomes. From 900 patients screened by the NRAD clinical lead, 624 were excluded because medical records were not returned or it was unlikely the patient had asthma or death was related to asthma. After detailed panel review, 45 of 276 patients were felt not to have asthma or insufficient information was available on the case. This highlights the potential inaccuracy of using medical codes to identify a specific condition using electronic health records. Compared to adults, fewer children were identified by the NRAD report, (167 adults, 28 children). The number of cases excluded were not reported as children or

adults, if even a small proportion were children, the missing data may have impacted the results.

2.8.2 National Respiratory Audit Programme (NRAP) in children

Previously known as National Asthma and COPD Audit Programme (NACAP) the NRAP programme is a voluntary data collection system open to all hospitals in the UK (Northern Ireland excluded). In England 114/154 hospitals are involved in NRAP, 2/14 hospitals in Scotland and 7/13 hospitals are involved in Wales. Twenty three other hospitals took part in NRAP but were excluded from analysis due to incomplete data sets.

The NRAP reporting for children and young people requires clinicians to enter data about every child admitted to hospital due to an asthma attack. Similar to the methodology of NRAD, patients were identified using ICD 10 codes for asthma however in contrast, clinicians directly involved in patient care entered details of the asthma admission into the NRAP database. The information gathered includes hospital arrival information (age, gender, transport to hospital), home smoking status acute observations (heart rate, oxygen saturations, peak flow), acute treatment (seniority grade of clinician who saw the patient, medication given) and discharge information (personalised asthma plan, emergency steroids and follow up arrangements¹⁶²).

Seventy eight percent of eligible hospitals initially engaged with the report with over 8000 patient details entered by clinicians into the dataset. However, only 66% of eligible hospitals submitted a full organisation audit record. It is

not clear why hospitals did not submit full records or if non submitting hospitals had common geographical regions, ethnicities or serviced areas of high or low deprivation. Despite the large number of patients captured by the report, the data gaps are potentially significant. Clinician input in two thirds of eligible hospitals shows enthusiasm in audit participation but as with NRAD is liable to potential data gaps. Additionally, as demonstrated by NRAD the use of ICD 10 codes to identify patients is not always accurate. Without this data, it is difficult to accurately assess the services provided to patients with asthma throughout the UK.

2.8.3 Near Fatal Asthma Surveillance

Almost 30 years ago, surveillance of fatal and near fatal asthma in children and young people was carried out in Germany by Schmitz et al (2000) (1st January 1996 - 31st December 1998⁹⁶). This surveillance study utilised a similar methodology to the BPSU. A monthly, postal questionnaire was sent to paediatricians throughout Germany to survey fatal and near fatal asthma attacks in children. The researchers categorised near fatal attacks and fatal attacks as death or mechanical ventilation (near-fatal attacks) due to symptomatic respiratory obstruction caused by chronic asthma, recurrent wheezy bronchitis or a first asthma attack in children of <16 years⁹⁶. This 3 year surveillance study observed 16 cases of fatal asthma and 45 cases of near fatal asthma. Patients were categorised into Type 1 (slow onset, over hours and to several days) and Type 2 (sudden onset, within one hour). The key finding of the paper observed a high proportion of type 1 attacks observed in near fatal asthma (36/42 attacks). The study included children age 0 – 16 years, the median age for near fatal asthma was 9.6 years.

Twenty one children (47%) presenting with near fatal asthma were reported to have respiratory infections. Male and female cases were similar (22 male, 23 female) in the near fatal asthma group. The study compared the presentation of fatal asthma compared to near fatal asthma and specifically addressed the use of short acting Beta 2 agonist (SABA) treatment prescribed prior to the attack. Both groups were noted to have a high proportion of patients prescribed SABA treatment (fatal attack 63% and near fatal 47%). In both fatal and near fatal asthma, the number of cases who were previously known to a specialised paediatric asthma service was low (2/16 in fatal asthma and 12/45 in near fatal asthma).

This surveillance study on near fatal and fatal asthma in children provides a useful insight on near fatal asthma in children and young people. The return rate of cards in response to the surveillance was very high (94 – 96%) indicating a high level of engagement with the surveillance. However, the authors comment that underreporting may have occurred specifically in relation to reporting of asthma deaths. National statistics reported 31 deaths attributed to asthma during the surveillance period, only 16 were reported in the study. Other limitations of the study and areas of further interest to be explored include data on the characteristics of the patients, inpatient treatment and discharge. The study included an age range of 0 – 16 years and in the near fatal asthma group 16 of 45 children were >0 and <5. As previously discussed it is challenging to differentiate other similar wheezing disorders from asthma in this age group. Although the study states ethnicity data was collected this is not presented in the final results. The definition

used for near fatal asthma was based on invasive ventilation however a clinical threshold for invasive ventilation was not stated. Compliance to medication is presented but it was not stated how this was measured. Environmental risk factors such as air pollution, atopic triggers and seasonal viral illnesses were not addressed. Duration of treatment, hospital stay or discharge outcomes data was not collected. The study concludes that although there are some similar characteristics between fatal and near fatal asthma, the high number of type 1 (slow onset) cases observed in near fatal asthma considers whether this is a separate entity to fatal asthma.

The German surveillance study performed by T. Schmitz et al (2000) invites us to re-examine and update the surveillance of near fatal asthma attacks in children and young people and explore these attacks in more detail.

Compared to Germany, data from 2000 – 2010 suggests the 10 year asthma mortality in the UK is now significantly higher⁹ (see figure 9 below). The data below uses the asthma mortality rate over a 10 year period occurring after the German surveillance (1996 – 1998). The graph demonstrates that the 10 year period post surveillance, asthma mortality in the UK (age 0 – 14 years) was significantly higher than Germany.

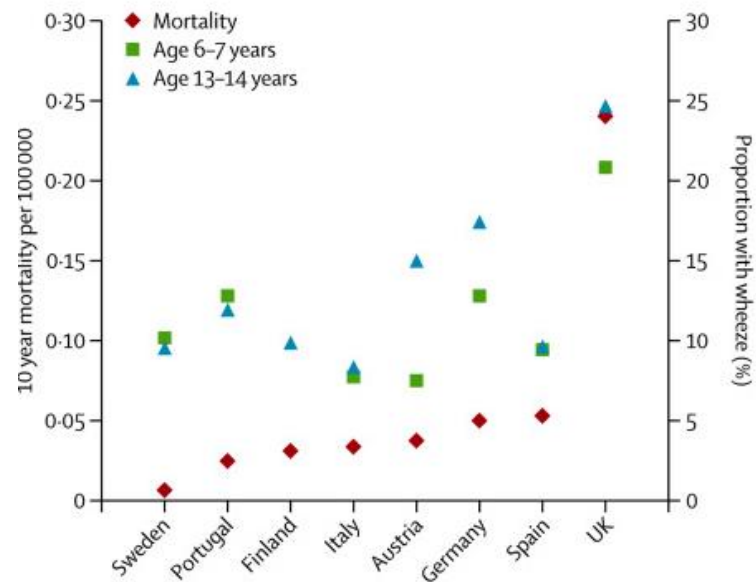


Figure 8 Asthma Mortality rate in children age 0 - 14 years and proportion with wheeze in eight European countries⁹. Reprinted with permission

The heterogenous nature of asthma and the wide spectrum of clinical presentation means that to explore near fatal asthma in children, a detailed characterisation of each case must be examined to determine if there are common themes observed for near fatal asthma cases. As demonstrated by narrative case 2 in chapter 1, the impact of environmental factors such as outdoor air pollution are now key considerations in the presentation of asthma attacks and need to be explored in greater detail when considering near fatal asthma attacks in children and young people.

3 Chapter 3: Systematic Review

In chapter 3 I will explore if other exposures specifically air pollution should be considered in association with fatal and near fatal asthma attacks.

As discussed in chapter 2, there are many factors which can impact a near fatal asthma attack. I was particularly interested in the narrative case presented in chapter 1 where outdoor air pollution had significantly contributed to the fatal attack of a 9 year old girl. In subsequent evaluation of relevant literature, I found several articles exploring outdoor air pollution and asthma exacerbations. I specifically wanted to focus a literature review on outdoor air pollution and near fatal and fatal attacks in children and therefore chose to complete a systematic review on this topic. I sought advice from the lead academic support librarian at the University of Edinburgh Marshall Dozier and after completing the course “Planning and Conducting a Systematic Review” through the Edinburgh Clinical Research Facility in October 2022, decided a systematic review would be the appropriate choice of literature review to explore this specific question. With assistance from Dr Bohee Lee, I constructed a search strategy and search results were screened by myself and Dr Kathryn Ferris. I composed the manuscript which was reviewed and edited by Professor Steve Cunningham, Professor Hilary Pinnock and Professor Jonathan Grigg.

This systematic review has now been peer reviewed and published.

Varghese D, Ferris K, Lee B, Grigg J, Pinnock H, Cunningham S. Outdoor air pollution and near-fatal/fatal asthma attacks in children: A systematic review. *Pediatr Pulmonol.* 2024 May;59(5):1196-1206. doi: 10.1002/ppul.26932. Epub 2024 Mar 13. PMID: 38477643.¹⁶³

3.1 Abstract

Background: Globally, observational studies have demonstrated an association between high levels of air pollution and asthma attacks in children. It remains unclear whether and to what extent exposure may be associated with increased near fatal/fatal attacks.

Objective: To systematically review the evidence for an association between ambient outdoor air pollution and fatal and/or near fatal asthma (NFA).

Methods: Following Cochrane methodology, we searched MEDLINE, EMBASE, Web of Science, Scopus and Open Grey electronic databases for studies reporting the association of fatal/NFA and air pollution (Particulate Matter (PM), sulphur dioxide, nitrogen dioxide, black carbon and ozone(O₃)) in children. NFA was defined as requiring intensive care (ICU) management.

Results: Two reviewers independently screened 1,358 papers. 276 studies identified asthma attacks related to air pollution, 272 did not meet inclusion criteria after full text review. Four observational studies described fatal/NFA, of which 3 addressed NFA. PM_{2.5} (per 12.5µg/m³ increase) and O₃ (per 22 ppb increase) were associated with NFA in one study (PM_{2.5} RR 1.26 CI (1.10-1.44)), O₃(1.19 (1.01 – 1.40)). PM₁₀ was associated with ICU admission in the context of thunderstorm asthma. Elemental carbon was associated

equally with NFA that did not require an ICU admission ($p=0.67$). Studies of fatal asthma including children did not demarcate age within analysis.

Conclusions: Ozone and $PM_{2.5}$ have been associated with NFA in children but synthesis is limited by the paucity of studies and methodological heterogeneity. Poor reporting of severities of asthma attack hinders the assessment of whether outdoor air pollution is associated with an increased number of NFA/fatal attacks in children.

Asthma affects over 300 million people globally. An asthma attack occurs when a trigger such as a virus, airborne allergens or air pollution causes an inflammatory response resulting in bronchoconstriction of small airways.

Asthma attacks range in severity from mild to fatal. Between 2001 and 2011, there were 13,749 deaths attributed to asthma in the UK, 265 of which were in children¹⁶⁴.

There is an emerging body of evidence examining the relationship between air pollution and respiratory health. Air pollution has been associated with recurrent respiratory infections^{42,165}, reduced lung function in childhood⁴² and a higher frequency of childhood asthma following exposure in early infancy^{49,165,166}. Compared to adults, the impact of air pollution in children is considered greater for several reasons: (1) smaller airway diameter leading to higher propensity for airway blockage from larger particulate matter⁴⁶, (2) length of time in playgrounds and outdoor activities is likely to be greater¹⁶⁶, (3) increased respiratory rate and preferential mouth breathing result in greater inhalation and deposition of pollutants^{60,167}, and (4) developing lungs are more sensitive to chemical and oxidative stress¹⁶⁸.

Air pollution is an umbrella term for chemicals and particles which contaminant the atmosphere¹⁶⁹, some of which can cause harm to when inhaled. Common components of outdoor air pollution include waste products

of industrial combustion and particulate matter (PM) from industry and natural sources. The World Health Organization (WHO) recognises particulate matter, sulphur dioxide (SO₂), nitrogen dioxide (NO₂), carbon monoxide (CO) and ozone (O₃) as the most significant outdoor air pollutants negatively impacting health⁴⁸. Sulphur dioxide is produced from crude oil and coal combustion¹⁷⁰. Nitrogen dioxide is derived from exhaust and car/vehicle fumes. Particulate matter can be any airborne particulate of a measured diameter (micrometres) and consists of primary and secondary components. Primary components include sea salt, elemental or black carbon, trace metals and mineral components¹⁷¹, secondary components include sulphate, nitrate, water and organic carbon¹⁷¹. Particulate matter is further categorised by diameter size, separated into PM_{≤2.5}, PM_{2.5} and PM₁₀.

Air pollutants are suspected to contribute to asthma symptoms in different ways. Larger particles can physically obstruct and aggravate airways at bronchiole level whilst smaller particles (PM_{2.5} and PM_{<2.5}) are able to enter the bloodstream across the alveolar capillary membrane⁴⁶ and can trigger an inflammatory cascade resulting in acute bronchospasm⁴⁶. Possible mechanisms have also been suggested describing the causation of asthma from air pollution including oxidative stress, airway wall remodelling, upregulation of inflammatory pathways and enhancing respiratory sensitisation to allergens^{44,172}.

Our aim was to perform a systematic review to determine if severe near fatal and fatal asthma attacks are associated with outdoor air pollution in children and young people.

3.2 Methods

This systematic review was registered on PROSPERO (CRD42022317704) and PRISMA-P protocol (Table 4) completed according to Cochrane methodology¹⁷³.

3.2.1 Information sources and search strategy

Electronic databases were accessed on 8th November 2022. MEDLINE and EMBASE (via OVID), Scopus, Web of Science, Central and Open Grey were searched for relevant articles. Forward and backward citation searching was carried out. Existing terms describing severe asthma attacks ‘critical asthma’ and ‘status asthmaticus’ were included in the search strategy. We recognise that patients presenting to front line services (general practitioner, emergency department) or hospital admission may present with milder symptoms which deteriorate to require intensive care or result in a fatal attack. To ensure all attacks of interest were captured, search terms were broad (Table 5) to encompass all severity and presentations of acute attacks in children related to air pollution.

3.2.2 Study selection and inclusion criteria

The primary outcome was the association of near fatal and fatal attacks with air pollution exposure. Cohort, case crossover and case control studies were included. To examine the literature for acute asthma attacks, children and young people presenting with, or receiving treatment for an asthma attack were included. An age range of 2 – 18 years was selected to exclude patients with other wheezing illness such as bronchiolitis. Papers which

included adults but had clearly demarcated the relevant paediatric age group in analysis were included. Air pollutants based on WHO highlighted outdoor air pollutants⁴⁸ (CO, NO₂, SO₂, PM (any size), O₃) and additionally black carbon and benzene were examined. Indoor air pollution exposure was excluded. Long term and short term air pollution exposure was included if the outcome was an acute asthma attack in any healthcare setting. Extreme weather events examining the relevant air pollutants were included. Language was restricted to English and translated English studies (Table 6). We relied on the author description of asthma attacks, authors were contacted if attacks were described as 'severe' or 'near fatal' without definition. As the terminology for near fatal asthma attacks is inconsistent in the literature, the full text of all remaining studies was reviewed for near fatal and fatal attacks to identify studies for analysis. For the purpose of this review, near fatal attacks are defined as management of an acute asthma attack in an intensive care/critical care setting.

3.2.3 Data Extraction

Results were screened using the Covidence online platform (Covidence systematic review software, Veritas Health Innovation, Melbourne, Australia. Available at www.covidence.org). Once duplicates were removed, two reviewers, (DV and KF) independently screened title and abstracts to identify studies reporting air pollution and acute asthma exacerbations in children. Any conflicts that could not be resolved by discussion were screened by a third reviewer (BL).

3.2.4 Quality assessment and bias

To assess study bias, an adapted quality scale used by Mustafic et al. (2012) for assessment of air pollutants impact on myocardial infarction was used¹⁷⁴. This tool evaluated three components (the validation of MI occurrence [0 to 1 point], the quality of air pollutant measurements [0 to 1 point], and the extent of adjustment for confounders [0 to 3 points]). We have adapted this to review near fatal and fatal asthma attacks for the purpose of this review. We have chosen to define near fatal asthma attack as intensive care admission however to reflect and acknowledge that criteria for intensive care admission may vary depending on each hospital, 1 point was awarded if indication for intensive care admission was stated and included the escalation of management to invasive ventilation. A fatal attack was awarded 1 point if cause of death was registered as asthma. Air quality measurements and extend of confounders (0 – 3 points) were awarded 0 to 1 point as per similar criteria set out by Mustafic et al.(2012) (Table 8).

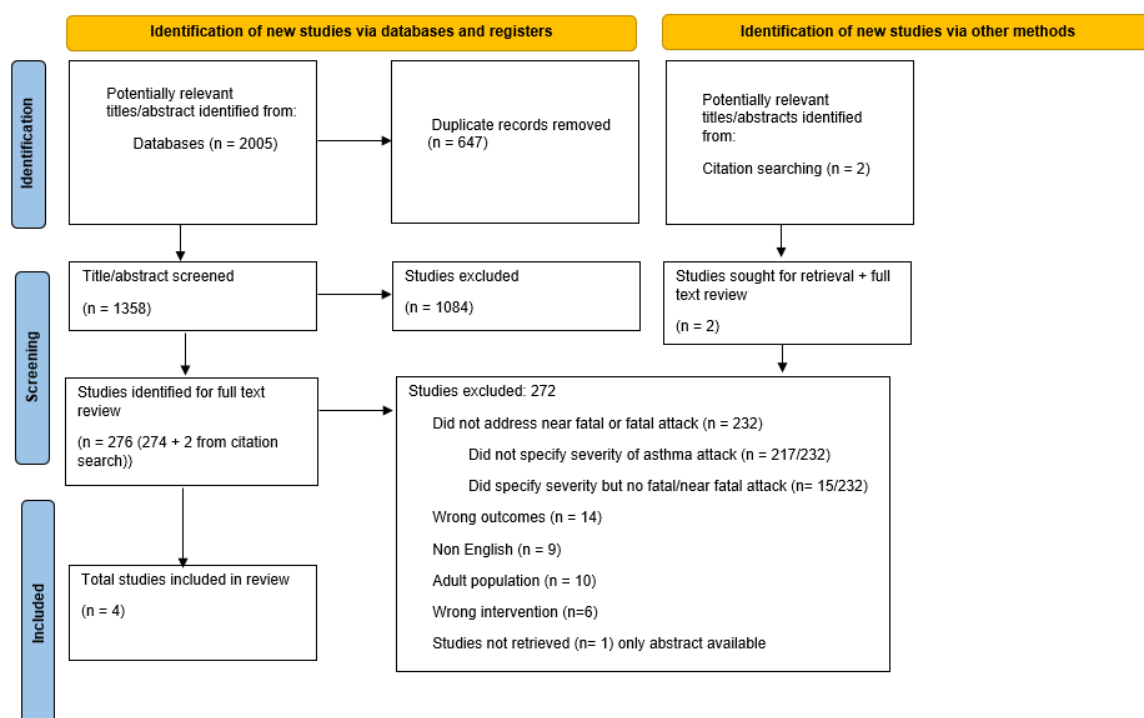
3.3 Results

After duplicates were removed 1,358 studies were screened for relevant air pollutants and asthma attacks in children, of which 276 studies met the criteria for a full text manual review. The majority of studies were excluded (n= 217 of 272, 80%) because the severity of asthma attack was not clinically described and could not be determined to the granularity of near fatal (intensive care admission) or fatal asthma attack (Table 7). Four studies

identified cases of fatal and near fatal asthma in children (see Figure 10 PRISMA P Results). Three studies addressed near fatal asthma attacks (defined as intensive care management) and one study presented a case series of fatal and near fatal attacks in an event of thunderstorm asthma. Although three studies identified intensive care admissions for near fatal asthma, only one study (Silverman et al. (2010)) was found to examine air pollutants as an exposure. The other two studies (McDowell et al. (2016) and Grunwell et al. (2021)) identified included air pollutants as part of a wider analysis of social deprivation and asthma admissions to intensive care. All identified studies were observational. Using the modified scoring from Mustafic et al. (2012) the quality of studies assessed can be viewed in Table 8. Studies scoring 3 in any category were deemed of high quality, low quality

if 0 in two categories and intermediate for any other score (Table 8)

PRISMA 2020 flow diagram for updated systematic reviews which included searches of databases, registers and other sources



Adapted from: Page MJ, McKenzie JE, Bossuyt PM, Boutron I, Hoffmann TC, Mulrow CD, et al. The PRISMA 2020 statement: an updated guideline for reporting systematic reviews. *BMJ* 2021;372:n71. doi: 10.1136/bmj.n71

Figure 9 PRISMA P Results
Near fatal asthma attacks

The only study that focussed on the impact of air pollutants and near fatal asthma, Silverman et al. (2010), reported ICU asthma admissions between April – August in relation to two air pollutants, ozone and PM_{2.5} (See Table 9). Over a seven year period, 74 hospitals were included in the study, with participants included if a diagnosis of asthma was coded on hospitalisation and coded as having an ICU admission or intubation or ventilation. Air pollution data was gathered from national data (US Environmental Protection Agency's Air Quality System¹⁷⁵ (Table 10). Pollution data was adjusted for

weather (humidity and temperature) and seasonal temporal trends. The study found the relative risk of ICU admission per interquartile increment of PM_{2.5} (12µg/m³) and ozone (22 ppb) was more significant in children age 6 – 18 years compared to adults (PM_{2.5} RR = 1.26 (CI 1.10 – 1.44) and ozone RR= 1.19 (1.01 – 1.40)). This risk of ICU admission was noted at an average lag of 0 day and 1 – day¹⁷⁶ suggesting increased risk with short term exposure.

McDowell et al. (2016) and Grunwell et al. (2021) both examined air pollution within analysis of social deprivation. As such, relative risk was not calculated for specific air pollutants.

McDowell et al. (2016) examined Elemental Carbon Attributed to Traffic (ECAT) measured using land use regression models from Cincinnati Children's Allergy and Air Pollution Study (CCAAPS). They observed no difference between ICU admission and non ICU groups admission (p= 0.67) in ECAT levels above the median (values not stated)⁹¹. Grunwell et al. (2021) identified near fatal asthma from hospital electronic records in children admitted to paediatric intensive care (PICU). Records were examined for a diagnosis of 'status asthmaticus'. Air pollutants were not separated for the analysis, air pollution data were combined with measures for education, health and environment and social and economic factors to create a Childhood Opportunity Index (COI) as a marker of social vulnerability. The COI data on air pollution was obtained from the Centres for Disease Control and Prevention using modelled data from 2010 and 2014^{177,178}. Levels of ozone and PM_{2.5} were similar in both groups¹⁷⁹.

Weather events

Darvall et al. (2018) describe two paediatric cases requiring ICU admissions for asthma in a case series of 35 adult and paediatric patients exposed to elevated PM_{2.5} and PM₁₀ after a thunderstorm in 2016⁷³. This was the largest event of thunderstorm asthma that has been described globally. This unique event resulted in 3460 patients seeking medical consultations and resulted in 9 deaths. Confounding factors including humidity and baseline medication use were considered. The study noted elevated levels of PM₁₀ ($\mu\text{g}/\text{m}^3$) >97th percentile for month and airborne grass pollen $\geq 100\text{grains}/\text{m}^3$. These levels however had been previously documented on other dates within the same year. Paediatric cases were not separated in the analysis.

Fatal Attacks

Fatal attacks were described by three papers assessed for eligibility by full text review. Each paper included all age ranges, children were not demarcated in analysis or reporting. All corresponding authors were contacted to ascertain if analysis on paediatric age could be attempted. None of the contacted authors responded.

Air pollutants

Researchers used inconsistent average time periods for the assessment air pollution data across the studies. (See Table 10). Exposure periods/lag times were not given for two of the studies addressing near fatal attacks (McDowell et al. (2016) and Grunwell et al. (2021)). Grunwell et al. (2021) used modelled

data which is commonly used in assessment of air pollution levels, was historical data from 2010, 2011 and 2014 (study period 2015 – 2019).

The most commonly studied air pollutants were ozone and PM_{2.5}. No included studies assessed NO₂ or SO₂ or considered these or other air pollutants in a combined multi-pollutant impact. Nitrogen dioxide and sulphur dioxide were included in studies of fatal asthma, though data for children could not be extracted as age related reporting was not provided or available via authors¹⁸⁰.

Ages

All three near fatal studies (Silverman et al. (2010), McDowell et al. (2016) and Grunwell et al. (2021)) included children aged 5 – 18 years (Table 9). McDowell et al. (2016) also included children < 5 years without stratifying age groups and as a result children with other similar wheezing conditions such as bronchiolitis may have been included in their analysis.

Heterogeneity of studies

The small number of heterogeneous studies precluded statistical synthesis and limited reporting to a description of the studies. There was a high degree of clinical heterogeneity as a result of differing methodologies (Table 9). Heterogeneity of study design did not allow a meta-analysis to be performed, limiting any conclusions that could be drawn from the studies identified. Studies were observational and measurement of pollution exposure differed greatly from study to study. Without specified time periods for exposure related to the asthma attack and consistent control groups in all studies,

estimation of exposure effect was not possible. Study heterogeneity in observational studies examining air pollution may be expected due to the range of possible study designs and differing methods of measuring air pollutants (dependant on local monitoring stations) ¹⁸¹.

Defining severity of attacks

This review has identified that whilst there is a substantial evidence base considering the association of an asthma attack and air pollution in children (*n= 232 of 272 excluded* - see Figure 10), the evidence considering the severity of asthma attack in relation to air pollution is far more limited (*n=4*). Of the 232 papers excluded, 217 had not specified whether a near fatal or fatal attack occurred (Table 6). Papers frequently addressed 'hospital attendance', 'emergency visit' or 'hospital admission' but did not specify if these events resulted in a fatal or near fatal attack. Children presenting to hospital with acute asthma can present with mild, moderate, severe or near fatal/fatal attacks and very few papers (*n=15*, see Table 7) defined this. Within the 217 that did not define severity, 147 used the International Classification of Diseases (ICD) code 'asthma' to identify presentations and patients (See Table 7).

3.4 Discussion

3.4.1 Principal findings

One of the key findings in this review is the almost absent reporting of the degree of attack severity in patients admitted to hospital with an asthma attack (*n = 217 of excluded papers* – see Table 7). Consequently, near fatal

and fatal attacks may have occurred but were not reported. Without this key information, conclusions on the severity of asthma attacks related to air pollution in children admitted to hospital are not possible. While many studies demonstrated an increase in the number of presentations with an acute attack, without quantifying the severity it is not possible to determine if more severe attacks are proportionally increased in association with high levels of outdoor air pollution. Potential reasons for the exclusion of these data may include (1) near fatal and fatal asthma attacks are infrequent, (2) use of diagnostic coding to identify attacks which limits the ability to identify the severity in those admitted to hospital. The use of diagnostic codes allows identification of cases but loses detail such as severity.

3.4.2 Common themes

Social Deprivation

A common theme in the two papers addressing near fatal asthma was the relationship between air pollution and social deprivation. McDowell et al. (2016) and Grunwell et al. (2021) both examined air pollution as part of environmental exposures related to socioeconomic status. Air pollution exposure was not a primary exposure in either study. As a result, neither study presented lag times or comparative periods of air pollution levels. This explains our inability to draw conclusions on the specific impact of air pollution on asthma from these two studies. Previous reports from the UK have shown a correlation between ICU admissions and deprivation¹²⁰,

highlighting the need for further research exploring the inter-relationship between deprivation and air pollution.

Air pollutants

In studies reporting a relationship of air pollutants to severity of asthma attack, there was varied reporting of pollutants, with ozone and particulate matter being most commonly reported. Standardised reporting of the air pollutants measured, duration of measured exposure (lag time) and average value (annual or 24 hour) and consistent reporting of the spread of the air pollution data in future studies would allow better synthesis of data. The use of retrospective air pollution data has benefits as is often readily available however it could be considered as a limitation when applied to an acute asthma attack which is likely to be attributed to air pollution levels in the days leading up to the acute attack.

Without experimental conditions the individual impact of singular air pollutants is difficult to determine. The combined effect of multiple air pollutants should be acknowledged and considered when interpreting the effect of air pollution on asthma attacks. For example, PM can be generated from road vehicle tyres in addition to vehicle fuel combustion waste products such as NO₂. Both are associated with asthma attacks in children. Examining one or another in isolation in relation to an acute asthma attack should acknowledge the potential impact of multiple air pollutants. Similarly, the relationship between airborne allergens as potential contributing factors for asthma attack triggers asthma attacks should also be considered. High

pollen counts have been associated with weather phenomenon such as thunderstorms which as shown by Darvall et al.(2018) also generate high levels of particulate matter. Separate analysis of individual pollutants may misrepresent any cumulative effect of exposure.

Exposure duration

The relationship between acute exposure and attacks was demonstrated by the significant weather event observed by Darvall et al.(2018) and Silverman et al. (2010).None of the studies commented on long-term exposure to air pollution. This is more challenging to quantify in the context of acute attacks. Antenatal, early childhood and infancy exposure to air pollution is associated with an increased asthma prevalence^{42,182,183}. Long -term exposure subsequently raises the questions of ‘how often?’ and ‘how long’ was an individual exposed. This can only be truly measured with individual exposure time and must consider cofounding factors such as weather, baseline asthma symptoms and inter-current viral illness. Whilst cohort studies assume individual exposure to outdoor air pollutants in the days/weeks leading up to the event, true exposure cannot be measured accurately without personal measurement devices^{184,185}. Though it may be useful to estimate individual air pollution exposure, it is not pragmatic or practical in near fatal or fatal asthma as such events are difficult to predict.

3.4.3 Limitations of the study

There were several limitations to our review. A very small number of papers met our inclusion criteria. Widening the age criteria to include adults may have resulted in a larger number of included studies but would not have answered our research question which focussed on children. Interpreting the resulting data would be unreliable as children are considered to be more sensitive to air pollutants. We therefore considered inappropriate to measure impact across all ages.

Many studies undergoing full text review described an admission to hospital as 'moderate' or 'severe' asthma attack. These non-standardised descriptions will not, in the majority of cases, equate to a near fatal asthma attack. 'Status asthmaticus' and 'critical asthma', included within our search terms have inconsistent definitions from a physiological and/or clinical perspective and so are unreliable. To differentiate near fatal asthma in this review, intensive care admission was used as a proxy marker of near fatal asthma attack. Although this creates a clear definition point, we are aware that using intensive care admission as a marker may have excluded cases that were not managed in intensive care due to resource or/and geographical limitations. In addition, individual units may have different thresholds for admission. This may have reduced the number of papers identified.

Although social deprivation was addressed as a common theme in two of the identified studies, all of the studies were conducted in high income countries. In those papers manually screened for near fatal and fatal events, 188 of the 272 papers screened were from high income countries. This should be

considered when addressing the impact of air pollution on fatal and near fatal asthma worldwide.

This review did not comment on the role of indoor air pollutants on asthma attacks however this is a key aspect to consider when evaluating environmental exposures. This has been shown to be particularly relevant in low to middle income countries where indoor air pollutant sources such as cooking stoves have been associated with poor respiratory health¹⁸⁶.

For the purpose of this review the validity of the studies was assessed using a modified assessment proposed by Mustafic et al¹⁷⁴. This was further modified to provide a relevant and structured approach to bias assessment for this paper however is not formally validated and is a limitation of this review.

3.4.4 Meaning of the study: possible implications

The association of air pollution with the severity of asthma attacks in children requires further research and vitally, quantification of the association. There is now a growing body of evidence associating air pollution and asthma presentations in children¹⁸⁷ and a landmark case in the UK has now reported that air pollution was a primary factor in the death of a child with a fatal asthma attack¹⁸⁸. This systematic review supports the need for additional data considering whether air pollution may increase risk of asthma attack severity and possible death from asthma. To ensure clear conclusions can be examined regarding air pollution data in children and young people experiencing near fatal and fatal asthma attack real time, datasets with

clearly defined pollutant and multi-pollutant models with adjustment for confounding variables and identifiable air pollution exposure time periods are required.

Such data could provide impetus to the need for cleaner air to improve children's health outcomes, as has been highlighted as a priority in environmental policies in the UK¹⁸⁹

3.5 Conclusion

The small number of available studies suggest that outdoor air pollution (specifically ozone and PM_{2.5}) may be associated with near fatal asthma. These studies add to the consistent evidence that air pollution is contributing to asthma attacks and prevalence in children. Clearly defined clinical severity of asthma attacks reported in association with air pollution should be reported in future studies, to enable the identification of fatal and near fatal attacks.

3.6 Outdoor air pollution and near fatal asthma surveillance

The results of the systematic review support the need to further identify near fatal asthma cases in children and young people with a clear definition and highlight how the classification of acute asthma severity can be lost in the literature. In future, a core outcome set specifically categorising the severity of asthma attack would be useful to identify near fatal and fatal attacks within coded data. The heterogeneity of study methodology in the impact of outdoor air pollution also demonstrates the difficulty in identifying the effect of both acute and background air pollution exposure and near fatal asthma.

Chapter 4 will discuss how I have used the finding from the systematic review to initiate a surveillance study on near fatal asthma in children and young people in the UK and examine the impact of outdoor air pollution on NFA cases.

Table 3.1 PRISMA-P

Title		Outdoor air pollution and fatal or near fatal asthma attacks in children. A systematic review.
Identification	1a	Identify the report as a protocol of a systematic review <i>This is a systematic review protocol</i>
Update	1b	If the protocol is for an update of a previous systematic review, identify as such <i>This review is not an update on a previous systematic review</i>
Registration	2	If the protocol is for an update of a previous systematic review, identify as such <i>Registered on PROSPERO (CRD42022317704)</i>
Authors:		Deepa Varghese, Kathryn Ferris, Bohee Lee, Steve Cunningham, Hilary Pinnock, Jonathan Grigg
Contact	3a	Provide name, institutional affiliation, e-mail address of all protocol authors; provide physical mailing address of corresponding author <i><u>Dr Deepa Varghese</u> Department of Child Life and Health, University of Edinburgh, Asthma UK Centre for Applied Research, Usher Institute, University of Edinburgh</i> <i>Dr Kathryn Ferris Queen's University Belfast, Asthma UK Centre for Applied Research, Usher Institute, University of Edinburgh</i>

		<i>Dr Bohee Lee Asthma UK Centre for Applied Research, Usher Institute, University of Edinburgh</i> <i>Professor Jonathan Grigg The Blizard Institute, Queen Mary's University, London, United Kingdom</i> <i>Professor Hilary Pinnock Asthma UK Centre for Applied Research, Usher Institute, University of Edinburgh</i> <i>Professor Steve Cunningham Department of Child Life and Health, University of Edinburgh</i>
Contributions	3b	Describe contributions of protocol authors and identify the guarantor of the review <i>Deepa Varghese: Main author</i> <i>Kathryn Ferris: second reviewer</i> <i>Bohee Lee: Search strategy and third reviewer</i> <i>Supervision team: Steve Cunningham, Hilary Pinnock, Jonathan Grigg</i>
Amendments	4	If the protocol represents an amendment of a previously completed or published protocol, identify as such and list changes; otherwise, state plan for documenting important protocol amendments <i>No amendments have been made at present to this protocol</i>
Support:		
Sources	5a	Indicate sources of financial or other support for the review

		<i>This review is not funded</i>
Sponsor	5b	Provide name for the review funder and/or sponsor <i>Not applicable</i>
Role of sponsor or funder	5c	Describe roles of funder(s), sponsor(s), and/or institution(s), if any, in developing the protocol <i>Not application, student project via University of Edinburgh</i>
INTRODUCTION		
Rationale	6	Describe the rationale for the review in the context of what is already known <i>Asthma attacks are episodes of acute bronchoconstriction which are often due to multi factorial triggers. Common triggers include respiratory virus infection and aero allergens. The effect of air pollution as a trigger for an asthma attack was previously unknown. Now, emerging clinical evidence suggests an increase in asthma attacks in areas with high ambient outdoor air pollution. Children are felt to be more susceptible to the effect of outdoor air pollution in light of smaller airways, faster respiratory rate and prolonged time outside. Asthma attacks have varying clinical presentation depending on the severity of symptoms and may be managed according by different healthcare professionals in different health care settings. Mild attacks may not require hospitalisation and can be managed in the community. A severe attack may also present to a community professional but then require ongoing management in hospital. Near fatal asthma attacks are the most severe form of survivable asthma attack. A near fatal attack will require hospital admission and</i>

		<i>in the majority of cases intensive care management.</i>
Objectives	7	Provide an explicit statement of the question(s) the review will address with reference to participants, interventions, comparators, and outcomes (PICO) <i>This review considers the evidence of the severity of the asthma attacks linked to air pollution and aims to answer if outdoor air pollution has been associated with severe asthma attacks specifically near fatal and fatal attacks in children.</i> <i>Population: children treated for an acute asthma attack during a period of measured high outdoor air pollution</i> <i>Intervention: air pollution</i> <i>Comparison: asthma attacks during periods of low ambient air pollution</i> <i>Outcome: severe asthma attacks requiring admission and management in intensive care or fatal attacks.</i>
METHODS		
Eligibility criteria	8	Specify the study characteristics (such as PICO, study design, setting, time frame) and report characteristics (such as years considered, language, publication status) to be used as criteria for eligibility for the review Population Children and young people with asthma (2years to 18 years) Intervention/exposure

		Particulate matter (PM), PM_{2.5} PM₁₀, fine PM, coarse PM, ultrafine PM, ozone (O₃), sulphur dioxide (SO₂), nitrogen dioxide (NO₂), traffic emissions, carbon monoxide (CO), benzene, black carbon. Comparison/control groups Expect majority observational studies or case control studies. Comparison will be non-fatal or near fatal attack. Outcomes Fatal or near fatal asthma attack. Defined by intensive care management of acute asthma attack or primary care review, hospital or emergency call out or attendance requiring escalation intensive care or invasive ventilation, resuscitation or fatal attack. Study Designs All studies included – expect observational or case control studies will be majority
Information sources	9	Describe all intended information sources (such as electronic databases, contact with study authors, trial registers or other grey literature sources) with planned dates of coverage

		<i>Electronic databases: EMBASE, MEDLINE, Scopus, Web of science</i> <i>Forward and backward literature searching of references</i> <i>Grey articles</i>
Search strategy	10	Present draft of search strategy to be used for at least one electronic database, including planned limits, such that it could be repeated See Table 5 - search strategy
Study records:		
Data management	11a	Describe the mechanism(s) that will be used to manage records and data throughout the review <i>Data extraction tables will be used to facilitate review of studies</i>
Selection process	11b	State the process that will be used for selecting studies (such as two independent reviewers) through each phase of the review (that is, screening, eligibility and inclusion in meta-analysis) <i>Two independent reviewers will select studies based on inclusion criteria. Both reviewers will screen titles and abstracts. A third reviewer will resolve any conflicts.</i>
Data collection process	11c	Describe planned method of extracting data from reports (such as piloting forms, done independently, in duplicate), any processes for obtaining and confirming data from investigators <i>Data will be extracted independently, observation studies will be screened using Newcastle Ottawa checklists. After peer review, data validity was reviewed using an adapted quality scale from Mustafic et al 2012</i>
Data items	12	List and define all variables for which data will be sought (such as PICO items,

		funding sources), any pre-planned data assumptions and simplifications. <i>No funding sources have been sought for data.</i>
Outcomes and prioritization	13	List and define all outcomes for which data will be sought, including prioritization of main and additional outcomes, with rationale <i>Main outcomes: Abstracts and titles will be screened for studies involving children > 2 years, asthma attacks (clinical) and air pollution. Studies meeting these criteria by two independent reviewers will then be screened by DV for fatal and near fatal attacks. Due to the nature of description of asthma attacks, narrow search terms may exclude near fatal attacks. Equally severe attacks are not clearly defined and can vary from hospital presentation to fatal attack. Manual screening of all relevant studies will prioritise primary outcomes.</i>
Risk of bias in individual studies	14	Describe anticipated methods for assessing risk of bias of individual studies, including whether this will be done at the outcome or study level, or both; state how this information will be used in data synthesis <i>A small number of likely observational studies is expected based on background reading of Near Fatal and Fatal asthma in children. Depending on the identified studies, meta-analysis may not be possible if mixed methods are used. Similar studies will be compared in a descriptive analysis. Random effects model if possible, will be carried out.</i>
Data synthesis	15a	Describe criteria under which study data will be quantitatively synthesised <i>Data quality will be assessed using Newcastle Ottawa Scale. After peer</i>

		<i>review this methodology was reconsidered, data validity was reviewed using an adapted quality scale from Mustafic et al 2012</i>
	15b	If data are appropriate for quantitative synthesis, describe planned summary measures, methods of handling data and methods of combining data from studies, including any planned exploration of consistency (such as I^2 , Kendall's τ)
	15c	Describe any proposed additional analyses (such as sensitivity or subgroup analyses, meta-regression)
	15d	If quantitative synthesis is not appropriate, describe the type of summary planned
Meta-bias(es)	16	Specify any planned assessment of meta-bias(es) (such as publication bias across studies, selective reporting within studies) <i>Meta-analysis will be considered if sufficient number of studies (3 or more)</i>
Confidence in cumulative evidence	17	Describe how the strength of the body of evidence will be assessed (such as GRADE) <i>If applicable, strength of evidence will be assessed using GRADE assessment tool.</i>

Table 3.2 Search Strategy

Search Strategy							
Search Set	MEDLINE (MeSH terms)	EMBASE (Subject headings)	CENTRAL	Web of science	Scopus	Open Grey	Citation searching
1	exp Asthma/ or exp Asthma-Chronic Obstructive Pulmonary Disease Overlap Syndrome/ or exp Status Asthmaticus	severe asthma/ or exp asthma/ or exp asthmatic state/ or exp severe persistent asthma/	asthma and air pollution and exacerbation and children	Asthma	(air AND pollution AND asthma AND exacerbations AND children)	Air pollution	Review articles
2	exp Bronchial Hyperreactivity	exp *asthmatic state/ or exp *severe asthma/		Exacerbation		Asthma	Systematic reviews
3	exp Bronchial Spasm	Near fatal asthma.mp.		Air pollution			
4	(asthma* adj3 (exacerb* or deteriorat* or acute or sever* or wors* or attack* or crisis or critical or fatal	1 or 2 or 3		Children			

	or near fatal)).ti,ab,kf,sh.						
5	1 or 2 or 3 or 4	exp *disease exacerbation/ or exp *complication/		1 and 2 and 3 and 4			
6	exp Air Pollutants/	exp critical illness/ or exp disease severity/					
7	exp Particulate Matter/	exp fatality/ or fatal.mp.					
8	exp Sulfur Dioxide/	5 or 6 or 7					
9	exp Nitrogen Dioxide/	4 and 8					
10	exp Ozone/	exp air pollution/					
11	exp benzene/	exp particulate matter/					
12	exp black carbon/	exp sulfur dioxide/					
13	(Air pollut* or particulate matter or particle pollut* or	exp nitrogen dioxide/					

	nitrogen dioxide* or SO ₂ or O ₃).ti,ab,kf,sh.						
14	6 or 7 or 8 or 9 or 10 or 11 or 12 or 13	exp black carbon/					
15	(child* or pediatri* or paediatri*).ti,ab,sh.	exp benzene/					
16	exp Child/	exp ozone/					
17	15 or 16	10 or 11 or 12 or 13 or 14 or 15 or 16					
18	((hospital* or emergenc* or consult* or review* or intensive* or critical* or ICU) and (admission or admi* or attend* or visit or util*)).ab,kf,sh.	Exp child/					
19	5 and 14 and 17	9 and 17					
20	18 and 19	18 and 19					
Total papers	442 (8 th Nov 2022)	560 (8 th Nov 2022)	20 (8 th Nov 2022)	482 (8 th Nov 2022)	499 (8 th Nov 2022)	0	2

Table 3.3 Inclusion exclusion criteria

3. Inclusion and exclusion criteria	
Inclusion	Exclusion
Population - Children age 2 years to 18 years treated for an exacerbation of asthma - Studies including adults up to the age of 25 if relevant paediatric population (2 – 18 years) included - Studies including paediatric deaths (age 2 – 18 years) where asthma identified as cause of death or contributed to death	Population - Children < 2 years where no definitive asthma treatment defined. - Children treated for other respiratory illness including bronchiolitis, bronchiectasis, recurrent respiratory infection - Adults >18 years with occupational wheeze not related to air pollution - Chronic obstructive pulmonary disease
Intervention - Studies must include measurement or measured exposure to of one of the following: Particulate matter (PM), PM_{2.5} PM₁₀, fine PM, coarse PM, ultrafine PM, ozone (O₃), sulphur dioxide (SO₂), nitrogen dioxide (NO₂), carbon monoxide(CO), benzene, black carbon. - Extreme weather related outdoor air pollution if resulting in increased particulate matter (any size)	Intervention - Indoor air pollution exposure - Animal models/studies
Comparison Control group in defined geographical areas of low levels of outdoor air pollution	Comparison For randomised control trials no clear control group without measured/defined area of low level or no outdoor air pollution

○ Control group observed over specified time period with low levels outdoor air pollution ○ Control group from population with measured minimal exposure to high levels of outdoor air pollution	
Outcome ○ Fatal or near fatal asthma exacerbation ○ Intensive care management of acute asthma attack ○ Primary care review, hospital or emergency call out or attendance requiring escalation intensive care or invasive ventilation, resuscitation or fatal attack	Outcome ○ Subsequent development of asthma post exposure ○ Asthma exacerbations not related to acute exposure ○ Escalation in chronic asthma treatment post exposure to high levels of outdoor air pollution ○
Study Design ○ Randomised control trials ○ Case control studies ○ Case cross over trials ○ Cohort studies ○ Grey literature	○ Editorials, letters to editor ○ Review articles ○ Opinion pieces
Language ○ Published studies in English language ○ Translated into studies with asthma, wheeze and severity of attack clearly defined	

Table 3.4 Excluded papers

Papers excluded as severity not defined	Number	Percentage of excluded papers
Severity addressed but fatal/near fatal attack not included	15/232	6%
Use of ICD Code or severity not defined (inc systematic reviews)	217/232	94%
Reason for exclusion after full text review		Number of papers
Did not identify a fatal or near fatal asthma attack		232
Incorrect outcome (acute asthma attack not addressed)		14
Publication not translated to English		9
Adult population (children not demarcated in analysis)		10
Incorrect intervention (outdoor air pollutant exposure not addressed)		6
Unable to obtain full text (abstract only)		1
Total		272

Table 3.5 *Modified validity score (Mustafic et al 2012)*

	<u>0</u>	<u>1</u>	<u>2</u>	<u>3</u>
Definition of near fatal asthma/fatal asthma (0 - 1)	0 points if ICU admission criteria was not defined by invasive ventilation	1 point was awarded if indication for intensive care admission was stated and included the escalation of management to invasive ventilation. 1 point fatal attack was awarded 1 point if cause of death was registered as asthma.		
Air pollutant measurements	0 points if measurement frequency was not stated or if >25% of data missing	1 point if measurement frequency was stated and <25% of data missing		
<u>Adjustment of cofounders</u>	0 points if no adjustment made for long-term trends or seasonality or temperature	1 point if only these <3 adjustments had been made	2 points if additional adjustment was made, either for humidity or weather event	3 points if adjustment had been made for seasonal viral infection, atopy, familial smoking

Table 3.6 Data Extraction Table

Author	Near Fatal /Fatal	Year (Study period)	Location	Setting	Study type	Population	Intervention			Comparison	Outcome	Pollutant measurement quality score (0-1 point)	Diagnosis of near fatal/fatal asthma (0 -1)	Adjustment quality score (0-3 points)
							Air pollutant		Lag time					
Jai N Darvall et al.(2018)	Near Fatal and Fatal	2016 (2 days)	Australia	Intensive Care	Retrospective multi centre observational study	Patients with asthma admitted to intensive care	Age	PM ≤ 2.5 PM 10 $\mu\text{g}/\text{m}^3$	2 days	Annual Intensive Care Admissions	Intensive care admission (all cause)	1	0	2
							9 and 12 years (n = 2)							
							Number of patients							
Robert A. Silverman et al (2010)	Near Fatal	2010 (1999 – 2006)	America	Intensive Care	Time series analysis	Paediatric asthma admissions	Age	Ozone (22 ppb per IQR change) PM2.5 ($12.5\mu\text{g}/\text{m}^3$ per IQR change)	Average 0 - 1 day	Non ICU admissions	Effect of age on air pollution risk for admission with very severe asthma	1	1	2
							6 – 49 years (>6 and 6 – 18 grouped)							
							Number of patients							
							6008							
							Age					1	0	0

Karen M. McDowell et al (2016)	Near Fatal	2016 (enrolled August 2010 – October 2011)	America	Intensive Care	Prospective Cohort Study	Paediatric asthma admissions	1 – 18 years	Black carbon	Not stated	Non intensive care admissions	Intensive care admission for severe asthma			
							Number of patients 771 (160 ICU admissions)							
Grunwell et al (2022)	Near Fatal	2022 (2015 - 2019)	America	Intensive Care	Retrospective cohort	Paediatric Intensive care	Age	PM 2.5 ($\mu\text{g}/\text{m}^3$) Ozone	Not stated	Not stated	Intensive care readmissions for severe asthma	0	0	0
							6 – 17 years							
							Number of patients 4425 (1705 PICU admissions)							

*Sites referenced in Ryan et al.(2007)¹⁹⁰

**airborne allergens, home tobacco smoke exposure, atopy, gender and financial hardship were recorded as part of cohort – no separate air pollution analysis carried out.

4 Chapter 4: Surveillance of Near Fatal Asthma in Children and Young People – study methodology and data permissions

This chapter will discuss how I facilitated the permissions, launched and completed an observational surveillance study in the UK which aimed to determine the frequency of near fatal asthma in children and young people during an 18 month observation period(1st October 2022 – 1st April 2024). I will discuss the methods applied to describe near fatal asthma attacks in detail regarding their prehospital, inpatient and discharge care. I went on to observe if there was an association with environmental exposures such as outdoor air pollution, weather, intercurrent viral illness and pollen levels. The impact of potential risk factors observed such as gender, ethnicity and social deprivation were assessed.

As discussed in Chapter 2.6, this was a BPSU study. This system was chosen to facilitate the identification of the number of reported cases of near fatal asthma in a defined time period within paediatric settings. Initial study application wished to explore near fatal asthma in older adolescents and include adults to age 25 years. Unfortunately, the BPSU methodology does not include adult patients and there is no equivalent reporting system for rare respiratory disease or near fatal asthma reporting in those over 16 years of age. Initial study application also included the study of fatal asthma over this period, however this data was not possible to obtain due to GDPR restrictions in the 18 month time frame allotted for the study.

This chapter will discuss the process of BPSU application, the steps required to facilitate the study launch, how the study was conducted and the planned data analysis.

The process of BPSU application was carried out and finalised by Professor Steve Cunningham prior to my involvement in the project. The protocol and draft questionnaire were in progress prior to my joining the study team. My role from February 2022 (appointment to the project and research post) involved finalising the protocol, submitting and obtaining relevant ethical approval and national permissions to facilitate study launch with the BPSU. All data collection, analysis and data linkage was undertaken by myself with supervision from Professor Steve Cunningham (PI).

4.1 Study funding

The study funding was secured by Professor Steve Cunningham through application to the Chief Scientists Office Scotland (CSO). This grant awarded fund to investigate a “Prospective survey of Near Fatal Asthma in Children and Adolescents to inform a future care bundle to reduce risk of death in this population”.

4.2 BPSU Application

The first stage of the study required application to the British Paediatric Surveillance Unit which was completed by Professor Steve Cunningham (Principal Investigator). There is a two stage application process to the BPSU scientific committee. Phase one application reviews the research question, clarifies the case definition to ensure this is clear but also answers the

research question. The phase two application involves the development of a questionnaire.

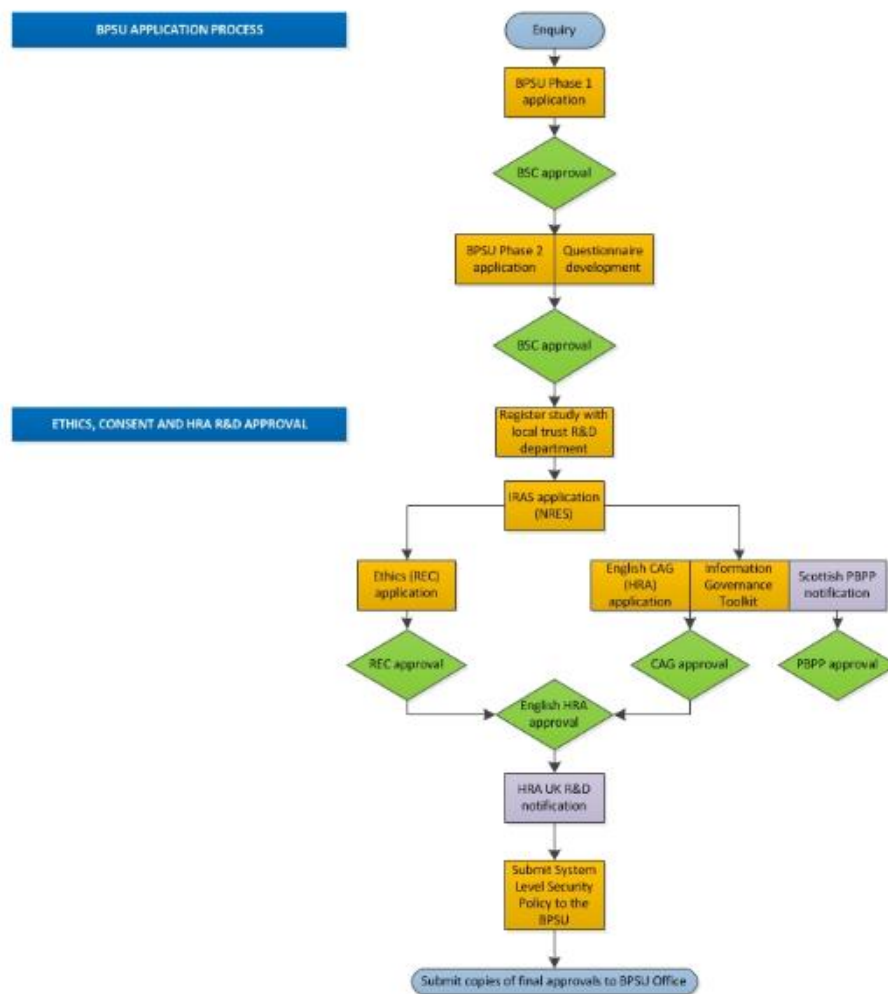


Figure 11 BPSU application process

4.2.1 Phase 1 Application

Phase 1 application was led and completed by Professor Steve Cunningham and Dr Ann McMurray.

4.2.1.1 Case Definition

The BPSU requires a clear case definition and to qualify as a rare illness – an incidence of <360 cases per year. They also stipulate that any study data should be accessible from patient case notes (no new or additional

information should be collected by study). In Chapter 2.8, I discussed in detail two prominent data sets regarding asthma care in the UK (NRAD and NRAP). Both of these datasets relied on ICD 10 codes to identify cases which without further interrogation do not provide granularity on the severity of the asthma attack¹⁶². For this study, a clinical definition was chosen to ensure near fatal asthma attacks could be identified by a reporting clinician.

Case criteria

Key to the methodology of this study is the use a definition for near fatal asthma based on of an e-delphi defined criteria to identify near fatal asthma attacks. As stated in Section 1.1, near fatal asthma (and all terms for asthma attacks) has been poorly defined and previously described with interchangeable terms such as status asthmaticus, critical asthma syndrome and severe asthma. These terms are commonly used to describe acute attacks without clear definition for clinical symptoms or physiological parameters, such as oxygen saturations or measured partial pressure of carbon dioxide. Loose definitions of near fatal asthma reinforce how difficult it can be to recognise patients at risk of an asthma related death. A consistent definition is key to identifying cases and consequently standardising management in national guidelines. An e-delphi consensus was carried out by Dr Ann McMurray et al¹⁹¹ which surveyed clinicians who were involved in caring for children and young people. There were 104 respondents from 25 countries and a definition for near fatal asthma in children and young people was reached. This defined near fatal asthma as:

'A person experiencing near fatal asthma is exhausted, with severe dyspnoea, unable to speak with a silent chest. Respiratory arrest is considered imminent and invasive ventilation will likely be required. They will be responding poorly to emergency asthma therapies. This is associated with hypoxaemia, hypercarbia and a falling pH¹⁹².

The case criteria for this BPSU study were derived from this definition of near fatal asthma. In contrast to previous studies in the UK which have identified severe acute asthma cases through coding^{120,193}, the cases were identified by a clinician who had been involved in the management of a near fatal attack. The use of electronic health records and diagnostic codes were not used to search for cases.

The basis of the definition used in the BPSU surveillance was formed from the e-Delphi consensus. Initial BPSU phase one application rejected this definition in accordance with the likelihood of high case number return exceeding 360/year. The initial research team therefore adjusted the definition as suggested by the BPSU to add specific biochemical parameters such as blood gas values, physiological observations including oxygen saturations. These values were obtained from the e-Delphi consensus process conducted by McMurray et al(2022). The e-Delphi process did not reach a consensus on values for SpO₂ and PaCO₂ but a preference was noted for SpO₂ <85% and PaCO₂ >60mmHg/8kPa¹⁹⁴. These parameters were adapted to form the clinical definition which was then resubmitted to the BPSU scientific committee. The research team were aware the additions of these parameters may exclude patients (blood gas not obtainable due to

machine error, saturations not recorded correctly) and raised these concerns. After review, this 'tighter' definition was felt to be clearly identifiable and was accepted by the BPSU.

Age range

In children < 5 years of age common differential diagnoses for presentation with hypoxia, cough, breathlessness and wheeze include: bronchiolitis, pre-school wheeze and asthma exacerbation. To ensure patient with bronchiolitis and pre-school wheeze were not included in this study a lower age limit of 5 years was chosen. As previously stated, initial study application wished to examine children and young adults (up to age 25) however an equivalent surveillance adult system to the BPSU did not exist. The BPSU only permits surveillance up to the age of 16 but as we wished follow up patients for 24 months, we placed an upper age limit of 15 years (to the day before 16th birthday) at the time of NFA. In the UK, the majority of paediatric services will accept admissions in children under 16 years old, with those age 16 and older likely to be cared for and present to adult emergency and respiratory services. The location of adult services may be in different geographical locations separate from those for children. To ensure data collection could be carried out whilst a patient remained under paediatric services an upper limit of 15 years was chosen for the age limit. Whilst adolescents are at higher risk of severe asthma attack and it was highly desirable to include adolescents within the survey, it was recognised that this was not possible beyond the BPSU.

The agreed definition is stated in Figure 11.

Cases defined as (1) and/or (2) and/or (3)
(1) Any child aged 5-15 years surviving* an acute episode of asthma, who when presenting self-ventilating with severe dyspnoea (e.g., inability to speak) and all the following features: a)Pulse oxygen saturation below 92% despite maximal oxygen therapy (i.e., 10-15l/min oxygen flow via non-rebreather mask) during acute presentation and b) pH $\geq$ 7.2 and/or pCO ₂ $\geq$ 60mmHg or 8kPa and c)Escalation to use of intravenous bronchodilator infusion
(2) Any child aged 5-15 years surviving* an acute episode of asthma, who had a respiratory arrest and/or required cardiopulmonary resuscitation as part of their presentation.
(3) Any child age 5-15 years surviving* an acute episode of asthma for which he/she was invasively ventilated.
*surviving to hospital discharge

Figure 10 Study Criteria

4.2.1.2 Study Group

The initial group involved clinicians and researchers from the UK who represented those involved in the care of children with near fatal asthma and also those who could provide research insight into key environmental factors such as outdoor air pollution. Initial BPSU application advised to widen the study group ensuring representatives from the Republic of Ireland were included in the study team.

The Near Fatal Asthma Study Group includes:

Table 4.1 Near Fatal Asthma Study Group

Name	Affiliation	Role
Professor Steve Cunningham (PI)	University of Edinburgh, NHS Lothian	Respiratory Paediatrician. <i>Specialist review of children experiencing near fatal asthma both</i>

		<i>in an inpatient setting and outpatient setting.</i>
Dr Ann McMurray	NHS Lothian, National Paediatric Respiratory and Allergy Nurses Group	Paediatric Respiratory Research Nurse Specialist. <i>Specialist review and day to day contact with children and families experiencing near fatal asthma. Acute, inpatient and outpatient management.</i>
Dr Lisa Finlay	NHS Dumfries and Galloway	General Paediatrician. with respiratory interest <i>Manages children and young people with near fatal asthma acutely, may facilitate transfer to tertiary centre for critical care management.</i>
Dr Des Cox	Children's Health Ireland	Respiratory Paediatrician. <i>Specialist review of children experiencing near fatal asthma both in an inpatient setting and outpatient setting.</i>
Dr Mark Lyttle	University Hospitals Bristol Foundation Trust, Paediatric Emergency Research in the UK and Ireland	Paediatric Emergency Care Consultant. <i>Acute management of patients presenting to emergency department with near fatal asthma.</i>
Dr Peter Davis	University Hospitals Bristol Foundation Trust, Paediatric Critical Care Society	Paediatric Critical Care Consultant <i>Inpatient management of patients admitted to critical care with near fatal asthma</i>
Dr Tom Clemens	University of Edinburgh, Department of Social Science and Geography	<i>Knowledge and expertise of environmental exposures which can be applied to cases of near fatal asthma</i>

This range of clinicians and researchers were key in developing a questionnaire in Phase 2 of the application that would reflect relevant research questions but also to ensure that data within the questionnaire was accessible to clinicians who work in relevant departments.

4.2.1.3 Protocol Development

The study protocol was written and reviewed by the study team and finalised once ethical approvals and relevant permissions were obtained. (See appendix). The study aims listed in the protocol are listed below:

Primary Endpoint

The annualised frequency of near fatal asthma attacks in children and young people aged 5- 15 years in the UK and ROI.

Secondary Endpoints

(1) Epidemiology

a. The clinical characteristics of CYP experiencing NFA (i.e., ethnicity, past asthma

history, current medication, initial vital signs/physiological measures)

b. The environmental exposures of CYP at the time of experiencing NFA (environmental pollution, pollen, viral, weather)

c. The sociodemographic status of CYP affected by NFA

(2) Acute Treatment

a. Pre-hospital recognition and treatment

b. Initial assessment and treatment on arrival in ED or a PAU

c. The care (support/treatment) provided to children with NFA in paediatric critical

care

(3) Subsequent Care

a. Changes in asthma treatment following NFA

b. The frequency of follow up in a hospital clinic in the 12 months following an NFA

attack (to include attendance and non-attendance rates)

c. The level of specialist training of the clinicians who provide follow up care in a

hospital clinic in the 12 months following a NFA attack

d. To describe what clinical services are offered to and attended by children and

their families following a NFA attack

(4) Longer term risk

a. The frequency of subsequent acute asthma related hospital attendances in the

24 months following a NFA attack

b. The frequency of asthma death in children within this cohort in the 24 months

of the survey (when compared with 10-year average)

4.2.1.4 Public and Patient Involvement(PPI)

During the Phase 1 application the study team sought colleague review and opinion on the project. The PPI group was facilitated by Dr Tracy Jackson from the Asthma UK Applied Centre for Research. This gained valuable insight concerning the identification and data linkage aspect of the attacks and PPI approval letter shared thoughtful and beneficial perceptions on the study (Appendix 1 : Public and Patient Involvement (PPI) Letter of Feedback and Support). Regarding the need for the project, one member commented:

“I think that's really, really important. Because, you know, there are times, especially as a parent if you're panicking you've taken your child, a young child, especially to hospital and you're panicking because you know something's not right they can't breathe. To know that they're going to get the care like as a sort of standard across the board” (Parent, female).

The PPI perspective were also useful for providing valuable insight into the patient opinion on the data collection methodology.

4.2.1.5 DPIA

A Data Protection Impact Assessment (DPIA), submitted to the University of Edinburgh Data Protection Officer, was carried out prior to application for ethical approval to aid in the identification of data protection risks. This aided the highlighted the data categories which would be accessed in the study (Appendix 3 : Data Protection Impact Assessment, University of Edinburgh)

4.2.2 Phase 2 Application

Phase 2 of the BPSU application began once the BPSU had approved the final definition, study team and duration of the project. Phase 2 of the application involved questionnaire development.

In recognition that the patient journey during a hospital admission would involve several different paediatric departments, the questionnaire was structured to have discreet sections. This included

1. Patient details
2. Prehospital care
3. Inpatient and discharge care
4. Baseline details

The design of the questionnaire aimed to encourage clinicians who looked after patients on a specific part of their hospital journey to complete the relevant section (see figure below)

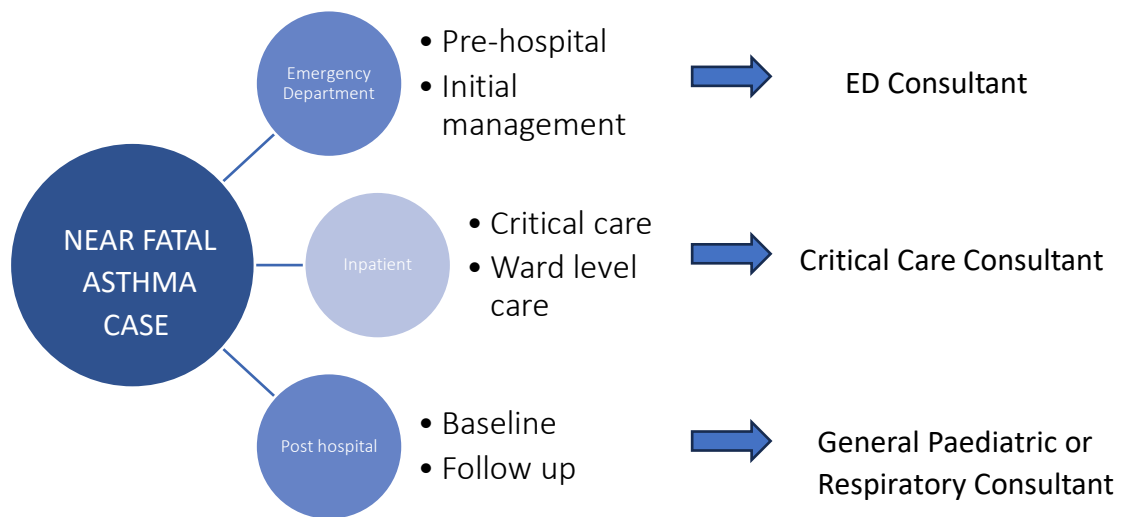


Figure 11 Clinicians completing NFA Questionnaire

4.2.2.1 Research Electronic Data Capture (REDCap)

REDCap is an online platform for building research surveys and managing databases. Produced by Vanderbilt University, this is a secure data collection tool meeting Health Insurance Portability and Accountability Act (HIPAA) standards. To maximise data entry, the study planned to integrate the use of REDCap within the data reporting to allow emergency and critical care clinicians to quickly access the data reporting platform using a QR code. REDCap will not store any clinical data but simply act as a conduit to the data entry platform. The use of REDCap in the study would be led by Dr Mark Lyttle.

4.2.2.2 Paediatric Emergency Research in the UK and Ireland (PERUKI)

To facilitate the involvement of emergency care clinicians, during the phase 2 application the study applied for PERUKI adoption (<https://www.peruki.org>). This would list the study as an active research study and highlight this to PERUKI members. The use of the REDCap platform would facilitate the input

of Emergency Care clinicians as it was recognised that emergency departments are often busy environments and can present challenges to data entry. PERUKI adoption was successful (Appendix 4: Paediatric Emergency Research in the United Kingdom and Ireland Support Letter)

4.2.2.3 *Caldicott Guardian Support*

In Scotland, the Caldicott Guardian exists to ensure the transfer of identifiable information between NHS organisations and non NHS organisations is shared for justified purposes and the minimum amount of data required is shared¹⁹⁵. The Caldicott guardian in Scotland is a senior health professional or member of a clinical governance board. For this study, application to the Caldicott Guardian for NHS Lothian was made by Professor Steve Cunningham. The study was approved by Heather Charles (Head of Research Governance, Research and Development NHS Lothian)(Appendix 5: Caldicott Guardian Support Letter)

My role in the project began after phase 2 applications had been completed. This stage comprised of protocol finalisation, ethics and permissions application and study launch and data collection, analysis and dissemination.

4.2.2.4 *GDPR Training*

During Phase Two of the application, any researcher who would require access to the Safe Haven (Dr Tom Clemens, Dr Ann McMurray, Professor Steve Cunningham and Dr Deepa Varghese) were required to complete the Medical Research Council training course 'GDPR – What you need to know'. This was an online course with online modules and assessment. Any

researchers accessing the safe haven were required to complete this course gaining a suitable level of understanding on information governance.

4.3 Ethical Approval and National Permissions

The next step in the study launch involved obtaining ethical approvals and relevant permissions for the study to commence. This incurred significant, unexpected time delays for the project. Ethical approval initially projected was to be obtained by February 2022 but was not achieved until May 2022. As discussed below further delays occurred in Confidential Advisory Group and Public Benefit and Privacy Panel approvals.

4.3.1 Ethical Approval

The study was given favourable ethical opinion by South East Scotland Research Ethics Committee (Reference 22/SS/0030) on 11th May 2022. Details of the ethical approval are provided in Appendix 6: South East Scotland Research Ethics Committee Approval Letter. Ethical approval required clear justification for non-consented access to data and emphasis of National Opt Out on public information leaflet. An amendment was sought in June 2023 due to the migration of HIC Dundee safe haven provider to AWS by Amazon.

4.3.2 Confidential Advisory Group (CAG)

The confidential advisory group is a facet of the Health Research Authority (HRA). This body is applicable to health care data in England and Wales. The CAG ensures that confidential patient information is used legally and in the public interest. Confidential information is defined as by the 2006 NHS act section 251.

(a)the identity of the individual in question is ascertainable—

(i)from that information, or

(ii)from that information and other information which is in the possession of, or is likely to come into the possession of, the person processing that information, and

(b)that information was obtained or generated by a person who, in the circumstances, owed an obligation of confidence to that individual.¹⁹⁶

It is recognised by HRA that as part of the NHS, medical research is an essential activity and that in some circumstances consent to obtain information may not be practical. In these cases, the use of non-consented data is support by CAG under a section 251 approval. Applications for Section 251 approval will be reviewed by a governing panel who will decide if there is sufficient public interest to temporarily lift the common law duty of confidentiality. Patients in England and Wales are able to opt out of data sharing and this is emphasised in any study that has section 251 approval.

For this project to proceed we required CAG approval to access confidential patient data in England and Wales. This involved submitting relevant documentation to demonstrate why the study a) could not ask for consent b) had significant public interest to access confidential information. The study was given provisional CAG approval (Reference 22/CAG/0055) on (14th April 2022) (see Appendix 7: Confidential Advisory Group Approval Letter CAG approval). Provisional approval was subject to corresponding approval from Public Benefit and Privacy Panel (PBPP) for Health and Social Care (HSC)

Scotland. As PBPP required a separate application and review board approval 22nd September 2022 there were significant delays in project commencement. CAG approval was granted in conjunction with PBPP approval (23rd September 2022).

4.3.3 Public Benefit and Privacy Panel (PBPP) for Health and Social Care

In Scotland, the study required approval from the PBPP. This is a governance structure that exists within Scotland to ensure data requests are in public interest and meet information governance requirements¹⁹⁷.

Information Governance (IG) is a process to ensure personal, patient and sensitive data is handled confidentially, securely and legally. In Scotland, to access health data, the PBPP ensure through an application process and panel review that data requests have public benefit and interest. The process of application via BPSU to PBPP was previously streamlined with a template application used for BPSU studies. The use of the template was removed in 2019 and now all BPSU studies are reviewed individually. This significantly delayed the start of the project and PBPP panel review and amendment process also caused significant delays.

PBPP review required extensive knowledge of the information governance regulations for Scotland and requirements for each health board within Scotland. As we were unable to predict where a case would present, all health boards would be required for the study. As each of the 14 NHS health boards in Scotland have a privacy notice which allowed for personal information to be accessed in the context of research, this was accepted by the panel and local research and development approval was not required by

every site. PBPP approval was granted September 2022. (Appendix 9 : Privacy Advisory Committee Approval Letter)

After initial PBPP review, some adjustments to the application form and protocol were required. The key reservations raised by the PBPP included:

1. Storage of reporting clinician details using REDCap and the QR Code
2. The use of NHS Lothian computers (when study led by University of Edinburgh)

It was vital the study retained BPSU methodology but the use of the QR code was an additional feature in the study. As the start of the study was already delayed, the decision to remove the use of the QR code in Scotland allowed PBPP application to move forward. PBPP were accepting of this change. To ensure the study was well publicised in Scotland, the study was promoted at regional meetings:

1. Ensure local paediatricians with respiratory interest or those who would follow up cases of NFA have been sent key information. These clinicians have been identified by Scottish Paediatric Respiratory Interest Group (SPRInG) network, Scottish Lung in Childhood (SLIC) network.
2. Emergency clinicians have been briefed via PERUKI network webinar

NHS Lothian computers are ISO 27001 certified and therefore were considered the preferred option by the study team to access and process the data within the safe haven provided by HIC Dundee.

4.3.4 Privacy Advisory Committee

The Privacy Advisory Committee Northern Ireland is a facet of Health and Social Care Northern Ireland. This follows standards set by Code of Practice on Protecting the Confidentiality of Service User Information 2009 (updated 2019)¹⁹⁸. In Northern Ireland there is no equivalent to Section 251 adhered to by CAG England and Wales and therefore decisions regarding personal data and special category data will be reviewed by the Privacy Advisory Committee¹⁹⁸. Application to the Privacy Advisory Committee required a discussion with the committee chair. Approval was granted in August 2022. (Appendix 9 : Privacy Advisory Committee Approval Letter)

4.3.5 GDPR Considerations

In a surveillance study of near fatal asthma in children and young people, access to special category data regarding ethnic or racial origin and data concerning health is required. Relevant health care details include clinical observations, clinical examination findings and clinician diagnosis, management plan and treatment.

For this study ethical approval and national permissions from regulatory bodies were required to access special category data. Three legal clauses which were explored for the study methodology to obtain access to surveillance data;

- 1) consent
- 2) substantial public interest
- 3) archive, statistical or research purpose.

A consent process was considered but due to the small numbers of expected cases, non-consenting participants in small numbers would not misrepresent

the characteristics of the patient group and skew any observations that were drawn from the study. The study sought access to the data based – substantial public interest in the area of public health. It was recognised that detailed information on near fatal asthma presentation, care and follow up is vital to prevent further asthma deaths in children and establish a bundle of care for children and young people experiencing near fatal asthma. Through detailed analysis of near fatal asthma attacks, research will inform whether risk factors such as ethnicity, social deprivation are relevant for near fatal asthma but also determine if triggers such as outdoor air pollution, weather and intercurrent viral infections are linked to near fatal asthma attacks.

4.3.6 Data sharing agreement Republic of Ireland

Studies run by the BPSU do not require additional ethical approval from a regulatory body in the Republic of Ireland. There is an active agreement that studies run by the BPSU and the Irish Paediatric Surveillance Unit are classed as audit by the National Office of Health Protection, Health Service Executive Ireland. (Appendix 10 : Republic of Ireland BPSU Agreement).

4.3.7 Data Sharing Agreement, University of Edinburgh

To enable to storage of the study data within the safe haven HIC Dundee, a data sharing agreement was required between University of Edinburgh and HIC Dundee. This application required thorough knowledge of the protocol, GDPR principles and BPSU methodology.

The data controllers for this study are jointly NHS Lothian and University of Edinburgh. The study team and researchers are affiliated with the University of Edinburgh, data sharing agreement therefore was required between HIC

Dundee and University of Edinburgh. Delays in obtaining this contract postponed the launch of the study (Approval gained 19th October 2022).

4.4 Project timeline

The project was planned to start recruitment in February 2022. Due to the delays in ethics application and permissions, case notification began in October 2022.



Figure 12 Project timeline

4.5 Reporting Platform Design Process

Study methodology reflected three aims

1. Describe the frequency of near fatal asthma in children and young people over an 18 month period.
2. Describe near fatal asthma attacks in detail in children and young people including prehospital, inpatient and follow up care.
3. To determine if risk factors such as air pollution, viral triggers, weather, gender, ethnicity or social deprivation were observed in near fatal asthma attack in children and young people in the UK during the surveillance period.

Once ethical approvals and permissions were granted, the study design in partnership with Health Informatic Centre (HIC) Dundee could begin.

Although the questionnaire had been structured, the transfer of this to an online platform and the methodology of the data collection was still required.

4.5.1 BPSU Monthly e-reporting cards and migration to online reporting

All consultant paediatricians who are members of the Royal College of Paediatrics and Child Health (RCPCH) are encouraged to sign up to the British Paediatric Surveillance Unit. Over time, the BPSU has adapted its methodology of reporting.

4.5.1.1 *Previous BPSU systems*

The BPSU reporting cards were historically paper forms which were posted to clinicians. Clinicians would complete the reporting card if they had or had not encountered a case of one of the listed conditions and return it to the BPSU. The research team would be informed of the reported case and post a questionnaire to the clinician who would complete it and return to the researcher. Over time this was updated to a monthly email, emailed or posted questionnaires which were returned to the researcher.

4.5.1.2 *Updated BPSU system*

In 2021, the BPSU began the process of migration to a new online system of data collection. They retained the process of sending the monthly e-reporting emails but also allowed clinicians to login to an online account and report a case at any time. The monthly reporting card would then reflect any cases seen in the past month but these could be completed at the clinicians convenience. Data would be entered by the clinician directly into a data platform which links to a safe haven. Using this system, researchers can review the questionnaire online and subsequently submit to the safe haven.

This system allows secure data entry by the clinician but also a high level of security of data storage for the researcher.

The near fatal asthma surveillance study was the second study to use the online platform. To reflect the different clinicians who would see a case at different stages of their inpatient or outpatient journey (see Figure 11), the questionnaire and accessibility on the online platform was divided into distinct stages to allow clinicians the option of only completing the relevant section. Instructions were provided to the reporting clinician regarding completion of the relevant section.

The BPSU methodology assumes that children age 5 – 15 years experiencing near fatal asthma will be cared for by a paediatrician therefore using the BPSU as a surveillance for reporting cases would allow adequate geographical coverage of the UK and Ireland and ensure patients presenting to secondary and tertiary care could be reported to the study. We did not include primary care in the reporting as this was not part of the BPSU methodology (affiliated with the RCPCH) and we were confident that all patients meeting study criteria would be managed in a hospital setting even if initial presentation was in primary care.

4.5.1.3 Safe Haven – Health Informatics Centre (HIC) Dundee

A safe haven or Trusted Research Environment (TRE) is a secure digital or physical environment which was been created to store and analyse confidential data. Access to a safe haven is restricted and requires appropriate training and authorisation for use. In Scotland, a safe haven must

align and meet the standards set by Scottish government by the Chapter for Safe Havens in Scotland¹⁹⁹. Health Informatics Centre Dundee (HIC) is the predefined safe haven in use by the BPSU. HIC is affiliated with the University of Dundee (<https://www.dundee.ac.uk/hic>). HIC has existed for 15 years and for 12 years has operated as a trusted research environment²⁰⁰. HIC Dundee complies with an information security standard (ISO)27001. ISO 27001 certification allows data to be held, processed and analysed within a highly secure environment. An ISO standard has three facets – confidentiality, information integrity and availability of data²⁰¹. To store information within a safe haven, researchers must complete Medical Research Council Course e-course on Research Data and Confidentiality. Only projects assigned to dedicated users can be accessed within the safe haven. This facilitates a safe environment for data storage in line with GDPR standards set by the Medical Research Council. Within the safe haven, data can be pseudonymised or anonymised. Data analysis and data linkage can occur with pseudonymised data. Standard operating procedures for HIC Dundee can be found on their website²⁰⁰.

All patients can opt to remove their data for research through the National Data Opt out (<https://digital.nhs.uk/services/national-data-opt-out>). This was made clear to patients through the study website (<https://www.rcpch.ac.uk/work-we-do/bpsu/bpsu-study-near-fatal-asthma>) and public information leaflet (Appendix 11 : Patient Information Leaflet).

4.5.2 Frequency of attacks and duplicate reporting

To determine the frequency of attacks a time period of 18 months was pre-defined prior to study commencement. Initially a 24 month period was requested but this was unfortunately unable to be facilitated by the BPSU. The frequency was defined by the number of attacks in 18 months. Although clinicians could retrospectively report a case, the initial report (without detailed questionnaire) prompts clinicians to enter a date of attack (later in questionnaire asked to specific date and time of NFA). This was not mandatory but was available to the researcher if entered and the case submitted to allow the researcher to potentially identify duplicate cases. If questionnaires were not completed or submitted to the researcher, initial date could also be used to estimate frequency even if full questionnaires were not completed.

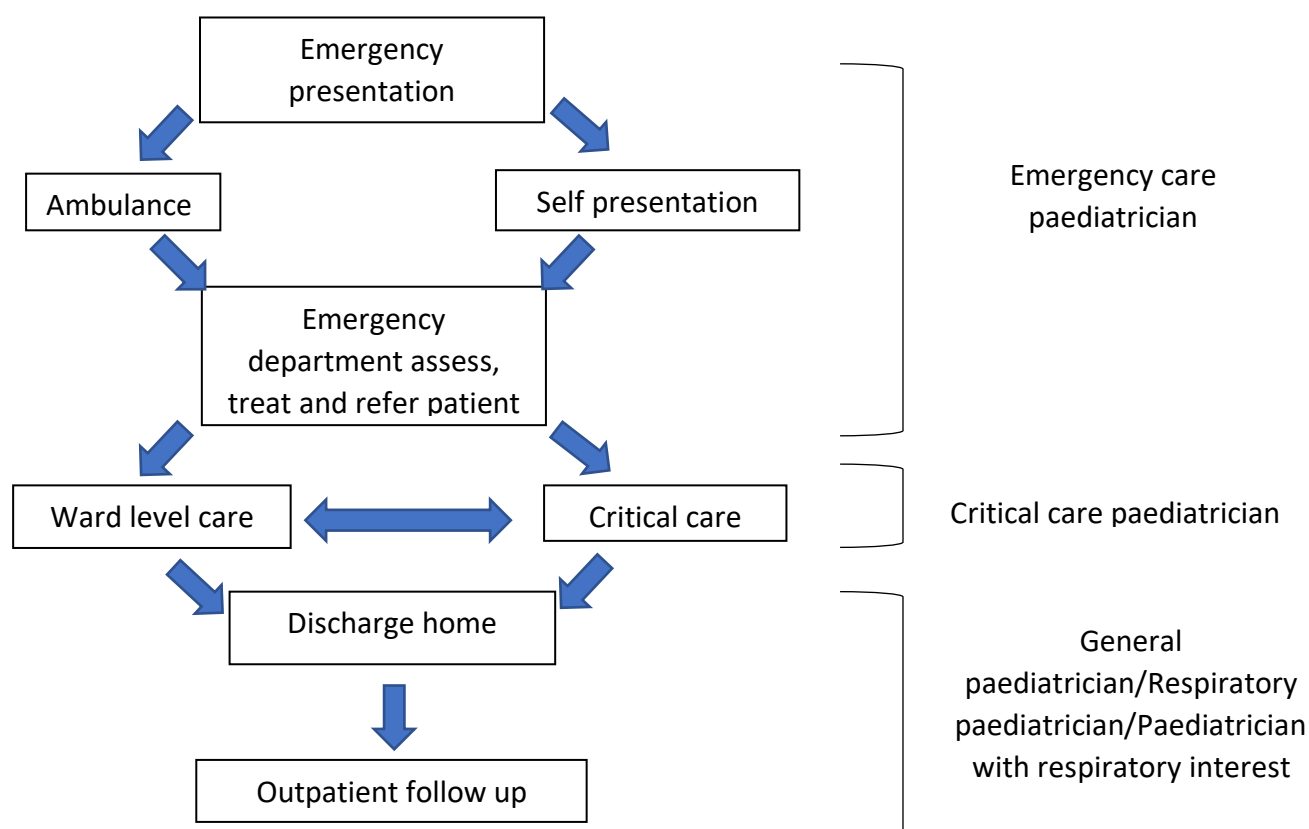
As clinicians from differing clinical areas could report the same attack in the same patient, (for example an ED clinician and respiratory clinician could report the same case) a system to identify duplicate cases was required. As no identifiable information was collected on e-reporting cards, duplicate cases could not be identified from these. Researchers however were provided with the name of the reporting clinician and could contact clinicians via the HIC online platform. To minimise duplication reporting from clinicians from the same clinical area, once a clinician responded to a reporting card the researcher internet searched of the name of the reporting clinician to identify their place of work. If two simultaneous reports were from the same hospital or geographical area the researcher contacted the clinicians via the

HIC platform and alerted them of potential duplicate reporting. If the clinicians had differing roles e.g., a report from ED and a report from general paediatrics clinicians were still alerted to the potential duplicate reporting but advised the clinician had reported from a different department.

4.5.3 Prehospital, inpatient and follow up care

To describe near fatal attacks in detail, further information about each attack was required which would allow the researchers to observe any risk factors associated with near fatal asthma attacks. If a clinician reported 'yes', they would be directed to the HIC platform to complete the questionnaire online (Appendix 12 : Near Fatal Asthma Questionnaire). To ensure GDPR standards were met, only clinicians directly involved with the patients care accessed medical notes and completed the study questionnaire.

A hypothesised a patient journey reflected which clinicians may be involved in data entry in the case of near fatal asthma(Figure 13).



As demonstrated above, a single patient may interact with many clinicians and therefore multiple reports about the same patient could be fed back to the researchers. It was important therefore that the minimum amount of patient identifiable details were included in the surveillance data to allow identification of duplicate reports. The questionnaire would also consider that one clinician is unlikely to have details for the entirety of the hospital admission and the questionnaire would require a design that reflected discreet sections to allow reporting clinicians to only complete the relevant section.

A key element of near fatal asthma management includes outpatient follow up and long term outcomes. To include this a 12 month and 24 month follow up questionnaire was proposed which would be sent to the primary consultant of the patient. (Appendix 13: 12 Month Follow Up Questionnaire, Appendix 14: 24 Month Follow Up Questionnaire)

4.5.4 REDCAP Integration

The initial use of REDCap had hoped to function in emergency departments to allow ED clinicians to enter details 'there and then' by scanning a QR code which was link to the safe haven to allow data entry. The use of the QR code had been intended for clinicians of all grades to use. Unfortunately, this functionality was not compatible with BPSU methodology or safe haven data protection protocol. Instead, REDCap and the QR code were used as access a quick screen for eligibility and knowledge of the emergency department questions within the study. Entry of a case on REDCap by any clinician in the emergency department will trigger an email to the Paediatric Emergency Research in the UK and Ireland (PERUKI) lead clinician at each site stating

the date of attack with no further clinical detail. The lead PERUKI clinician at each site agreed to follow up any cases entered on REDCap on the specific data and if eligible, entered the details into the HIC reporting site using their BPSU login. The use of the QR code was not adopted by PBPP review in Scotland and therefore was not rolled out in ED services in Scottish hospitals.

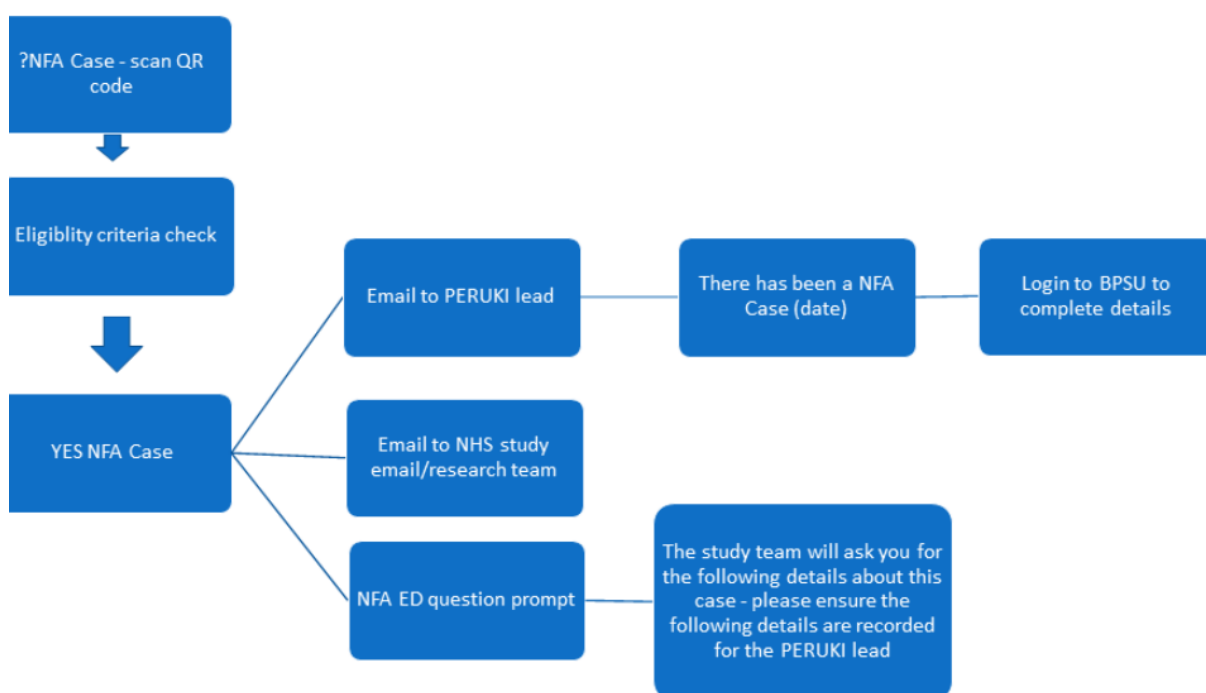


Figure 14 REDCAP PERUKI flow chart

4.5.5 Risk factors

Full postcode was sought to allow researchers to determine outdoor air pollution levels at the time of the attack. Clinicians were only asked to provide clinical details available from hospital notes.

4.6 Study Promotion

During the early stages of the study there were some unexpected delays to obtaining the relevant permissions (Chapter 4.3) The BPSU mandated that communication about the study should not be released until a study date of launch was confirmed (date). Once confirmed the study was highlighted on social media platforms, national training groups and through the RCPCH e-newsletter.

4.6.1 PERUKI

The study was supported by the PERUKI group and publicised on their website. PERUKI members were alerted to the study and associated materials were made available on the PERUKI shared group Google Drive folder. Additionally, the study was presented at a PERUKI online meeting (May 2022). This presentation allowed the study team to explain the rationale and study objectives to PERUKI lead members, and also clarify the data entry process. The project received positive feedback by email from PERUKI members. It was emphasised to emergency clinicians that the prehospital and initial hospital care was the only required section emergency clinicians were encouraged to submit. Reporting emergency clinicians were asked to nominate a lead inpatient clinician who could complete the remainder of the questionnaire and the follow up questionnaire. PERUKI were updated throughout the study and will be acknowledged in any publications.

4.6.2 Paediatric Critical Care Scientific Group(PCCSG)

We expected a significant proportion of patients would require management in paediatric critical care and therefore it was important that critical care clinicians were aware of the study and involved in data collection. We were

invited to discuss the study at the Paediatric Critical Care Scientific Group Meeting (April 2022). This was a useful opportunity, where we received feedback from critical care clinicians present that they were cautious about the time needed to complete data entry and this would be challenging in a critical care environment. We advised that we as the study team would try and support them in this task as much as possible and pre-circulate the critical care section questions to try aid data entry. We discussed the possibility of a pre filled prompt in electronic health record systems in the commonly used critical care platform 'Metavision' but we were advised that this would not aid data entry as the information would still require transcription to the HIC Dundee platform.

4.6.3 Royal College of Paediatrics and Child Health (RCPCH)

We used the RCPCH Annual Conference (May 2023) as an opportunity to promote the BPSU study and ensure that general paediatricians were aware of the study.

4.6.4 National Paediatric Respiratory and Allergy Nurses Group(NPRANG)

The study was regularly publicised through the NPRANG newsletter. This was a valuable opportunity and we were able to discuss the study with specialist nurses who are involved in the care of children experiencing near fatal asthma. We explored with the BPSU if it would be possible for specialist nurses to report during the NFA study as we hoped to increase reporting through this very supportive network. Unfortunately, the BPSU were unable to amend their methodology to allow this.

4.6.5 British Thoracic Society (BTS) – Winter Meeting

Dr Ann McMurray was invited to discuss the work on the near fatal asthma children and young people at the British Thoracic Society Winter Meeting in November 2022. This meeting was available to British and international members of the British Thoracic Society in the UK.

4.6.6 British Paediatric Respiratory Society (BPRS)

Respiratory paediatricians in the UK are invited to join the British Paediatric Respiratory Society. The BPRS circulate a monthly newsletter to members. We expected the majority of specialist paediatric respiratory clinicians to be members of the BPRS. The monthly newsletter highlighted the study and provided study contact details. We circulated study updates and encouraged respiratory clinicians to report cases.

4.6.7 Paediatric Respiratory Trainee Group

During the surveillance period, I contacted a network of paediatric trainees who are specialising in paediatric respiratory medicine. The study was highlighted to this group of trainees who work across the UK. Trainees were asked to consider if they had encountered any cases of near fatal asthma, if they had we asked them to determine if the local consultant had reported the case to the BPSU and if not, highlight the study to them and forward the research team contact details.

4.7 Data collection

During the study, any questionnaire submitted to the safe haven was reviewed within the HIC Dundee platform. To track clinician reporting progress, a data management sheet was created. This did not contain any clinical or clinician details. Clinicians' BPSU unique identifier numbers were

stored to track reporting and response rates. This was password protected.

No other information was stored outside the safe haven.

4.8 Data Analysis

Data analysis is carried out within the safe haven. Cases completed by clinicians have been reviewed by the researcher (DV) and submitted to the safe haven via the online platform.

Once reported and submitted the safe haven cases are accessed by researchers via an NHS computer. Prior to migration, the safe haven was remotely accessed via a VMware Horizon HTML Access. Each user could navigate to the VMware HIC Dundee login and access the safe haven using an individual login and secure password. Once remote access was obtained, the user would have access to their project only. Submissions from the online platform were individually uploaded to the user project folder and could be analysed. Cases were identified by individual unique case number.

After the migration of HIC Dundee to a TRE AWS by Amazon (August 2023) the safe haven was accessed by a link <https://hic-tre.dundee.ac.uk>. To access this, researchers used their email address or username and unique secure password. Access then requires authentication using a onetime code (Authenticator App hosted by Microsoft). The one time code expires every 30 seconds. Once access was granted, users are then required to create a workshop and connect to the safe haven. Submitted cases would appear in each individual project.

Post migration an error was noted in the uploaded case reports; data was missing and columns did not correspond to the correct information. This error was addressed with HIC Dundee. Unfortunately, this fix incurred a significant time delay to data analysis (3 month delay in analysis).

Once HIC resolved this process, all the previous cases had to be re uploaded to the safe haven. Previously the cases were able to be individually uploaded to the safe haven by the researcher (to allow blank or error cases to be omitted). Unfortunately, after the fix from HIC, all previous cases had to be uploaded simultaneously therefore blank and error cases were submitted to the safe haven.

The data was then cleaned before analysis. All column headings were numbered by HIC for the process of building the data platform. A key was provided by HIC to allow the researcher to align the column headings to the corresponding questions.

4.8.1 Data Cleaning Steps

1. Columns renamed as per HIC key
2. Date of event – format changed to English UK day/month/year
3. Blank submissions removed (no clinical details entered)
4. Identify duplicates – format NHS/CHI/Hospital numbers, spaces/dashes removed. 10 digit numbers all in same column.
Duplicates identified by NHS/CHI number – searched within data sheet for matching numbers. Each identified duplicate case then crossed checked with date of event and DOB. two patients with x2 admissions

5. Criteria check, cases not meeting criteria – crosschecked with HIC platform and evidence of incorrect data entry. One case didn't check invasive ventilation but entered data in this column in questionnaire therefore not excluded.
6. Timings changed to 24hour clock. Date formats standardised (UK DD/MM/YYYY)
7. It was noted that tick box questions were uploaded as "true" if the response was ticked. When the data sheet was uploaded it was noted that "false" was also present inconsistently throughout the data. It was confirmed with HIC that "false" was equivalent to an unticked box or blank box and these should not be interpreted. "False" responses were removed from the dataset.

4.8.2 Duplicate cases

Due to the different clinical staff entering patients details either within the same hospital or at differing/referring hospitals, duplicate cases were expected.

Duplicate reports were expected to have matching answers where relevant. It became apparent there were conflicts in the data entered within duplicate cases. Some of these were related to subjective questions that would depend on the clinicians' interpretations such as 'time of NFA attack'. It was also noted that some details that would not be expected to be subjective such as "time of ED attendance" generated conflicts. To resolve conflicts, the clinicians entering the data were contacted to clarify responses. This did not

yield many responses (2 clinicians responded to queries). To ensure that duplicate reports could be consolidated to allow case analysis rules to allow interpretation of results were applied to the duplicate data.

Once duplicate cases were consolidated using duplicate case rules, the data set was reviewed to allow initial analysis.

4.8.3 Section analysis

4.8.3.1 *Patient details*

Consultant in charge of care: Consultant role was accessed via internet search. Consultant roles were categorised:

1. General Paediatrician
2. General Paediatrician with respiratory interest
3. Critical Care
4. Emergency Care
5. Respiratory Paediatrician

Most recent listed consultant role found via internet search was used to determine category of consultant in charge.

4.8.3.2 *Age of patient*

Age of patient was determined from their date of birth at the 'date of attack'.

This calculation revealed one patient <5 years who did not meet inclusion criteria. The reporting clinician was contacted to confirm the date of birth and date of NFA attack which confirmed the patient did not meet inclusion criteria.

The patient was excluded. Three patients were identified who were between 15 and 16 years. Inclusion criteria for the study stated children inclusive of 5

– 15 years therefore these children were included in study data. Average age was calculated (no incomplete data).

4.8.3.3 *Ethnicity*

Ethnicity in the questionnaire was selected from a drop down menu based on UK Government 2021 ONS Census listed ethnicities²⁰². Other free text category could also be selected. As small number suppression is applied to the data, ethnicities were then further grouped into

1. White
2. Asian
3. Black/African
4. Other

Where the following categories were coalesced to form these four groups:

White

- Any other white background
- English/Welsh/Scottish/Northern Irish/British
- White
- Irish

Asian

- Asian/Asian British
- Indian
- Bangladeshi
- Pakistani

Black/African

- White and Black Caribbean
- Black/African/Caribbean/Black British
- African

Other

- Any ethnicity not listed above

4.8.3.4 *Criteria*

Study criteria (Figure 10 Study Criteria) were counted depending on whether the patient met one, two or all of the criteria.

4.8.3.5 *Time between NFA identified and ED attendance*

Reporting clinicians were asked to identify a time when the NFA attack was recognised (Defined by giving 10 puffs of short acting beta2 agonist) Time, between NFA and ED attendance was recorded. The intention of this question was to ascertain if NFA attack time could be identified and if so, is there a critical time period of opportunity for intervention and approximately how long is that critical time period.

The data revealed some discrepancies, for example the time of NFA was after the time and date of ED attendance. Blank ED attendance or NFA attack times were disregarded and as a result time between NFA recognition and ED attendance could not be calculated. The reporting clinician was also asked to report the number of doses of short acting beta 2 agonist (SABA) given between NFA and ED attendance.

4.8.3.6 Admission

Duration of admission was calculated from date and time of ED attendance to stated discharge date and time. If discharged date or ED attendance date was not stated this could not be calculated. Any admission >100 days was clarified with reporting clinician to ensure an erroneous entry had not been made.

4.8.3.7 Clinical observations

Pulse arterial oxygen saturation (SpO₂)

Saturations in room air documented and additionally were grouped by the researcher into the follow categories;

- 100% - ≥ 92%,
- <92% - ≥90%,
- <90% - ≥80%,
- <80% - ≥ 70%,
- <70%

British Thoracic SIGN guidelines determine life threatening events as patient that present with oxygenation saturations <92%.

Highest noted carbon dioxide during admission was recorded by clinicians.

<8kPa

≥8 - <10 kPa

≥10 – <15 kPa

≥15 – < 20kPa

≥20kPa

4.8.4 Planned Analysis

Descriptive analysis of reported attacks were carried out. These are described in detail for pre hospital, in hospital and follow up of patients presenting with near fatal asthma.

4.8.5 Data Quality

Incomplete data points were anticipated due to clinician input failure., Clinicians were contacted by the online platform and then by email to complete missing data points. If clinicians did not respond to communication from the researcher the questionnaire contained a blank response for the specified question. Researchers could return the incomplete questionnaire to the clinician via the online platform but no clinicians (n = 4) completed and returned the data. The original submission was uploaded to the safe haven by HIC if this occurred.

Early discussions with PICANet took place to determine if routinely collected critical care data could be used to complete gaps in missing data points. This would have involved patient identifiers being removed from the safe haven to allow data to be matched from PICANet. The removal of patient identifiers from the safe haven was not possible and therefore this method could not be explored to resolve data gaps.

4.8.6 Data linkage

The use of HIC Dundee safe haven allowed detailed patient information, such as postcode, to be entered by clinicians into the HIC Dundee database. This level of personal information was requested for this project to support the capacity for new knowledge based on data linkage to be performed within the safe haven. Relevant external data sets which are either publicly

available or permission has been granted, can be uploaded to the HIC safe haven for the purpose of data linkage. Any results from data linkage however must remain in line with GDPR regulations. Researchers can access pseudonymised data within the safe haven with small number suppression (<5) applied to data when disseminated. The following sections discuss the data linkage that will be applied.

4.8.7 Weather Patterns

As demonstrated by Darvall et al 2019 (see Chapter 3: Systematic Review), near fatal asthma attacks have been observed in extreme weather events. Thunderstorm asthma is a well described phenomenon where high winds and heavy rainfall combined increase the number and suspension of pollen and air pollution particles in the atmosphere. Larger particulates such as pollen are fractured by electrical forces generated by the thunderstorm increasing the level of circulating pollen and increasing the likelihood of inhalation to larger airways²⁰³. As discussed in 'Acute Asthma Triggers Chapter 2.2.2', cold weather is also recognised as a trigger for asthma attacks. To observe if near fatal asthma attacks in children and young people were associated with weather patterns, meteorological information will be examined in the 48 hours prior to near fatal asthma attack. Reviewing meteorological information, specifically any extreme weather events, can be accessed through publicly available weather data.

Several weather sources were considered for weather data linkage (Table 3). After careful consideration and discussion with Dr Tom Clemens, it was decided that using data from Met Office Datapoint to capture extreme

weather events (storms, extreme temperature changes and thunderstorms). These will be captured over the study period and any observed associations will be noted. Dates of extreme weather events will be obtained from the Met Office (<https://www.metoffice.gov.uk/>).

4.8.8 Viral triggers

Viral infections are known to trigger asthma attacks. Asthma hospitalisation in children have been associated with associated with the school calendar^{204,205}. The contribution of specific viral infections has been examined²⁰⁶ and the role of rhinovirus infections has been described. No specific viral infections have been associated with near fatal asthma attacks to our knowledge. We will describe trends of seasonal circulating viral infections in children as well as those associated with specific near fatal asthma attacks.

Obtaining this data will rely on viral swabs taken at the time of the event, clinician input and access to UK viral data surveillance. In the UK, surveillance data is divided by country with different labs reporting overall data points. In England and Wales (majority of cases expected), two data sources are used. Public health England and Wales report data using Second Generation Surveillance System (SGSS) and Respmart. SGSS is used by the majority of laboratories in England and Wales but will not routinely provide surveillance for the most common respiratory viruses. Respmart provide greater detail but is only in use in 17 laboratories in the UK. Numbers are reported per 100000 population. Viral prevalence data for

England and Wales is released in upper tier local authority level and publicly available from <https://ukhsa-dashboard.data.gov.uk/>.

4.8.9 Fungal spores and pollen counts

Airborne fungal spores, in particular of *Alternaria alternata*, have been suggested as a trigger for near fatal and fatal asthma in studies in both children and adults²⁰⁷ and was noted to be of significance in the National Review of asthma deaths.¹⁰ Fungal spores however will vary in concentration across seasons and weather exposure²⁰⁸. Data on fungal spore levels in the UK are monitored and published by the University of Worcester. Levels are monitored only in high season (July to September). Data is publicly available from <https://www.worcester.ac.uk/documents/alternaria-seasons-charts-2020-to-2022.pdf>.

Similarly, pollen counts across the UK are available from fixed monitoring sites and reported from these regions:

- Scotland
- Northern Ireland
- Northwest England
- Northeast England
- Wales
- West Midlands
- East Midlands
- Southwest England
- South Central England
- East of England
- Southeast England

Pollen levels in each of these regions will be noted during the study period, to ensure anonymised dissemination of data, reporting numbers will be matched to a generalised pollen calendar for the UK. (Available from

<https://www.worcester.ac.uk/about/academic-schools/school-of-science-and-the-environment/science-and-the-environment-research/national-pollen-and-aerobiology-research-unit/pollen-calendar.aspx>)

4.8.10 Air pollution

Outdoor air pollution is known to trigger asthma exacerbations in children and young people. For this study, I planned to examine outdoor air pollution levels 5 days (lag time 0- 5) prior to the near fatal asthma attack and compare annual modelled background air pollution exposure at each case postcode. To determine this time period, advice was sought from Dr Abigail Whitehouse (Senior Clinical Lecturer in Children's Environmental Health and Honorary Consultant in Paediatric Respiratory Medicine, Queen Mary University, London). Air pollution data was obtained from Department for Environment, Food and Rural Affairs (DEFRA). Annual mean observations (1km x1km modelled background air pollution data <https://uk-air.defra.gov.uk/data/pcm-data>) and the AURN publicly available data (<https://uk-air.defra.gov.uk/networks/network-info?view=aurn>). Air pollution monitoring in the UK is provided by fixed stations which are positioned in areas of high vehicle traffic or urbanised areas. Modelled data can provide estimated outdoor air pollution levels at postcode level. As full postcode data will be requested from clinicians reporting cases, modelled background air pollution exposure can be determined at postcode level. It is noted that there is a time lag in publicly published DEFRA annual modelled air pollution data. If the data for the corresponding year of NFA attack is not available, the exposure will be calculated based on the most recent annual data available.

To determine air pollution exposure around the time of the attack (lag time), initial analysis planned to use postcode data to determine the AURN monitoring station which is closest to the postcode. This can be determined using the XY coordinates corresponding to the AURN monitoring station and XY coordinates of the postcode belonging to each case. AURN data can be accessed through the R studio programme 'Openair' (<https://cran.r-project.org/web/packages/openair/index.html>)²⁰⁹. Using Openair, lag time of 5 days could be calculated based on postcode. This analysis was tested within the safe haven but unfortunately Openair could not be used in real time within the safe haven. As individual postcodes could not be removed from the safe haven Openair could not be used to determine lag time. To overcome this I hoped to download AURN from <https://uk-air.defra.gov.uk/networks/network-info?view=aurn>. This is publicly available data and gives air pollution data collected from each site. As individual postcodes could not be removed from the safe haven I attempted to download AURN data from corresponding time periods around NFA attack for all air pollutants which could then be uploaded to the safe haven and used for analysis of lag time. If this was possible, a control time period could also be examined to allow a case crossover analysis²¹⁰. Unfortunately the size of download to preserve anonymisation of cases (i.e. data from all monitoring stations for specific air pollutant over date range) could not be carried out from the AURN site. Even when lag time was reduced to 48 and 24 hours this data was not publicly available for download. I contacted AURN to review if this data could be supplied for an individual research project within the

time constraints planned for the submission of this thesis but AURN data from each monitoring site was not available for download (Data from AURN has verification period of approximately 6 months) and furthermore not all AURN monitoring sites monitored the air pollutants of interest in this analysis. Lag exposure time based on AURN data could not therefore be calculated for each case using this methodology.

As discussed in Appendix 2 : 'Near-fatal and fatal asthma and air pollution: are we missing an opportunity to ask key questions?' personal exposure monitors will provide a detailed individual exposure to air pollution. These are not widely available and therefore data from personal exposure monitors will not be used in the study.

Indoor air pollution is not routinely monitored by UK government standards. Whilst the impact of indoor air pollution on asthma is widely recognised²¹¹, reporting clinicians are unlikely to have access to indoor air pollution monitors. This was not included on the near fatal asthma questionnaire.

4.9 Twelve month and 24 month follow up

Patients will be followed up with a short questionnaire at 12 months and 24 months (see appendix). Clinicians who submitted the initial report will be contacted to complete this if they are from the following groups

- General paediatric
- General Paediatrics with respiratory interest
- Respiratory paediatricians

Intensive care clinicians and emergency care clinicians will not be contacts for follow up. Follow up questionnaires will be 'triggered' by the researcher at the 12 and 24 month follow up point post questionnaire submission. Follow up questionnaires will be completed on the HIC platform. If response to follow up questionnaires is poor, an amendment to follow these to be completed with minimal identifiable data will be considered. 24 month follow up will be completed by April 2026. Due to delays in set up time for the study, the 12 and 24 month surveillance questionnaires do not form part of this thesis.

4.10 Surveillance end point

In previous years, the BPSU has been known to have a high response rate (88% in 2020). Compliance with reporting cases is decreasing as is clinician sign up to the BPSU. We are unclear why this is the case and the BPSU are attempting to encourage clinician participation. BPSU data from 2020 is highlighted in Figure 15.

Table 2: Outcome of follow-up of the cases reported in 2020 for conditions under surveillance

Condition under surveillance	Date when reporting began	Valid reports	%	Duplicates	Errors	(D&E) %	Not yet known	%	Total
CRU	Jun-91	93	45	42	67	52	6	3	208
PIND	May-97	2,505	51	607	1,277	39	489	10	4,406
ICH	Nov-18	28	29	31	34	66	5	5	98
SC	Nov-18	40	52	9	6	19	22	29	77
FPIES	Jan-19	98	47	7	78	41	26	12	209
CFS	Feb-19	131	46	2	23	9	126	45	282
HSV	Jul-19	76	39	34	9	22	75	39	194
PNE	Jan-20	45	42	10	7	16	44	42	106
COV	Mar-20	549	54	116	193	30	160	16	1018
PMIS	Mar-20	748	49	192	89	18	508	33	1537
ASU	Sep-20	7	7	0	27	28	61	64	95
ESK	Sep-20	18	21	1	3	5	62	74	84
CNO	Oct-20	42	36	6	18	21	51	44	117
RES	Nov-20	29	36	2	15	21	35	43	81
Total		4,409	49	1,059	1,846	32	1,670	19	8,984

CRU	Congenital rubella	COV	Neonatal complications of coronavirus disease (COVID-19)
PIND	Progressive intellectual and neurological deterioration	PMIS	Paediatric multisystem inflammatory syndrome, Kawasaki disease and toxic shock syndrome
ICH	Ichthyosis	ASU	Glucocorticoid induced adrenal suppression
SC	Sydenham's chorea	ESK	Conservative care in end-stage kidney disease
FPIES	Food protein induced enterocolitis syndrome	CNO	Chronic recurrent multifocal osteomyelitis/ chronic nonbacterial osteomyelitis
CFS	Severe chronic fatigue syndrome	RES	Outcome of resuscitated term babies with no heart rate detected at 10 minutes of age
HSV	Neonatal herpes simplex virus		
PNE	Clinical characteristics of pneumococcal meningitis		

Figure 15 BPSU 2020 reporting data

BPSU numbers from 2020 show between 7% and 54% of reported cases were valid. This is consistent with survey responses from healthcare professionals excluding the BPSU. In physicians and surgeons the average response rate to surveys has been found to below 50% (29% in paediatricians)²¹² and vary dependent of speciality and whether information is gathered in person or online. Online surveys had lower response rates ²¹³. The aim for this study was to encourage reporting clinicians to complete the questionnaire highlighting the importance of the information gathered on near fatal asthma in children and young people and gap in clear management,

follow up care and risk factors associated with this group. Aware that each case took on average 3 months to chase, the study endpoint would be achieved either 3 months after surveillance ceased or when reporting achieved 80% completion rate.

5 Chapter 5: Results

This chapter will describe the results collected from the surveillance study from 1st October 2022 to 1st April 2024. I have chosen to use descriptive analysis to present my results. I considered this as the most appropriate method to present this surveillance data. Where relevant, measures of central tendency and dispersion were used to describe the data within the constraints of the small number of observed cases. These descriptive statistics are novel in the characterisation of near fatal asthma in children and young people in the UK. I have explored the presentations in detail and where relevant, noted meaningful associations within the data set.

5.1 BPSU Survey Response

Over the 18-month period monthly e-reporting cards were sent to BPSU registered clinicians. Clinicians could also access the reporting website at their convenience in parallel to or instead of the emailed reporting card.

The surveillance period ended on 1st April and clinicians were given 1 month to report any final case details for the analysis presented in this thesis. For the results in this thesis, clinician responses for any cases submitted between 1st October 2022 and 30th April 2024 are presented.

In 2024, 5138 paediatric consultants were registered with the RCPCH (England, Wales Scotland)²¹⁴, 118 RCPCH paediatric consultants were registered in Northern Ireland (2017 figures)²¹⁵ and 257 paediatric consultants were registered with the Royal College of Physicians

Ireland(RCPI) in the Republic of Ireland (2021)²¹⁶. This gives an approximate total of 5513 consultants across the UK and Republic of Ireland available to sign up to BPSU reporting cards.

Throughout the study the overall reporting response to the BPSU cards is shown in Figure 15. On average, 66% of the clinicians registered with the BPSU responded to a reporting card every month. Unfortunately reporting figures from March 2024 were not available.

Month	response rate
Oct-22	67.6
Nov-22	65.4
Dec-22	66.2
Jan-23	61.3
Feb-23	67.0
Mar-23	56.4
Apr-23	71.3
May-23	65.5
Jun-23	67.1
Jul-23	69.4
Aug-23	71.4
Sep-23	65.7
Oct-23	66.9
Nov-23	70.0
Dec-23	68.2
Jan-24	68.0
Feb-24	57.0

Figure 15 BPSU Reporting Card Responses

The pattern of reporting varied over the 18 month surveillance period (see Figure17) . Some clinicians entered cases month by month whilst others chose to “collect” all the reports from a clinical centre and reported in one month. Error reports were common and often multiple error reports were submitted by the same clinician. This affected the monthly reporting figures which did not then correspond with the number of NFA cases.

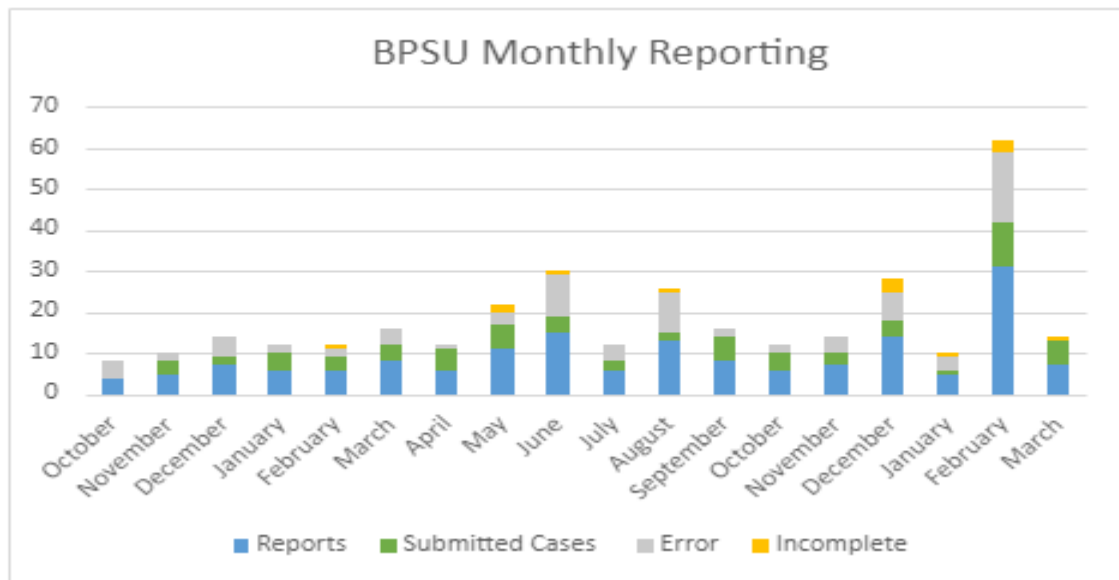
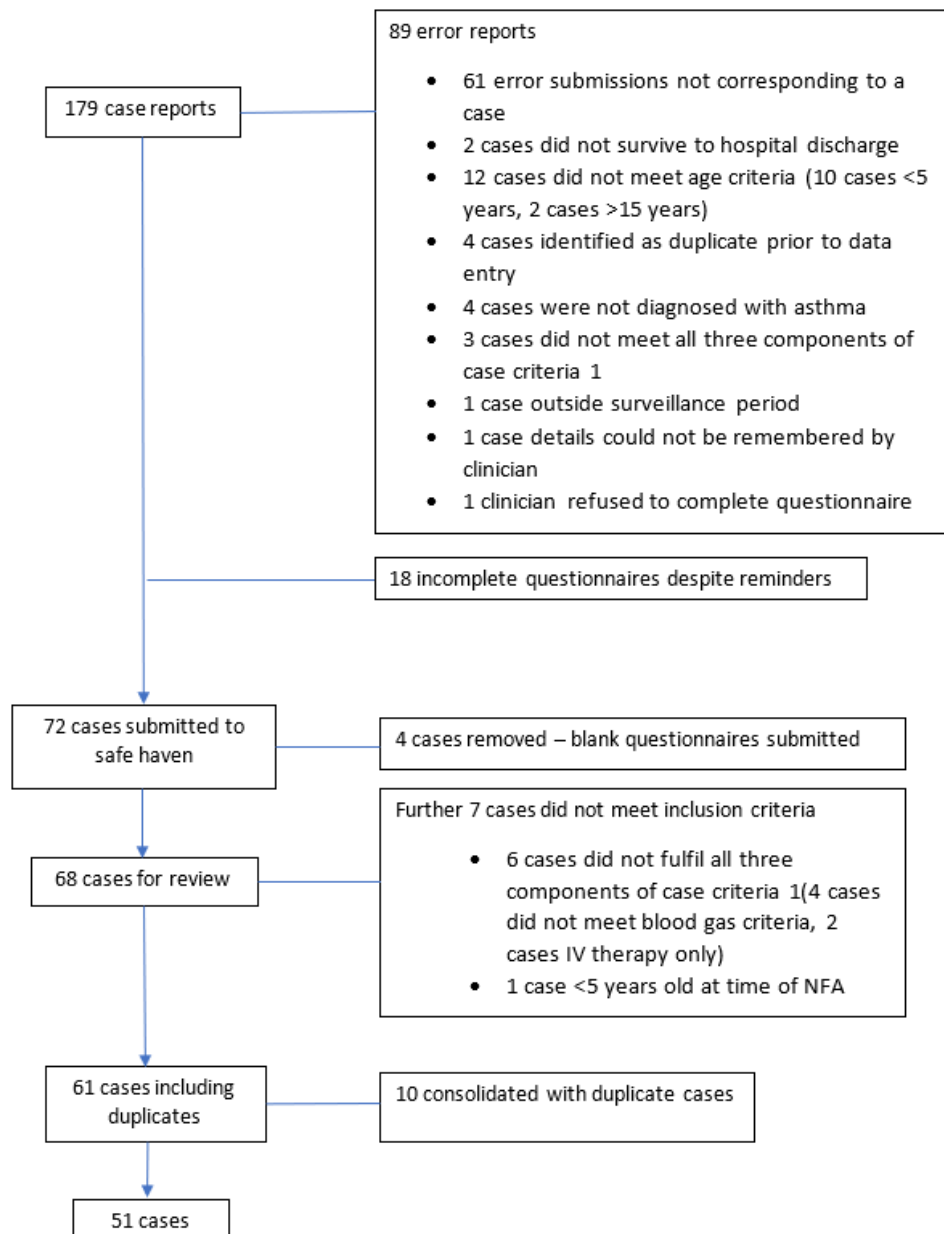


Figure 17 BPSU monthly reporting pattern – note high number of reports in February 2024 corresponding to a single clinician entering seven reports observed over the entire study period.

The new HIC reporting system enabled clinicians to report at their convenience or using the monthly reporting cards. Of the 179 reports, 89 were erroneous reports (50%), 72 were submitted (40%) and despite multiple reminders, follow up emails and attempts to contact the clinician through members in their department 18 (10%) cases remain unreported. (see Figure 16). Seventy-two cases were submitted to the safe haven for further analysis. Of these, four cases were identified as blank and when contacted, all clinicians reported these had been submitted in error (i.e., did not correspond to a case). Prior to AWS migration (see Chapter 4.5.1.3), cases with no supporting clinical data could be excluded from safe haven upload. Post AWS migration, these cases could not be excluded. After duplications and error reports were removed, 51 cases were identified for analysis.

- 46 cases were reported from England
- 5 cases were reported from Scotland, Wales, Northern Ireland and Republic of Ireland



Case reporting throughout the study period noted three spikes in case numbers in March 2023, May 2023 and October 2023. The lowest cases were reported in April 2023 (n = 0).

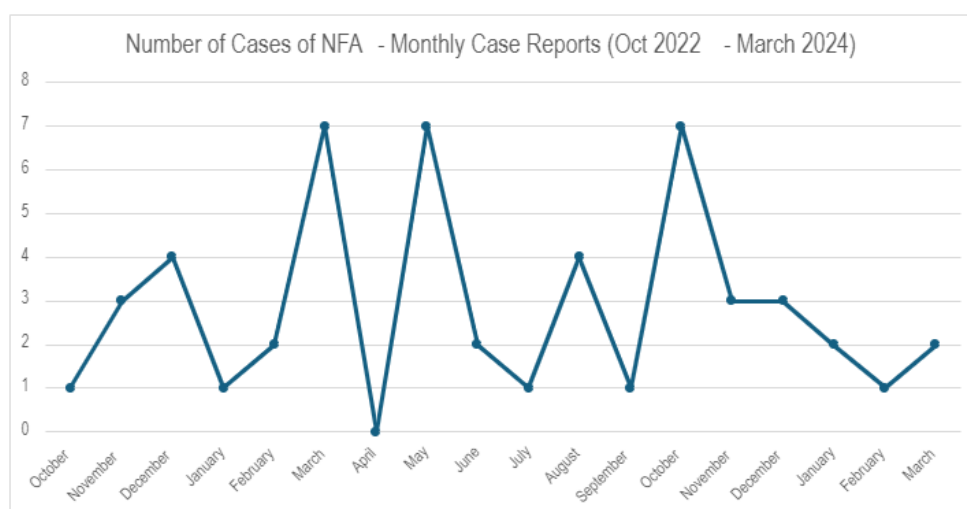


Figure 16 NFA Monthly Case Numbers

5.2 Summary of cases

The summary statistics of the patients observed in the surveillance period are outlined in Table 12. Aggregate data is presented. Two patients in the surveillance were noted to have two discrete attacks of near fatal asthma within the study period. One patient was discharged and readmitted 3 months later, the second patient was discharged and readmitted one month later. This equates to 49 patients for 51 reported cases during the surveillance period. Analysis of each attack (including age distribution) will examine the 51 cases of near fatal asthma. Each attack is reported as an individual case report ('N' within the results relate to number of individual case reports unless otherwise stated).

5.2.1 Patient Demographics

Table 5.1 Summary characteristics

Data	N	%
Age distribution (N=51/51)		
Median	10.67 years	
5 - ≤10	22	43%

>10- 15	29	57%
Sex (N=49/49)		
Male	30	61%
Female	19	39%
Ethnicity Background(small number suppression applied) (N=49/49)		
White	31	63%
South Asian	12	24%
African/Caribbean	5	10%
Not reported or Other Ethnicity	<5	3%
Deprivation Indices for English cases (n =42/49) (Quintiles)		
1 (Most deprived)	14	33%
2	8	19%
3	8	19%
4	8	19%
5 (Least deprived)	4	10%

Ages

Age at time of attack was calculated from date of birth and date of attack.

Fractional age (in years) was calculated. Age distribution is show in Figure 14 below. The median patient age was 10.67 years (IQR 8.16 – 13.7 years).

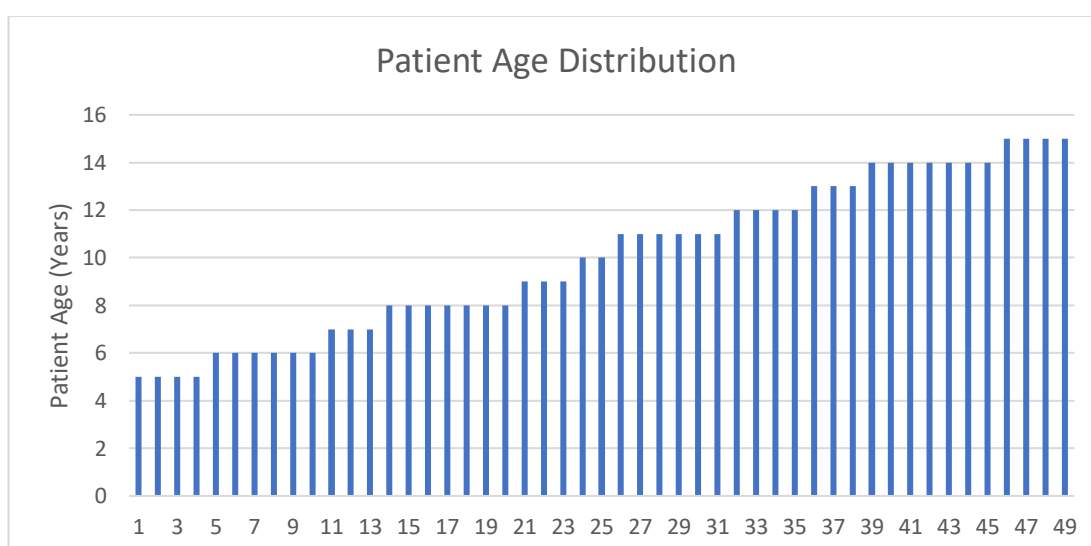


Figure 17 Patient Age Distribution

Gender

Of the 49 patients, 30 patients (61%) were observed to be male and 19 patients (39%) were noted to be female. Schmitz et al (2000) in previous surveillance of NFA in Germany found equal presentation of male: females for NFA. In patients >10 – 15 years old, 10 patients were female, 19 patients were male.

Ethnicity

Eleven different ethnicities were observed in the patient group based on UK consensus categories. Due to small number suppression, aggregate cases have been grouped into categories. Three clinicians did not report an ethnicity for the case, these have been grouped with ethnicities reported as 'other' and the reports for an ethnicity where there were <5 cases.

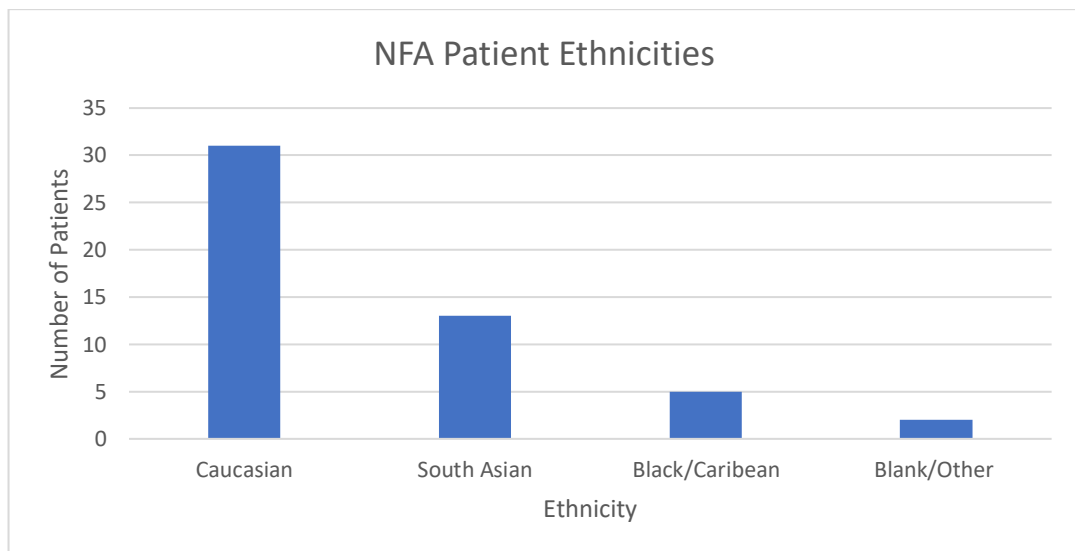


Figure 18 NFA Patient Ethnicities

Deprivation

Five of the 49 patients did not have reported postcodes (not reported from England/Wales/NI/Scotland or submitted from ROI where postcodes not used to identify geographical areas). Deprivation indices could not be calculated for these patients. Reporting clinicians were contacted to complete the outstanding postcode data however there were no responses. Deprivation scores for England were calculated from postcodes corresponding to LSOA based on deprivations indices from 2019 (<https://www.gov.uk/government/statistics/english-indices-of-deprivation-2019>). As highlighted by Table 13 (above) one third of patients were from the most deprived quintile of England.

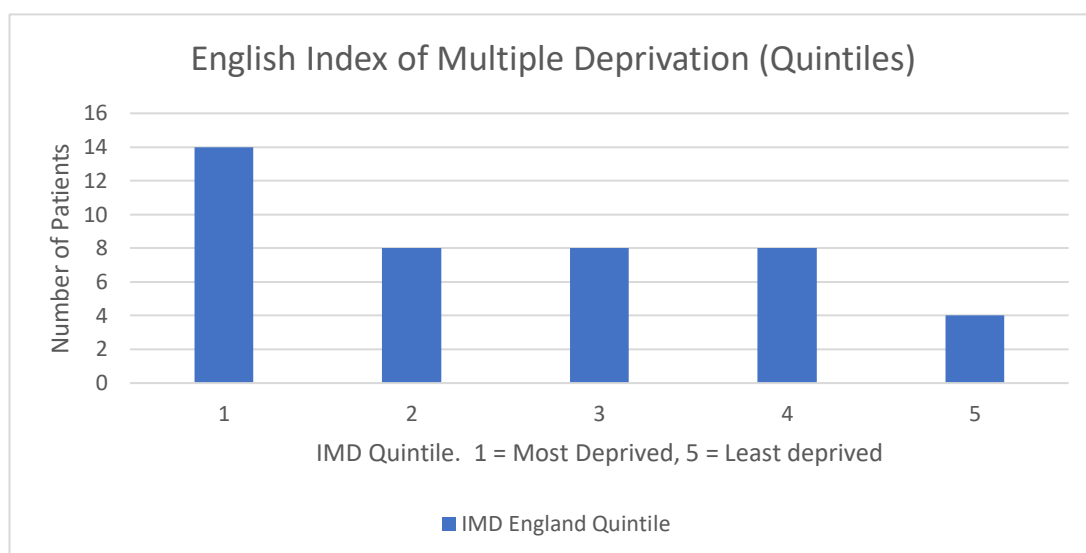


Figure 19 Deprivation IMD Quintiles showing data from patient from England (n = 44) Most deprived centile = 1, least deprived = 5.

As deprivation indices based on the criteria discussed in Chapter 2.5.5 are not comparable between nations, a unified scoring system was applied to patient postcodes from these areas allow inclusion and analysis of deprivation scores from patients from the UK. I chose to use The Townsend

Deprivation Index to calculate a comparable deprivation score across the UK.

The Townsend Deprivation Index

(<https://statistics.ukdataservice.ac.uk/dataset/2011-uk-townsend-deprivation-scores>) is calculated based on four census variables²¹⁷

- Households without a car
- Overcrowded households
- Households not owner-occupied
- Persons unemployed.

Patient postcode was again matched to postcode area and Townsend

Deprivation Index calculated for each patient. Forty three postcodes were available for the 49 patients to calculate Townsend Deprivation Scores.

Table 5.2 Townsend Scores for patients from the UK

Townsend Score Quintile	Number of patients	Percentage (n/43)
1 (least deprived)	1	2.3%
2	9	20.9%
3	5	11.6%
4	7	16.3%
5 (most deprived)	21	48.8%

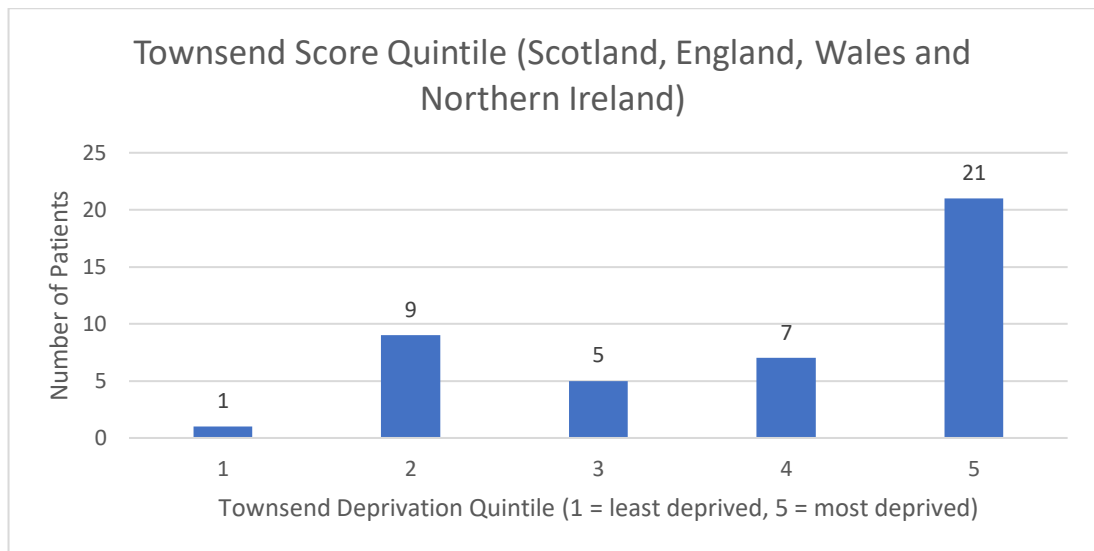


Figure 20 Townsend Score Quintiles
1 = Least Deprived, 5 = Most deprived

As shown by figure 17 and table 13, 21 patients (48.8% 21/43) were from the most deprived quintile of the UK evaluated by Townsend Score. Figure 16 highlights similar findings when compared to IMD scores for England demonstrating 1 in 3 patients (33%, 14/42) patients from England were from the most deprived quintile.

Republic of Ireland

As the geographical areas used by Townsend scores are not applicable to the Republic of Ireland, Pobal HP Deprivation Indices (<https://www.pobal.ie/pobal-hp-deprivation-index/>) were used to assess deprivation from ROI. <5 cases from the ROI scored between 6 and 1 (affluent to extremely disadvantaged).

5.2.2 Repeated patient presentations

The two patients presenting with two attacks are described below in detail to highlight the differences between each presentation. Both describe differing management and triggers for each attack.

Patient 1:

Known to have asthma with two previous asthma admissions 12 months prior to NFA attack (including previous admission to PICU). Review primary care prior to first attack (oral steroids) and represented to primary care with symptoms consistent with NFA. Required invasive ventilation. Follow arranged in primary and secondary care (timescales unclear). Second attack 3 months later consistent with NFA occurred at home later also required invasive ventilation. Changes to medication and interval interactions with healthcare unclear.

Patient 2:

First attack: Attended ED in the 7 days prior to NFA and received oral prednisolone. At time from NFA onset to hospital attendance received 24 puffs of salbutamol. Delivered to ED by parent with presentation consistent with NFA. Patient required invasive ventilation. Second attack 30 days later consistent with NFA also required invasive ventilation. Review in ED in 7 days preceding this attendance, no oral steroid provided. At time of NFA at home, considered too breathless to use inhaler successfully.

5.3 Case Criteria

A reminder of the case criteria for the study is stated below:

Cases will be defined as (1) and/or (2) and/or (3)

(1) Any child aged 5-15 years surviving* an acute episode of asthma, who when presenting self-ventilating with severe dyspnoea (e.g., inability to speak) and all the following features:

10- a) Pulse oxygen saturation below 92% despite maximal oxygen therapy (i.e., 15l/min oxygen flow via non-rebreather mask) during acute presentation and

b) pH $\leq$ 7.2 and/or pCO₂ $\geq$ 60mmHg or 8kPa and

c) Escalation to use of intravenous bronchodilator infusion

(2) Any child aged 5-15 years surviving* an acute episode of asthma, who had a respiratory arrest and/or required cardiopulmonary resuscitation as part of their presentation.

(3) Any child age 5-15 years surviving* an acute episode of asthma for which he/she was invasively ventilated. *surviving to hospital discharge

The cases that met each criterion are displayed below in table 14 and Figure 18.

Table 5.3 Case criterion met

Case Criteria Met	Number of Cases (n = 51)	%
1	10	19.6
2	5	9.8
3	12	23.5
1 and 2	3	5.9
1 and 3	7	13.7
2 and 3	5	9.8
1 and 2 and 3	9	17.6

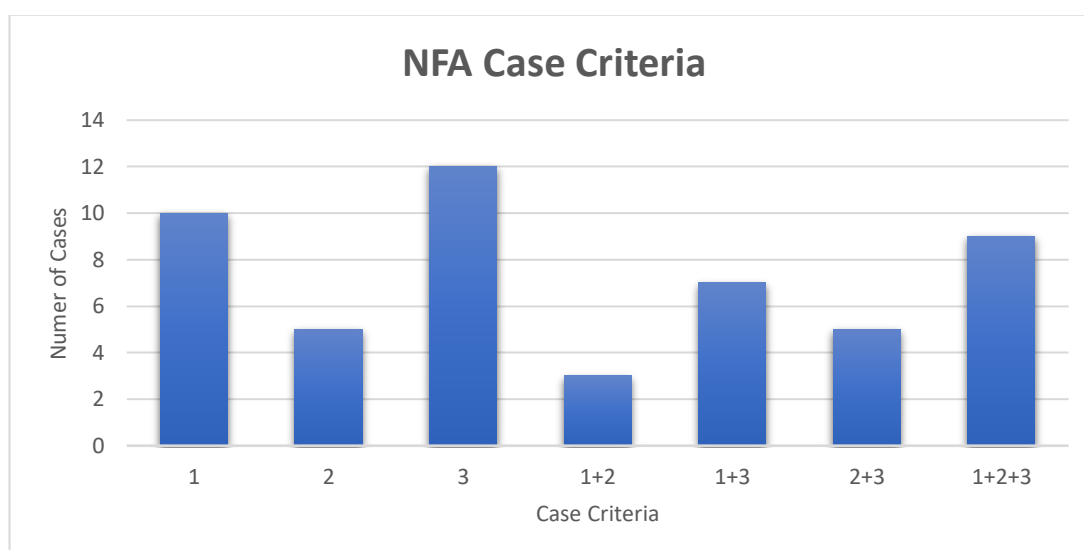


Figure 21 NFA Cases by Criteria

The most common criteria met was invasive ventilation ($n = 12/51$, 23.5%) followed by the combination of hypoxia, hypercapnia and IV bronchodilator use ($10/51$, 19.6%). Previous studies have defined near fatal asthma by invasive ventilation or admission to intensive care as a criterion. The data from our study shows 33 cases ($33/51$, 64.7%) were invasively ventilated. This study also included cases who were hypoxic, hypercapnic and required intravenous therapy (see criteria 1). Eleven cases ($11/51$, 21.6%) met criteria 1 only within the data set. Of these cases, 3 were provided with management in ICU, 8 did not require escalation and were managed with ward level care. If previous criteria of intensive care management had been used, 8 cases (15.7%) would have been excluded. Twenty two cases ($22/51$, 43%) in the study experienced a respiratory arrest or required cardiopulmonary resuscitation and in five cases ($5/51$, 9.8%) this was the qualifying study criteria. Sixteen of the 22 cases that had a respiratory arrest or received CPR number received care in intensive care during their admission.

5.3.1 Type 1 and Type 2 attacks

Previous surveillance on near fatal asthma in children in Germany by Schmitz et al (2000) (discussed in chapter 2), divided NFA and fatal asthma into type 1 and type 2 attacks. Type 1 was slow onset (≥ 60 mins) and Type 2, rapid onset (< 60 mins). In the study by Schmitz et al (2000), near fatal asthma cases were defined as cases requiring mechanical ventilation. Categorisation of type 1 or type 2 was defined as “from onset of symptoms until intubation for mechanical ventilation”⁹⁶. We considered if it would be possible to

categorize the attacks in our data set into type 1 or Type 2. However, in contrast to Schmitz et al (2000), clinicians were asked to identify the start of near fatal asthma symptoms as when emergency dosing of salbutamol (10 puffs) was administered. This time point was recorded and this study is unique in recognising this as the starting point near fatal asthma attack. Time to mechanical ventilation was not used. The duration of NFA symptoms was calculated between start of NFA and arrival to ED (see below).

Event details	
Date of Event	00/00/0000
Actual or estimated time of event (A) (First use of an emergency dose of 10 puffs MDI, i.e., onset of attack no longer responding to normal dose of short acting bronchodilator)	00 : 00
Date of arrival at ED	00/00/0000
Time of arrival at ED (B)	00 : 00
How long (hours:mins) from first bronchodilator use to hospital admission? (time from A to B)	0 0 hours 0 0 mins
Date of discharge home	Click or tap to enter a date.

Figure 15 Example from NFA questionnaire: Clinicians asked to identify time of NFA onset

Table 5.4 Duration of NFA Pre Hospital

	N/51	% (including Don't /blank response)	N/ completed data (%)
Time from recognition of NFA (10 puffs of SABA) to ED arrival (Completed data 31/51)			
<60 mins	11	21.6%	11/31 (35.5%)
≥60 mins - <120 mins	5	9.8%	5/31 (16.1%)
≥120 mins - <240 mins	12	23.5%	12/31 (38.7%)
≥240 mins	3	5.9%	3/31 (9.7%)
Blank or 'Don't know' response	20	39%	-

Twenty cases were unable to be categorized into Type 1 or Type 2 because the event time (5 cases) or ED arrival time (3 cases) was not reported by clinicians and in 10 cases, clinicians reported the time of NFA was after arrival at ED (i.e., NFA was recognised in the ED department) and in two cases the time of NFA was reported at the same time as arrival in ED (in both cases met criteria for cardiorespiratory arrest).

As discussed in chapter two, differing parameters are used to define type 1 and type 2 attacks. (Type 2 <60 mins or <120 mins). Of the 31 cases that could be categorized into types 1 or 2, 11/31 (35%) cases had an attack time <60 minutes, 5/31 (16%) cases were noted to have an attack time ≥60 but <120 mins, 15 (48%) were noted to have an attack time ≥120 mins (See Table 15). The median attack time was 110 mins (IQR 31mins – 185 mins).

5.4 Prehospital treatment

We asked clinicians to record any pre hospital treatment. The breakdown of case characteristics is displayed in Table 16 and discussed below.

We asked clinicians to identify how many doses of SABA had been given between the recognised time of near fatal asthma attack and arrival in ED. A high proportion of responses were incomplete (45%, 23/51 incomplete). The highest number of puffs given prior to admission was 100 (n = 1) and the lowest was 0 (n = 1). The median number of SABA doses was 10 (IQR 5 – 30).

Clinicians were also asked to state if oral steroids were taken as treatment prior to the attack. Forty four clinicians responded yes or no, 2 clinicians did

not indicate a response and 5 clinicians responded 'Don't know'. Of the 44 responses, 32 cases 32/44 (72.7%) did not have oral steroids prior to the NFA and 12 (12/44, 27.3%) did have oral steroids. The median course of oral steroids was 2.5 days (IQR 1 day – 4.5 days).

Table 5.5 Prehospital and first responder NFA characteristics

	N/51	% (including Don't /blank response)	N/ completed data (%)
Number of doses of Salbutamol MDI given pre ED arrival (Completed data 28/51)			
≤10 puffs	15	29.4%	15/28 (53.6%)
>10 puffs	13	25.5%	13/28 (46.4%)
Blank or 'Don't know' response	23	45.1%	-
Oral steroid prior to ED arrival (Completed data 44/51)			
Yes	12	23.5%	12/44 (27.3%)
No	32	62.7%	32/44 (72.7%)
Blank or 'Don't know' response	7	13.8%	-
Pre hospital asthma symptoms (Completed data 49/51)			
Yes	40	78.4%	40/49(81.6%)
No	9	17.6%	9/49 (18.4%)
Blank or 'Don't know' response	2	3.9%	-

Approximately 4 out of 5 cases were recognised to have had prehospital asthma symptoms (not defined in questionnaire). All the cases who received SABA treatment and oral steroids were recognised as having pre hospital asthma symptoms. In the 9 cases who did not have pre hospital asthma symptoms, all of these cases were known to have asthma prior to NFA. One

identified cold weather as a trigger, two identified food allergies as a trigger. Three of these cases required CPR and four were given intramuscular (IM) adrenaline (2 of which had known food allergy).

With acknowledgement that the questions on pre hospital treatment did not have 100% completion, the data highlights the wide variation in pre hospital management of NFA. The data highlights the variation in treatment with oral steroids, short acting beta 2 agonists and IM adrenaline. Further interrogation of pre hospital treatment would be useful to ascertain the context of pre hospital treatment (clinician administered or patient/carer administered) and guide point. A more detailed examination of this critical time period would aid standardisation of pre hospital care when NFA is recognised.

5.5 Prehospital symptoms, service interaction and location and time of NFA and identified triggers.

Prehospital observations aimed, where possible, to build a picture of the timelines leading up to the near fatal attack, time from recognition to initial management and immediate observations from first responders.

5.5.1 Service Interaction Pre NFA

Twenty cases interacted with clinical services prior to the attack. Of these 20 cases, almost half (9/20 cases) interacted with more than one service prior to NFA. Of the 12 cases who received oral corticosteroids –7 had interacted with clinical services in the seven days prior to the NFA attack. Interestingly, 9 cases had an unspecified hospital admission in the 7 days pre near fatal asthma attack. Two cases represented with a respiratory arrest. All the cases

except one were known to have asthma pre near fatal attack and were on asthma medications.

5.5.2 Location of NFA

The majority of cases were at home when they experienced the near fatal attack (86.3%). Twenty cases occurred on weekend days (Saturday/Sunday) and 31 cases during the week (Monday – Friday). All children were of school age (5 – 15 years) however clinicians were not asked if child was off school as unwell or if school was attended on the day of the attack. Only two attacks were noted to be at school. The 5 children who had attacks at ‘other’ locations were not specified. Attacks occurred more frequently in the evening between 18.00 and 23.59 (16/45 completed cases). Most of the children were with a parent when the NFA occurred (86.3% of the 50 completed cases).

Table 5.6 Prehospital NFA Characteristics

	N/51	% (including Don't /blank response)	N/ completed data (%)
Service interaction pre 7 days NFA (Completed data 41/51)			
Yes	20	39.2%	20/41 (48.8%)
No	21	41.2%	21/41 (51.2%)
Blank or 'Don't know' response	10	19.6%	-
<i>Service Interaction (multiple per case permitted)(Completed data 35/51)</i>			
111/NHS 24	2	-	2/35(5.7%)
Primary Care/OOH	9	-	9/35 (25.7%)
ED	13	-	13/35 (37.2%)
Outpatient	2	-	2/35(5.7%)
Hospital admission	9	-	9/35 (25.7%)

Cases interacting with more than one service			9/20(45%)
Location of NFA (Completed data 51/51)			
home	44	86.3%	
school	2	3.9%	
other	5	9.8%	
Time of NFA onset (Complete data 45/51)			
00.00 – 05.59	9	17.6%	9/45(20%)
06.00- 11.59	7	13.7%	7/45(15.5%)
12.00 – 17.59	13	25.5%	13/45(28.9%)
18.00 – 23.59	16	31.4%	16/45(35.6%)
Blank or 'Don't know' response	6	11.8%	-
Who were they with? (Completed data 50/51)			
Parent	44	86.2%	44/50(86.3%)
Other	5	9.8%	5/50 (10%)
Alone	1	2.0%	1/50 (2%)
Blank or 'Don't know' response	1	2.0%	-

5.5.3 NFA Triggers

Twenty five cases had a reported trigger for the NFA. Multiple triggers were identified for 1 case. Sixteen cases were reported to have viral triggers associated with the near fatal asthma attack. Only 8 of these had further details submitted:

- Influenza A (n = 2),
- Rhinovirus (n = 3),
- SARSCoV2 (n = 1)
- Parainfluenza (n = 1),
- RSV (n = 1)

Three cases had a food allergy exposure identified as a trigger and all three of these cases were known to have a food allergy.

Of the cases with no trigger identified, 5 cases had interacted with hospital (as an admission) in the seven days prior to the attack. Four cases had interacted with the GP and four with ED. Eighteen of the 24 were known to have asthma. One case was known to be a tobacco smoker/e-cigarette user and seven had household exposures to tobacco smoking or e-cigarettes.

Table 5.7 NFA Case Triggers

	N/51	% (including Don't /blank response)	N/ completed data (%)
Any trigger associated with event (Completed data 49/51)			
Yes	25	49.0%	25/49 (51.0%)
No	24	47.1%	24/49(49.0%)
Blank or 'Don't know' response	2	3.9%	-
<i>Associated trigger (multiple per case permitted)</i>			
Viral infection	16		
Exercise	3		
Food allergy exposure	3		
Animal allergy exposure	2		
Allergic pollen exposure	0		
Other	Cold weather (n = 2) Bacterial chest infection (n = 2) Vaping (n = 1)		

First clinical observations

Clinicians were asked to select one or more of the stated clinical observations on first presentation. Severe dyspnoea and unable to talk were the most frequently observed.

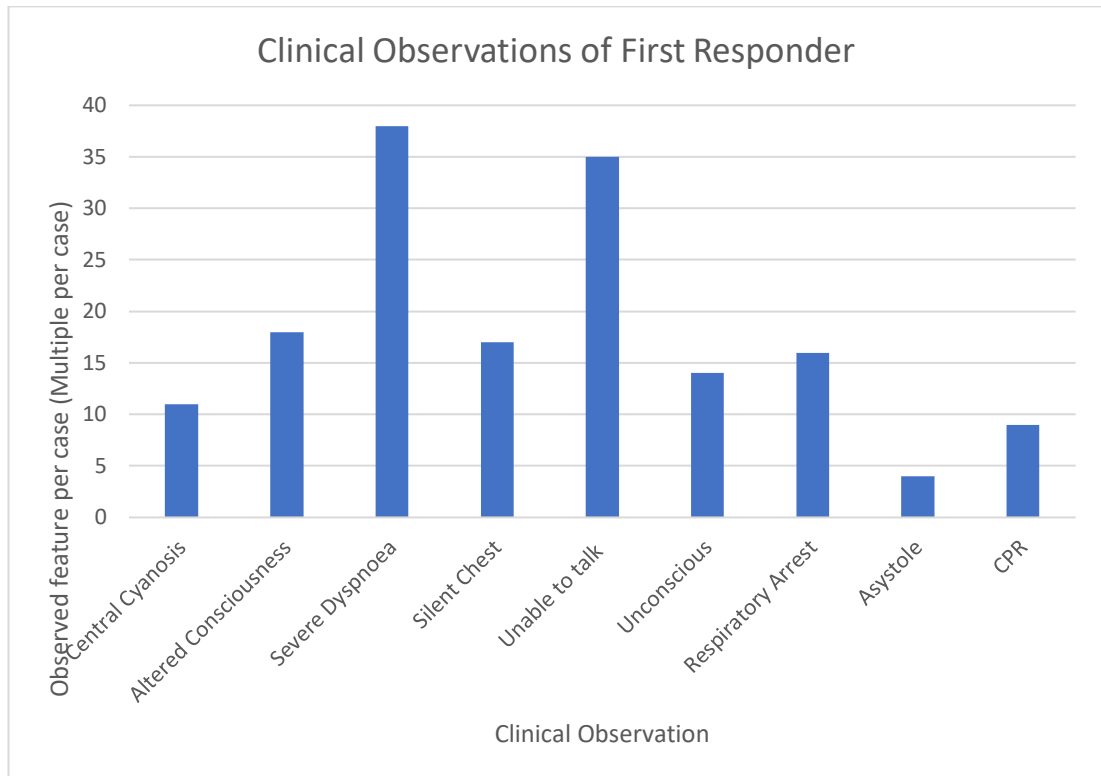


Figure 22 Clinical Observations from First Responder

5.5.4 First Responders

Twenty four cases (47.1%) first responder observations were gathered by a paramedic. Two cases presented to a GP with NFA symptoms. Five cases were in hospital when they experienced an NFA. Five of the first responders in these cases were hospital clinic staff.

5.5.5 SpO₂ and PaCO₂

SpO₂ in room air at NFA presentation were reported by 28 clinicians. Twenty three clinicians did not complete this section or selected 'don't know

response'. Of the 28 cases with completed SpO₂ data, over a third of case (10/28, 35.7%) were noted to have SpO₂ less than 70% and 3 cases (5.9%) were noted to have saturations >92%. British Thoracic guidelines categorise life threatening asthma as SpO₂ <92%⁴. The results from this study highlight that a significant number of cases had saturations much lower than this. We anticipated that there would be gaps in SpO₂ in room air, as commonly oxygen would be provided at triage and if a child were visibly severely unwell it would not be appropriate to remove oxygen to determine SpO₂ in room air. This likely corresponds to the incomplete/'don't know' responses.

Two cases were noted to have PaCO₂ >20 kPa. Twenty one cases (41.2%) had a PaCO₂ between 10 – 15 kPa. The median value for PaCO₂ was 11.2 kPa, (IQR8.35 – 14.8) All cases with a PaCO₂ ≥ 14kPa were invasively ventilated. Cases who experienced cardiorespiratory arrest (n = 22) had a higher median PaCO₂ (14.25 kPa).

5.5.6 Intramuscular Adrenaline

Eleven cases were administered IM adrenaline prior to hospital admission.

Three of the cases given IM adrenaline were known to have food allergies, two of these cases had food allergy identified as the trigger for NFA. Four of the 11 cases receiving IM adrenaline had required out of hospital cardiopulmonary resuscitation.

Table 5.8 First Responder Observations

	N/51	% (including Don't /blank response)	N/ completed data (%)
First responder making clinical observations (Completed data 51/51)			
ED Staff	19	37.3%	

GP	2	3.9%	
Paramedic	24	47.1%	
Hospital staff	5	9.8%	
Other - Police	1	2.0%	
Initial observations (multiple per case permitted)			
Central cyanosis	11	-	
Altered conscious level	18	-	
Severe dyspnoea	38	-	
Silent chest	17	-	
Unable to talk	35	-	
Unconscious	14	-	
Respiratory arrest	16	-	
Asystole	4	-	
CPR prehospital	9	-	
Pulse arterial oxygen saturation (in room air)	28/51		
<70%	10	19.6%	10/28(35.7%)
≥70 - <80%	2	3.9%	2/28 (7.1%)
≥80 - < 90%	9	17.6%	9/28 (32.1%)
≥90 - < 92%	4	7.8%	4/28 (14.3%)
≥92 - 100%	3	5.9%	3/28 (10.7%)
Median saturations	83%		
Blank or 'Don't know' response	23	45.1%	
Highest Blood gas PaCO₂(kPa)	51/51		
<8	11	21.6%	
≥8 - <10	7	13.7%	
≥10 - < 15	21	41.2%	
≥15 - <20	10	19.6%	
≥20	2	3.9%	
Median PaCO ₂	11.2kPa		

pH	44/51		
<7.1	30	58.8%	(30/44)68.2%
≥7.2	14	27.5%	14/44(31.8%)
Blank or 'Don't know' response	7	13.7%	-
Pre hospital adrenaline	47/51		
Yes	11	21.6%	11/47(23.4%)
No	36	70.6%	33/47(76.6%)
Incomplete data	4	7.8%	-

5.6 Inpatient journey and discharge

Inpatient characteristics focused on patient journey through different departments and inpatient management.

Patient journey

The median duration of admission 5.5 days (IQR 3 – 10 days), the longest admission was 180 days. Of the cases that stayed > 4 days (n = 23), 11 were discharged with oral steroids and 4 cases were reported to have the same medications on admission and discharge. Twenty two of the 23 cases were invasively ventilated during admission.

Table 5.9 Duration of Hospital Stay

Duration of hospital stay (51/51)	Number of cases n/43(%)
1 day	1 (2.3%)
2 days	7 (16.3%)
3 days	10 (23.3%)
4 days	2 (4.7%)
>4 days	23 (53.4%)
Incomplete data	8

We asked clinicians to plot inpatient journey. The pattern of patient journey is visualised below. Data was completed by 50/51 clinicians. Forty two of the 50

(84%) cases were reported to have care in the ED on Day 1, 24/50 (48%) were escalated to intensive care on day one.

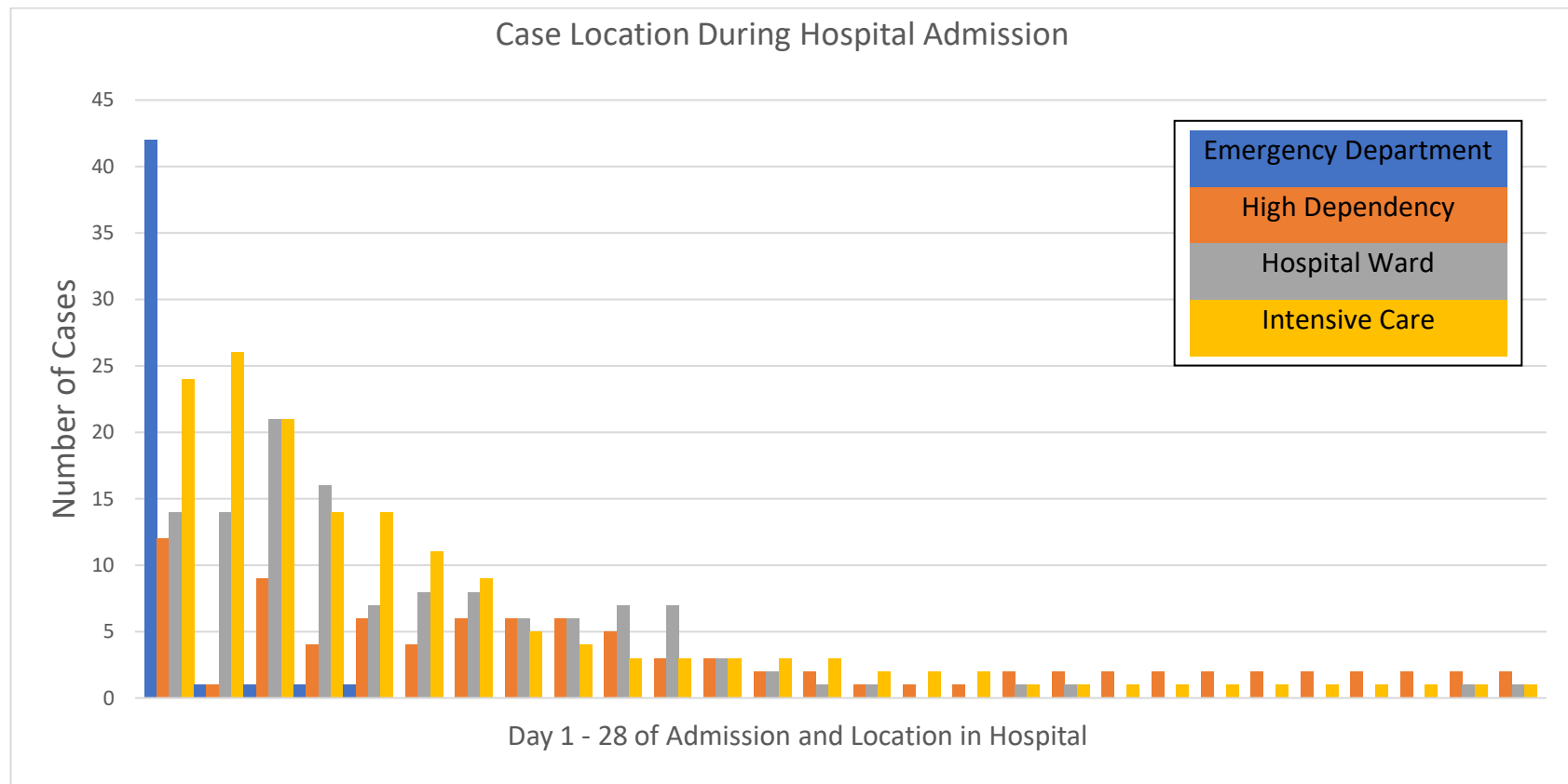


Figure 23 Case Journey During Admission

Medication administration during hospital admission

Two clinicians did not complete data on medications administered during hospital stay. The summary of the available data is plotted below. All cases were reported to receive with nebulised salbutamol and IV steroids during admission. Twenty seven cases were given IV salbutamol, 34 cases received aminophylline, 44 cases were treated with IV magnesium sulphate (see Figure 24). One case was reported to have treatment with nebulised lidocaine.

Seven cases had DNase administered during admission. All cases who had DNase reported were invasively ventilated. One case was reported to have a 'respiratory infection' as a trigger for NFA and one case reported to have 'vaping' as a trigger. All of the cases reported to receive DNase had a duration of admission > 4 days.

Four cases were reported to have a bronchoscopy. All cases were invasively ventilated and admitted to intensive care. Three of the four cases were previously known to have asthma. One case was reported to have parainfluenza as a viral trigger for NFA. Two of the four cases had a hospital admission >4 days.

Inpatient Medication

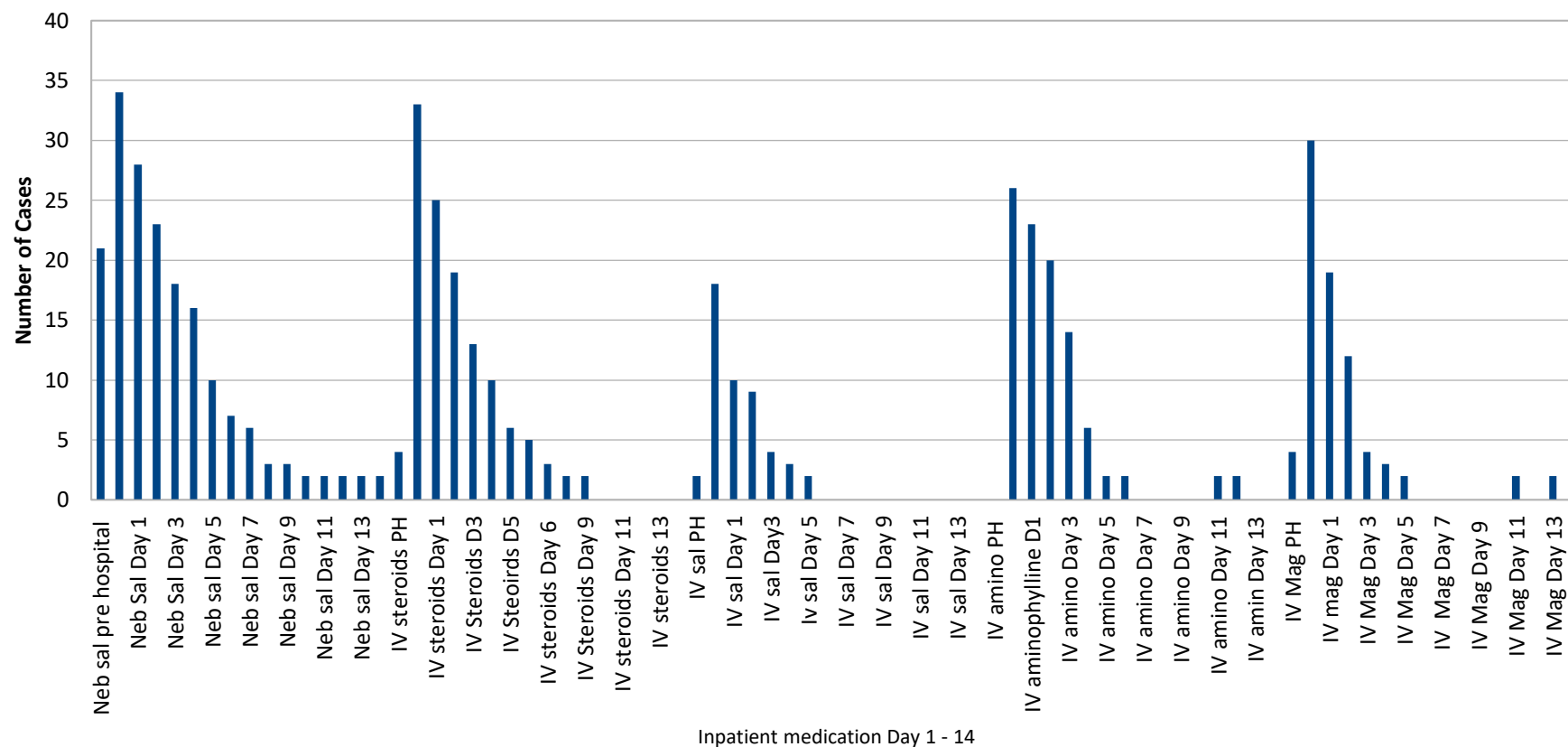


Figure 24 Inpatient Medication

Recovery

Forty eight clinicians responded to the question on discharge health status.

Forty one cases (85.4%) were reported as 'back to normal self' on discharge.

Four cases(8.3%) recovered with sequelae (n = 3 neurological sequelae(6.3%), iatrogenic, n = 1 ((2%)). Data was not provided for 3 cases (Don't know) and 3 clinicians did not respond to this question (blank response).

Discharge and follow up

Thirty four clinicians reported on oral steroids on discharge. Twenty five cases (25/34, 73.5%) were discharged home with an oral steroid course, 9/34 (26.5%) had no steroids on discharge. The shortest course prescribed on discharge was 1 day, the longest course 35 days. 17 clinicians did not provide a response or responded 'don't know'. Thirty eight clinicians gave information about a spacer on discharge. Thirty four (34/38, 89.5%) cases were discharged with a spacer, 4 cases (4/38, 10.5%) were documented as no spacer on discharge. Thirty one clinicians reported on asthma action plans on discharge, 23 cases (23/31 74.2%) were discharged with an asthma action plan, 8 cases (8/31, 25.8%) were recorded as no asthma plan on discharge and 20 cases were recorded as blank/don't know. Three of the 8 cases were previously known to have asthma, seven of 8 cases were on asthma medications on admission. Four of the 8 cases were reported to have a spacer on discharge (two clinicians did not respond to this question). Six of

the 8 cases were reported to be referred to a respiratory paediatrician on discharge and six are reported to have follow up with an asthma nurse.

Follow up

Clinicians were asked to provide details of the follow up arrangements made for each case (multiple responses recorded).

Table 5.10 NFA Clinician Follow Up

Follow up clinician	Number of cases
GP	18
Asthma/Respiratory Nurse	29
General Paediatrics	7
General Paediatrics with Respiratory Interest	20
Respiratory paediatrician	28

The graph below demonstrates the highest level of recorded follow up (primary care, secondary care, tertiary care).

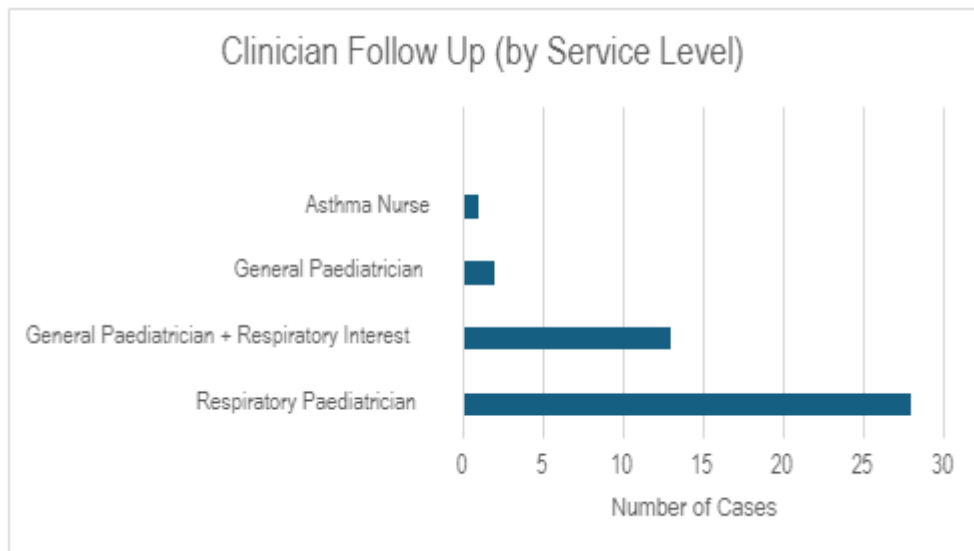


Figure 25 Clinician Follow Up

Forty four clinicians responded to the question regarding follow up. Twenty eight (28/44 (63.6%) cases were reported to have follow up in tertiary care (respiratory paediatrician), 15/44 (34.1%) were reported to have follow up in secondary care either with general paediatrics or a paediatrician with respiratory interest. One case (1/44 , 2.3%) was reported to have asthma nurse follow up – no other clinician follow up was indicated.

5.7 Baseline characteristics

Forty four clinicians responded to the question on baseline characteristics.

Thirty six (36/44 81.2%) of the cases were known to have asthma prior to the near fatal asthma attack.

Eight cases (8/44 18.2%) were not previously known to have asthma, . Seven of these 8 cases were invasively ventilated and had interacted with clinical services in the 7 days prior to NFA. Four of the eight cases were given oral steroids prior to NFA. Three of these were on regular asthma medications (salbutamol only) at the time of NFA attack despite not

previously being known to have asthma. Three cases (3 of 8) had no previous asthma medications and were not previously known to have asthma. None of these three cases had associated atopy.

Of the 36 cases previously known to have asthma, 25 (25/36, 69.4%) had a first diagnosis of wheeze under 5 years of age (18 of the 25 were age 2 and younger at time of first wheeze). Forty two cases were receiving asthma treatment at time of admission.

Nineteen cases (19/44, 43.2%) had a previous admission with asthma in the last 12 months and 4 cases (4/39, 10.2%) had >3 courses of steroids in the last 12 months. Twenty three cases (23/48, 47.9%) had been reviewed by a hospital consultant (consultant role not specified) in the 12 months prior to the attack. Nine cases (9/48, 18.8%) were reported to have had previous admission to PICU with asthma requiring ventilation. Six cases (6/46, 13.0%) were previously known to have food allergy and 4/6 were reported to have an adrenaline auto injector. Two of these 4 were given adrenaline as part of NFA treatment, both had food allergy identified as NFA trigger.

Thirty seven clinicians responded to the question relating to skin prick testing. Two cases of the 37 (5.4%) were reported to have skin prick testing carried out, both cases were positive for house dust mite.

Four cases (4/37 10.8%) were reported to vape or smoke and 15 cases (15/39 38.5%) had household exposure to vaping or smoking. Seven children (7/38 18.4,) were reported to have mental health issues, 4 children (4/31, 12.9%) were known to have mental health issues in family.

5.8 Medications

Forty two clinicians had completed sections of the questionnaire on admission and discharge medications. Eleven cases (11/42 26.2%) were discharged on the same medications as admission. Twenty three patients (23/42 54.8%) had an increase in medication – either addition/increase of inhaled corticosteroid, addition or increase in long acting Beta 2 agonist (LABA) or addition of theophylline. No cases were admitted or discharged on monoclonal antibody therapy. Three cases (3/42, 7.1%) were discharged on SABA only. Eight clinicians did not state medication changes or left admission medications blank.

The below graph highlights the dosage changes observed from admission to discharged in inhaled corticosteroid use (beclomethasone equivalent). The most common ICS dosing was to increase from 200mcg to 500mcg (5/42 cases, 11.9%) follow by on remaining on 200mcg of ICS on discharge (4/42, 9.5%) and increased from 200mcg to 400mcg(4/42 9.5%). The graph identifies that an escalation in ICS does not occur at all levels (none to highest dose on admission).

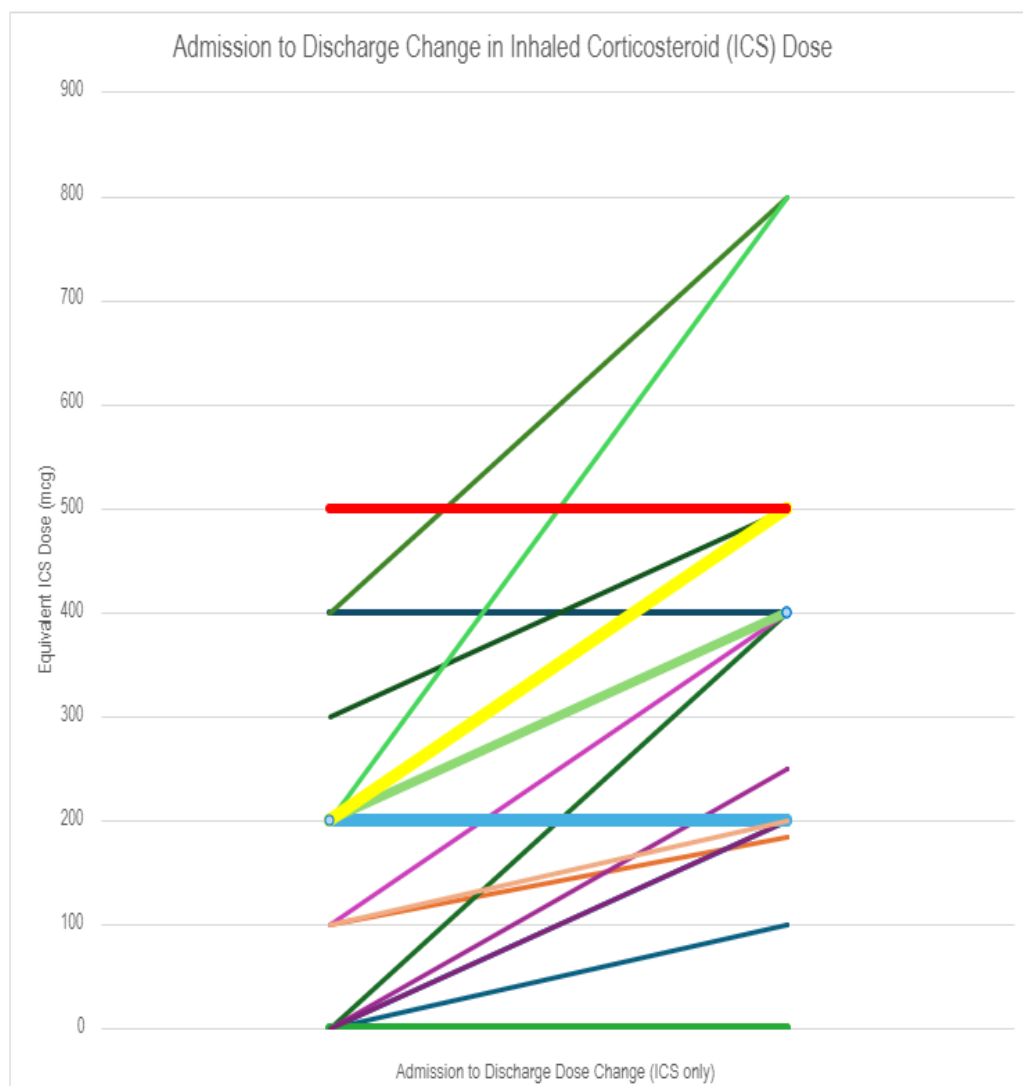


Figure 26 Inhaled Corticosteroid Dose change from admission to discharge

5.8.1 Comparison to National Guidelines

Compared to national guidelines (BTS/SIGN) many of the cases did not comply with recommendations for discharge of a patient experiencing a severe asthma attack. The table below summarises the key recommendations from BTS guidelines compared with the surveillance response.

Table 5.11 Surveillance Response Compared to BTS/SIGN Guidelines

BTS/SIGN Recommendation	Surveillance Case Response Meeting	Surveillance Case Response Not

	Guideline Recommendation	Meeting Guideline Recommendation
Oral corticosteroids: Ensure the child has started a 3-5 day course of oral corticosteroids before discharge	25/34 cases (73.5%) (NB duration variable)	9/34 cases (26.5%)
Inhaled corticosteroids should be considered as part of the long-term asthma management	23/42 cases (54.8%)	Not evaluated in questionnaire data.
Ensure the child has an updated asthma action plan	23/31 cases (74.2%)	8/31 cases (25.8%)
Consider specialist referral for children who have experienced life-threatening attacks, particularly if they have a history of frequent severe exacerbations.	28/44 (63.6%)	16/44 (36.4%)

The table highlights how national recommendations were not followed in a significant number of cases. The guidance however should be interpreted with caution with reference to follow up post attack. BTS guidelines suggest “**Immediate follow-up** with a **pediatric asthma specialist** or the child’s primary care provider should be arranged within **48 hours** to ensure recovery and assess ongoing management needs”⁴. Specialist referral is only recommended as a consideration. The guidance could be interpreted that primary care follow up in isolation would be satisfactory post NFA. This would not be considered adequate follow up for NFA due to the risk of future severe attack.

5.9 Data linkage

5.9.1 Fungal spore counts

Fungal spore counts for *Alternaria alternata* are currently available from 2022 (2023 and 2024 data not yet available). Fungal spore counts in the UK are not routinely monitored from September to May as counts are generally low. From June to September to daily count data is available from period. As data for 2023 and 2024 are not yet released it has not been possible to include this data in the final analysis. The data from 2022 are available however as previously stated, reporting is carried out after August as counts are low. As our study started in October 2022, relevant fungal counts are not comparable for 2022. In 2022, peaks in *Alternaria* were noted in July and August²¹⁸. This does not correspond to peaks in NFA cases reported from 2023 from our study data.

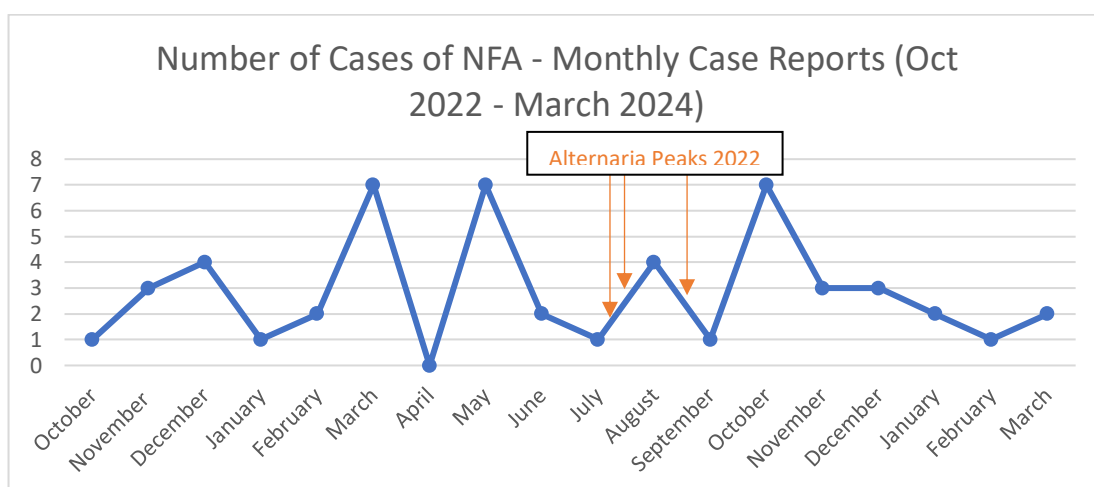


Figure 27 Monthly Cases Compared to *Alternaria* Peaks in 2022

5.9.2 Pollen counts

As discussed previously in Chapter 4.8.9, pollen counts are monitored at fixed locations across the UK. The Met Office information is supplied by the

University of Worcester and regional stations across the UK are highlighted in the figure below.

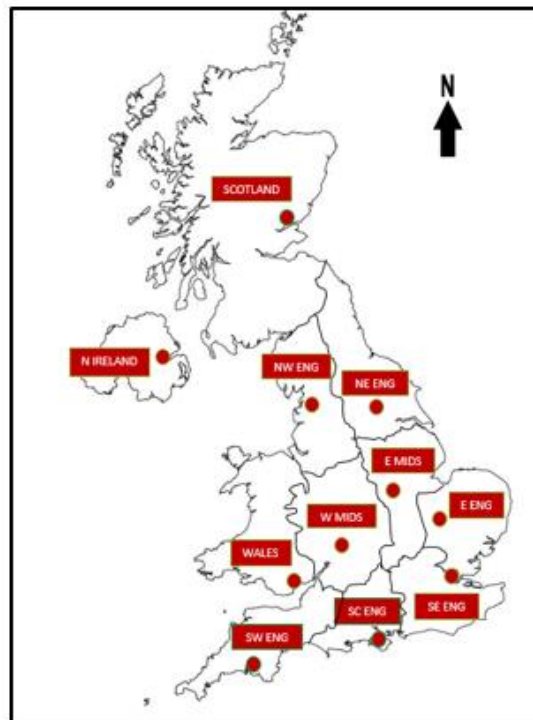


Figure 28 Pollen Forecast Regions in the UK²¹⁹

As individual NFA cases must remain anonymised and regional reporting of pollen levels in specific months could identify cases (only 3 months with >5 cases in study, one month outside pollen season). Dr Beverley Adams-Groom, Senior Palynologist and Pollen Forecaster, School of Science and Environment, University of Worcester was contacted in April 2024 to discuss if pollen count data from 2023 and 2024 would be available for analysis for this thesis. Unfortunately, 2023/2024 data is not yet publicly available. No clinicians identified pollen exposure as a trigger in the clinical questionnaire.

5.9.3 Weather events

Several weather events were noted during the study period and are listed below:

Table 5.12 Extreme Weather Events

Year	Start Date	End Date	Weather Event	
2022	8th December	18th December	Low temperatures	- Daily between -5 and -10
2023	17th February	February	Storm Otto	
2023	12th April	12th April	Storm Noa	
2023	5th August	5th August	Storm Antoni	
2023	18th August	19th August	Storm Betty	
2023	4th September	10th September	September heatwave	Maximum daily temperatures exceed 30degrees
2023	27th September	28th September	Storm Agnes	
2023	18th October	21st October	Storm Babet	
2023	1st November	2nd November	Storm Ciaran	
2023	13th November	13th November	Storm Debi	
2023	9th December	10th December	Storm Elin and Fergus	
2023	27th December	28th December	Storm Gerrit	
2024	2nd January	2nd January	Storm Henk	
2024	21st January	24th January	Storms Isha and Jocelyn	
2024	28th January	28th January	Record high temperature	

When compared to the trend of reported cases, there are no correlations with NFA attacks. As chapter 3 noted, a significant increase in near fatal asthma has been correlated to a severe thunderstorm event in Australia, data was obtained from thunderstorm warnings generated by the Met Office UK from the National Severe Weather Warning Service (NSWWS) (Accessed through Met Office Archive https://digital.nmla.metoffice.gov.uk/SO_a3062731-4abc-43b4-8a8a-477c76231d31/). Severe weather warnings were reviewed for the

18 month study period. During this time, the number of thunderstorm warnings per month was recorded. Individual dates and weeks of thunderstorms have not been included as NFA cases could be identified from specific dates. Thunderstorm warnings have been indicated on the graph below corresponding to NFA attacks. Geographical areas have not been identified to preserve anonymity of cases.

There was a noted peak in NFA cases and thunderstorm warnings in May 2023. In 3 months including May 2023, NFA cases corresponded to specific days with thunderstorm warnings (<5 cases in 2 other months).

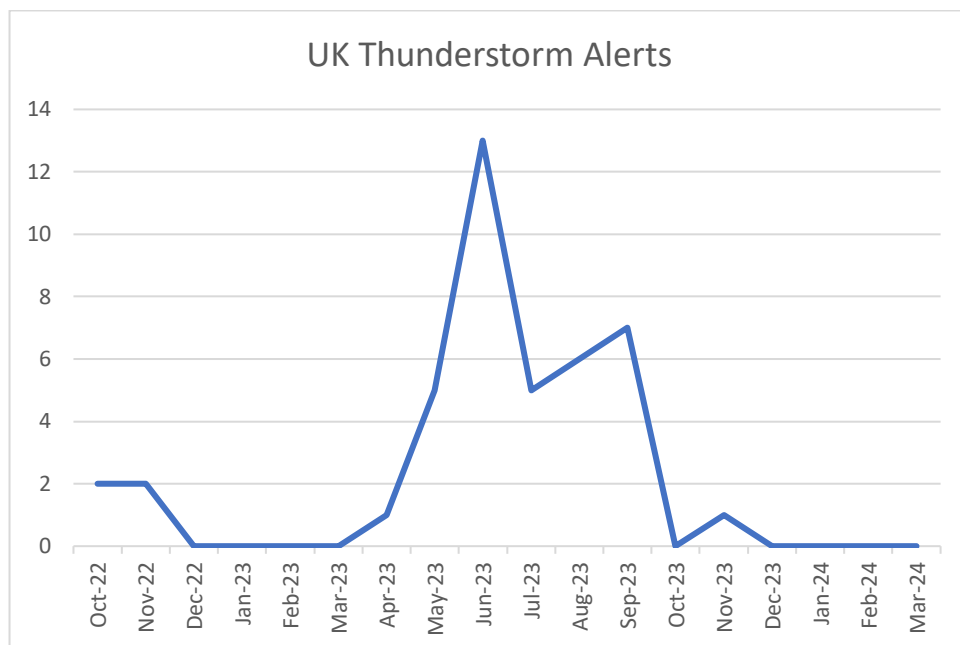


Figure 29 UK Thunderstorm Alerts from NSWWS

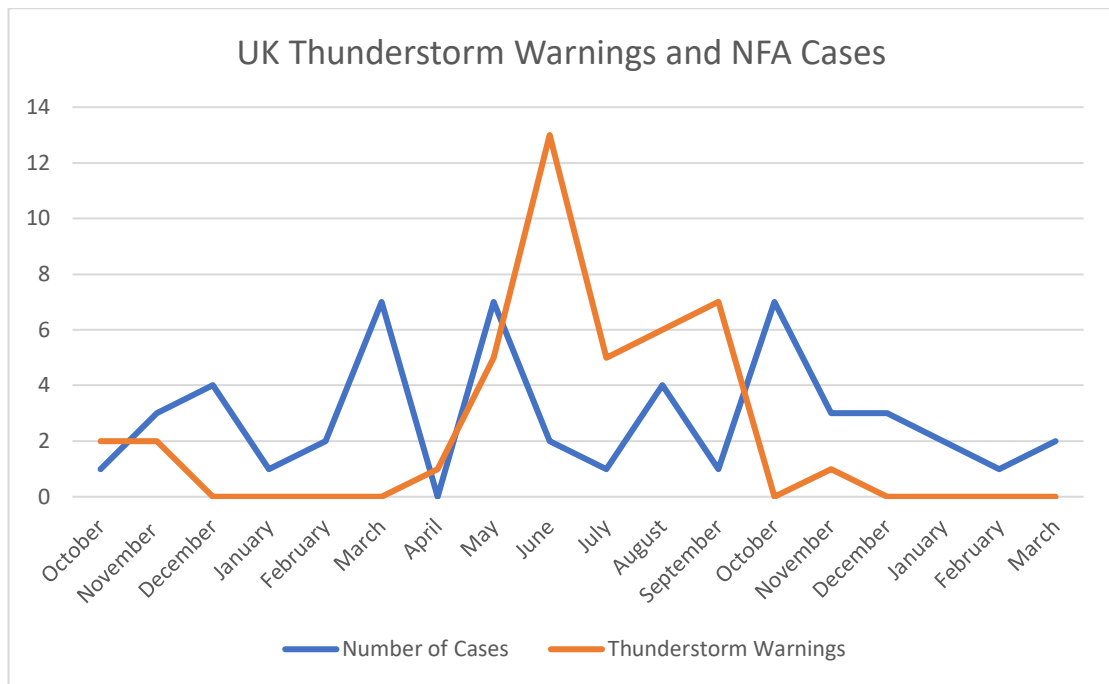


Figure 30 Thunderstorm Warnings Compared to NFA cases

5.9.4 UK Viral Prevalence

Sixteen cases of near fatal asthma were reported by clinicians as triggered by viral infections. Of these, eight clinicians were able to provide specific viruses attributed the near fatal attack.

Monthly reports of viral prevalence were provided by UK Health Security Agency (UKHSA <https://www.gov.uk/government/statistics/national-flu-and-covid-19-surveillance-reports-2024-to-2025-season>). Due to the small number of reported viral infections in the study data, trends in UK viral prevalence corresponding to the week of attack have been highlighted in the graphic below. Five different viruses were identified associated with NFA cases – RSV, Parainfluenza, Rhinovirus, SARSCoV2 and Influenza A. UKHSA data allows crude visualisation of UK viral trends during in the week leading up to the attack. Specific regions have not been highlighted below, only trends from English data is highlighted. No cases from ROI identified

specific viral triggers. Numbers of positive viral samples are given for all ages in the UK population.

RSV

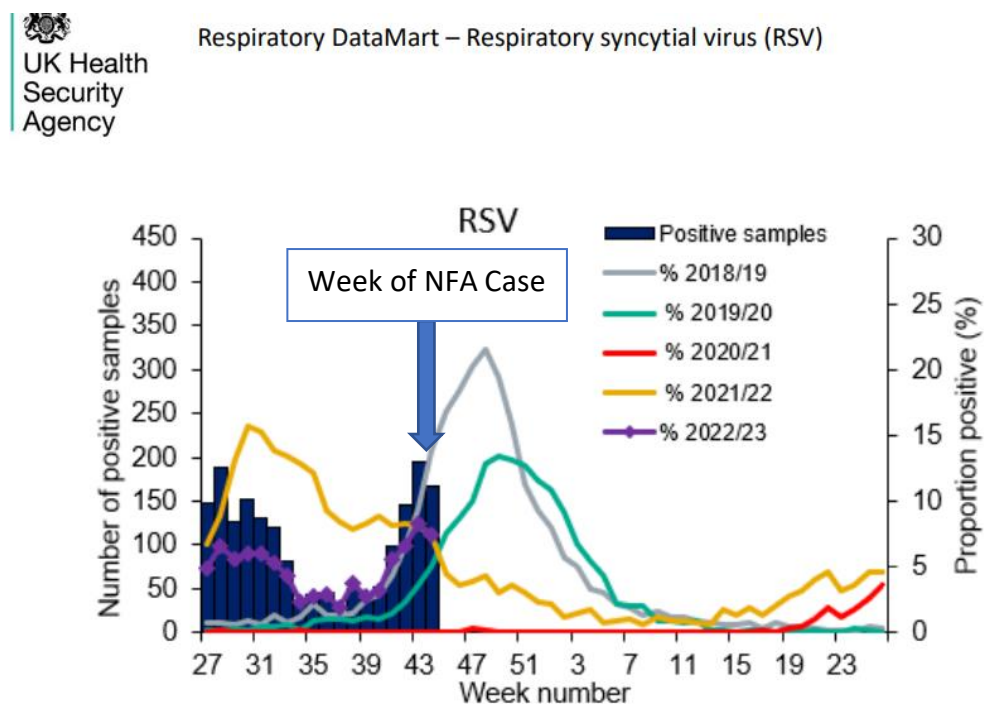


Figure 31 UKHSA RSV Reporting Numbers²²⁰

Graph shows an increase in RSV reporting during the week of NFA attack.

Decline in RSV reported numbers shown after week of attack (Week 43).

Data obtained from UKHSA Respiratory Datamart System.

Influenza A

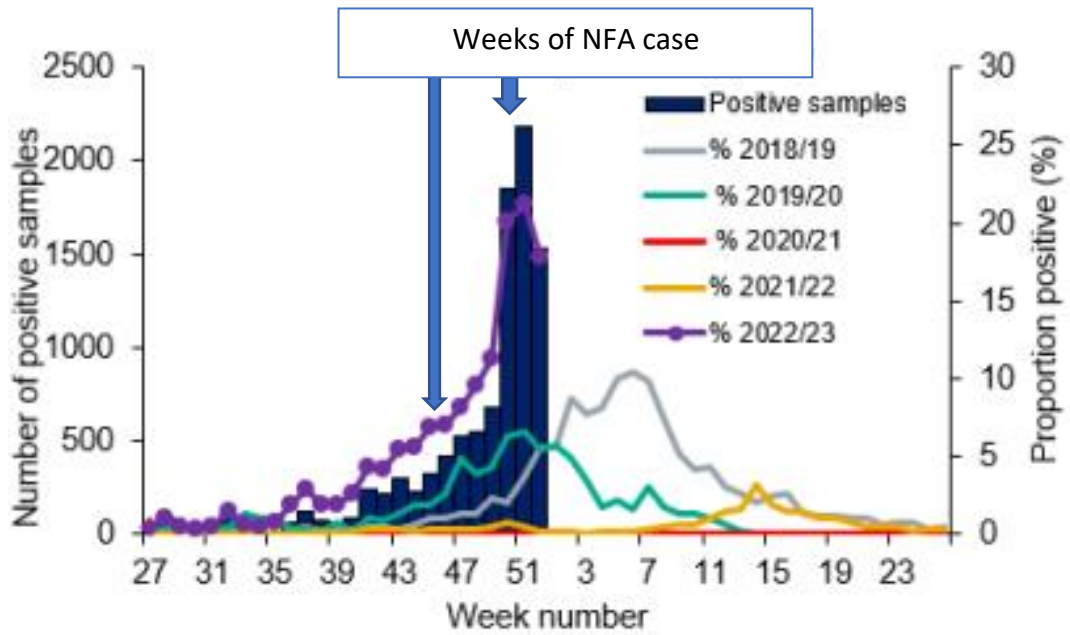
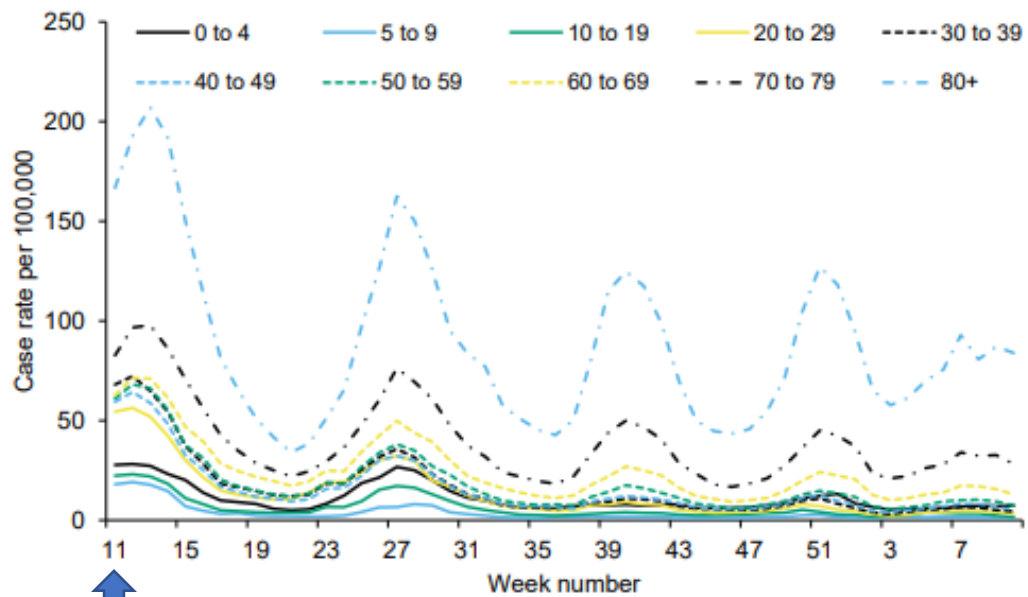


Figure 32 UKHSA Influenza Reporting Numbers²²⁰

Influenza A numbers peak at week 51 which corresponds to a case of NFA.

Graph demonstrates seasonal pattern for untyped Influenza A (Further typing not specified in clinician response in NFA questionnaire). Increase in reporting demonstrated throughout regions of England.

SARSCoV2



Week of NFA

Figure 33 Weekly confirmed COVID-19 case rates per 100,000²²¹

The graph highlights a small rise in numbers of SARSCoV2 numbers in children age 5 – 9 and young people age 10 – 19 at week 11 (corresponding week to NFA). Data is provided by UKHSA Second Generation Surveillance System (SGSS).

Rhinovirus

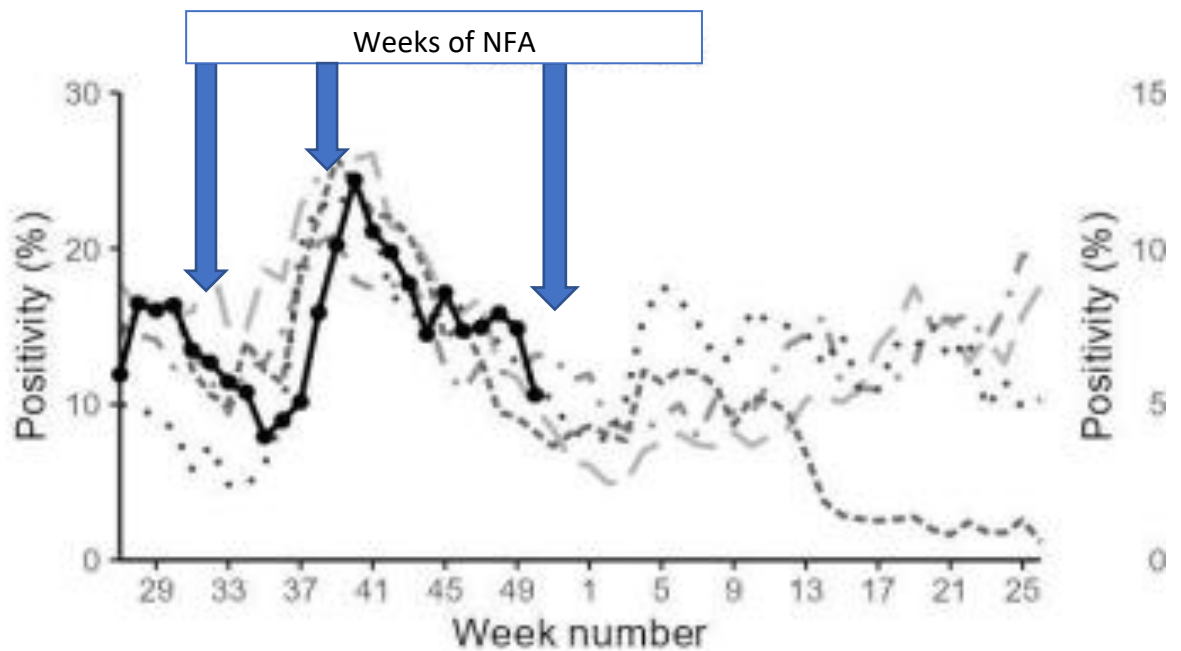


Figure 34 UKHSA Weekly Reporting Figures Rhinovirus²²²

Three cases of Rhinovirus were reported as triggers for NFA during the study. The above graph shows the weekly reporting for positive rhinovirus samples in the corresponding NFA weeks (previous years shown in dashed lines). All ages are shown. There does not appear to be a peak in rhinovirus cases corresponding to NFA cases. Interestingly, the peaks on the graph do not correspond to the start of school term, as discussed in Chapter 2.2.2 previous trends with increased rhinovirus infections have been observed around the start of school terms. One case shown occurs within 3 weeks of English school term commencement.

Parainfluenza

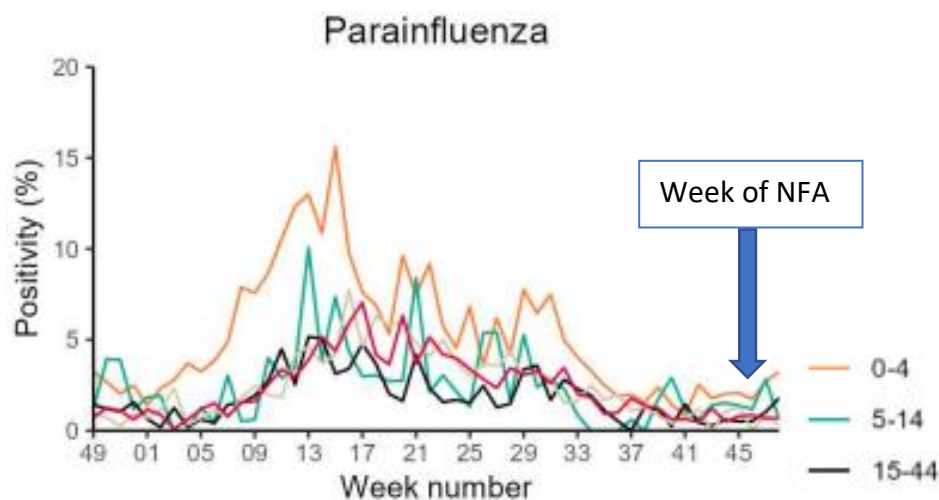


Figure 35 UKHSA Reporting Figures Parainfluenza²²¹

There does not appear to be a correlation in peak of cases of parainfluenza in the week of the NFA reported case. Age 5 – 14 years appear to have a

small peak after the NFA attack. Data is shown from UKHSA reported data for England (Respiratory Data Mart system).

5.9.5 Air pollution

To observe any impact from outdoor air pollution related to near fatal asthma cases, levels of outdoor air pollution acutely (3 days prior to attack) and background exposure (1km x1km modelled background data) were sought. Publicly available data sources (<https://uk-air.defra.gov.uk/data/pcm-data>) were used to obtain data. Verified data for 1km by 1km analysis was not available for 2023 and 2024 therefore data was used from 2022. I sought advice of Dr Tom Clemens, Senior Lecturer in Health and Environment in the School of Geosciences, University of Edinburgh regarding the use of data from 2022 for cases occurring in 2023 and 2024. It was discussed that data from 2022 would provide a relatively accurate estimation of background exposure. For acute exposure, each case was mapped by XY coordinates to nearest Automatic Rural and Urban Network monitoring station(available from <https://uk-air.defra.gov.uk/networks/network-info?view=aurn>). Where possible data was extracted from each site 3 days prior to the event. Unfortunately, there was inconsistency in which air pollutants were monitored at each site. Rural stations often did not capture PM_{2.5} and NO₂. Analysis is therefore based on 1km by 1km air pollution data from 2022 (background exposure only). Acute exposure has not been captured by this analysis.

44 patient postcodes were available to use for analysis (5 postcodes not available from questionnaires, either not reported or from ROI and two patients with two discreet attacks).

The following air pollutants were measured by DEFRA and examined for analysis - PM₁₀, PM_{2.5} NO₂, SO₂, Ozone and Benzene. Data for CO was also available but levels only measured until 2010. As the majority of cases (maximum age 15, inclusion until 16th birthday) were born after this date therefore background CO was not included in analysis.

Thresholds for outdoor air pollution have been compared to WHO standards. WHO standards take into account global economic and social differences aiming to provide pragmatic achievable guidelines on a global scale. Compared to UK guidelines, WHO standards for air pollution levels are stricter to reflect the disproportionate health impacts of air pollution on populations in lower and middle-income countries.

5.9.5.1 PM₁₀

For the 44 patients, the annual median PM₁₀ observed level was 12.2µg/m³ (IQR 10.8 µg/m³ – 14.7 µg/m³). The highest noted background annual exposure was 21.12µg/m³. The WHO recommended mean exposure should not exceed 15µg/m³. Eleven of the 44 cases (25%) exceeded the WHO limit for annual PM₁₀ exposure. The UK Air Quality Standards Regulation (2010)²²³ should not exceed 40µg/m³.

5.9.5.2 PM_{2.5}

Of the 44 patients examined for background PM_{2.5}, the median annual exposure was 7.4 µg/m³ (IQR 6.5 µg/m³ - 8.8 µg/m³) and highest exposure was 10.3 µg/m³ annual background exposure. The recommended WHO limit for background annual PM_{2.5} exposure is 5µg/m³. Forty two of the 44 cases (95%) exceeded the WHO recommended background PM_{2.5} exposure. The

median annual exposure was also above WHO recommendations. UK Air Quality Standards Regulations express a level of 20 $\mu\text{g}/\text{m}^3$ should not be exceeded annually.

5.9.5.3 NO_2

The median NO_2 annual background exposure for the 44 cases of NFA was 11 $\mu\text{g}/\text{m}^3$ (IQR 9.1 $\mu\text{g}/\text{m}^3$ – 15.9 $\mu\text{g}/\text{m}^3$). Twenty seven cases of 44 (61.4%) exceeded the WHO limit of 10 $\mu\text{g}/\text{m}^3$. The UK regulations for NO_2 state NO_2 annual exposure should not exceed 40 $\mu\text{g}/\text{m}^3$.

Twelve of the 44 cases (12/44, 27.3%) cases had excess WHO recommended levels of exposure for all three air pollutants (PM_{10} , $\text{PM}_{2.5}$ and NO_2). All of these cases were reported from England. Interestingly of these 12 cases, 5 were from the second least deprived quintile of IMD (England) and 0 cases were from the least deprived. Of the 12 cases exceeding WHO limits for PM_{10} , $\text{PM}_{2.5}$ and NO_2 , 7/12 had viral triggers identified for NFA, 5 had a respiratory arrest/required cardiorespiratory resuscitation and 6 required invasive ventilation. Eleven were known to have asthma, 5 had a previous admission requiring ventilation and 6 had an asthma admission in

the 12 months prior to NFA attack. Seven of the 12 cases were of Asian ethnicity.

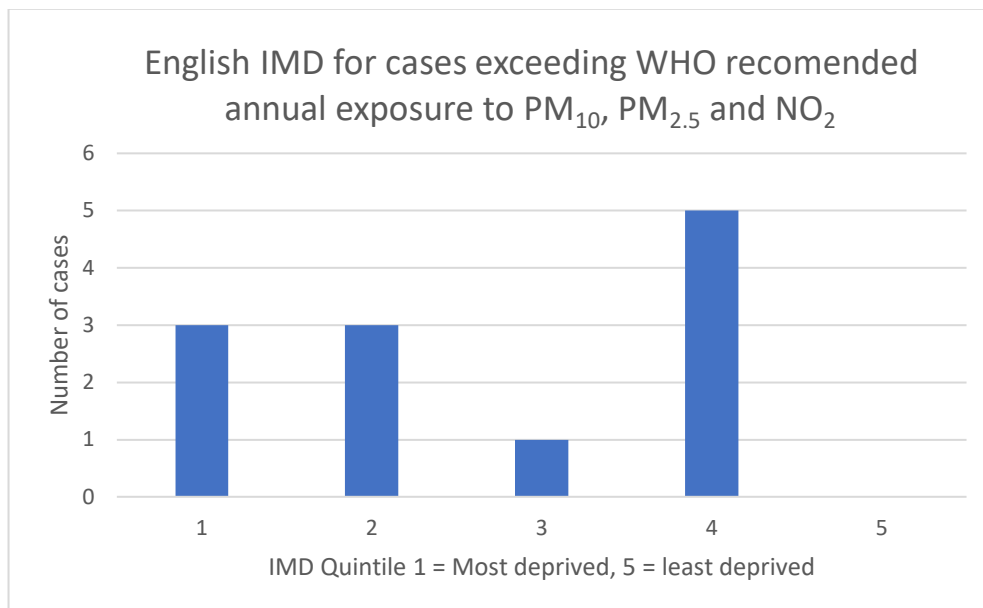


Figure 36 English IMD for cases exceeding annual modelled background exposure for PM₁₀, PM_{2.5} and NO₂

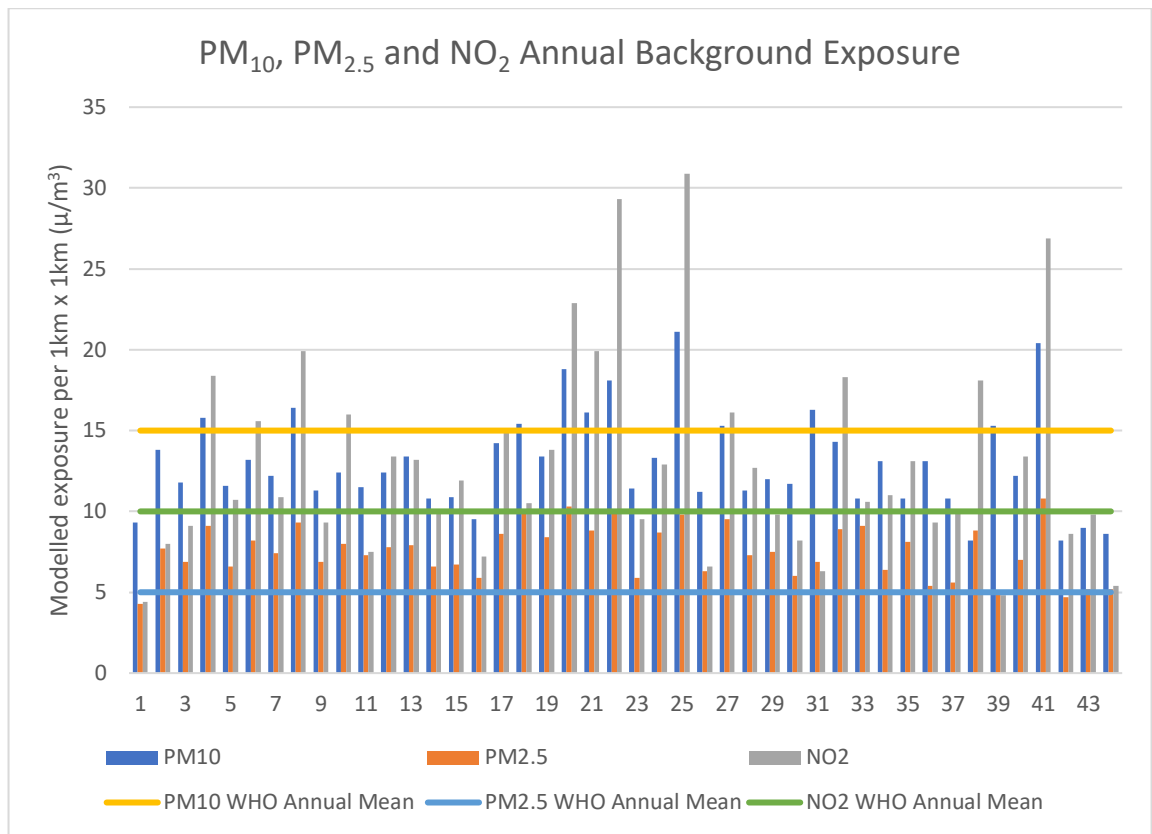


Figure 37 PM₁₀, PM_{2.5} and NO₂ modelled background exposure(2022) at 1km x1km radius of NFA case.

5.9.5.4 SO₂, Ozone and Benzene

Background annual exposure to SO₂ (µg/m³) was calculated at each case postcode. WHO and UK recommendations were not available as annual exposure (peak levels and hourly exposure). For Ozone, number of days of 8 hourly exposure >120 µg/m³ was calculated for each case. UK and WHO thresholds are also not comparable. The WHO has also not set a recommended limit for Benzene exposure. Annual mean background exposure (µg/m³) was calculated for each case.

5.10 Excluded cases sub analysis

There were 6 cases that were submitted to the safe haven that did not meet inclusion criteria but clinicians felt the presentations were in keeping with near fatal asthma. One case was below the age threshold (age 5 when data submitted but <5 years when attack occurred). In two cases, the research team were contacted by clinicians who felt the presentation of these cases were consistent with near fatal asthma but they were unable to obtain successful gases to demonstrate acidosis or hypercarbia. We had not stated 'clinician concern' as a criterion and therefore have not included these patients in the main study analysis. Subgroup analysis of this group noted similar age demographics and gender distribution (M>F). The median admission duration was 4 days. Four patients were noted to have viral triggers for NFA, two patients were attributed to rhinovirus infection and one to enterovirus infection. No patients were administered adrenaline as treatment. The median number of SABA puffs given pre admission to hospital was 17. The median saturations in air at first review were 85% and mean PaCO₂ was 8.4kPa. Two patients were cared for in critical care. All patients returned back to their normal self prior to discharge. Only one patient was not known to have asthma prior to admission, two patients had been admitted to critical care and ventilated for asthma before recent NFA attack. All patients were under 5 years when first diagnosed with wheeze and four patients were exposed to vaping/e-cigarette/tobacco smoke in their household.

This patient group had a lower mean PaCO₂ compared to the NFA group (8.4kPa compared to 11.2kPa).

5.11 Summary and Discussion of Surveillance Results

The results of the surveillance study show that near fatal asthma was more frequent in males (30/49, 61%) and children from areas of higher socioeconomic deprivation (21/49, 48.8% from lowest Townsend score quintile and 33% (14/42) of cases from England in lowest IMD quintile). The majority of patients were of white ethnicity (31/49, 63%), a high portion of children were from South Asian background (12/49, 24%). Two thirds of the cases with NFA (64.7%, 33/51) required invasive ventilation and 43% (22/51) experienced a respiratory arrest or required cardiopulmonary resuscitation. Two patients had two discrete NFA attacks during the surveillance period however detailed discharge information was incomplete in both cases to determine if opportunities for intervention prior to repeated NFA were missed. The majority of patients were reported to have asthma symptoms prior to the near fatal attack (40/49 cases, 78.4%) and 20/41 cases (48.8%) had interacted with clinical services in the 7 days prior to NFA. Twenty seven percent (12/44) had received oral steroids leading up to NFA presentation. The recognition of asthma symptoms and interaction with health care services prior to attack highlights there may be early opportunities to recognise and responds to NFA symptoms prior to an attack however future detail about the early presentations is required. Sixteen cases presented in respiratory arrest and all of these patients were reported to have symptoms prior to NFA attack. On presentation cases were observed to have significant hypoxia 35% (10/28) had SpO₂ <70% in air on presentation. As oxygen may have been applied prior to SpO₂ measurement in an unwell child it is likely

that severely low SpO₂ measurements may be underestimated. Forty of the 51 cases (78%) were observed to have a PaCO₂ ≥8kPa. Interestingly, 21% (11/47 cases) received IM adrenaline. At present IM adrenaline is not part of UK or GINA guidelines in the acute management of asthma. It has been suggested there is a role for emergency IM adrenaline administration but there is limited evidence for use in children and adolescents^{224,225}. More than half (53.4%) of the reported cases (completed data for 43/51, n= 23/43) required a hospital admission for >4 days, and just under half (48% 24/50 completed responses) required ICU admission suggesting a significant use of hospital resources for these patients. This supports previous evidence on NFA in children suggesting an increase in subsequent severe asthma attacks⁹³.

Unfortunately, the study observed 6.3% of patients suffered from neurological sequelae post NFA (3/48 cases).

On discharge, 11 patients (11/42, 26%) were reported to be discharged on the same medications as admission i.e., no change or escalation in treatment. Three patients were discharged on SABA alone (3/42 7.1%). Most children were discharged with a spacer for medication administration (34/38, 89.5%) but only 23 cases (23/31, 74.2%) had an asthma action plan on discharge. Again, this highlights a potential area of opportunity for intervention to increase preventor medication and improve asthma education. Follow up varied with, just under two thirds of patients (28/44 63.6%) were followed up by a respiratory paediatrician and one cases was reported to have only asthma nurse follow up(not stated if within tertiary service or

primary care). Local follow up at each hospital may be dictated by service availability (some hospitals will not have tertiary level respiratory follow up available) however level of follow up is not consistent for all the cases and questions if referral to tertiary service would highlight the significance of the NFA event.

Eight cases presented with a near fatal attack as their first asthma attack (8/44 18.2% responded the case was not known to have asthma prior to NFA attack). Interestingly 3 of these 8 were prescribed salbutamol prior to attack despite no diagnosis of asthma.

Nineteen cases (19/44, 43%) had an admission for asthma in the previous 12 months, 4 cases had >3 courses of steroids and 9 cases (9/48, 18. 8%) had a previous ICU admission requiring ventilation. This echoes the findings of previous studies suggesting an increased risk of subsequent near fatal attacks and again highlights another potential opportunity for education and intervention for this children and young people. Nine patients (9/35, 25.7%) had a hospital admission in the 7 days prior to NFA again presenting another potential opportunity for intervention prior to NFA attack.

Four children in the study were reported to use e-cigarettes or smoke and 38.5% (15/39) were exposed to household smoking or e-cigarette use. This again highlights a vital opportunity in asthma education to promote smoking/e-cigarette cessation.

One of the key findings from this surveillance observed a high level of annual background exposure to PM_{2.5}. 95% of cases (42/44) were exposed to background PM_{2.5} exceeding WHO recommendations.

The surveillance studies results support previous knowledge of near fatal asthma in regards to gender and deprivation. Novel findings from this study show a high percentage of south Asian children experiencing near fatal asthma which has not be described for near fatal asthma in children in previous studies. The surveillance suggests there are multiple opportunities for intervention to prevent further near fatal asthma attacks.

5.11.1 Context of data

We compared themes from previous literature on near fatal asthma in children and young people to the observations from our dataset.

1. Diagnosis

When recognising near fatal asthma, the use of PaCO₂ has previously been suggested by several studies^{78–82} although a consensus on the diagnostic limit has not been reached. These studies suggest PaCO₂ 5.9 – 6.6 kPa. We observed a median PaCO₂ 11.2PKa in our group of patients which is significantly higher than previously observed. This questions whether this observational study has identified more severely decompensated patients or if previous definitions have not attempted to delineate the severity NFA. A broader definition for PaCO₂ thresholds may include larger numbers of patients but may then dilute the identification of NFA. Using PaCO₂ in isolation as a marker of severity has not previously been shown to be a

useful criterion for NFA but the PaCO₂ results observed in this study highlight the severity of the NFA presentations.

2. Baseline characteristics

A history of asthma at presentation or first presentation with near fatal asthma attack has also been observed in previous studies^{93,95} with previous diagnosis of asthma noted in 87% - 90%^{68,70} and first presentation to intensive care with first diagnosis of asthma in 10 – 13%^{68,70}. In our dataset, 16% of patients were not previous known to have asthma although three patients within this group were receiving asthma medications.

3. Type 1 vs Type 2 presentation

A previous national surveillance of near fatal and fatal asthma conducted in Germany in 1998 (Schmitz et al 2000) observed 42 cases with near fatal asthma. Of this group they describe 36 cases (85%) with Type 1 (slow onset) near fatal asthma and type 2 (rapid onset) in 6 cases (15%). This differs to the observation from our dataset with 11/31 cases (35%) patients categorised to Type 1 and 20/31 (65%) patients displaying Type 2 onset. Our study used a clinician identified a specific time (time at which 10 puffs SABA administered to time to ED presentation as end point) as NFA onset time in contrast to Schmitz et al (2000) who did not specific an onset time but used time until intubation as an end point. There are challenges in using both definitions – we noted poor clinician responses to this question (31/51) however Schmitz et al reply on invasive ventilation as an endpoint – the criteria for intubation and the onset of symptoms

were not specified. This may explain the discrepancy between the two study findings.

6 Chapter 6: Challenges and Solutions During Data Collection and Analysis

This chapter will describe and discuss the process of data collection during the study period, the challenges that occurred during data collection and how these were addressed.

6.1 Questionnaire completion

BPSU reporting clinicians were sent a monthly email from the BPSU (Appendix 15: BPSU Monthly Email). This contained a link which directed clinicians to the e-reporting card (Appendix 16: BPSU Reporting Card BPUS reporting card). As discussed in chapter 4, a submitted e-reporting card would have previously alerted researchers to a potential case and they would contact the clinician by email.

With the introduction of the HIC Dundee reporting platform, a further step was required by the reporting clinician (illustrated below in Figure 34).

Instead of waiting to be contacted by the researcher, the clinician could immediately follow the link on the reporting card to the HIC reporting platform. Although this was intended to streamline the process, it created some user difficulty as expanded below for both the researcher and reporting

clinician.

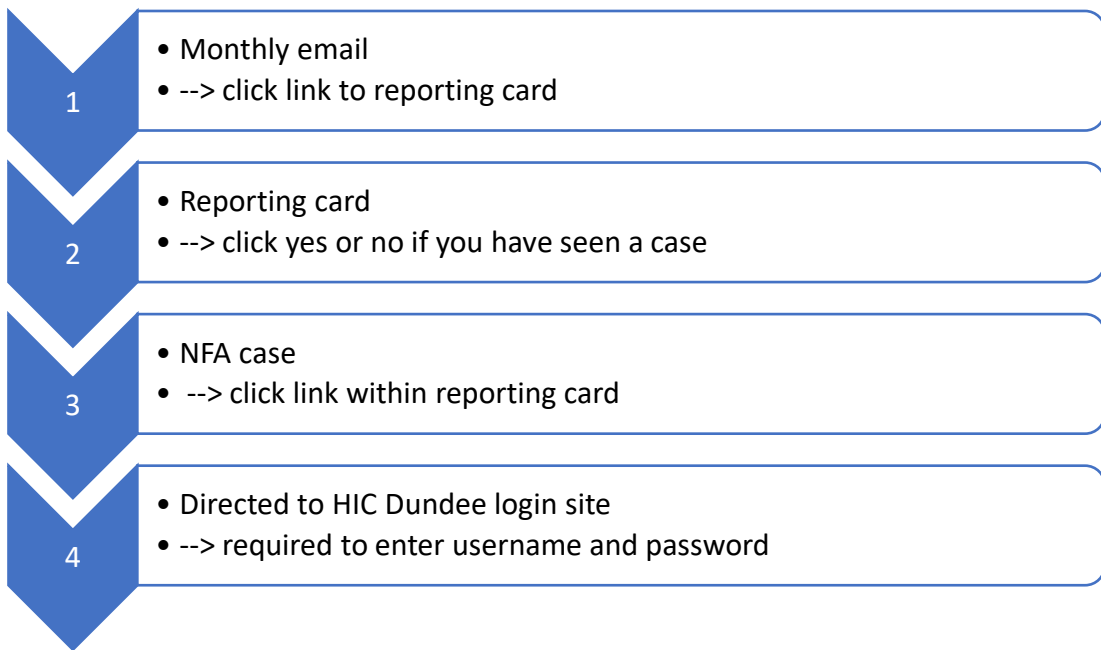


Figure 38 Figure 26 Click steps to access questionnaire

6.1.1 Clinician barriers to reporting using HIC Dundee Platform

6.1.1.1 Accessing the questionnaire

The transition to the new HIC Dundee reporting platform from an email containing the questionnaire to an online reporting platform was considered difficult to navigate by many clinicians. The additional step required (instead of researcher emailing form, clinician would have to login to HIC online platform) was a significant pattern change from the previous BPSU methodology. Many clinicians did not appreciate this additional step existed and waited for the research to send a questionnaire. Additionally, the NFA was only the second study to use this new methodology, the process was not yet streamlined.

The process of logging into the HIC online reporting platform also created a barrier for some clinicians. If login details for the HIC online reporting platform

needed to be obtained or were not remembered the flow of the reporting process was interrupted. Login details took 48 hours to reset (must be reset by member for BPSU administrative team, only available Monday – Friday 0900 - 1700). If a clinician could not login the frustration of waiting for details deterred them using the online platform and reporting was not completed.

Additionally, it appeared that there were two ways a clinician could login to the online platform, 1) by following the link on the reporting card or 2) logging into the HIC site directly and bypass the reporting card email. As many clinicians missed the link for the online reporting platform on the card or had to wait for login details, they opted to log directly into the HIC online reporting site. This meant they did not complete or submit a reporting card which resulted in under reporting of cases to the BPSU.

To try to navigate this, the research team used a functionality within the HIC Dundee reporting platform. The platform allowed messaging from the researcher to the reporting clinician and vice versa. Posting a message on the HIC reporting platform would trigger an email to the reporting clinician with a 'prompt' alerting them a message has been sent to their HIC account about their reported case. The reporting clinician would then need to log in to the HIC reporting platform to see and respond to the message. Once a case was reported, a pre-prepared message would be sent by the HIC platform from the researcher which provided instructions on how to generate a questionnaire. Again, the message text was only observable within the HIC reporting platform therefore the reporting clinician was required to login to see the message. Emails generated by the HIC reporting platform are

generic stating 'you have received a message'. If a clinician did not respond, the researcher assumed they had not been able to login to their HIC online reporting platform account. In this case, early email contact was made by the researcher directly the clinician with details on how to login or contacts if login had been forgotten. I developed a plan for timely support of responding to clinicians to enable reporting and completion of case data (see Figure 35). Of the 179 reports, 71 clinicians (40%) responded at step one, 17 (9%) responded at step 2, 7 (4%) responded at step 3, 66 (37%) responded at step 4 and 18 (10%) did not respond to any of the communication(step 5).

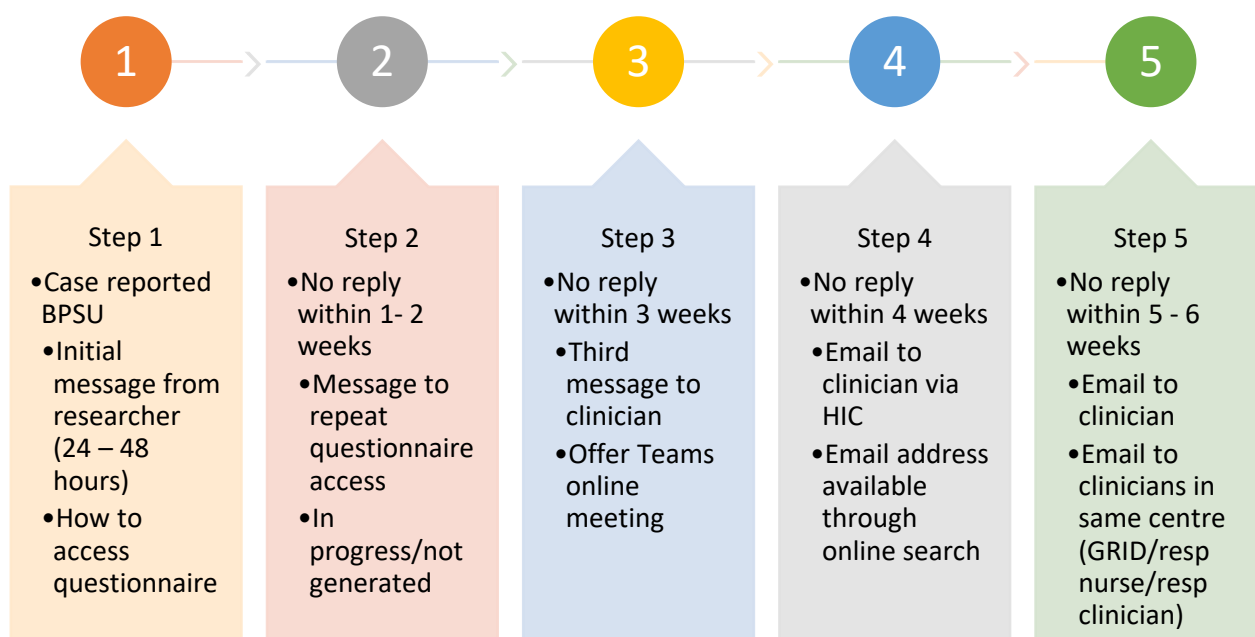


Figure 39 Report response stages

6.1.1.2 Completing the questionnaire

The functionality of the HIC online reporting platform allowed the researcher to view if a questionnaire was 'awaiting details', 'not started', 'in progress' or 'submitted'. Figure 28 below demonstrates the process used and the different

stages of response.

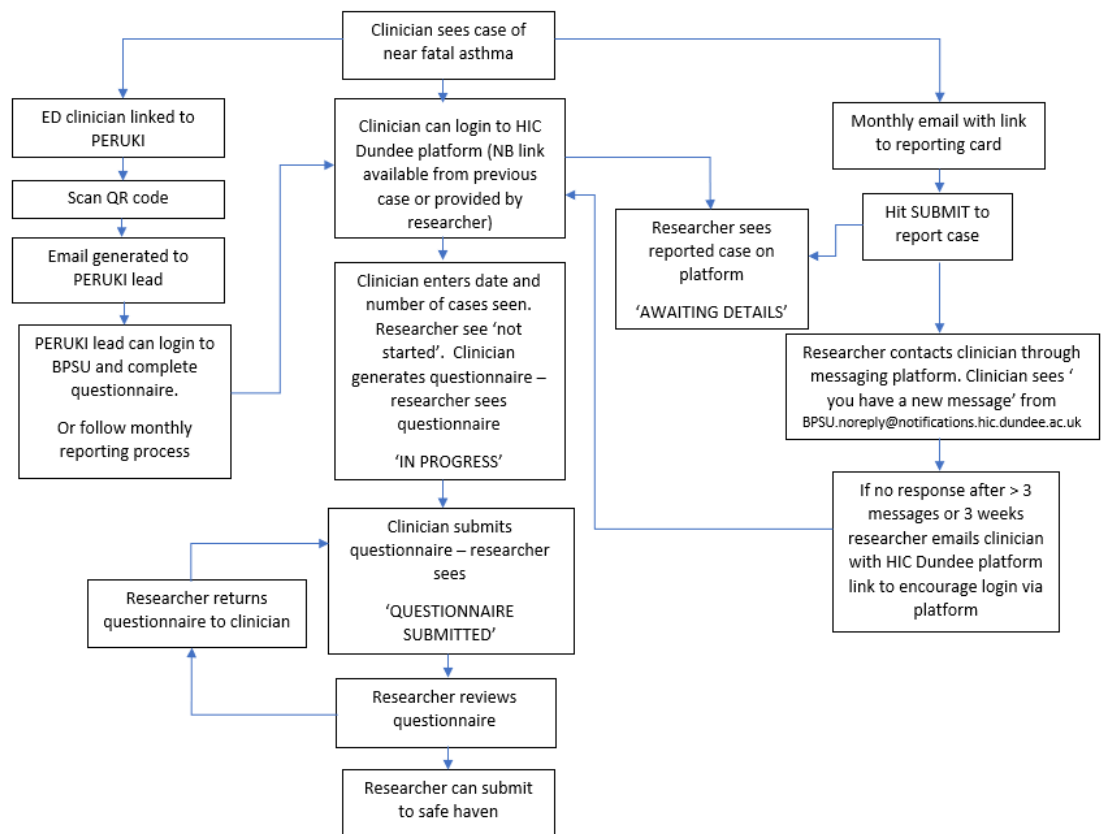


Figure 40 HIC response process

AWAITING DETAILS : Any questionnaires that were reported from the e-reporting card but no further details were given were marked 'awaiting details'. Reporting a case generated a unique BPSU case number on the online platform. This was visible to the researcher as well as the name, clinician BPSU number and the date they reported the case. As previously stated, it became evident throughout the study that many clinicians were waiting to be contacted by the researcher to be provided with a questionnaire. This left many reports in the 'awaiting details' stage.

During the study, I approached the BPSU team and HIC Dundee programmers to request learned experience improvements to the structure of the email, reporting card and messaging system. Unfortunately, these changes were not possible within the timescale and resource allocation available.

NOT STARTED: In this scenario, clinicians had registered a case, entered a date and how many cases they had encountered but not yet generated a questionnaire. As above, the researcher could only see the case number, clinician name and reporting number and date of report. Any clinicians who did not respond to messaging on the HIC online platform and had not generated a questionnaire were contacted by the researcher by email with instructions on how to generate the questionnaire. Clinician email addresses were obtained by online search or through the BPSU. Visual prompts such as highlighting the button that would generate the questionnaire were discussed with HIC but again unable to be actioned in the study period.

IN PROGRESS: These were clinicians who had generated a questionnaire but not submitted any details of the case. Clinicians could save their progress through the questionnaire but this was not available to researchers. It was difficult to determine how best aide the clinician when their questionnaire was in progress as completing the questionnaire relied on the clinician logging into their account and completing the data entry. Reminder emails were sent to clinicians and those who did not respond after 6 months were sent a formal email from the BPSU. Researchers could not see any of the 'IN PROGRESS' questionnaire details.

SUBMITTED: A questionnaire had to be 'submitted' by the reporting clinician for any case details within the questionnaires to be available to the researcher. This allowed the researcher the opportunity to review each questionnaire and if essential data points were incomplete could be returned to the clinician for completion. Any questionnaires submitted prematurely or in error could be returned to the clinician by the researcher on the online platform. Once a questionnaire was reviewed by the researcher and checked it would be submitted to the safe haven by the researcher. Until a questionnaire was submitted it was difficult for the researcher to support the clinician with the questionnaire as it was not clear where the stumbling blocks were. Online calls were offered to allow screen shares and email support was given to clinicians where possible.

RETURNED: If a researcher returned a questionnaire to a reporting clinician for clarification/further input, the information would only be submitted to the safe haven if the clinician resubmitted the data. This process in theory allows researchers flexibility to confirm any outstanding data points but unless the clinician returned the questionnaire, it could not be submitted to the safe haven. After several returned questionnaires were not sent back to the researcher it became clear that the process of returning questionnaires was not successful. Questionnaires with data points missing were carefully reviewed by the researchers and clinicians were contacted via the messaging platform if key details only were missing. If the clinician replied, the researcher could manually add these details to the data once it was uploaded to the safe haven.

The research team were aware that the HIC reporting system created difficulties for reporting clinicians and the design of the study platform was not clinically intuitive. Although HIC could make some changes to the live site, the process and structure of the platform was fixed and had limited potential for alteration. Aware of issues with the site functionality, reporting clinicians were encouraged to contact the study team to facilitate data entry. Meetings were offered via MS Teams to demonstrate the study site (using a researcher test site) or to allow reporting clinicians to screen share any error messages. Despite these interventions some reporting clinicians found the data entry platform challenging and did not complete questionnaires.

6.1.2 Consultant data entry

BPSU methodology states that only consultant paediatricians are eligible to receive e-reporting cards.

During the course of this study, I approached the BPSU to enquire if it would be possible to allow rotational training doctors or specialist nursing staff to complete the questionnaire on a consultant's behalf. Unfortunately, the BPSU denied this request. They felt this would not be possible due to the rotational nature of paediatric training schemes in the UK which often results in frequent changes in contact details such as email addresses. Non responding i.e., no response to BPSU e-reporting cards utilises resources and non-responses may impact the validity of reported numbers therefore the BPSU is not open to trainees becoming a denominator monthly respondents. We discussed if it would be possible for a reporter to be identified from the

HIC platform to allow a consultant to transfer reporting for a specific submitted case to a specified clinician or trainee to facilitate data entry, the reporting card however would still be registered to the consultant. After discussion with the HIC programming team it was suggested this could be possible however this change was unable to be completed during our study period. As they could not facilitate this change during the study period the BPSU allowed us to nominate trainees on behalf of the consultant to complete the questionnaire with the agreement the trainee would create a login for the study and once the study has finished, be removed from the BPSU register. To recognise the trainee efforts the study team produced a certificate to encourage and reward any trainees and specialist nurses that helped with data entry. Trainee submissions counted for 9 of the 51 cases (17%). As a researcher, I found trainees were able to follow the online reporting platform instructions and submitted cases quickly compared to consultants.

6.1.3 Barrier for researchers

Prior to the introduction of the HIC online reporting platform researchers would be directly notified of a 'yes' report submitted on a BPSU reporting card. With the introduction of the HIC online reporting system, there was no automated response to the researcher that a report has been submitted. The researcher would only be notified if a completed questionnaire had been submitted. To ensure reports were picked up quickly and early contact was made with clinicians, the reporting platform was checked daily throughout the project by one of the research team (DV).

6.2 Irish Paediatric Surveillance Unit

The BPSU study included clinicians and case reporting in Republic of Ireland. During the surveillance period it was noted in email conversations with clinicians in the Republic of Ireland that 'blue cards' were being used to report cases with similar case criteria. Blue cards are the method of reporting to the Irish Paediatric Surveillance Unit (IPSU) which exists in parallel to the BPSU and operates in a similar way. Reporting cards are blue and printed on paper which are posted out monthly to clinicians registered with the IPSU. Cases registered with the IPSU are not automatically fed into the BPSU however previously the BPSU has worked with the IPSU to prevent duplication of data. During the course of this study, it became clear that some cases ($n \leq 5$) were being reported from ROI on the BPSU card and not on the IPSU card and some vice versa. In a rare condition such as near fatal asthma with small reporting numbers, it is important to ensure each case is registered with loses of even one or two patients impacting the overall data.

During a visit to Dublin for the Irish Faculty of Paediatrics Annual General Meeting (May 2023) I took the opportunity to discuss the reporting for the BPSU Near Fatal Asthma study. It was assumed by many of the clinicians in ROI that reporting with the IPSU would automatically ensure BPSU reporting. When informed of this potential conflict in reporting, we contacted the chair of the IPSU to try to identify a solution. After meeting with IPSU it was confirmed that the systems were intended to run in parallel and it was not possible to link the two reporting methods.

It also became apparent that IPSU cases were not being followed up by any allocated clinician. After discussion with the BPSU it was decided that an allocated clinician (Dr Des Cox) would collate the IPSU cases and enter the details on the BPSU system. In future, methods to better align IPSU and BPSU methodology are planned to be discussed by the BPSU committee.

6.3 Survey Fatigue

Survey fatigue describes the lack of enthusiasm experienced when multiple surveys and requests for information are asked of a population or study group. We were aware that post COVID 19 Global Pandemic, which saw a rise in healthcare surveys for professionals²²⁶, clinicians may be less enthusiastic to engage with BPSU surveillance. Surveillance data can become difficult to interpret with incomplete or unreturned data so maximising engagement was a key priority for the research team.

Factors that enhance survey fatigue for healthcare professionals include –

- Length of survey (too long)
- Participant time concerns
- Technology – poor designs, accessibility
- Intrusion into non-working hours^{226,227}

I was aware these could become a problem in our study. Based on recommendations²²⁸, I attempted to combat survey fatigue by:

- Splitting the questionnaire into discrete sections to shorten the length any individual speciality clinician would be required to complete.
- check box answers yes/no/don't know where possible

- use of logic for question stems – follow up question appeared depending on a yes/no/don't know answer
- personalised messaging when contact clinicians
- shorter sections for acute specialities such as ED and critical care
- Minimise free text responses
- Clear guidance instructions on how to complete the survey and which sections were required
- Flexibility of timing of data entry- form could be saved and accessed again

Through HIC Dundee a pilot site was created and the study team invited clinicians from ED, critical care, general paediatrics and respiratory paediatrics to complete the questionnaire with feedback. This ensured we were able to adjust any unclear terminology, check the functionality of the site and trial the reporting process.

As demonstrated in Chapter 5, the critical care details of each case were poorly completed (8 cases with critical case data completed). We questioned why this may be the case and attempted to engage critical care clinicians at the PCCSG ASM (Section 4.6.2). Critical care clinicians are involved in data reporting through PICANet and the burden of another reporting system appeared to cause reluctance in reporting. To try to minimise this burden the critical care section of the questionnaire was made as direct as possible with tick box questions and optional data entry for ventilation settings but response to this section was overall still poor.

6.4 Definition Review

After the study had been running for 10 months, I met with the Professor Cunningham and Dr Ann McMurray to discuss case reporting and numbers. We discussed reasons why reporting was low and if any other opportunities could be used to publicise the study or support reporting clinicians.

We noted that error reports were common either due to patient not meeting criteria 1 (without blood gas) or age range. After discussion we felt that although broadening criteria might increase case reporting, may reduce the accuracy of finding defined near fatal asthma attacks. We did acknowledge blood gas sampling in unwell children can be challenging and user dependant. We circulated amongst PERUKI clinicians that if a blood gas could not be obtained due to technology failure (i.e., gas dropped, machine analysis error) but a patient met the remaining two features of criteria 1, that these patients would be considered in the study and should be included if reporting clinicians felt their presentation was one of near fatal asthma. Two patients were subsequently reported that did not meet criteria but were felt by ED clinicians to have presented with NFA. These two patients were not included in overall analysis but formed part of sub analysis(Chapter 5.10).

We also noted a small number of patients than expected were reported from highly populated areas with tertiary centres such as London. Dr McMurray facilitated an opportunity to discuss this with London Asthma Leadership and Implementation Group for Children and Young People (LALIG). We presented the study at this meeting and subsequently had an increase in reported cases.

6.5 HIC Dundee programming challenges including ethics amendment and changing HIC platform

6.5.1 Data Analysis Delays

Unfortunately, during the study there was a significant delay in the access of data within the safe haven. From May 2023 until February 2024 researchers were unable access data uploaded to the safe haven. Although study data could continue to be submitted during this period, no data could be accessed by researchers in the safe haven. This was due to the migration of HIC Dundee to a trusted research environment (TRE), AWS Cloud by Amazon. This was a back end change and did not affect the study methodology. The BPSU required renewed governance approvals for this change and during the 10 month period it took to obtain renewed approvals from relevant national committees, access to the safe haven was suspended.

6.5.1.1 *Ethics amendment time delay*

A formal ethics amendment and a CAG and PBPP amendment was required. These were obtained within 2 months of submission as they were considered a minor amendment. During the course of the study, the chair of PAC NI stepped down and a new chair was appointed. There was a significant delay in obtaining PAC NI permission. Unfortunately, there was a lack of response from PAC NI for 5 months. At this point it was considered that data from Northern Ireland would be excluded from the study if permission could not be obtained. After 6 months of unanswered communication PAC NI agreed to the amendment. This significantly delayed data analysis in the study. During this time period, proposed data analysis tables were made in Microsoft Excel

and proposed data linkage code was written in R studio statistical software (<https://posit.co/download/rstudio-desktop/>).

6.5.1.2 *HIC Dundee reporting platform*

As discussed in Chapter 4.5.1, the online platform provided by HIC Dundee created some challenges in usability for clinicians. Although researchers could provide feedback to HIC Dundee on the site, the structure of the site and platform could not be altered on an individual study basis. Researchers were unable to alter the platform, respond to error messages or clinician feedback. Changes could only be made through HIC Dundee. This created difficulties as HIC resources and staff constraints varied in their ability to adjust the platform based on feedback. Suggested changes could not always be facilitated such as some functionality and aesthetic changes that would have made the platform user friendly. To discuss these, bimonthly meetings were arranged with BPSU representatives for HIC. This helped the communication of the researcher suggestions but unfortunately the resource and time constraints of HIC did not allow all changes to be made.

Some clinicians had registered with the BPSU with an infrequently used email address or an incorrect email address. This could also not be corrected by the research team and changes had to be made through the BPSU. This hindered the login process and slowed the pace of data collection.

6.6 Triangulation of cases with Paediatric Intensive Care Audit Network for the UK (PICANet)

PICANet is a network established by the University of Leeds, Leicester and Sheffield. It is a database that records the details of children in critical care in

the UK and Ireland. PICANet is commissioned by Healthcare Quality Improvement Partnership (HQIP) and National Clinical Audit Programme (NCA)²²⁹. Previous interrogation of PICANet data on asthma admissions in children suggested we could expect approximately 300 admissions during the 18 month surveillance period¹²⁰. We reviewed our numbers in July 2023 (approx. 10 months of study data). At this point 77 reports were submitted with 28 completed questionnaires. 29 of these reported were errors and all of the reported cases had required management in critical care. The numbers of reported cases were much smaller than expected. To determine if this was true frequency or under reporting, we applied to obtain interim data from PICANet to determine if the number of patients invasively ventilated for asthma (ages 5 – 15 years) matched our data.

We discussed this data request with PICANet. We opted to include any patient with a diagnosis of asthma (either primary reason for admission) or secondary diagnosis. This was necessary to ensure that patients who were admitted with cardiopulmonary arrest (may primary admission diagnosis) due to asthma (secondary diagnosis) we included in the data set from PICANet. We could not filter other admission diagnosis i.e., if a patient admitted with a surgical pathology but also had asthma – this would be included in our PICANet numbers.

To ensure the appropriate patients were selected we were required to provide READ Codes for the PICANet data. READ Codes are discussed in Chapter 2.5. To ensure these were correctly applied to the data set I met with Dr Lyn Palmer Data Research Nurse Department of Population Health

Sciences, University of Leicester. The most common 80% of respiratory diagnosis READ Codes are used in PICANet data sets. This enables clinicians coding data to find and categorise patient admissions with the most common conditions. Near fatal Asthma is rare and therefore no READ Code existed in the PICANet dataset for NFA. The READ Codes selected were

Table 6.1 READ Codes for PICANet

Xa9zf	Acute asthma	304527002
XE0YW	Asthma attack	708038006
Ua1AX	Brittle asthma	225057002
H33z.	Asthma unspecified	195967001
Xa0lZ	Asthmatic bronchitis	405944004
XE0YX	Asthma NOS	195967001
X101t	Childhood asthma	233678006
Xa7uu	Expiratory wheeze	9763007
Xa7ut	Inspiratory wheeze	31572008
XE0YQ	Allergic atopic asthma	389145006
XM09W	Respiratory arrest	87317003
XE0qs	Wheezing	56018004
Xa0Ns	Bronchospasm	4386001

We chose to ask for simple data request for children admitted age 5 – 15 years:

- Number of children admitted with above codes
- Number of children invasively ventilated throughout the study period

Obtaining PICANet data required permission from HQIP (Data request made by PICANet). This was successful however on discussion with the PICANet Confidential Advisory Group we were requested that data was used only for triangulation of cases within the study and not published prior to PICANet verification and public release. This has limited the data available that can be

presented in this thesis. Receiving the PICANet data allowed us to review if BPSU reporting was reflective of national acute asthma attacks admitted to critical care. The comparison with PICANet data is described in the following section, PICANet case numbers have not been included.

PICANet supplied a month – by month dataset of cases meeting the above criteria and READ Codes. This was directly compared to the monthly case reports of NFA attacks. The PICANet data comparison noted the BPSU reports were much lower than expected compared to the PICANet admissions and invasively ventilated asthma admissions. We noted there was a significant number of cases admitted to critical cares in November/December 2022 in PICANet data but this was not reflected in our study reports. We considered several explanations for this:

5. PICANet data included asthma admissions admitted with non-primary asthma presentation not meeting case criteria.
6. Under reporting from BPSU – may be due to study start point one month prior to surge of critical care cases, clinicians could have been unaware of the study
7. Retrospective cases were be added to our data
8. Incorrect READ Codes applied to cases
9. PICANet data will also include any children that were admitted to critical care and died (fatal asthma not included in our study)

With the knowledge of this under reporting we republicised the study via the above listed channels in Chapter 4.6 highlighting the gap in cases for

November /December. We also considered amending our case criteria (see Chapter 6.4).

To review how PICANet pulled cases based on the read codes provided we obtained data for the study period from Metavision in the Royal Hospital for Children and Young People Edinburgh. Using the case criteria, a search was carried out by Dr David Armstrong. Initially 61 patients were pulled from metavision meeting study criteria (READ codes for diagnosis used) for the study period, once age criteria applied 33 patients were removed. Twenty eight patients were remaining with <5 patients matching study criteria (small number suppression applied). This highlighted that using PICANet as a data search tool during the study may not accurately represent cases meeting our NFA criteria.

6.7 Reflection On The BPSU Methodology

This chapter has highlighted many of the challenges and barriers faced using the BPSU methodology to identify NFA cases. Whilst the BPSU is a longstanding and useful surveillance network for rare paediatric diseases, this chapter highlights how changes advances in data access, storage and legislation now pose barriers to BPSU methodology which previously may not have been in place. The use of the safe haven for data storage, linkage and analysis allow storage of personal and special category data however have limited the analysis of environmental exposures at postcode level. Use of the new BPSU data collection platform has also exposed the shift in clinician investment in BPSU data collection. The BPSU methodology recognises the unique and invaluable input from clinicians to identify cases which as

demonstrated by the PICANet and metavision interrogation above may be missed however to ensure ongoing participation from busy and time poor clinicians it should be considered if widening the pool of contributing clinicians or changing their surveillance methodology and data collection platform would encourage greater clinician participation and ensure survival of the BPSU for future studies.

7 Chapter 7: Discussion

In this chapter I will summarise the main finding of this thesis project and discuss the relevance of these finding in context of what is already described in the literature on near fatal asthma in children and young people.

The objectives of this thesis were

1. To conduct a systematic review on ambient outdoor air pollution and its association with severe asthma attacks in children. As a secondary outcome review the multiplicity of factors that may contribute to near fatal asthma.
2. Through an observational surveillance study, measure the annual frequency of NFA attacks in children and young people in the UK and Republic of Ireland, and to describe key characteristics and potential risk factors.
3. Using the data set identified in the surveillance study, assess the effect of environmental and infective factors on NFA attacks in children and young people, to include air pollution, weather, pollen levels and prevalent respiratory viruses.
4. Assess if any conclusions from the data could be enhanced by further analysis of near fatal asthma cases using alternative methodology

7.1 Systematic review findings

A key element identified from the background to this thesis was requirement for a systematic review on near fatal and fatal asthma and outdoor air pollution. One of the main findings from this review highlighted the lack of

granularity in identifying and reporting the severity of asthma attacks, when ICD codes are used to identify asthma attacks from hospital records. The small number of papers available from the review (n = 4) highlight the gap in data on near fatal asthma attacks and outdoor air pollution in children. Outdoor air pollution was identified as a causative factor in the death of a child from asthma in landmark UK case described in chapter 1.2. This review strengthens the need to consider outdoor air pollution as a risk factor for near fatal asthma. The role of outdoor air pollution in asthma exacerbations is well described²³⁰, Orellano et al (2017) describe an increased risk of exacerbations (in children significant increased risk with NO₂, SO₂ and PM_{2.5} exposure) but the severity of attacks were not described. Clinicians need to consider whether and to what extent outdoor air pollution may be contributing to more severe asthma attacks. Current literature poorly categorises asthma without defined severity and as a result categorising near fatal asthma in the same group as mild or moderate asthma. This loses a key opportunity to learn more about this group of patients.

7.1.1 Is the solution in diagnostic codes?

The international classification of disease system was initially created to catalogue the causes of mortality. This expanded over time to code hospital diagnoses and surgical procedures²³¹. The correct use of codes is user dependent. In a surveillance of sepsis in intensive care, a study in Canada demonstrated significant under presentation of sepsis using ICD codes²³². Even if a code exists it must be used correctly and appropriately.

New codes can be suggested and will be reviewed by WHO-FIC Network committee and reference groups to establish if significant need for the code is evident²³³. Similarly, the 'Systematized Medical Nomenclature for Medicine–Clinical Terminology' or SNOMED codes are increasingly used within areas of the NHS to monitor diseases. In the interrogation of PICANet for this study, I discussed how SNOMED codes were chosen with Lyn Palmer (PICANet Research Nurse) and it was noted that PICANet only adopted the top 80% of most used codes for intensive care admission as the system could not support all SNOMED codes. The consequence of this may be rare conditions such as near fatal asthma will not be included in PICANet coding even if a relevant code was available. There is currently no code for near fatal asthma. The ICD 11 which is in current circulation does have the ability to quantify the severity of asthma (mild, moderate or severe)²³⁴ but does not specify if this is acute or chronic asthma and does not define severe. As a consequence, a patient who requires monoclonal antibody therapy for daily severe asthma symptoms could be coded equivalent to a life threatening asthma attack or a severe asthma attack without differentiation. 'Unspecified asthma with status asthmaticus' is included in ICD 11 but no case definition is given. Identification of near fatal asthma and recognition of the risk of fatal asthma is vital, appropriate coding of the severity of acute asthma attack may aide clinicians correctly identifying this high risk patient group. Correct use of the code will depend on a clear definition that is recognised.

7.2 Surveillance of Near Fatal Asthma in Children and Young People in the UK

The characteristics of the children and young people presenting in this study are novel and add to existing knowledge of near fatal asthma in children. To our knowledge this is the first UK surveillance study of near fatal asthma in children and young people using clinician questionnaires to identify near fatal asthma attacks. This study highlights the importance and necessity in expanding the body of evidence on near fatal asthma in children and young people. The detailed characterisation of near fatal asthma attacks including follow up data has not previously been described in the UK. There are no current guidelines in the UK addressing the follow up care of children with near fatal asthma. This study demonstrates that the identification of near fatal asthma which includes hypoxia/hypercarbia and IV therapy (basis of E-Delphi) cannot be identified solely from intensive care admissions and this study demonstrates these critically unwell children are being managed outside a critical care environment. In this dataset we demonstrated that discharge management including medication changes, follow up clinician and spacer use, personal action plans are not yet standard practice. This study has provided insight into the social demographics of patients experiencing near fatal asthma and highlighted again that children from deprived socioeconomic backgrounds were more commonly observed in the dataset. We present for the first time that children from South Asian background were observed to have an increased frequency of NFA compared to children from Black/Caribbean background. This study has also highlighted the degree of hypoxia and hypercarbia observed in children presenting with near fatal

asthma which has not previously been described. The surveillance data highlights the severity of acute presentations requiring respiratory and cardiopulmonary resuscitation and in respiratory failure (high PaCO₂, low SpO₂). These cases had opportunities for intervention (contact with clinical services prior to NFA). The descriptive data demonstrates that NFA is not managed consistently and there is a gap in the current BTS/SIGN guidelines addressing recommendation for NFA recognition, management and follow up. As demonstrated by the table in Chapter 5, current guidance (in life threatening asthma) has low compliance specifically in relation to the variation of medications on discharge (three children on SABA only therapy on discharge). This is troubling as current guidelines suggest inhaled ICS treatment as a preventer in life threatening asthma. When compared to key benchmarks in place from NRAP surveillance (see below) for all asthma presentations, the administration of steroids occurred in all cases (timeline not documented) but not all patients had a personalised asthma action plan on discharge.

NRAP benchmarks (2021)

- *Steroids administered within one hour of hospital arrival*
- *Current (patients) tobacco dependency addressed*
- *Current (parents/carers) tobacco dependency addressed*
- *Inhaler technique checked*
- *Personalised asthma action plan issued/reviewed*

The discord between the results of the surveillance data, current guideline recommendations and NRAP benchmarks highlight the urgent need to clearly identify this group of patients and ensure clear management strategies are in place to prevent further NFA or fatal asthma attacks.

7.2.1 Age

The age distribution of cases shown in Chapter 5.2.1 appears linear. This is counter to some expectation of an increase in teenage years as there is a transfer of responsibility for both chronic care but also acute care responses^{235,236}.

7.2.2 Gender

This dataset observed more male cases (30/49, 61%) of near fatal asthma compared to females (19/49, 39%). This is consistent with previous observations noted for asthma exacerbations in children^{90,93}. As discussed in chapter 2, post pubertal females are higher risk of asthma exacerbation with increasing age, our data had small number and did not reflect a post pubertal shift towards female NFA cases. Although numbers are small – we anticipate that asthma generally improves in adolescent males, and not as commonly in females. This data (>10 to 15 years) suggests that whilst males may generally improve, their propensity to near fatal asthma attacks is increased.

7.2.3 Ethnicity

The surveillance of near fatal asthma noted 24% (12/49) of cases were of South Asian ethnicity. The majority of cases of near fatal asthma (63% n = 31/49) were white background. I compared this to the data available from 2021 census (England and Wales). In children age 5 – 15 years the distribution of ethnicity was^{136,237}:

- **White:** 70.2%
- **Asian:** 14.5%
- **Black:** 7.5%
- **Mixed:** 6.5%
- **Other:** 1.3%.

When compared to my surveillance data results there is a higher proportion of children from Asian background experiencing NFA compared to 2021 census data.

Table 7.1 Surveillance Data compared to ONS 2021 Census Data

		2022- 2024 NFA attacks	2021 England Census
White	31	63%	70.2%
South Asian	12	24%	14.5%
African/Caribbean	5	10%	7.5%
Not reported or Other Ethnicity	<5	3%	-

A recent study in the UK examining paediatric intensive care unit admissions from January 2008 to December 2021 supports our study findings highlighting Asian and Black children had a higher incidence of unplanned PICU admission compared to White (RR 1.29 [95% CI: 1.25–1.33] and 1.50 [95% CI: 1.44–1.56])²³⁸. This is supported by historic data from Parslow et.al (2009) which also demonstrated and increased incidence in intensive care admission for south Asian children (1.36, 95% CI 1.32 to 1.40)²³⁹. These studies did not look specifically at asthma admissions. In the UK, previous meta-analysis has noted has shown in children age 5 – 15 years, south Asian children have a lower frequency of wheeze (9.6% CI 8.0 – 11.2) compared to

white 14.6% (11.5–17.8%) or black children 16.2% (12.8–19.6%)²⁴⁰.

However, when considering hospital admissions, Black and South Asian people (children ages 5 – 15) had an increased risk of hospital admission with asthma 1.5 (1.2–1.9)²⁴⁰. It has also been observed that in south Asian children age 2-4 years, are more likely to have multiple wheeze 2.21 (1.19–4.09) compared to white children and 1.43 (0.77–2.65).

7.2.4 Social Deprivation

Our data observed that one third of the cases were associated with the lowest deprivation quintile in England. This data is in line with previous PICANet interrogation of admissions to intensive care with asthma in the UK^{120,239}. When Townsend indices were applied to our surveillance data set 48.8% of patients were in the lowest quintile (most deprived). Globally, race and social deprivation have been strongly associated with increased risk to intensive care admission for asthma in children^{91,241,242}. This study supports previous research acknowledging children from lower socioeconomic backgrounds are at high risk for asthma, intensive care admission and near fatal asthma. This risk must be addressed at government but also clinician levels. It is vital these patients have an understanding of near fatal asthma, when to seek help and have enhanced contact with asthma specialist services. Clinicians must ensure environmental exposures are minimised where possible and where relevant, families are highlighted to local authorities. In the UK this disparity has been highlighted by prominent charities such as Asthma and Lung UK²⁴³.

7.2.5 Outdoor air pollution

A significant finding in the results of this study found that 95% (41/44 cases) were exposed to background levels of PM_{2.5} exceeding WHO recommended thresholds. In addition, 11/44 cases (25%) exceeded thresholds for PM₁₀ and 27/44 (61.4%) exceeded recommended levels for NO₂.

Outdoor air pollution exposure, specifically PM_{2.5} has been linked to the development of asthma in early and middle childhood²⁴⁴ but also to an increase in acute asthma attacks in children and reduction in lung function (FEV₁)²⁴⁵. PM₁₀ has also been implicated in increasing asthma symptoms in children^{246,247} and high exposure to NO₂ prior to an attack triggered by viral infection has also been observed to increase the severity of asthma attack symptoms²⁴⁸. As demonstrated by the findings of the systematic review, over 200 papers were identified examining outdoor air pollution and asthma attacks in children and although small numbers addressed near fatal asthma, it is clear from the results of this surveillance study that further examination of near fatal asthma and outdoor air pollution is required. The results of this systematic review and surveillance study add to the overwhelming body of evidence supporting the need to address high levels of outdoor air pollution to reduce the burden of asthma prevalence in children and the number of acute asthma attacks in children and young people.

There is recognition amongst paediatricians in the UK that outdoor air pollution exposure needs to be reduced to improve respiratory lung health in children²⁴⁹. The RCPCH has issued a statement calling on the UK Government to tackle air pollution, specifically exposure to PM_{2.5} and NO₂²⁵⁰.

This also addressed the UK Government Air Quality Guidelines position on recommended air quality levels which are not in line with WHO recommendations. The UK Air Quality Strategy 2022 – 2024 has aimed to reduce PM_{2.5} annual mean exposure to 10µg/m³ by 2040²⁵¹ which is still double the WHO recommended level. Without further policy change and an awareness in the need for reduction in air pollution levels, high levels of exposure will continue to be observed in near fatal asthma as cases such as Ella Kissi Debrah (Box 2) may unfortunately become more common.

7.2.6 NFA discharge and follow up

The results of this surveillance study show the multiple potential intervention opportunities for children with near fatal asthma presentation to prevent future attacks. Strikingly, 20/41 cases (48.8%) had interacted with a clinical service in the 7 days prior to NFA attack. Nine cases had a hospital admission in the 7 days prior to attack, unfortunately discharge information from that admission is not available but all patients were known to have a diagnosis of asthma and seven of these had oral corticosteroids prior to NFA. As noted in the case from William Gray¹⁵ (Box 1), presentations with NFA can be unrecognised and appropriate follow up not in place. Also highlighted by NRAD¹⁵⁷, multiple health care interactions prior to fatal asthma attack have also been observed. This questions if asthma education is occurring at these points for children and families and also if healthcare professionals are aware of the risk of near fatal asthma. Asthma care guidelines stipulate all patients should have a personalised asthma action plan^{4,12} but our surveillance noted that even after a near fatal asthma attack, 8 cases (8/31,

25%) did not have an asthma action plan on discharge. In paediatric asthma care repeated use of SABA only inhalers without ICS has been considered dangerous and increases the risk of near fatal and fatal asthma attack²⁵² and SABA overuse²⁵³. Three cases in the surveillance study were reported to be discharged on SABA only therapy. Of interest, no patients in the study were reported to be on injectable asthma therapy, this raises the question if there is a treatment gap for these patients and requires further research. Both GINA and BTS/SIGN guidelines suggest the use of monoclonal antibody therapy (in accordance with local policy) in difficult to treat asthma to reduce severe exacerbations^{4,12}. We did not include Asthma Control Scores (ACS) or equivalent measures of background control in this questionnaire however 4 cases (4/39, 10.2%) had > 3 courses of oral steroids in the 12 months prior to NFA attack suggesting poor baseline control and it could be argued that if age appropriate and non-biologic therapy maximised, monoclonal antibody therapy would be indicated in these cases.

Patients with previous NFA are known to have increased risk of future severe and or fatal asthma attacks and two patients (2/49, 4%) had two attacks of NFA within the study period. Nine cases (9/48, 18.8%) had a previous ICU admission for asthma requiring ventilation in the 12 months prior to the attack again demonstrating the increased risk of near fatal asthma. Again, this shows there are key opportunities for intervention, asthma education and risk reduction for further NFA attacks.

7.2.7 Context of data

We compared themes from previous literature on near fatal asthma in children and young people to the observations from our dataset.

1. Diagnosis

When recognising near fatal asthma, the use of PaCO₂ has previously been suggested by several studies^{78–82} although a consensus on the diagnostic limit has not been reached. These studies suggest PaCO₂ 5.9 – 6.6 kPa. We observed a median PaCO₂ 11.2kPa in our group of patients which is significantly higher than previously observed. This questions whether this observational study has identified more severely decompensated patients or if previous definitions have not attempted to delineate the severity NFA. A broader definition for PaCO₂ thresholds may include larger numbers of patients but may then dilute the identification of NFA. Using PaCO₂ in isolation as a marker of severity has not previously been shown to be a useful criterion for NFA but the PaCO₂ results observed in this study highlight the severity of the NFA presentations.

2. Baseline characteristics

A history of asthma at presentation or first presentation with near fatal asthma attack has also been observed in previous studies^{93,95} with previous diagnosis of asthma noted in 87% - 90%^{68,70} and first presentation to intensive care with first diagnosis of asthma in 10 – 13%^{68,70}. In our dataset, 16% of patients were not previous known to have asthma although three patients within this group were receiving asthma medications.

3. Type 1 vs Type 2 presentation

A previous national surveillance of near fatal and fatal asthma conducted in Germany in 1998 (Schmitz et al 2000) observed 42 cases with near fatal asthma. Of this group they describe 36 cases (85%) with Type 1 (slow onset) near fatal asthma and type 2 (rapid onset) in 6 cases (15%). This differs to the observation from our dataset with 11/31 cases (35%) patients categorised to Type 1 and 20/31 (65%) patients displaying Type 2 onset. Our study used a clinician identified a specific time (time at which 10 puffs SABA administered to time to ED presentation as end point) as NFA onset time in contrast to Schmitz et al (2000) who did not specify an onset time but used time until intubation as an end point. There are challenges in using both definitions – we noted poor clinician responses to this question (31/51) however Schmitz et al (2000) rely on invasive ventilation as an endpoint – the criteria for intubation and the onset of symptoms were not specified. This may explain the discrepancy between the two study findings. The findings of the NFA surveillance data echo and build on the conclusions from the NRAD Report (2014). The NRAD recommendations addressed fatal asthma however a similar approach should be applied to NFA to prevent fatal attacks. The NRAD recommendations suggest changes to the systems in the provision of care, diagnosis, identifying risk, implementation of guidelines, improved patient education and self-management, and improved quality of completion of medical certificates of the cause of death¹⁵⁷. All of these areas (improved coding of NFA instead of completion of medical certificates) are shown as needing intervention from the NFA surveillance. The NRAD report

was published in 2014, 10 years later the NFA surveillance indicate that there are still significant steps required to improve asthma care in CYP and prevent further attacks.

7.2.8 Study limitations

7.2.8.1 *Overall numbers*

Fifty one attacks were captured by the surveillance study. We suspect that during the study, there was underreporting of cases. Eighteen cases remain outstanding and amongst BPSU clinicians, there was an average of 66% response rate to BPSU cards throughout the study.

As this is the first UK surveillance of near fatal asthma in children, there is no comparative number for this dataset. Using PICANet, we carried out a review at 10 months to determine if PICANet numbers were reflective of BPSU reporting. PICANet numbers of asthma admissions and the number of those admissions that required invasive ventilation were higher than BPSU reported numbers but as discussed in chapter 6 (section 6.6), PICANet cases were obtained using SNOMED codes and may not have accurately captured our study population.

During the study, significant effort was made to publicise the study to relevant paediatricians as described in Chapter 4. BPSU sign up is voluntary and although 4277 paediatricians are BPSU members¹⁴⁶ and 5138 consultants were registered with the RCPCH²¹⁴ (England, Wales and Scotland) and clinicians who were not part of the BPSU during the study period could not contribute to the surveillance. BPSU reporting card return rates are also lower than previous years (in 2021 88.3%¹⁴⁶). It is not clear why this decline

has occurred but may coincide with the introduction of the new online reporting platform. During the study we received feedback from several clinicians that the platform was not user friendly and paper forms were requested. One clinician reported

“(I) find the BPSU web site cumbersome and not easy to navigate”

and several clinicians reported difficulties in navigating the site

“I’ve tried 2 internet browsers (Chrome and Microsoft Edge) but I can’t progress.”

The high number of error reports evidences the difficulties clinicians experienced in using the site. During the study we provided support for clinicians entering data by offering online meetings to demonstrate the site usage, example power point slides to clearly show how to access the questionnaire and support by email when needed.

The BPSU methodology states only consultant paediatricians can sign up to receive reporting cards. As discussed in chapter 5 we recognised consultants were struggling to engage with the reporting platform and approached the BPSU to open the reporting to trainees. This was not accepted and unfortunately impacted the number of reported cases. We received feedback regarding this issue from one consultant who refused to complete the questionnaire stating

“I didn’t fill in details as initially had issues with website and it looked like a lot of work.”

As discussed earlier in year- I am only BPSU person here. I would guess that there have been multiple asthmatics that would fit criteria but they haven't been screened.

I would like to help but genuinely looking at diary for next month I have one deadline after another after another and my own research is on the back burner for another month."

Although many consultants did take time to complete the questionnaire, we were conscious that the above sentiment was shared by many. In discussion with a respiratory consultant specialising in paediatric asthma they stated:

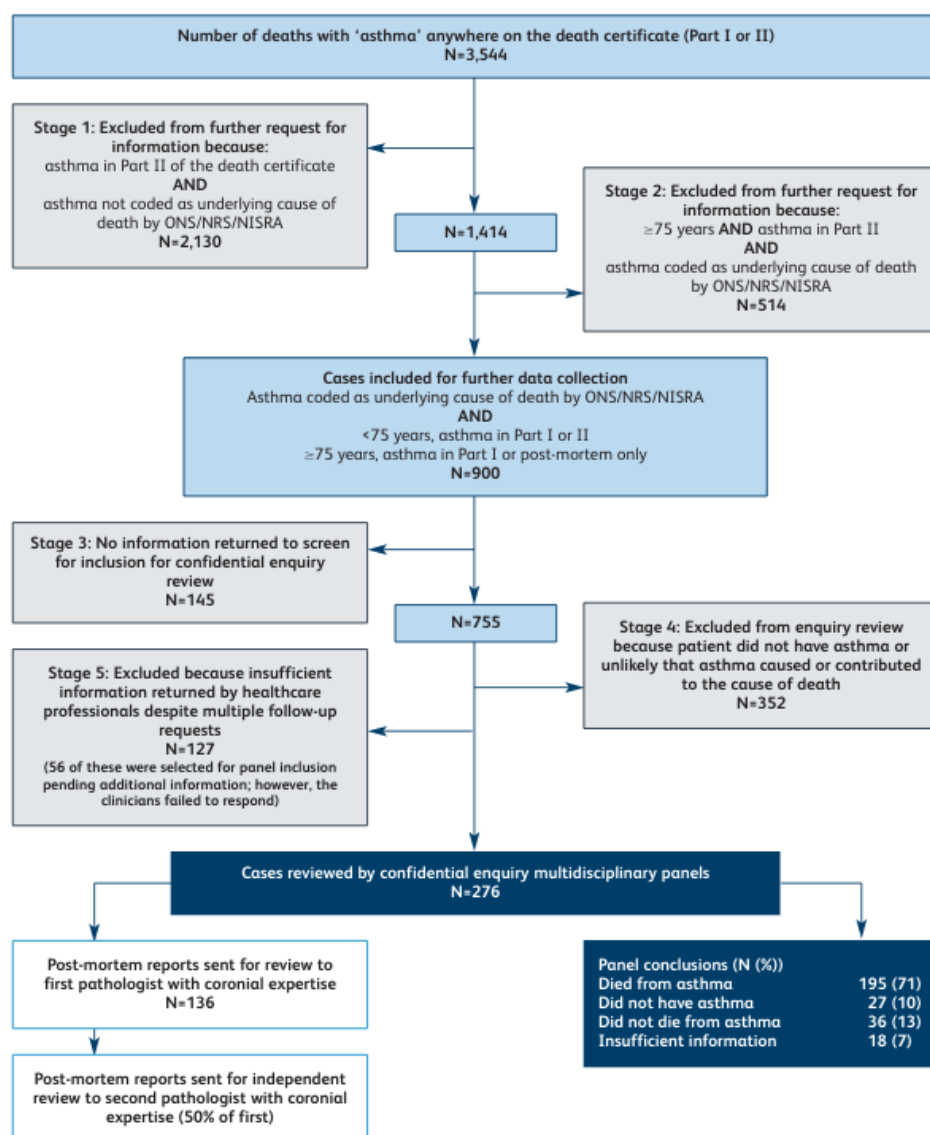
'Oh, the BPSU emails – I just ignore them. I filled it out once and it was just so much work, I don't have time for them, they wanted so many details'.

This attitude questions whether or not the BPSU was the right platform to use to conduct this surveillance study. The BPSU is unique in providing a network to all paediatric specialities which was crucial for this study as clinicians in district general hospitals, emergency departments, critical cares and respiratory paediatrics would require questionnaire access. The BPSU has also been in existence for many years and is well known in the surveillance of rare paediatric conditions. However, the methodology was rigid and did not allow adjustments such as including junior trainees which may have supported increased reporting numbers and questionnaire completion. These issues and those discussed in chapter 6 have been reported to the BPSU for consideration in future studies.

7.2.8.1.1.1 UK and Global Surveillance studies, how does this study compare?

NRAD and NRAP

In chapter 2, two other UK surveillance studies were discussed – NRAD and NRAP. We compared the response to this surveillance study to reported response from NRAP and NRAD. NRAP reports only 66% of hospitals returned full data sets despite prompting and agreement for involvement in national initiative. The NRAD reporting is demonstrated below in figure 23. Of 900 cases meeting inclusion criteria, 290 (32%) cases did not return sufficient information to be included in the report (145+127+18). Figure 23 also demonstrates the pitfalls of coding as 352 patients that met inclusion criteria were excluded after review as they were not felt to have asthma (or asthma had not contributed to the death). Both NRAD and NRAP show similar levels of engagement to the BPSU report cards through our study duration. No specific strategies were suggested by either report to increase study engagement.



^aData from the Office for National Statistics (ONS) for England and Wales, the Northern Ireland Statistics and Research Agency (NISRA) and the National Records of Scotland (NRS)

Figure 41 NRAD Case identification

INOSPU

Internationally, the BPSU forms part of the International Network of Paediatric Surveillance units (INOPSU). This is comprised of 12 different

surveillance networks globally for rare paediatric illnesses accessing > 10000 clinicians.

To compare BPSU reporting rates with INOPSU data we contacted each INOPSU chair to determine how data is collected and their response rates.

Table 7.2 INOPSU Country data reporting

Country	Emailed	Paper/Email/online database	Response rate
Australia	9 th November 2023	Paper form then postal return (available online or contact researchers)	>90%
Canada	9 th November 2023	Online reporting, emailed questionnaire	42%
Germany	9 th November 2023	Web based questionnaire	90% hospitals respond (estimate)
Irish	9 th November 2023	Paper forms/email	No information
New Zealand	9 th November 2023	REDCap used for reporting, email/post questionnaire	Not stated
Netherlands	9 th November 2023	Closed in December 2021 due to lack of reporting	
Portuguese	9 th November 2023	Bounce back email. Unable to contact	
Belgium	9 th November 2023	Not stated	69% hospitals respond (estimate)
Switzerland	9 th November 2023	Online login to report cases – does not send questionnaires, reports only.	100% return rate

The INOPSU network shows a variety of different methodologies to obtain surveillance data. The most successful of these appears to be the Swiss Paediatric Surveillance Unit (reporting only). Australian and German systems

appear to have the most success in reporting and surveillance rates but use different systems.

7.2.8.2 *Case criteria*

The case criteria for this study were based on a previous e-Delphi consensus. After BPSU panel review, the definition was refined to include specific limits for hypoxia, hypercapnia and treatment thresholds. During the study we were contacted by clinicians who felt they had encountered a patient with near fatal asthma but they did not meet the inclusion criteria. Clinicians were encouraged to report these cases however as discussed previously study case criteria was not adjusted. The description of near fatal asthma as identified by the e-Delphi consensus by McMurray et al (2019) would have included these patients. This suggests that the criteria in this study was restrictive in the identification of patients with near fatal asthma during the surveillance period.

The age criteria were set to ensure that paediatric patients were able to be followed up within the study period and a lower limit of 5 years was chosen to filter submissions of patients with preschool wheeze and bronchiolitis. During the study, several error reports were due to age restrictions (n= 13). Of these, 11 patients number were <5 years and 2 patients were >5 years. Adolescents patients (15 – 19 years are known to be high risk for severe asthma attacks²³⁵ and those 16 years and older were not included in this study due to lack of surveillance platform. The large number of patients <5 years reported to in the surveillance should consider in future if near fatal asthma can be diagnosed at a younger age and whether/to what extent

wheeze syndromes should be delineated by age rather than defined severity of attack. Follow up of these patients would determine if they are at risk of a future near fatal or fatal asthma attack.

7.2.8.3 Risk factors

We observed the patterns of gender, ethnicity and social deprivation on the cases reported during the surveillance period. Other features of near fatal asthma that could have been reviewed but were not included in this study were obesity which as discussed in chapter 2 is known to be a risk factor for asthma and severe exacerbation³⁸.

As the data was collected as part of the BPSU study, I did not as part of this project have the opportunity to compare the NFA cases to a control group. This could have been achieved by comparing NFA data with acute asthma hospital admissions in children 5 - 15 years in the UK during the surveillance time period or PICANet admissions to critical care both for asthma and non asthma presentations in the surveillance period. Without a comparison group, analysis of the impact of risk factors including environmental exposures (outdoor air pollution and pollen exposure) was limited and descriptive only. This should be considered as part of future analysis and would require permission and collaboration with the relevant data sources.

7.2.8.4 Data linkage limitations

We aimed in this study to provide data linkage with 1km x1km air pollution data for each asthma event. At present this data for 2023 and 2024 is not available. Data is expected once validated and verified by DEFRA and this process takes 12 – 24 months. Due to data availability, air pollution levels lag

time (0 – 5) days prior to NFA could not be obtained and uploaded to the safe haven for all the cases. Outdoor air pollution levels and acute attacks were not evaluated by this study, conclusions associating acute exposure to high levels of outdoor air pollution therefore are limited.

Pollen, fungal and viral data were crude measurements from publicly available data sources. A more detailed analysis of these factors would strengthen any observed association with near fatal asthma.

Data linkage with environmental factors must also consider the personal exposure of each individual to an environmental exposure such as outdoor air pollution, weather or pollen count. For example, if the UK pollen count is known to be particularly high but the patient is not residing in the UK at the time (e.g., holiday abroad) the exposure becomes irrelevant. Activity diaries may be useful to provide context to environmental exposures and as discussed, the review article (see appendix) personal exposure air pollution monitors should be considered to determine accurate indoor and outdoor air pollution exposure.

7.2.8.5 *Fatal attacks during study period*

During the study period, we were alerted by clinicians when an asthma death had occurred. This prompted the question of whether or not there were supplementary ways to review the frequency of asthma deaths alongside the near fatal asthma attacks. We searched local newspaper articles for ‘asthma death’ ‘collapse, asthma’ and checked local social media. We asked the NPRANG community if a death had occurred in their hospital/region (yes or no – no clinical details obtained) and if so, we searched local media streams

for reported news of asthma deaths. We compared fatal attack numbers found online with Office of National Statistics reports. This contained up to date from 2021 which noted 12 deaths in children age 1 -19 coded as asthma (ICD10 J45/J46). The number of deaths found by media search was <10. Follow up of this cohort of NFA patients is ongoing (24 month follow up) and aims to capture any fatal attacks.

7.2.9 Study positives

7.2.9.1 *Case identification without use of coding*

One of the key strengths of this study and methodology is the use of clinicians to identify near fatal asthma cases which did not rely of identification of cases through medical coding. The use of a clear definition allows clinicians to initiate report notification and removes patients who are incorrectly coded or not included due to lack of coding granularity. The use of medical codes to identify rare conditions as demonstrated by the systematic review in chapter 3 can overlook severity of an illness and this study methodology was able to avoid that pitfall. By using specific treatment thresholds (invasive ventilation) this study also avoided the use of intensive care as a threshold and as demonstrated in the results, 8 of the 11 patients meeting criteria 1 were not cared for in intensive care (15.7%). These patients would not have been included if only intensive care data had been interrogated.

The BPSU methodology however relies on the good will and effort from the reporting clinician. Without this, BPSU studies could not operate. We recognised, as working demands increase, this model may not be sustainable. In future it should be considered if BPSU methodology would

allow a research team to 'recruit' BPSU reporters, gain accruals for study participation and allocate local reporters at each site. This would facilitate consultant reporting but local allow researchers to access relevant patient records and complete study data.

7.2.9.2 Non consenting data acquisition

In this study, consent for patient data was not required for study inclusion.

Patients were provided with a public information leaflet detailing in the study and highlighting the procedure to opt out of data use in national surveillance.

No patients contacted the research team during the study to opt out of data collection. This was encouraging and echoed the sentiments from the PPI consultation which highlighted PPI enthusiasm to allow data sharing to benefit the care of patients experiencing near fatal asthma.

7.2.9.3 Description of near fatal asthma attacks in detail

The use of the questionnaire allowed detailed clinical description of each near fatal asthma case. Although all questionnaire were not fully completed, the wide range of clinicians able to enter data for each patient allowed a detailed patient journey to be relayed to the researcher team and present a picture of the near fatal attack journey. As researchers were not involved in the data collection, reporting bias was minimised. The multiple sections of the questionnaire also facilitated the input of clinicians from differing clinical areas which is of benefit when considering a condition such as near fatal asthma that involves clinicians in multiple roles. The detailed description of attacks has enabled future recommendations regarding the care of near fatal asthma to be suggested by this study.

7.2.9.4 *Four nation collaboration and Republic of Ireland reporting*

The study involved reporting and data collection from the UK and Republic of Ireland. This overview has provided a snapshot of frequency of near fatal asthma in a large geographical location. Obtaining permissions from each nation required a knowledge of each application process but also time to apply to each individual permissions board. This highlighted the different legislature required for each nation and questions if this process could be streamlined in the future to facilitate researchers in their application. At present there is not a standard to allow this when acquiring routine data across Scotland, Wales, England and Northern Ireland. Examples of data banks moving to 4 nation collaboration include the BREATHE programme in Health Data Research UK (HDRUK) which incorporates data from Data Loch (East Lothian, Scotland), SAIL Databank (Wales) and Honest Broker Service (Northern Ireland) and BREATHE Health Data Research Hub (England). The collaboration of datasets and the coding of specific conditions within HDRUK would allow researchers to access four nation data but is limited by the included data sets (BREATHE - only East Lothian included from Data Loch at present, other Scottish regions not currently included). Use of large collaborative datasets would facilitate researchers to identify cases from retrospective data using coding but would not have been able to facilitate the clinical question of frequency using our study criteria.

7.3 Future considerations

This study has initiated research in near fatal asthma in children and young people in the UK. Future considerations must address how to ensure the momentum of this study facilitates future research.

7.3.1 Bridging the gap between coding and surveillance

This thesis has explored the difficulties in identifying near fatal asthma patients both through surveillance and coding. The question of how to bridge this gap to ensure that patients with rare diseases such as near fatal asthma are not lost is challenging to answer. Disease registries may provide some benefit in ensuring near fatal asthma patients are correctly coded but rely on clinician input to keep up to date. Public health surveillance strategies could be targeted to identify near fatal asthma but would rely on a well-recognised and circulated definition of near fatal asthma in children. If electronic health records are used on a national scale, provisions must be allowed for the varied documentation systems throughout the NHS as discussed in chapter 2.5. At present, a combination of these methods – clear definition use, granularity of coding and recognition of near fatal asthma from clinicians and centralised care within specialist services may be a step in the right direction but requires nationwide governmental recognition that asthma services are not adequate in their current state to care for children with near fatal asthma. Services across the UK and Republic of Ireland must be standardised to ensure the risk of near fatal and fatal asthma is recognised.

7.3.2 Severe asthma registry

One consideration in identifying and monitoring the care of patients with near fatal asthma is a disease registry. As mentioned in Chapter 2, this too is another form of surveillance which can provide valuable information on disease progression and management. In adults, the Severe Asthma Registry exists for patients with difficult to treat asthma^{254,255}. It has been discussed if this would be of benefit in paediatric patients in the UK as similar

registries have been replicated in Europe²⁵⁶. This registry has been suggested in paediatrics with a recommendation that patients included would meet the definition below²⁵⁷:

- A previous severe exacerbation (admission in last year, admission to the intensive care unit)
- Previous brittle / anaphylactic reactions especially if associated with food allergy
- Those already known to have difficult-to-treat asthma (BTS/SIGN steps 4 and 5)

A severe asthma registry has been initiated in adults in primary care with results pending²⁵⁸. If, however 'At Risk' registers were to be introduced in paediatrics, as this study has demonstrated intensive care should not be used as a threshold and instead clearly defined near fatal asthma attack should form criteria. The benefit of at risk registers would allow disease monitoring but also provide a network of patients for implantation of guidelines on the management of near fatal asthma. Data entry however, as shown by this study or other national studies is reliant on clinician buy in, time and effort and if a registry is not filled out or regularly updated its use becomes less beneficial. Patient consent is also required for a disease registry and in small numbers of patient (i.e., for NFA in children), non consent from specific groups will significantly impact reporting numbers.

7.3.3 Policy changes in near fatal asthma management

This study demonstrates the lack of consistent asthma management in near fatal asthma follow up. Asthma attacks are driven by a continual inflammatory

cycle²⁵⁹ which must be broken in order to control asthma symptoms. Patients with no change in medications on discharge after a near fatal attack may have ongoing inflammation which must be treated in reduce further asthma symptoms. The results of the surveillance study question if patients with a NFA attack should have an increase in therapy on discharge to break this inflammatory cycle to prevent future attack.

Asthma is a life threatening chronic condition. It is however a common condition which is managed in primary, secondary and tertiary care. Evidence indicated that children with near fatal asthma are high risk for future severe or fatal asthma attacks. It should be considered whether these children should be followed up in tertiary care by a respiratory paediatrician to ensure the risk of future attack is not only recognised but can be managed with access to specialist services including spirometry, asthma nurse contact and specialist review. In the coroner's report discussed in Chapter 1.2, William Gray was 'lost to follow up' after a near fatal attack and as a result, the risk of future fatal attack was not recognised. If this strategy is to be implemented, consideration of current asthma service provision would need to be reviewed and allocation of resources to allow tertiary services to absorb and manage this group of patients is required from both a funding and organisational perspective. It could be argued however, if William Gray's previous attack had been identified as NFA and there were clear guidelines on onward management, his death could have been prevented even if he had not been reviewed by a tertiary asthma paediatrician. At present, children with near fatal asthma could be followed up in a 10 minute GP

appointment, a 15 minute general paediatric appointment in-between other non-asthma pathology or in a general respiratory clinic. Asthma deaths in the UK in children are continuing to rise and it must be considered if special asthma paediatrician care would serve this high risk population appropriately.

As previously discussed in Chapter 6 I have reflected on whether the BPSU surveillance methodology optimally captured and described NFA cases.

Other strategies to identify NFA could include detailed case note review which has been successful in areas such as maternal death (MBRRACE - UK report²⁶⁰). This reporting system uses nominated staff members at each reporting site and detailed case note review of each maternal death. This method of identifying a responsible reporter could be adopted or integrated into the BPSU methodology to aid surveillance report completion and improve data quality. Improvement in the BPSU surveillance engagement and questionnaire completion would enable clearer conclusions from NFA data, detailed analysis of risk factors and recommendations for prevention of future NFA attacks.

7.3.4 Other management strategies

We noted that no children in the dataset were receiving treatment with monoclonal antibody therapy (MAB). There is limited evidence to support the use of MABs in near fatal asthma however as discussed by Drazen et al (2024), key to asthma management involved breaking the inflammatory cycle. The use of benderlizumab for an adult with near fatal asthma has been presented^{261,262} but further research is required in this in both children and adults.

7.4 Recommendations and conclusion

This study has presented the frequency and a description of near fatal asthma attacks over 18 months in the UK. Near fatal asthma is rare and this study present novel features associated with this patient group.

To aid future work in this area the following recommendations are made from this thesis:

1. A clear definition of near fatal asthma should be recognised internationally and coded appropriately within the ICD
2. Patients experiencing near fatal asthma are at increased risk of fatal and subsequent near fatal attack. This risk should be managed by specialist tertiary asthma services to ensure provision of appropriate follow up care and consideration of medication increase post near fatal attack.
3. Children from deprived socioeconomic areas were observed to have near fatal attacks more frequently, additional resources should be provided for these families and deprivation risk should be recognised by health care professionals. Support for these children and families should be initiated
4. Consider the use of near fatal asthma at risk registries to allow disease monitoring, targeted follow up and patient and clinician support networks.
5. Outdoor air pollution specifically PM_{2.5} must be addressed by local authorities and governmental policy to reduce exposure to levels exceeding WHO thresholds. Reduction of annual exposure thresholds in the UK should be updated to comply with WHO standards to decrease the exposure of children experiencing near fatal asthma to high levels of outdoor air pollution.

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9 Appendices

Appendix 1: Public and Patient Involvement (PPI) Letter of Feedback and Support



THE UNIVERSITY
of EDINBURGH



Asthma UK Centre
for Applied Research



Professor Steve Cunningham
Child Life and Health
University of Edinburgh
Edinburgh
EH16 4TJ

7th February 2022

Dear Steve,

Research into Near Fatal Asthma in Children and Young People

On behalf of the Asthma UK Centre for Applied Research Patient and Public Involvement (PPI) group, I can confirm that we held two discussion groups with members of the public (including parents and young people with asthma) to give them the opportunity to know more about your study and to provide their opinions on the methods used and the data being requested.

Using patient data can be a controversial issue and our public members found your presentation interesting and appreciated the time taken to consider and include their perspectives. They were in favour of including postcode and ethnicity data, and were satisfied that the security around the data was sufficient that they would feel safe with it being collected. Some parents reflected on their personal experiences of attending hospital with their child and the low likelihood of them signing a consent form, therefore they thought the process used by BPSU provided the best opportunity to obtain data that would help those living with asthma.

I have included some quotes from the members below:

Thoughts about the project

"I think that's really, really important. Because, you know, there are times, especially as a parent if you're panicking you've taken your child, a young child, especially to hospital and you're panicking because you know something's not right they can't breathe. To know that they're going to get the care like as a sort of standard across the board"
(Parent, female)

The BPSU consent process

I think it's really well thought through and the detail, but like so knowing that there's that level of protection, data protection, I think that's just really reassuring and it's all for the greater good I'd be happy with it.
(Young person, female)

I say yes as well, it'd really help. It's good like that it's got like the data protection as well, so it's not going to get lost or given to someone you don't want it to have,
(Young person, male)

I agree with the other mum and it's not something that you would want to go near when you're in a hospital when you are worried and dealing with your child you don't want 'can you please sign this form?'
(Parent, female)

It's going to sound awful if I say this, but to be completely honest once the event is over you've got your child home or well again. That form is likely going to go in the bottom of a pile of other things you've got to deal with,
(Parent, female)

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Appendix 2: Near-fatal and fatal asthma and air pollution: are we missing an opportunity to ask key questions?

Review

Near-fatal and fatal asthma and air pollution: are we missing an opportunity to ask key questions?

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ABSTRACT

There is an increasing body of evidence supporting the link between asthma attacks and air pollution in children. To our knowledge, there has only been one reported case of a fatal asthma attack in a child associated with air pollution and this was in the UK. This article considers why there is a lack of evidence on fatal/near-fatal asthma and air pollution. We also explore three challenges. First, fatal and near-fatal asthma events are rare and not yet well understood. Second, measuring and interpreting personal exposure to air pollution with sufficient temporal and spatial detail are challenging to interpret in the context of individual fatal or near-fatal asthma attacks. Third, current studies are not designed to answer the question of whether or to what extent air pollution is associated with fatal/near-fatal asthma attacks in children. Conclusive evidence is not yet available and systems of data collection for both air pollution and fatal and near-fatal asthma attacks should be enhanced to ensure risk can be determined and impact minimised.

INTRODUCTION

Ella Kissi-Debrah was the first person in the UK whose death, at 9 years of age, was attributed to air pollution.¹ Residing in a busy, traffic dense area of London, Ella was exposed to high levels of traffic-related air pollution. Her severe asthma symptoms and eventual death were attributed to exposure to high levels of outdoor air pollution. Asthma deaths in the UK are among the highest in Europe.² While clinicians are aware of this statistic and measures have been suggested to reduce risk,³ strategies to reduce air pollution exposure are not at the forefront of our consultations and clinicians lack the tools and knowledge to limit exposure. If outdoor air pollution could be a significant contributing factor to near-fatal and fatal asthma attacks, why are we not doing more to understand and prevent further cases?

AIR POLLUTION

Hippocrates in 400 BC wrote of air pollution concerns in *Air, waters and places*.⁴ A more contemporaneous, but archaic vision of air pollution is the London smog of December 1952 when a weather event combined with high levels of industrial air pollution caused a visible smoke cloud which was estimated to cause 4000 deaths.⁵ Current harmful levels of air pollution are often not visible to the naked eye and yet silently contribute to an estimated 28 000–36 000 deaths per year in the UK.⁶

Outdoor air pollution levels are a global health concern and are estimated to contribute to

4.2 million premature deaths globally.⁷ Air pollution has a negative impact on health in utero, during childhood and in adulthood.⁸ The WHO identifies sulfur dioxide (SO₂), nitrogen dioxide (NO₂), ozone (O₃), carbon monoxide and particulate matter (PM) as the main air pollutants negatively impacting on health outcomes. Other pollutants such as benzene have also been attributed to negative health outcomes in children with asthma.⁹ The main sources of each vary (table 1). PM is made up of solid and/or liquid materials of differing size which can be primary or secondary components¹⁰ and is further quantified by size: <1 µm, ≤2.5 µm and ≤10 µm. Outdoor air pollutants are typically measured from a distribution of fixed location monitoring stations. Local levels are modelled based on these measurements combined with meteorological patterns, taking into account the chemical reaction of different pollutants in the atmosphere.¹¹ In the UK, levels of air pollutants are reported in relation to the Air Quality Standards Regulations 2010 which mandate limits for certain air pollutants. UK air pollution levels are currently higher than that recommended by the WHO (see table 2).

Asthma and air pollution

Asthma is one of the key respiratory conditions impacted by outdoor air pollutants. It is postulated that air pollutants physically obstruct and aggravate airways at bronchiole level.¹² Small particles and oxides can trigger the inflammatory cascade, resulting in acute bronchospasm in asthmatic airways.^{12–14} Children are more vulnerable to the effects of air pollution compared with adults as they spend more time outdoors, have smaller airways and inhale a larger volume per kilogram per body mass compared with an adult.¹⁵ Globally, there is increasing evidence that outdoor air pollution adversely affects children with asthma. Air pollutants, such as PM, have been found in placental phagocytes suggesting small particulates can enter the circulation and damage organ development.^{16 17} Exposure to air pollution in pregnancy and infancy has been associated with the subsequent development of asthma, allergic sensitisation and rhinitis in childhood.^{18–20} Children exposed to air pollution can have lower lung function,²¹ increased asthma medication use,^{22 23} and an increase in primary care, emergency care and hospital admissions.^{9 24–28} The impact of viral infections in combination with air pollution has also been studied showing an increase in viral exacerbation of asthma when combined with higher air pollution exposure.²⁹

Table 1 Air pollutants and sources

Pollutant	Most common source ^{10 46 47}
Sulfur dioxide	Combustion of sulfur-containing fuels, for example, coal
Nitrogen dioxide	Power generation, industrial combustion and road transport
Ozone	Created by photochemical reactions involving nitrogen oxides and volatile organic compounds
Carbon monoxide	Produced from combustion of gas, oil, coal and wood
Particulate matter	Primary components: sea salt, black carbon, trace metals mineral components, road transport–fuel combustion and tyre/brake wear, road dust Secondary components: sulfate, nitrates
Benzene	Vehicle exhaust, evaporation of petrol

CHALLENGES IN INTERPRETING AIR POLLUTION DATA

There are several factors to be considered when applying large-scale air pollution data to an individual and an asthma attack at a specific time point. First, the monitoring and reporting of air pollution vary from country to country due to regional variations in the types of air pollutants monitored and location of fixed monitoring stations. Urban areas are likely to have more stations within a smaller geographical radius compared with rural locations. Second, daily weather patterns are a significant contributing factor to air pollution exposure, and extreme weather events such as thunderstorms, dust and sand storms will affect levels of air pollutants such as PM.³⁰ Third, air pollution is a broad term which is likely to refer to a mixture of pollutants, of which several or all may have an effect on asthmatic airways. Components such as PM could refer to particles such as sea salt which is benign, or toxic industrial gaseous waste. Studies commonly address air pollutants individually and although this is useful, air pollutants are highly spatially correlated and thus the effects should be mixed together in epidemiological analyses to fully estimate the effect on a respiratory condition such as asthma. Fourth, annual mean levels are often reported as thresholds for air pollution (see table 2). Concentrations can vary significantly over relatively short time scales and therefore annual means may overlook substantial peaks and troughs in a congested area. Although air pollution modelling is improving as advanced algorithms provide better spatial and temporal detail estimates (including hourly estimates at 100×100m spatial resolution), more frequently recorded, granular data would support better research though such data are less commonly available.

Personal exposure

Ideally, personal exposure to air pollutants should be considered when evaluating the impact of air pollution on health. In practice,

this is difficult to achieve. An individual's exposure to outdoor air pollutants will be less if they remain indoors when outdoor pollution levels are high. Children are more likely to be exposed based on activities of daily living as compared with adults, as children spend a higher proportion of their day outdoors. Young children are closer to traffic-related air pollutants because of their small stature compared with adults which may increase exposure to air pollutants.³¹ Without personal exposure measurement, the effect of air pollution globally, country-wide or even regionally on an individual at the time of an attack can only be estimated based on modelled data. Exposure to indoor air pollutants has not been covered in this article but must also be taken into account when evaluating potential triggers of asthma attacks and risk factors for poor respiratory health.³²

Air pollution data related to fatal and near-fatal asthma attacks are gathered retrospectively. Exposure to air pollutants around the time of an event is difficult to measure directly without personal exposure devices. Use of personal air pollution monitors has been studied in children with asthma,^{33 34} but it may be challenging in the context of asthma attacks which are unpredictable and may not occur when a participant is wearing a device. Measuring levels of air pollutants in a child's 'microenvironment' using personal monitoring devices may be useful when considering sources of daily exposures,³⁴ but this has not yet been demonstrated in fatal or near-fatal asthma attacks. Efforts to evaluate individual exposure (for example, from macrophages and presence of sputum carbon³⁵) demonstrate a possible mechanism to assess exposure, but again are of uncertain feasibility in relation to an acute severe attack. Activity diaries may be useful aids to guide personal exposure but linking personal exposure to an event will be highly individualised to each patient. The use of portable/personal devices such as spirometry may also help elucidate an association between exposure and health effects while reducing exposure misclassification. Even the most robust observational study will struggle to estimate the actual exposure to air pollution around the time of an attack.

NEAR-FATAL AND FATAL ASTHMA IMPACTED BY AIR POLLUTION: ARE THERE MORE CASES TO COME OR HAVE WE MISSED MANY IN THE PAST?

Fatal and near-fatal asthma attacks cause concern and anxiety for paediatric clinicians, parents, children and young people (CYP). Fatal and near-fatal asthma is rare, but the UK has one of the highest death rates from asthma in children age 10–24 years.³⁶ Asthma attacks in children accounted for >19 000 admissions in England and Wales in 2022.³⁷ Despite heightened awareness of the importance of diagnosing and appropriately managing

Table 2 WHO versus UK-recommended levels^{7 48 49}

Air pollutant	UK-recommended level		European Union		WHO-recommended level	
Sulfur dioxide $\mu\text{m}/\text{m}^3$	24-hour average	125	24-hour average	125	24-hour average	40
Nitrogen dioxide $\mu\text{m}/\text{m}^3$	Annual	40	Annual	40	Annual	10
Ozone $\mu\text{m}/\text{m}^3$	24-hour average	No limit set	24-hour average	No limit set	24-hour average	25
	Annual	No limit set	Annual	No limit set	Annual	60
	24-hour average	No limit set	24-hour average	No limit set	24-hour average	100
	8-hour mean	100	8-hour mean	120	8-hour mean	No limit set
Carbon monoxide $\mu\text{m}/\text{m}^3$	24-hour average	10	24-hour average	No limit set	24-hour average	4
PM _{2.5} $\mu\text{m}/\text{m}^3$	Annual	20	Annual	25	Annual	5
	24-hour average	No limit set	24-hour average	No limit set	24-hour average	15
PM ₁₀ $\mu\text{m}/\text{m}^3$	Annual	40	Annual	40	Annual	15
	24-hour average	50	24-hour average	50	24-hour average	45
PM, Particulate Matter.						

Review

Box 1 International e-Delphi-defined near-fatal asthma definition⁵⁰

A near-fatal asthma attack occurs if:

- ⇒ A person is exhausted, with severe dyspnoea, unable to speak with a silent chest.
- ⇒ Respiratory arrest is considered imminent and invasive ventilation will likely be required.
- ⇒ They will be responding poorly to emergency asthma therapies. This is associated with hypoxaemia, hypercarbia and a falling pH.

Box 2 Suggested questions for clinicians reviewing children experiencing asthma exacerbation

- ⇒ How do you get to school? Do you walk beside a busy road? Do you travel to school by car?
- ⇒ Do you need your inhaler when you are walking beside a busy road?
- ⇒ Do you play outside close to a busy road at break time?
- ⇒ Do you know about clean air walks to school?
- ⇒ Is your patient's home positioned beside a source of traffic-related air pollution such as a busy road and if so, how do they ventilate their home, that is, windows open or closed during peak traffic times?

asthma, the National Review of Asthma Deaths report concluded that care was inadequate in 13 of the 28 deaths in CYP that they investigated. People experiencing a near-fatal attack are at high risk of future severe attacks and it is important for clinicians caring for children with asthma to evaluate the risk factors and features associated with near-fatal and fatal attacks with an aim to reducing future risk.

Near-fatal attacks are difficult to identify in the literature. The definition of near-fatal asthma (and terminology used) overlaps with severe, life-threatening asthma, status asthmaticus, and the use of 'diagnostic codes' to identify 'asthma' cases in routinely collected data does not further differentiate the severity of attacks within hospital. Near-fatal events can be defined (see Box 1), but studies using routine data from hospital records to identify asthma attacks typically use 'asthma' alone to find cases. While this may correctly identify a case of asthma, it does not necessarily record the severity of presentation or any subsequent hospital deterioration. If a child had a sudden collapse due to asthma and required resuscitation, this could be coded as asthma and in the same category as a child brought in to the emergency department who was discharged on the same day. This contributes to the loss of granularity of data on near-fatal and fatal events, where such attacks may exist but often poorly coded and consequently not identifiable within routine data. Although large studies have demonstrated an increased frequency of acute asthma presentations associated with air pollution exposure,²⁸ attack severity is not reported. We have only identified one study meeting the definition in Box 1 which has examined the effect of O₃ and PM_{2.5} on near-fatal asthma in children,³⁸ which demonstrated an increase in admissions to intensive care. Two other studies included air pollution levels when assessing social deprivation and near-fatal asthma, but neither focused on this as a primary or secondary outcome.^{39 40} There thus is a small body of literature examining asthma mortality and air pollution and there remains a significant and important gap in the literature regarding the impact of air pollution exposure on near-fatal and fatal asthma attacks in CYP.

There are factors such as social deprivation which confound both severe asthma and air pollution. Higher concentrations of NO₂, PM₁₀ and SO₂ are observed in areas of social deprivation in England, Scotland and Northern Ireland,⁴¹ and children from areas of higher deprivation are also more likely to be admitted to intensive care for asthma.⁴² The degree of association between social deprivation, asthma and air pollution requires further observation but should be highlighted. In the UK, there is a current surveillance study examining near-fatal asthma which will examine social deprivation and air pollution data around the time of event.⁴³

CONCLUSION

We have an opportunity now to build on past work on near-fatal and fatal events and air pollution. By including air pollution in

the asthma risk factors assessed in a clinical history, we can start to shape the body of evidence on fatal and near-fatal attacks. By increasing awareness of air pollution in conversations with our patients or their parents in the same way we would discuss smoking, atopy, pets, etc, we start to highlight air pollution as a risk factor. While the policy changes on air pollution exposure at local and regional levels are controlled by politicians, as clinicians, we must now start to engage and consider the potential impact of air pollution on our individual patients. The question of how much exposure is dangerous cannot yet be answered accurately, but we can start to ask the right questions (see Box 2). Some initiatives are already in place looking at 'clean air walks to school', but we need to encourage our patients that these can make a difference.

The body of evidence is growing, but better data will be required to support policymakers to deliver safer and lower exposure to air pollution levels in CYP with asthma. Reducing PM_{2.5} by 1 µm/hour could prevent 9300 new cases of asthma/year,⁴⁴ and it is predicted that if the UK becomes net zero, we could reduce >20 000 cases of childhood asthma.⁴⁵ The death of Ella Kissi-Debrah has highlighted the devastating influence of outdoor air pollution and the urgent need for further research to understand the impact that air pollution may have on near-fatal and fatal asthma in children. By keeping air pollution in mind in our clinical practice, we can raise awareness, add to the evidence and find out more about near-fatal and fatal asthma cases associated with air pollution.

Suggestions

1. Help to identify the severity of asthma attacks in routine data. We need to know more about fatal and near-fatal attacks in children. Consider a coded definition for near-fatal asthma (see Box 1) to increase the granularity of future data on near-fatal asthma.
2. Add air pollution questions to your asthma history (see Box 2)—think when are they exposed (daytime activities, how long and how often).
3. Consider reporting any cases of e-Delphi-defined near-fatal asthma to the British Paediatric Surveillance Unit Study (October 2022–April 2024).

X Deepa Varghese @NearFatalAsthma

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Appendix 3: Data Protection Impact Assessment, University of Edinburgh



THE UNIVERSITY of EDINBURGH

Assessment Details

Name R - Near fatal asthma in children v.2

Approver Rena Gertz

Respondent Ann McMurray, Deepa Varghese, Steve Cunningham

Stage In Progress

Date Completed

Result

Assessment Questions

1 Overview

1.1 Research Outline

Summarise what the research aims to achieve and what type of processing it involves. You may find it helpful to refer or link to other documents, such as a project proposal. Explain why and how the processing of information is necessary to that work?

Response

This a surveillance project of the UK and ROI to determine the frequency and risk factors for near fatal asthma in children. The project will be run by the British Paediatric Surveillance Unit (<https://www.rcpch.ac.uk/work-we-do/bpsu>) using their standard methodology. Data will be submitted and held by Dundee University Health Informatics Centre (<https://www.dundee.ac.uk/hic>). The surveillance offers the opportunity for the first time to understand both the frequency of near fatal asthma (a major risk factor for asthma death) and potential risk factors including ethnicity, deprivation and environmental exposures (viral, pollen, weather and pollution). As a recent landmark case identified pollution as a contributing cause of death in a child with asthma this data is considered paramount. We outline in the protocol how personal data will be handled and protected, in particular by the use of Safe Haven analysis within HIC. A protocol for the study is attached.

1.2 Describe the information flow

You should describe the collection, use and deletion of personal data here and it may also be useful to refer to a flow diagram or another way of explaining data flows – where you are getting the data from, where it will be stored and where it could be transferred to. You should also say how many individuals are likely to be affected by the project.

e.g. Data will be collected from research participants via online forms

↓

Data will be stored encrypted on departmental drives

↓

Pseudonymised dataset will be provided to Department X along with report

Response

Please refer to Section 5, 6 and 7 of the protocol, together with Figure 1 (an appendix).

1.3 Why is the processing necessary?

Why is it necessary to process the data you have described in the Activity Outline?

This and the next question are most important as they form the justification for your research being proportional. You will need to argue the benefits of your research, why it is important and why the planned activities are necessary to achieve these benefits.

Response

Prior severe asthma attacks are frequently a prelude to fatal asthma attacks. There is no data on the frequency of near fatal asthma attacks in the UK, and no data on the characteristics of those affected (including ethnicity), nor the risk factors (such as pollution) that may place them at additional risk. Near fatal asthma attacks in children will be uncommon and so it will be vital to capture all cases. BPSU methodology enables this to be achieved. Use of Dundee HIC enables us to process data in a safe environment whilst being able to analyse data to give meaningful outputs. The outputs of this research should allow for better identification of those at risk to help clinicians focus care; potential environmental factors that enhance that risk to enable public health decision making; future risk of near fatal and fatal asthma attacks enabling services to be configured to support children appropriately to reduce

1 / 12

that risk.

1.4 How will the activity help you achieve your objective(s)?

Describe how what you plan to do will help you achieve your purpose - describe how you ensure that the personal data is proportionate to the objective. Is there a less intrusive way of achieving your aim?

Response

We outline the use of personal data in the protocol (section 7.1.1). We consider this use of personal data proportionate to the objectives identified. PPI members of the Asthma UK Centre for Applied Research agree with this proportionality and use of data in this way. BPSU methodology has approvals from the Confidentiality Advisory Group (CAG) and Patient Benefit and Privacy Panel (PBPP). We will use the safe haven of Dundee HIC to ensure data security and to minimise access to personal data by members of the research team. The protocol outlines how we will limit reporting of personal data to minimise identification of individuals. The proposal has been reviewed by the BPSU research committee (including PPI members) and the methodology proposed is considered the least intrusive way to achieve these aims.

2 Compliance with Privacy Laws

2.1 Check

Data Protection legislation is relevant to any DPIA, and this section forms the data protection compliance check which should always be carried out. The Data Protection Officer will be able to advise you on the relevance of other privacy laws.

2.2 What type of personal data are you processing?

For guidance on what personal data is, consult the [definitions](#).

Response

☒ Patient data

Justification

None

2.3 Common Law duty of confidence

This only applies when you use, for example medical data or similar types of data that individuals would not expect to see disclosed. Describe how you have obtained consent.

Response

☒ No

Justification

BPSU methodology does not require consent. The BPSU reporting methodology has received Confidential Advisory Group approval to allow its facilitated studies to collect unconsented patient information. It was accepted that to do so would reduce and bias case ascertainment, i.e. certain groups or types of individual might be more likely to refuse consent. In a study of a rare disorder, such as near fatal asthma, in which the number of cases is small, refusal to contribute data by one or two individuals will result in under-ascertainment of cases and incorrect conclusions on frequency and associations. If all the refusals occurred in a single region or were from children who had a less severe disorder, then this would 'bias' the results. To avoid bias, a BPSU surveillance study is undertaken without seeking individual consent and uses limited identifiable data via Safe Haven to protect confidentiality.

2.4 Human Tissue Act and the Medicines for Human Use (Clinical Trials) Regulations

Note: This only applies to medical research. Describe how you have obtained consent.

Response

☒ No

Justification

We do not obtain human tissue nor use medicines within this project.

2.5 List the personal data you are going to process?

For guidance on what personal data is, consult the [definitions](#).

Response

We will request that the following personal information is submitted to the online questionnaires. This information will be available to contributing clinicians within the BPSU HIC database and accessed by their login. It will not be visible to or accessible by the research team.

Personal Data

CHI/NHS/ROI Hospital number.

This data will be held securely within the BPSU HIC database. It will be visible to contributing clinicians only and to them when logging into the BPSU HIC database. This data will be utilised to determine duplicate submissions. The BPSU HIC database will perform searches to identify potential duplicate case submission. The research team will be notified of the potential duplicate case submission study numbers and can liaise with the relevant submitting clinicians to confirm or refute a duplicate case. Duplicate cases will have data amalgamated within the BPSU HIC database.

Date of birth:

This data will be held securely within the BPSU HIC database. It will be visible to contributing clinicians only and to them when logging into the BPSU HIC database. This data will be utilised to determine duplicate submissions. This will allow us to determine age at the time of NFA event (which will be summarised as years and months of age or decimal age to one decimal point).

Full post code:

This data will be held securely within the BPSU HIC database. It will be visible to contributing clinicians only and to them when logging into the BPSU HIC database. Full post code will allow us to determine both sociodemographic status and external pollution exposure (at 1km x 1km level), and within London and Glasgow a more detailed (100mx100m) determination of pollution exposure. Data linkage for these outcomes will be made within the HIC Safe Haven. Post code district (i.e. EH52) will be made available to researchers for summarising location of cases, analysing events by weather and pollen exposure, and virus prevalence in the community.

Special Categories of Personal Data

Ethnicity:

This data will be held securely within the BPSU HIC database. It will be visible to contributing clinicians only and to them when logging into the BPSU HIC database. The BPSU HIC database will provide summary data to researchers. Ethnicity will be a characteristic available within the safe haven for analysis in relation to other risk factors, i.e. deprivation or pollution exposure, but reported only in summary form.

Health:

This data will be held securely within the BPSU HIC database. It will be visible to contributing clinicians only and to them when logging into the BPSU HIC database. The BPSU HIC database will provide summary data to researchers. Health data will be reported only in summary form. The data will explore both commonly identified clinical factors, but also for the first time describe in detail the variance in medical management (acute and intensive care) that could lead to future clinical trials and guideline development to standardise care.

2.6 Which of the legal bases in Article 6 (1) will provide a lawful basis for the processing?

For research the legal basis will typically be task carried out in the public interest or 'public task'.

Consult the document [Guidance – how to determine the legal basis for processing personal data](#) for information on the other potential legal bases.

Response

Public
Tasks

Justification

None

2.8 Special Categories of Personal Data

If special categories of personal data are going to be processed, which of the legal bases in Article 9 (In addition to the Article 6(1) legal bases) will provide a legitimate basis for that processing? Consult the [special category guidance](#) for information on determining the legal basis for special category data.

For research the legal basis for special category personal data will typically be Article 9 (2) (j) - necessary for research in the public interest or 'archive, statistical and research purposes'.

Note – special categories of personal data are personal data consisting of information as to (a) the racial or ethnic origin of the data subject, (b) political opinions, (c) religious beliefs, (d) Trade Union membership, (e) physical or mental health, (f) sexual life, (g) genetic data and (h) biometric information. Added to this is also criminal conviction data.

Response

Archive, statistical and research
purposes

Justification

Ethnicity:

Ethnicity is an important factor in respiratory health outcomes, particularly in relation to asthma. This data will be key to understanding risk in different ethnicities of near fatal asthma and how to inform public health and clinical practice.

This data will be held securely within the BPSU HIC database. It will be visible to contributing clinicians only and to them when logging into the BPSU HIC database. The BPSU HIC database will provide summary data to researchers. Ethnicity will be a characteristic available within the safe haven for analysis in relation to other risk factors, i.e. deprivation or pollution exposure, but reported only in summary form.

Health:

This data will be held securely within the BPSU HIC database. It will be visible to contributing clinicians only and to them when logging into the BPSU HIC database. The BPSU HIC database will provide summary data to researchers. Health data will be reported only in summary form. The data will explore both commonly identified clinical factors, but also for the first time describe in detail the variance in medical management (acute and intensive care) that could lead to future clinical trials and guideline development to standardise care.

2.9 How are individuals being made aware of how their personal data will be used?

How are individuals being made aware of how their personal data will be used? If you supply participants with a Participant Information Sheet (PIS), please attach the PIS.

There is a template PIS available within the [Research and the General Data Protection Regulation](#) guidance.

Response

BPSU methodology does not require consent. Participants will not be directly aware of the study, however information on how to opt-out is available on the BPSU website (including study-specific website) and public information leaflet (attached). Opt-out can be done by directly contacting their local clinician.

2.10 Does the activity involve the use of existing personal data for new purposes?

Response

☒ No

Justification

None

2.11 Is there a way to check that the data collection procedures are adequate, relevant and not excessive in relation to the purpose for which the data will be processed?

Response

The study has been reviewed by the BPSU steering committee (with PPI members), and will be further reviewed by the ACCORD team, an ethical review committee, CAG (Confidentiality Advisory Group), PBPP (Public Benefit and Privacy Panel).

2.12 How will the personal data be checked for accuracy?

Response

Identifiers as outlined in the protocol will enable duplicate cases to be identified. Any missing or apparent discrepancies in personal data identified by Dundee HIC team will have the BPSU study number provided to the study team who can ask the local clinician to review and correct or confirm those data fields. It will not be possible with this methodology for monitors to check source data.

2.13 Will there be set retention periods in place in relation to the storage of the personal data?

Will there be set retention periods in place in relation to the storage of the personal data? If 'Yes', you will need to include details of this in your PIS.

If you apply the research exemption that the data is intended for future use, you can select 'No'.

Response

☒ Yes

Justification

None

2.14 What technical and organisational security measures will be in place to prevent any unauthorised or unlawful processing of the personal data?

Response

Please see Dundee HIC DPIA as attached

2.15 Has the personal data been evaluated to determine whether its processing could cause unwarranted damage or distress to data subjects?

Response

☒ Yes

Justification

We have consulted widely with PPI representing asthma (Asthma UK Centre for Applied Research) who have been supportive of the proposal and the use of personal information as outlined in the protocol. We also have the support of Asthma UK (the principal patient organisation for people with asthma in the UK) for the proposed study.

2.16 Do you use a data processor?

Response

☒ Yes

Justification

Dundee Health Informatics Centre (as outlined in protocol sections 6 and 7)

2.17 Do you have a contract or data processing agreement in place?

If you don't have a data processing agreement in place, please contact the relevant team below:

- *If the data processing relates to research (other than industry-related research), please contact the Edinburgh Research Office, at RSO.Contracts@ed.ac.uk*
- *If the data processing relates to the Roslin Institute, please contact the dedicated legal team the Roslin Institute at EBCampusLegal@ed.ac.uk*
- *For any other data processing activities (including industry-related research) please contact the Legal Services team at legalservices@ed.ac.uk*

In each case, please use the subject **DPIA - Request for Data Processing Agreement** in your email.

Response

This has been requested to RSO

2.18 Will you share the data with an external third party?

Response

☒ No

Justification

None

2.20 Will you be transferring personal data to a country outside of the European Union or the European Economic Area (EEA)?

[Countries in the EU](#)
[Countries in the EEA](#)

Response

☒ No

Justification

None

2.24 If the data will be anonymised, is it likely that a 'motivated intruder' will be interested in attempting re-identification by linking the data with other information available to them?

For guidance on 'motivated intruders', please see [here](#).

Response

☒ Yes

Justification

Possibly, but the use of summary data (no reporting <5 cases) will significantly minimise this potential risk.

2.25 From the Data Protection compliance check in this section we have concluded:

Have you satisfied all the requirements asked for above? If you answer no, then please give a reasoning why and why you believe the DPIA should still be approved.

Response

We have concluded that if the research project goes ahead as detailed here, it is data protection compliant.

Justification

None

3 Screening

3.1 Screening

Answer the following questions to determine any potential privacy risks in your research.

You will then be asked to explain what practical steps you will take to ensure that you identify and address privacy risks. Who should be consulted about potential risks (members of your research team, supervisor, research sponsor...)?

3.2 Will the research involve the collection of new identifiable or potentially identifiable information about individuals?

Response

☒ Yes

Justification

As researchers we do not have the information outlined so this will be new to us. The personal data requested is set out in the Protocol attached at Section 7.1.1.

3.3 Will the research compel individuals to provide information about themselves, i.e. where they will have little awareness or choice?

Response

☒ Yes

Justification

BPSU standard methodology is being applied where this is no consent for this surveillance project. Please see protocol section 4.2

- 3.4 Will identifiable information about individuals be shared with other organisations or people who have not previously had routine access to the information?

Response

☒ Yes

Justification

The identifiable information will be shared by Dundee Health Informatics Centre (as outlined above). Some personal data and summary personal data will be shared with the researchers as outlined above.

- 3.5 Are you using information about individuals for a purpose it is not currently used for or in a new way, i.e. using data collected to provide care for an evaluation of service development?

Response

☒ Yes

Justification

This is a research project and so the information will be used for research purposes as outlined in the protocol.

- 3.6 Will there be new or significantly changed consolidation, inter-linking, cross-referencing or matching of personal data from multiple sources?

Response

☒ Yes

Justification

We will use Dundee HIC as a safe haven to enable data linkage for the analyses set out in the Protocol section 8.2

- 3.7 Where information about individuals is being used, would this be likely to raise privacy concerns or expectations, i.e. will it include health records, criminal records or other information that people may consider to be sensitive and private and may cause them concern or distress?

Response

☒ No

Justification

This is an 18-month observational surveillance study with a two year follow-up period. We will be using standard BPSU methodology to use minimal identifiable data without consent for reasons previously explained with a robust plan to minimise the risk of disclosure and maintain confidentiality.

This methodology is well established with over 120 national surveillance studies been conducted in a similar fashion since the establishment of BPSU in 1986. The BPSU surveillance studies are undertaken without seeking individual consent and use as limited identifiable data as possible to protect confidentiality. Identifiable data which are not clinical data will be destroyed at the end of the study.

We have also consulted with public and patient representatives to gauge perspectives on our proposals. Members of the Asthma UK Centre for Applied Research PPI group have been significantly supportive of the proposed study and use of data. Asthma UK is also supportive as the lead patient organisation in the UK.

- 3.8 Will the project require you to contact individuals in ways which they may find intrusive, i.e. telephoning or emailing them without their prior consent?

Response

☒ No

Justification

None

- 3.9 Will the project result in you making decisions in ways which can have a significant impact on individuals, i.e. will it affect the care a person receives?

Response

☒ No

Justification

None

- 3.10 Does the project involve you using new technology which might be perceived as being privacy intrusive, i.e. using biometrics, facial recognition or automated decision making?

Response

Justification
None

- 3.11 Is a service being transferred to a new supplier (re-contracted) and the end of an existing contract?

Response

☒ No

Justification
None

- 3.12 Is processing of identifiable/potentially identifiable data being moved to a new organisation (but with same staff and processes)?

Response

☒ No

Justification
None

- 3.13 Consultation to address privacy risks

Explain what practical steps you will take to ensure that you identify and address privacy risks highlighted in the preceding questions. Who should be consulted about potential risks (members of your research team, supervisor, research sponsor...)?

Response

Potential privacy risks can be addressed to Prof Steve Cunningham, Professor of Paediatric Respiratory Medicine, University of Edinburgh (Steve.cunningham@ed.ac.uk) and he will engage with other relevant members of the research team to resolve any potential risks.

Dundee HIC have provided a risk assessment within a DPIA shell document (Step 5) and the proposed measures to reduce risk (Step 6).

4 Risk Identification

- 4.1 Risk identification and assessment

Together with the other stakeholders, now list all the risks you can identify. Below, you will find a list of common risks. If any of these apply, choose them by answering 'yes' and providing a short description of the risk and how you would mitigate the risk.

If the risk applies - select 'Yes'. As a result you will be required to:

- 1. Provide a brief explanation / consequence of the risk occurring*
- 2. Provide a brief explanation of the mitigating factors that will be undertaken to either eliminate or lower the risk*
- 3. In considering the defined mitigation measures, determine the likelihood of the risk occurring to be Low, Medium or High*
- 4. In considering the defined mitigation measures, determine the impact on the data subjects and on the University to be Low, Medium or High*

If the risk does not apply, select 'No'

- 4.2 Possibility that information is shared inappropriately.

If this risk applies, click 'yes' and give a brief explanation of why the risk applies.

If the risk does not apply, click 'no'

Response

☒ Yes

Justification

This could always be a risk, but is considered minimised by security and procedures in place within HIC (see attached Dundee HIC DPIA)

- 4.3 What can you do to eliminate or at least reduce the risk?

Explain all mitigation measures you will put in place.

Response

Outlined in Dundee HIC DPIA (attached to 4.2)

- 4.4 Is the overall residual risk after the mitigation measures low, medium or high? Provide an explanation

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4.4 Is the overall residual risk after the mitigation measures low, medium or high? Provide an explanation for your choice.

Response

☒ Low

Justification

Security and systems in place within HIC. Outlined in Dundee HIC DPIA (attached to 4.2)

4.5 Personal data may be used for a new and different purpose without the knowledge of the data subjects, perhaps due to a change in the context in which the data is used.

If this risk applies, click 'yes' and give a brief explanation of why the risk applies.

If the risk does not apply, click 'no'

Response

☒ No

Justification

Protocol is provided. Any changes will be subject to review.

4.8 New surveillance methods such as CCTV, email monitoring etc. may be an unjustified intrusion on people's privacy.

If this risk applies, click 'yes' and give a brief explanation of why the risk applies.

If the risk does not apply, click 'no'

Response

☒ No

Justification

Does not apply

4.11 Actions taken against individuals as a result of collecting information about them might be to their detriment or cause damage/distress.

If this risk applies, click 'yes' and give a brief explanation of why the risk applies.

If the risk does not apply, click 'no'

Response

☒ No

Justification

No action will be taken against individuals as a result of this research

4.14 People cannot participate in research anonymously because participants may become identifiable again due to data linkage, low participant numbers, geographical location, transfer of data, or access of data.

If this risk applies, click 'yes' and give a brief explanation of why the risk applies.

If the risk does not apply, click 'no'

Response

☒ Yes

Justification

The proposed research is surveillance of an uncommon form (near fatal asthma) of a common condition (asthma). There will be low patient numbers and data linkage. The protocol and Dundee HIC DPIA shell outlines how we will handle, analyse and transfer data, and minimise any potential risks associated with the project.

4.15 What can you do to eliminate or at least reduce the risk?

Explain all mitigation measures you will put in place.

Response

For risks within Dundee HIC please see Dundee HIC DPIA shell attached.
For the within the research team, please see NFA Protocol BPSU survey 1.0 attached (section 6, 7, 8.2)

4.16 Is the likelihood of the risk manifesting after the mitigation measures low, medium or high? Provide an explanation for your choice.

Response

☒ Low

Justification

See Dundee HIC DPIA (attached to 4.15) and protocol (attached to 4.15)

- 4.17 **Vulnerable people may be particularly concerned about the risks of identification or the disclosure of information if anonymity is what people were led to expect.**
If this risk applies, click 'yes' and give a brief explanation of why the risk applies.
If the risk does not apply, click 'no'
Response
☒ Yes
Justification
 We have consulted with people with asthma and groups representing people with asthma who are supportive of our methodology and use of identifiable data as outlined in the protocol (attached to 4.15)
- 4.18 **What can you do to eliminate or at least reduce the risk?**
Explain all mitigation measures you will put in place.
Response
 See Dundee HIC DPIA (attached to 4.15) and protocol (attached to 4.15)
- 4.19 **Is the likelihood of the risk manifesting after the mitigation measures low, medium or high? Provide an explanation for your choice.**
Response
☒ Low
Justification
 See Dundee HIC DPIA (attached to 4.15) and protocol (attached to 4.15)
- 4.20 **Collecting information, matching and linking identifiers or whole datasets might mean that data are no longer anonymous if anonymity is what people were led to expect.**
If this risk applies, click 'yes' and give a brief explanation of why the risk applies.
If the risk does not apply, click 'no'
Response
☒ No
Justification
 The summary grouping of outcomes is outlined in the protocol (attached to 4.15). Restriction of outputs <5 individuals would be maintained for data linkage studies.
- 4.23 **Excess information collection or information not properly managed can lead to creation of duplicate records.**
If this risk applies, click 'yes' and give a brief explanation of why the risk applies.
If the risk does not apply, click 'no'
Response
☒ Yes
Justification
 With BPSU methodology it is possible that multiple clinicians could register the same individual.
- 4.24 **What can you do to eliminate or at least reduce the risk?**
Explain all mitigation measures you will put in place.
Response
 An explanation of how this is resolved is provided in the protocol (attached to 4.15). Some personal identifiers will be seen by the research team to resolve this as per standard BPSU methodology.
- 4.25 **Is the overall residual risk after the mitigation measures low, medium or high? Provide an explanation for your choice.**
Response
☒ Low
Justification
 None
- 4.26 **If a retention period is not established information might be used for longer than necessary.**

If this risk applies, click 'yes' and give a brief explanation of why the risk applies.

If the risk does not apply, click 'no'

Response

☒ No

Justification

The retention period is outlined in the protocol (section 11.6)

- 4.29 **The use of biometric information or potentially intrusive tracking technologies may cause increased concern and cause people to avoid engaging with the University.**

If this risk applies, click 'yes' and give a brief explanation of why the risk applies.

If the risk does not apply, click 'no'

Response

☒ No

Justification

None

- 4.32 **Public distrust about how information is used can damage the University's reputation and lead to less willingness to participate.**

If this risk applies, click 'yes' and give a brief explanation of why the risk applies.

If the risk does not apply, click 'no'

Response

☒ No

Justification

None

- 4.35 **Data loss causing damage or distress to individuals or damage the University's business.**

If this risk applies, click 'yes' and give a brief explanation of why the risk applies.

If the risk does not apply, click 'no'

Response

☒ No

Justification

Data loss is always possible, but within this project as participants are not made aware then loss will cause damage or distress to them.

- 4.38 **Despite proper security, is there an increased possibility of external unlawful access to the data such as hacking?**

If this risk applies, click 'yes' and give a brief explanation of why the risk applies.

If the risk does not apply, click 'no'

Response

☒ Yes

Justification

Always possible. The Dundee HIC DPIA shell outlines the risk and mitigation procedures (attached to 4.2)

- 4.39 **What can you do to eliminate or at least reduce the risk?**

Explain all mitigation measures you will put in place.

Response

The Dundee HIC DPIA shell outlines the risk and mitigation procedures (attached to 4.2)

- 4.40 **Is the overall residual risk after the mitigation measures low, medium or high? Provide an explanation for your choice.**

Response

☒ Low

Justification

None

- 4.41 **Using an external data processor or sharing with another data controller increases the risk of unlawful access to personal data.**

If this risk applies, click 'yes' and give a brief explanation of why the risk applies.

If the risk does not apply, click 'no'

Response

☒ Yes

Justification

We will use Dundee HIC as outlined in the protocol.

- 4.42 **What can you do to eliminate or at least reduce the risk?**

Explain all mitigation measures you will put in place.

Response

We will use the measures outlined in the protocol and the Dundee HIC DPIA (as attached).

- 4.43 **Is the overall residual risk after the mitigation measures low, medium or high? Provide an explanation for your choice.**

Response

☒ Low

Justification

None

- 4.44 **Are you transferring personal data to a non-EEA country using Standard Contractual Clauses as a safeguard?**

Since the European Court of Justice decision in July 2020, a special risk assessment is required for transfer of personal data in particular to the US but also to other non-EEA countries. Please assess how likely it is that despite the use of the Standard Contractual Clauses the data is likely to be accessed, for example under the Patriot Act in the US.

If the answer to this question is 'yes', then this question will be approved by your Head of School.

Response

☒ No

Justification

None

- 4.47 **Any other risk you have identified - describe below.**

If this risk applies, click 'yes' and give a brief explanation of why the risk applies.

If the risk does not apply, click 'no'

Response

☒ No

Justification

None

- 4.50 **Any other risk you have identified - describe below.**

If this risk applies, click 'yes' and give a brief explanation of why the risk applies.

If the risk does not apply, click 'no'

Response

☒ No

Justification

None

- 4.53 **Any other risk you have identified - describe below.**

If this risk applies, click 'yes' and give a brief explanation of why the risk applies.

If the risk does not apply, click 'no'

Response

☒ No

Justification

Appendix 4: Paediatric Emergency Research in the United Kingdom and Ireland Support Letter

Paediatric Emergency Research in the United Kingdom & Ireland

Prof Steve Cunningham
Centre for Inflammation Research
University of Edinburgh

Niall Mullen
Chair

Tom Waterfield
Vice Chair

17/06/2022

Dear Prof Cunningham,

Damian Roland
Past Chair

As Chair of Paediatric Emergency Research in the United Kingdom and Ireland I am pleased to inform you that the PERUKI Research Steering Committee has voted to adopt your study entitled "Near fatal asthma – surveillance".

Shrouk Messahel
Secretary

Please find accompanying this letter:

- Feedback from the RSC including comments and questions on your proposal. While it is not essential to address every issue, or to respond to this feedback, we hope that working through these will optimise uptake and deliverability of your trial.

Emily Walton
Treasurer

~~Kene Madueme~~
Trainee member

As an adopted study we request you acknowledge the group on presentation slides and posters, and include it in the main list of authors and methods section of all manuscripts.

Mark Lyttle
Inaugural & past
chair

Formed in 2012, our group is a collaborative dedicated to improving the quality of emergency care of children through rigorous multi-centre research. We are comprised of more than 70 Emergency Departments caring for children in the nations of England, Ireland, Northern Ireland, Scotland, and Wales.

In summary, on behalf of our group, I would like to reiterate our support of the proposed study.

Kind regards

Dr Niall Mullen
Chair, Paediatric Emergency Research in the UK & Ireland (PERUKI)



PERUKI

Appendix 5: Caldicott Guardian Support Letter

Lothian NHS Board

Queen's Medical Research Institute
47 Little France Crescent
Edinburgh, EH16 4TJ

www.nhslothian.scot



Professor Steve Cunningham
Professor of Paediatric Respiratory Medicine
Child Life and Health,
Centre for Inflammation Research
University of Edinburgh,
Royal Hospital for Children and Young People,
50 Little France Crescent
Edinburgh BioQuarter
Edinburgh
EH16 4TJ
United Kingdom

Date 25 February 2022

Enquiries to Research & Development
Direct Line 0131 242 3330
Email accord@nhslothian.scot.nhs.uk

Director: Professor Alasdair Gray

Dear Professor Cunningham,

Letter OF SUPPORT: Near Fatal Asthma in Children and Young People

Within NHS Lothian, the Caldicott Guardian has granted delegated authority for review of specific research activity to the NHS Lothian R&D office. On this basis, this letter is in support of the above research project, co-sponsored by the University of Edinburgh and NHS Lothian and funded by the Chief Scientist's Office (CSO).

The project will use an established surveillance platform and methodologies in the UK (British Paediatric Surveillance Unit) to identify cases of near fatal asthma in children and young people.

Confidentiality Advisory Group (CAG) approval is being sought under section 251 of the NHS Act 2006, as patient consent will not be sought to access confidential patient information. We request the use of personal data for case verification, but also for analysis through the Health Informatics Centre (HIC) Safe Haven platform at the University of Dundee, with limited identifiers analysed within NHS Lothian. The legal basis of the approval request is for public health benefit.

Note that this letter should not be considered as NHS Lothian Caldicott approval.

Yours sincerely

Heather Charles
Heather Charles (Feb 25, 2022 13:11 GMT)

Head of Research Governance, Research & Development, NHS Lothian



Headquarters
Waverley Gate
2-4 Waterloo Place
Edinburgh EH1 3EQ

Chair Professor John Connaghan CBE
Chief Executive Calum Campbell
Lothian NHS Board is the common
name of Lothian Health Board

Appendix 6: South East Scotland Research Ethics Committee Approval Letter



Lothian NHS Board

South East Scotland Research
Ethics Committee 01

2nd Floor, Waverley Gate
2-4 Waterloo Place
Edinburgh
EH1 3EG
Telephone 0131 536 9000
www.hra.nhs.uk

Date: 11 May 2022

Enquiries to: Sandra Wyllie
Mobile: 07814 764241
Email: sandra.wyllie@nhslothian.scot.nhs.uk

Please note: This is the favourable opinion of the REC only and does not allow you to start your study at NHS sites in England until you receive HRA Approval

11 May 2022

Professor Steve Cunningham
Professor of Paediatric Respiratory Medicine
University of Edinburgh
Dept of Child Life & Health
Royal Hospital for Children and Young People
50 Little France Crescent, Edinburgh
EH16 4TJ

Dear Professor Cunningham

Study title: Near Fatal Asthma in Children and Young People
REC reference: 22/SS/0030
Protocol number: 1.0
IRAS project ID: 310881

Thank you for your letter of 26th April 2022, responding to the Research Ethics Committee's (REC) 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.

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.

Good practice principles and responsibilities

The [UK Policy Framework for Health and Social Care Research](#) sets out principles of good practice in the management and conduct of health and social care research. It also outlines the responsibilities of individuals and organisations, including those related to the four elements of



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Waverley Gate
2-4 Waterloo Place
Edinburgh EH1 3EG

Interim Chair Esther Robertson
Chief Executive Calum Campbell
Lothian NHS Board is the common
name of Lothian Health Board

[research transparency:](#)

1. [registering research studies](#)
2. [reporting results](#)
3. [informing participants](#)
4. [sharing study data and tissue](#)

Conditions of the favourable opinion

The REC favourable opinion is subject to the following conditions being met prior to the start of the study.

Confirmation of Capacity and Capability (in England, Northern Ireland and Wales) or NHS management permission (in Scotland) 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 HRA and HCRW Approval (England and Wales)/ NHS permission for research is available in the Integrated Research Application System.

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 research should be registered in a publicly accessible database and we expect all researchers, research sponsors and others to meet this fundamental best practice standard.

It is a condition of the REC favourable opinion that **all clinical trials are registered** on a publicly accessible database within six weeks of recruiting the first research participant. For this purpose, 'clinical trials' are defined as:

- clinical trial of an investigational medicinal product
- clinical investigation or other study of a medical device
- combined trial of an investigational medicinal product and an investigational medical device
- other clinical trial to study a novel intervention or randomised clinical trial to compare interventions in clinical practice.

Failure to register a clinical trial is a breach of these approval conditions, unless a deferral has been agreed by the HRA (for more information on registration and requesting a deferral see: [Research registration and research project identifiers](#)).

If you have not already included registration details in your IRAS application form you should notify the REC of the registration details as soon as possible.

Publication of Your Research Summary

We will publish your research summary for the above study on the research summaries section of our website, together with your contact details, no earlier than three months from the date of this favourable opinion letter.

Should you wish to provide a substitute contact point, make a request to defer, or require further information, please visit: <https://www.hra.nhs.uk/planning-and-improving-research/application-summaries/research-summaries/>

N.B. If your study is related to COVID-19 we will aim to publish your research summary within 3 days rather than three months.

During this public health emergency, it is vital that everyone can promptly identify all relevant research related to COVID-19 that is taking place globally. If you haven't already done so, please register your study on a public registry as soon as possible and provide the REC with the registration detail, which will be posted alongside other information relating to your project. We are also asking sponsors not to request deferral of publication of research summary for any projects relating to COVID-19. In addition, to facilitate finding and extracting studies related to COVID-19 from public databases, please enter the WHO official acronym for the coronavirus disease (COVID-19) in the full title of your study. Approved COVID-19 studies can be found at: <https://www.hra.nhs.uk/covid-19-research/approved-covid-19-research/>

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).

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, including early termination of the study
- Final report
- Reporting results

The latest guidance on these topics can be found at <https://www.hra.nhs.uk/approvals-amendments/managing-your-approval/>.

Ethical review of research sites

NHS/HSC sites

The favourable opinion applies to all NHS/HSC sites taking part in the study, subject to confirmation of Capacity and Capability (in England, Northern Ireland and Wales) or management

permission (in Scotland) 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/HSC sites

I am pleased to confirm that the favourable opinion applies to any non-NHS/HSC sites listed in the application, subject to site management permission being obtained prior to the start of the study at the site.

Approved documents

The final list of documents reviewed and approved by the Committee is as follows:

Document	Version	Date
Copies of materials calling attention of potential participants to the research [NFACYP BPSU Follow Up Questionnaire Letter]	1.0	01 March 2022
Copies of materials calling attention of potential participants to the research [NFACYP BPSU Flyer]	2.0	26 April 2022
Copies of materials calling attention of potential participants to the research [22-03-01 Version 1.0 NFACYP BPSU Thank you for completing Questionnaire]	2.0	26 April 2022
IRAS Application Form [IRAS_Form_02032022]		02 March 2022
Letter from funder [NFACYP BPSU Award Letter]		22 January 2021
Letters of invitation to participant [NFACYP BPSU Covering message to respondents]	1.0	01 March 2022
Non-validated questionnaire [NFACYP Questionnaire]	1.0	01 March 2022
Other [Asthma Medication for HIC]	1.0	01 March 2022
Other [Required Security/Insurance Policy - British Bureau Cert]		21 February 2021
Other [Required Security/Insurance Policy - UoE]		01 August 2021
Other [Required Security/Insurance Policy - HIC UoD]		25 June 2020
Other [Required Security/Insurance Policy - NHS Lothian]		
Other [Required Security/Insurance Policy - Data Security UoD]		15 January 2021
Other [SCADR Completion Cert TC]		22 April 2021
Other [NFACYP BPSU Caldicott Support]		25 February 2022
Other [Additional Supporting Document] Response to REC PO	1.0	26 April 2022
Participant information sheet (PIS) [NFACYP BPSU Information Leaflet]	2.0	26 April 2022
Referee's report or other scientific critique report [NFACYP Asthma UK and BLF Support]		30 April 2021
Referee's report or other scientific critique report [NFACYP PPI&AUKCAR Support Letter]		07 February 2022
Research protocol or project proposal [NFACYP Study Protocol BPSU]	1.0	01 March 2022
Summary CV for Chief Investigator (CI) [CI Curriculum Vitae]		01 March 2022
Summary CV for student [Student Curriculum Vitae]		

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.

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 Learning

We are pleased to welcome researchers and research staff to our HRA Learning Events and online learning opportunities– see details at: <https://www.hra.nhs.uk/planning-and-improving-research/learning/>

IRAS project ID: 310881 Please quote this number on all correspondence

With the Committee's best wishes for the success of this project.

Yours sincerely

Dr Lucy Kershaw
Chair

Email: sandra.wyllie@nhslothian.scot.nhs.uk

Enclosures: "After ethical review – guidance for researchers"

Copy to: Ms Jo-Anne Robertson

Lead Nation
Scotland: gram.nrspcc@nhs.scot

Appendix 7: Confidential Advisory Group Approval Letter CAG approval



Health Research Authority

2 Redman Place
Stratford
London
E20 1JQ

Tel: 020 7104 8100
Email: cag@hra.nhs.uk

23 September 2022

Professor Steve Cunningham
Professor of Paediatric Respiratory Medicine
University of Edinburgh
Dept of Child Life & Health
Royal Hospital for Children and Young People
50 Little France Crescent, Edinburgh
EH16 4TJ

Dear Professor Steve Cunningham

Application title:	Near Fatal Asthma in Children and Young People
CAG reference:	22/CAG/0055
IRAS project ID:	310881
REC reference:	22/SS/0030

Thank you for submitting a **research** application under Regulation 5 of the Health Service (Control of Patient Information) Regulations 2002 ('section 251 support') to process confidential patient information without consent.

Supported applications allow the controller(s) of the relevant data sources, if they wish, to provide specified information to the applicant for the purposes of the relevant activity without being in breach of the common law duty of confidence. Support provides a lawful basis to allow the information to be processed by the relevant parties for the specified purposes without incurring a breach of the common law duty of confidence only. Applicants must ensure the activity remains fully compliant with all other relevant legislation.

The role of the Confidentiality Advisory Group (CAG) is to review applications submitted under these Regulations and to provide advice to the Health Research Authority on whether application activity should be supported, and if so, any relevant conditions. This application was considered at the CAG meeting held on 07 April 2022.

This outcome should be read in conjunction with the provisional support letter dated 14 April 2022.

Health Research Authority decision

The Health Research Authority, having considered the advice from the Confidentiality Advisory Group as set out below, has determined the following:

The application, to allow the disclosure of confidential patient information by reporting clinicians at hospital trusts and health boards who are part of the PERUKI network to the University of Dundee HIC safe haven server, and the disclosure of confidential patient information to the chief investigator at the University of Edinburgh on questionnaires returned via email or by post, is fully supported, subject to compliance with the standard conditions of support.

Please note that the legal basis to allow access to the specified confidential patient information without consent is now in effect.

Context

Purpose of application

This application from the University of Edinburgh set out the purpose of medical research that seeks to understand how often children aged 5-15 years in the UK and Republic of Ireland experience a near fatal asthma attack.

Near fatal asthma is the most severe form of asthma attack and the UK has the highest rate of asthma death for children in developed healthcare. Children who experience severe asthma attacks are more likely to subsequently die from asthma. Until recently, there was no agreed definition of near fatal asthma and the prevalence could not be estimated. The applicants recently created a definition using an international group of experts so that it is now possible to measure how frequently it occurs in our population. The closest estimate for the prevalence of near fatal asthma attacks is 200-250 children per year in the UK, based on admissions to paediatric intensive care with acute asthma. However, not all children who experience near fatal asthma will be admitted to intensive care and some intensive care admissions would not fit this definition.

The applicants will conduct a prospective epidemiological survey of clinicians in the UK and Republic of Ireland (ROI) using the British Paediatric Surveillance Unit (BPSU) Orange eCard system. This will be undertaken over 18 consecutive months with a follow-up phase at 1 and 2 years of age. The BPSU 'Orange e-Card' has a list of rare disorders under active surveillance which is sent electronically every month to over 4,000 British and Irish consultant paediatricians and other specialities. Clinicians will return the Orange e-Card to the BPSU, notifying any cases seen or 'nothing to report'. The clinicians name and contact details will be passed to the study team and the reporting clinician will be directed to the study online questionnaire, which will request details on the presentation of near fatal asthma, demographic details, investigation and management. A further outcome questionnaire will be sent at one and two years following the near fatal asthma attack. The questionnaires will be run through the University of Dundee HIC safe haven server. If clinicians are unable to use the online system, questionnaires will be sent out in an electronic document format to the reporting clinicians via the investigator's secure nhs.net email account. As a last resort, a paper questionnaire form will be sent by registered mail. It will be marked confidential and double enveloped for data collection with self-addressed envelope to be returned to the chief investigator's office in the University of Edinburgh. Limited confidential patient information will be included so that duplicate cases can be identified. These items of confidential patient information will be removed as soon as possible and held separately to the anonymised dataset used for analysis.

A recommendation for class 1, 2, 4, 5 and 6 support was requested to cover access to the relevant unconsented activities as described in the application.

Confidential patient information requested

The following sets out a summary of the specified cohort, listed data sources and key identifiers. Where applicable, full datasets and data flows are provided in the application form and relevant supporting documentation as this letter represents only a summary of the full detail.

Cohort	Patients aged 5-15 years considered to have experienced an episode of near fatal asthma and who meeting any one of the following: • Survived an acute episode of asthma, with the following features: ○ Pulse oxygen saturation below 92% despite maximal oxygen therapy (i.e. 10-15l/min oxygen flow via non rebreath mask) during acute presentation ○ pH $\leq$ 7.2 and/or pCO₂ $\geq$ 60mmHg or 8kPa ○ Escalation to use of intravenous bronchodilator infusion • Survived an acute episode of asthma and who had a respiratory arrest and/or required cardiopulmonary resuscitation as part of their presentation • Survived an acute episode of asthma for which they were invasively ventilated The applicants anticipate that 375 patients in the UK will be recruited and that the majority of cases will be recruited from England.
Data sources	1. Questionnaires completed by reporting clinicians working in emergency departments, and other clinical areas within the PERUKI network (Paediatric Emergency Research UK and Ireland). Clinicians in all clinical areas may encounter and report cases of Near Fatal Asthma (NFA) in CYP and complete questionnaires. This will include General Paediatric, Critical Care and Emergency Medicine doctors. Clinicians in Paediatric Critical Care Units will also be able to register cases via the same system as emergency clinicians (QR code with link to BPSU – HIC questionnaire)
Identifiers required for linkage purposes	1. NHS number 2. Hospital ID number 3. Date of birth 4. Date of death 5. Postcode – unit level
Identifiers required for analysis purposes	1. Postcode – unit level 2. Gender 3. Ethnicity

Confidentiality Advisory Group advice

This letter summarises the outstanding elements set out in the provisional support letter, and the applicant response. The applicant response was considered by a sub-committee of the CAG.

1. **The patient information leaflet requires revision to ensure that the study is explained as clearly and concisely as possible. Further details on how patients can opt-out also need to be included.**

The applicant provided an update. The CAG were content with the updated version provided, however the CAG recommend using the term anonymised rather than de-personalised in the patient leaflet. The applicant confirmed this would be changed.

2. **Provide confirmation that the confidential patient information collected will be deleted after two years.**

The applicant confirmed that this is proposed to be a maximum of three years and the CAG were content with the justification.

3. **Alternative means of detecting duplicate reports need to be explored. If no alternative is available, an explanation on why no alternatives can be used needs to be provided.**

In a call with HIC Dundee on 26.04.22, applicants explored the ability of the research team to be made aware of duplicate cases, without their exposure to identifiers (i.e. hospital number, date of birth). HIC Dundee will now provide the facility for researchers to identify duplicate cases without personal identifiers being visible. The CAG were content with this response.

Confidentiality Advisory Group advice conclusion

The CAG agreed that the minimum criteria under the Regulations appeared to have been met, and therefore advised recommending support to the Health Research Authority, subject to compliance with the specific and standard conditions of support as set out below.

Specific conditions of support

1. Favourable opinion from a Research Ethics Committee. **Confirmed 11 May 2022**
2. Security assurances are provided for the **University of Edinburgh and the University of Dundee**, in the form of an approval letter from the NHS Scotland Public Benefit And Privacy Panel For Health And Social Care, confirmed **23 September 2022**

As the above conditions have been met, this letter provides confirmation of final support. I will arrange for the register of approved applications on the HRA website to be updated with this information

Application maintenance

Annual review

Please note that this legal support is subject to submission of an annual review report, for the duration of support, to show that the minimal amount of patient information is being processed and support is still necessary, how you have met the conditions or report plans, any public benefits that have arisen and action towards meeting them. It is also your responsibility to submit this report every 12 months for the entire duration that confidential patient information is being processed without consent.

The next annual review should be provided no later than **23 September 2023** and preferably 4 weeks before this date. Reminders are not issued so please ensure this is provided annually to avoid jeopardising the status of the support. Submission of an annual review in line with this schedule remains necessary even where there has been a delay to the commencement of the supported activity, or a halt in data processing. Please ensure you review the HRA website to ensure you are completing the most up to date 'section 251' annual review form as these may change.

For an annual review to be valid, there must also be evidence that the relevant DSPT submission(s) for organisations processing confidential patient information without consent are in place and have been reviewed by NHS Digital. Please plan to contact NHS Digital in advance of the CAG annual review submission date to check they have reviewed the relevant DSPTs and have confirmed these are satisfactory.

Register of Approved Applications

All supported applications to process confidential patient information without consent are listed in the published 'Register of Approved Applications'. It is a statutory requirement for the Register to be published and it is available on the CAG section of the Health Research Authority website. It contains applicant contact details, a summary of the research and other pertinent points.

This Register is used by controllers to check whether support is in place.

Changes to the application

The application and relevant documents set out the scope of the support which is in place for the application activity and any relevant restrictions around this.

Any amendments which are made to the scope of this support, including but not limited to, purpose, data flows, data sources, items of confidential patient information and processors, require submission of a formal amendment to the application. Changes to processors will require evidence of satisfactory DSPT submission. The amendment form can be found in the Confidentiality Advisory Group pages on the Health Research Authority website.

Support for any submitted amendment would not come into effect until a positive outcome letter has been issued.

Changes to the controller

Amendments which involve a change to the named controller for the application activity require the submission of a new and signed CAG application form and supporting documentation to support the application amendment. This is necessary to ensure that

the application held on file appropriately reflects the organisation taking responsibility for the manner and purpose of data processing within the application, and that the legal support in place is related to the correct legal entity.

Applicants are advised to make contact with the Confidentiality Advice Team to discuss a change in controllership for an existing application in sufficient time ahead of the transfer of project responsibility to discuss the submission process timings.

Further information and relevant forms to amend the support is available on the HRA website.

Reviewed documents

The documents reviewed at the meeting are as follows.

Document	Version	Date
CAG application form (signed/authorised) [CAG - completed Form]		
Confidentiality policy [20-06-25 Required SecurityInsurance Policy HIC UoD]		
Confidentiality policy [21-01-15 Required SecurityInsurance Policy - Data Security UoD]		
Confidentiality policy [Required SecurityInsurance Policy NHS Lothian]		
Confidentiality policy [21-08-01 Version 1.0 Required SecurityInsurance Policy UoE]		
Covering letter on headed paper [22-03-01 Version 1.0 NFACYP CAG Cover Letter]		01 March 2022
Data Protection Registration [22-01-31 NFACYP Data Protection Registration UoE]		31 January 2022
GP/consultant information sheets or letters [22-03-01 Version 1.0 NFACYP BPSU Covering message to respondents]	1.0	01 March 2022
GP/consultant information sheets or letters [22-03-01 Version 1.0 NFACYP BPSU Reminder Letter]	1.0	01 March 2022
GP/consultant information sheets or letters [22-03-01 Version 1.0 NFACYP BPSU Follow Up Questionnaire]	1.0	01 March 2022
GP/consultant information sheets or letters [22-03-01 Version 1.0 NFACYP BPSU Thank you letter]	1.0	01 March 2022
Other [Attachment 4 NFACYP PPI&AUKCAR Support Letter]		
Other [21-04-24 SCADR Completion Cert]		24 January 2021
Other [Attachment 1 Republic of Ireland BPSU Ethical Approval]		
Other [21-02-21 Version 1.0 Required SecurityInsurance Policy British Bureau Cert]		21 February 2021
Other [22CAG0055 CAGSF1 CAT advice form]		
Other [21-06-15 NFACYP Grant Award Letter]		
Other [21-07-28 Study Approval BPSU]		
Other [21-04-30 NFACYP Asthma UK and BLF Support]		30 April 2021
Other [21-12-22 MRC GDPR Cert SC]		22 December 2021
Other [21-12-29 MRC GDPR Cert DV]		29 December 2021
Other [22-03-01 CI Curriculum Vitae]		01 March 2022
Other [22-01-10 MRC GDPR Cert AM]		10 January 2022
Other [20-10-15 Republic of Ireland Data Exchange Agreement]		
Other [22-03-01 Version 1.0 NFACYP Questionnaire]		

Other [22-03-01 Student Curriculum Vitae]		
Other [Attachment 3 Privacy Advisory Committee Northern Ireland BPSU]		
Other [22CAG0055 CAT assessment form template]		
Patient Information Materials [22-03-01 Version 1.0 NFACYP BPSU flyer]	1.0	01 March 2022
Patient Information Materials [22-03-01 Version 1.0 NFACYP BPSU Information Leaflet]		01 March 2022
Research protocol or project proposal [22-03-01 Version 1.0 NFACYP Study Protocol BPSU]	1.0	01 March 2022
Written recommendation from Caldicott Guardian (or equivalent) of applicant's organisation [Attachment 5 22-02-25 NFACYP BPSU Caldicott Support]		
20220923 HSC-PBPP Conditions Met 2122-0172 Cunningham		23 September 2022
22-04-26 Version 2.0 BPSU public information leaflet NFACYP - Tracked changes	2.0	26 April 2022
22-04-26 Version 2.0 BPSU public information leaflet NFACYP	2.0	26 April 2022
22-SS-0030 IRAS 310881 Favourable opinion 11.05.2022 (1)		11 May 2022

Membership of the Committee

The members of the Confidentiality Advisory Group who were present at the consideration of this item are listed below.

No conflicts of interest were declared.

Please do not hesitate to contact me if you have any queries following this letter. I would be grateful if you could quote the above reference number in all future correspondence.

With the Group's best wishes for the success of this project.

Yours sincerely

Caroline Watchurst
Confidentiality Advisor

On behalf of the Health Research Authority

Email: cag@hra.nhs.uk

Included: List of members who considered application
Standard conditions of support

Copy to: Sandra.Wyllie@nhslothian.scot.nhs.uk

**Confidentiality Advisory Group meeting attendance
07 April 2022**

Members present:

<i>Name</i>	
Dr Tony Calland MBE	CAG Chair
Dr Martin Andrew	CAG member
Ms Sophie Brannan	CAG member
Dr Sandra Duggan	CAG member
Professor Lorna Fraser	CAG member
Mr Andrew Melville	CAG member
Ms Diana Robbins	CAG member
Dr Murat Soncul	CAG Alternate Vice Chair

Also in attendance:

<i>Name</i>	<i>Position (or reason for attending)</i>
Ms Katy Cassidy	HRA Confidentiality Advisor
Ms Natasha Dunkley	HRA Head of Confidentiality Advice Service
Dr Paul Mills	HRA Confidentiality Advice Service Manager
Ms Mia Crispin	HRA Approvals Administrator (Observer)
Ms Emma Davies	HRA Information Governance Support Officer (Observer)

Standard conditions of support

Support to process the specified confidential patient information without consent, given by the Health Research Authority, is subject to compliance with the following standard conditions of support.

The applicant and those processing the information under the terms of the support will ensure that:

1. The specified confidential patient information is only used for the purpose(s) set out in the application.
2. Confidentiality is preserved and there are no disclosures of information in aggregate or patient level form that may inferentially identify a person, nor will any attempt be made to identify individuals, households or organisations in the data.
3. Requirements of the Statistics and Registration Services Act 2007 are adhered to regarding publication when relevant, in addition to other national guidance.
4. All staff with access to confidential patient information have contractual obligations of confidentiality, enforceable through disciplinary procedures.
5. All staff with access to confidential patient information have received appropriate ongoing training to ensure they are aware of their responsibilities and are acting in compliance with the application detail.
6. Activities must be compliant with the General Data Protection Regulation and relevant Data Protection Act 2018.
7. Audit of data processing by a designated agent is facilitated and supported.
8. The wishes of patients who have withheld or withdrawn their consent are respected.
9. Any significant changes (for example, people, purpose, data flows, data items, security arrangements) must be approved via formal amendment prior to changes coming into effect.
10. An annual review report is submitted to the CAG every 12 months from the date of the final support letter, for the duration of the support.
11. Any breaches of confidentiality around the supported flows of information should be reported to CAG within 10 working days of the incident, along with remedial actions taken/to be taken. This does not remove the need to follow national/legal requirements for reporting relevant security breaches.

Appendix 8: Public Benefit and Privacy Panel Approval Letter PBPP

Public Benefit and Privacy Panel for Health and Social Care (HSC-PBPP)

phs.PBPP@phs.scot

<https://www.informationgovernance.scot.nhs.uk/pbphsc/>



Professor Steve Cunningham
Professor of Paediatric Respiratory Medicine,
University of Edinburgh,
Department of Child Life and Health,
Royal Hospital for Children and Young People,
50 Little France Crescent,
Edinburgh. EH16 4TJ

Date: 23rd September 2022
Our Ref: 2122-0172 Cunningham

Dear Professor Cunningham

Re Application: Near Fatal Asthma in Children and Young People Version: v1.3

Further to your conditional approval issued by the Public Benefit and Privacy Panel for Health and Social Care on 22nd September 2022, I am writing to confirm that all conditions applied to the approval have now been satisfied. Your application and supporting documents have undergone proportionate governance review and have now been approved in full.

This approval is given to process data as specified in the approved version of the application, and is limited to this. Approval is valid for the period specified until 31st January 2026. Your approved application (v1.3) has been attached, with the version control box completed by HSC-PBPP. Should you need to submit an amendment, this version of your application should be updated (to v2.0), with all previous changes no longer highlighted but with any new changes highlighted.

You are required to notify the Panel Manager, via your eDRIS Coordinator, of any proposed changes to your proposal, e.g. purpose or method of processing, data or data variables being processed, study cohorts, individuals accessing and processing data, timescales, technology/infrastructure. Instructions and forms are available on our website: <https://www.informationgovernance.scot.nhs.uk/pbphsc/home/application-amendments/>

On conclusion of your proposal, as part of NHS Scotland Governance and monitoring we will require you to complete an End of Project reporting form to demonstrate that you have complied with the obligations outlined e.g. data destruction or submission of references for publications of findings.

I would take this opportunity to remind you of the declaration you have made in your application form committing you to undertakings in respect of information governance, confidentiality and data protection. It is the responsibility of the applicant and their organisation to ensure that their study complies with current legislation at all times during the study.

Requests for access to NHS Scotland data as part of this approved application must be supported by providing a copy of your approval letter and approved application to the relevant local board contacts and/or data providers.

Please note that summary information about your application and its approval, including the title and nature of your proposal, will be published on the panel website (<https://www.informationgovernance.scot.nhs.uk/pbphsc/>). Please note that our email address has changed and the previous addresses are no longer in use.

I hope that your proposal progresses well.

Yours sincerely,

Dr Marian Aldhous

Panel Manager
NHS Scotland Public Benefit and Privacy Panel for Health and Social Care
Email: phs.PBPP@phs.scot

Cc: Dr Rena Gertz, Main contact for Lead Organisation
Cc: Jo-Anne Robertson, Research sponsor

Appendix 9: Privacy Advisory Committee Approval Letter

To: Dr Deepa Varghese
Clinical Research Fellow,
University of Edinburgh

Privacy Advisory Committee, N Ireland

31st August 2022
(sent by email)

Dear Dr Varghese, Re: Proposed BPSU study: Near Fatal Asthma in Children and Young People

Thank you for giving me the opportunity to discuss the above study with you and with Professor Steve Cunningham, in particular the possible inclusion of data from Northern Ireland (NI).

There is a clear and strong public interest in this proposed epidemiological study.

We note that in England and Wales the study required Section 251 Approval. However at the present time the corresponding HSC (Control of Data Processing) Act 2016 (NI) is not yet operational and it will be some time before it is. Therefore we do not have a legal basis for setting aside the Common Law duty of confidentiality.

We have agreed arrangements which should enable the study to proceed within the existing legal framework in NI. These are based on the general arrangements for involving NI in BPSU studies, agreed with Dr Elizabeth Coates in 2018, then Head of Research Governance, Public Health England. Specifically that the cases from Northern Ireland will be reported on a unique NI questionnaire, where a case number will be used instead of a national identifier, days of life instead of DOB, and first half of postcode only. The completed questionnaire will be transferred by the treating Clinician to a Safe Haven for the study, via a secure link, for the further pseudonymisation applied to all study data before processing. Your information to clinicians in NI reporting cases should include this information.

In addition any data obtained from patients in NI should comply with the Section 251 conditions of approval set by CAG, including Data Protection and data security arrangements.

I hope the foregoing may be of assistance. If you require any further information or clarification please do not hesitate to get back to me.

Yours sincerely

Professor Roy McClelland OBE
Chairman Privacy Advisory Committee (N. Ireland)
R.J.McClelland@gub.ac.uk

CC Professor Steve Cunningham
Professor of Paediatric Respiratory Medicine
University of Edinburgh

Appendix 10: Republic of Ireland BPSU Agreement



National Office Health
Protection
Health Service
Executive
31/33 Catherine Street
Limerick

Tel: (061) 483347
Fax: (061) 464205

12TH, February 2010

Re: Need for ethical approval for participation in IPSU and BPSU studies.

To whom it may concern,

Paediatricians in Ireland provide data to surveillance studies organised by both the Irish Paediatric Surveillance Unit (IPSU) and the British Paediatric Surveillance Unit (BPSU). These studies require paediatricians to report on a monthly basis on any new case of a number of conditions listed on the IPSU and BPSU surveillance cards. Studies accepted for inclusion in both surveillance systems must meet a number of strict criteria, namely:

1. All studies must receive ethical approval from the institution where the principal investigator is based. In addition, studies included in the BPSU must be passed by the UK National Governance Information Board-Ethics and Confidentiality Committee.
2. No personally identifiable information is collected on cases reported to IPSU or BPSU. Only minimal identifier information, to exclude duplication, is collected.
3. No additional investigations or therapeutic interventions are requested on cases reported to IPSU or BPSU.
4. Study data must be easily obtainable from normal clinical notes. No additional data is required from cases, or their carers.

Based on the above, it is clear that IPSU and BPSU studies are a form of audit or surveillance, and do not represent interventional research. Therefore, provision of data to IPSU or BPSU studies does not require ethical approval from the institution where the paediatrician providing the data is based. Likewise, national level ethical approval is not required for IPSU studies, or participation in BPSU studies by paediatricians based in the Republic of Ireland, provided the criteria listed above have been.

Yours sincerely,


DR. KEVIN KELLEHER
ASSIST. NATIONAL DIRECTOR FOR POPULATION HEALTH – HEALTH PROTECTION
MEDICAL REGISTRATION NUMBER 19719

Appendix 11: Patient Information Leaflet

Near Fatal Asthma in Children and Young People
Version 3.0
19_May2022

What is the British Paediatric Surveillance Unit (BPSU)?

The aim of the BPSU is to encourage the study of rare conditions in children. It was founded in 1986 and its parent bodies are the Royal College of Paediatrics and Child Health, Public Health England and Great Ormond Street Institute of Child Health (University College London).

What does the BPSU do?

It allows doctors and researchers to find out how many children in the UK and the Republic of Ireland are affected by the rare disease or condition each year - this is called epidemiological surveillance. When a doctor sees a case of the condition they will inform the BPSU investigation team, who send the reporting doctor a short confidential questionnaire for more information about the affected child. BPSU researchers never contact families or children and surveillance studies don't ever affect a child's treatment. The purpose is ONLY to collect information to learn more about the condition.

How does the BPSU work?

Each month the unit sends an email to over 4000 consultant paediatricians; the email lists the rare conditions currently being studied. If a doctor has seen a child affected by one of these conditions they tick a box on the email and return it to BPSU.

What has the BPSU achieved?

The BPSU has now helped to undertake surveys of over 120 rare conditions, which may affect children. These have helped to increase understanding of why the conditions occur and can help to provide better diagnoses and treatments.

For further information contact:

British Paediatric Surveillance Unit, Royal College of Paediatrics and Child Health, 5-11 Theobalds Road, London, WC1X 8SH,
T: +44 (0) 207 092 6173/4

Email: bpsu@rcpch.ac.uk Website: www.rcpch.ac.uk/bpsu



Public Information Leaflet Surveillance of Near Fatal Asthma

This leaflet provides information about a new study of Near Fatal Asthma (NFA). It aims to provide information about the condition, why this study is important and what we hope to show by doing it. It includes the contact details of one of the researchers carrying out the study and a link to the website where the results will be published.

What is near fatal asthma?

Asthma attacks can vary from mild to fatal. Some children and young people have an asthma attack so severe that they are close to dying from it. This is called "near fatal asthma". People who have near fatal asthma or NFA, are more likely to have more severe asthma attacks and possibly die.

Why is this study important?

The UK historically and currently has higher rates of asthma deaths than any other country in Europe and North America, but data is lacking on how often NFA attacks occur. The results will tell us how doctors manage children when they have a near fatal asthma attack, and whether we can find better ways to treat attacks and deliver better asthma care for those who are high risk for future severe asthma attacks.

What are the aims of this study?

We want to know how often near fatal asthma attacks happens in children and young people in the UK and Republic of Ireland.

We hope that the information will help us in three ways:

1. identify some of the risks for near fatal asthma, and with additional future research use these results to:
2. give better care to children and young people who have near fatal asthma
3. reduce future risk of severe asthma attacks and/or death.

How long will the study go on for?

This study will last for 3 ½ years (18-months surveillance with 2-years follow up) starting in October 2022. The study will be taking place across the United Kingdom and Republic of Ireland. The study is led by researchers based at NHS Lothian and Edinburgh University.

How will the information be collected?

This is a surveillance study that uses questionnaires to research rare conditions. You do not have to complete any of the forms or fill out a questionnaire. The doctors who are looking after your child will complete questionnaires using information from medical records. Doctors will **not** provide names and addresses to the study team but they will provide details like **ethnic group, gender, post code and date of birth**. The data will be entered onto an encrypted secure database (a safe haven). A safe haven is an approved, regulated and encrypted secure database where safeguards limit access to depersonalised data by specially trained and authorised professionals and researchers. Researchers will not see information on full post code and date of birth, but this information will be safely and securely linked to other databases in the 'safe haven' to understand factors (such as local air pollution levels or pollen counts) that might make near fatal asthma attacks more likely to happen. Individual cases will not be identified in any reports. Any information made public will be reported as a minimum of 5 cases i.e. there were five cases in Scotland and less than 5 cases in the North of England.

The smallest amount of personally identifiable information will be used. We cannot withdraw or remove personal information from the study as this would make the research invalid but you can opt out of further details being collected. When the study finishes, personal information will be deleted or depersonalised. The University of Edinburgh and NHS Lothian are the sponsor and data controllers for this research study, which means they are responsible for looking after the information and using it properly. They will securely store anonymous information for at least 20 years.

For more details about how personal information is used in the study, please see the BPSU website <https://www.rcpch.ac.uk/work-we-do/bpsu/bpsu-study-near-fatal-asthma>

If you want access to the information in your child's medical records, then you should contact your child's NHS hospital or doctor.

What if I do not want to be involved?

If you think your child has had a NFA attack and do not want your child's data to be included in the study you must inform your doctor or the study team (see below). They will stop any further details about your case entering the study.

Hospitals will also record if patients do not want their medical records to be used for audit or research. You must tell your doctor or hospital if you do not want your records to be used.

In addition, individuals living in England can register a national data opt out. Registering an opt out means that none of your child's NHS information relating to care provided in England would be used for research or planning www.nhs.uk/your-nhs-data-matters/.

Who is funding and supporting this study?

This study is being funded by Chief Scientists Office for Scotland. The Asthma UK and British Lung Foundation Partnership are supporting this study.

Where will the results be published?

Once the study is completed, you will be able to find the results on the BPSU website: <https://www.rcpch.ac.uk/work-we-do/bpsu/bpsu-study-near-fatal-asthma>

Who has reviewed this study?

The study was given favourable ethical opinion by South East Scotland Research and Ethics Committee (Ref 22/SS/0030) the Health Research Authority Confidentiality Advisory Group (England and Wales) and the Public Benefit and Privacy Panel (Scotland). The National Office Health Protection in provides approval for Ireland.

If you have any questions, concerns or would like to opt out?

Prof Steve Cunningham, Royal Hospital for Children and Young People, 50 Little France Crescent, Edinburgh, EH16 4TJ

Email: loth.bpsunfa@nhslothian.scot.nhs.uk

Website: www.rcpch.ac.uk/bpsu/nfa

Telephone: 0131 312 0453

Appendix 12: Near Fatal Asthma Questionnaire

Near Fatal Asthma in Children and Young People
Version 1.0
01 March 2022

1

NFA Questionnaire Sections (and rationale)

Identifiers in RED are submitted online only and are not visible to researchers

Identifiers in BLUE are submitted electronically or on paper and may be visible to researchers

Initial questionnaire:

Section 1 Core data (+ as in standard BPSU)

Reporter Details

- Consultant Responsible for Care in this hospital
- Hospital Name
- Work Email address
- Has patient been referred from another centre (Yes/No)
- If Yes,
- Name of centre:
- Name of consultant in referring centre

Case Details

- NHS/CHI (to check duplicates)
- Hospital number
- Town of birth (ROI)
- Date of birth (Month/Year only if email/paper submission)
- Sex M/F
- Ethnicity (table)
- Full postcode - to link deprivation and with date of event for pollution, pollen, weather (Partial postcode if email/paper submission)

Near Fatal Asthma in Children and Young People
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01 March 2022

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Section 2

Near Fatal Asthma Event Presentation

How does this child meet the case definition for Near Fatal Asthma?

		Yes/No (tick)	
All of these	SpO ₂ <92% despite supplemental oxygen therapy		
	pH <7.2 and/or pCO ₂ >60mmg/8kPa		
	Use of intravenous bronchodilator infusion		
Respiratory arrest			
Cardiopulmonary resuscitation			
Mechanical ventilation			

Item	Field options	Data location	Relevance to outputs
Date of Event	Date (DD/MMM/YY)	clerking history or hospital medical records	Link to age, seasonality, pollen, weather.

Time of Event* (First use of an emergency dose of 10 puffs MDI, i.e. onset of attack no longer responding to normal dose of short acting bronchodilator)	Time (24 hour clock)	<i>clerking history or hospital medical records</i>	opportunities to intervene/delayed presentation/indoor outdoor exposures
Date of arrival at ED			
Time of arrival at ED			
Date of Discharge	Date (DD/MMM/YY)	<i>clerking history or hospital medical records</i>	Logic request for patient journey (days) and acute/PICU hospital management (days) sections

Did the child have acute asthma symptoms prior to NFA	(Yes/No)		
(If yes) Date of onset of asthma symptoms	Date (DD/MMM/YY)	<i>clerking history or hospital medical records</i>	Link to age, seasonality, pollen, weather.
(If yes) Time of onset of asthma symptoms	Time (24 hour clock)	<i>clerking history or hospital medical records</i>	opportunities to intervene/delayed presentation/indoor outdoor exposures
Did the child have acute illness prior to the onset of asthma symptoms ?	(Yes/No)		
(If yes) Date of onset of acute respiratory illness	Date (DD/MMM/YY)	<i>clerking history or hospital medical records</i>	Link to age, seasonality, pollen, weather.

(If yes) What was prior illness?	Cough Non-specific viral illness Breathlessness with activity Other, please state:	<i>clerking history or hospital medical records</i>	Opportunities to intervene

Leading up to this NFA event:

Was any trigger reported associated with this NFA?	Choice of one or more: Viral infection Exercise Allergic food exposure reaction Allergic animal exposure reaction Allergic pollen exposure reaction Other (state)	<i>clerking history or hospital medical records</i>	
Clinical services interacted with in 7 days prior to event	Tick all that apply: 111/NHS24 Primary Care/Out of hours ED Hospital clinic Hospital admission Not known	<i>clerking history or hospital medical records</i>	Opportunities to intervene
Calculate time from asthma onset to time of NFA (=X).	Number (drop down list) /DK (free text option)	<i>clerking history or hospital medical records</i>	Delay in seeking care. Red flag risk factor. Opportunities to intervene

In the X hours from asthma onset to NFA how many doses of inhaled short acting bronchodilator were used for the attack? (number of doses of 100microgramme MDI)			
Had oral prednisolone been prescribed prior to the NFA attack?	Yes/No		
How many days of acute prednisolone treatment had been provided prior to NFA attack?	(1-10 drop down)		

Pre-hospital care

Location at time of event	Choice of one: Home School Other location (state) with parent Other location (state) other adult Other location (state) no adult	<i>clerking history or hospital medical records</i>	Situational risk/delay in presentation
First clinical responder to this attack	Choice of one: First aider Paramedic General Practitioner ED staff	<i>clerking history or hospital medical records</i>	

	Hospital clinical staff Other (state)		
First responder assessment	All that apply: Central cyanosis Altered conscious level Severe dyspnoea Silent chest Unable to talk Unconscious Respiratory Arrest Asystole	<i>clerking history or hospital medical records</i>	Objective markers of event severity
Need for Cardiopulmonary resuscitation (CPR) pre-hospital	Yes/No	<i>clerking history or hospital medical records</i>	
If yes, duration of CPR	Minutes		

PreHospital/ED observations

Oxygen saturation in air measured	Yes/No/DK	<i>clerking history or hospital medical records</i>	Objective marker of event severity
Oxygen saturation in air measured: Yes	Lowest value recorded (%) 0-100	<i>clerking history or hospital medical records</i>	Objective marker of event severity
Oxygen saturation in air measured: Yes	Location: Scene or Hospital	<i>clerking history or hospital medical records</i>	Objective marker of event severity

Oxygen saturation in supplemental oxygen measured	Yes/No/DK	<i>clerking history or hospital medical records</i>	Objective marker of event severity
Oxygen saturation in supplemental oxygen: Yes	Lowest value recorded (%) 0-100	<i>clerking history or hospital medical records</i>	Objective marker of event severity
Oxygen saturation in supplemental oxygen: Yes	Oxygen flow at time of SpO ₂ recording		
Oxygen saturation in supplemental oxygen: Yes	Location: Scene or Hospital	<i>clerking history or hospital medical records</i>	Objective marker of event severity
Highest blood carbon dioxide measured during emergency treatment	Two digits (XX) mmHg (20-99) Or Two digits, one decimal place (XX.Y) kPa (03.0 – 30.0)	<i>clerking history or hospital medical records</i>	Objective marker of event severity
Lowest blood pH measured during emergency treatment	Three decimal points (X.XXX)		
Was there a hospital to hospital transfer for treatment of this event	Yes/No/DK	<i>clerking history or hospital medical records</i>	If no = non hospital transfer (referring details above)
Hospital transfer (Yes) – Name of hospital patient transferred to	Free Text	<i>clerking history or hospital medical records</i>	

Pre-hospital use of adrenaline IM	Yes/No	<i>clerking history or hospital medical records</i>	

*Duration of admission (day of admission = Day 1)

Please plot the patient journey to discharge	Emergency Department	Hospital Ward	High Dependency	Paediatric Intensive Care Unit
Day 1	Y/N	Y/N	Y/N	Y/N
Day 2	Y/N	Y/N	Y/N	Y/N
Day 3	Y/N	Y/N	Y/N	Y/N
Day 4	Y/N	Y/N	Y/N	Y/N
Day 5	Y/N	Y/N	Y/N	Y/N
Day 6	Y/N	Y/N	Y/N	Y/N
Day 7	Y/N	Y/N	Y/N	Y/N
Day 8 onwards (present by response logic)	Y/N	Y/N	Y/N	Y/N

(Tick all that apply for the 24 hour period midnight to midnight)

Acute/PICU In-hospital management:

(Separate Pre hosp/Ed/Hospital interventions to relevant sections: Other medicines may be added once tested to see how well respondents can rapidly answer these questions). Automatically add days if >7.

Nebulised Salbutamol	IV Steroids	IV salbutamol	IV aminophylline	IV magnesium	High Flow Nasal Cannula	If Yes (use logic), Maximum Flow rate	Non-invasive CPAP	If Yes (use logic), Maximum CPAP pressure	Non-invasive BiPAP	If Yes (use logic), Maximum BiPAP pressure (PIP)	Invasive Ventilation	If yes (use logic), Ventilation mode	If Yes (use logic), Maximum invasive ventilation pressure	And: ratio	And: ECLS	And: Volatile anaesthetic gases	Supplemental Oxygen (max %)	Sedation use (then sedation type if Yes).

						(litres)				& CPAP)			es (PIP & PEEP)					
Pre-hospital		Y/N	Y/N	Y/N	Y/N	Number	Y/N	Number	Y/N	Number	Y/N	ST/Oscillation etc	Number		Y/N	Y/N	Y/N	Y/N
ED		Y/N	Y/N	Y/N	Y/N	Number	Y/N	Number	Y/N	Number	Y/N	ST/Oscillation etc	Number		Y/N	Y/N	Y/N	Y/N
Day 1		Y/N	Y/N	Y/N	Y/N	Number	Y/N	Number	Y/N	Number	Y/N	ST/Oscillation etc	Number		Y/N	Y/N	Y/N	Y/N
Day 2		Y/N	Y/N	Y/N	Y/N	Number	Y/N	Number	Y/N	Number	Y/N	ST/Oscillation etc	Number		Y/N	Y/N	Y/N	Y/N
Day 3		Y/N	Y/N	Y/N	Y/N	Number	Y/N	Number	Y/N	Number	Y/N	ST/Oscillation etc	Number		Y/N	Y/N	Y/N	Y/N
Day 4		Y/N	Y/N	Y/N	Y/N	Number	Y/N	Number	Y/N	Number	Y/N	ST/Oscillation etc	Number		Y/N	Y/N	Y/N	Y/N
Day 5		Y/N	Y/N	Y/N	Y/N	Number	Y/N	Number	Y/N	Number	Y/N	ST/Oscillation etc	Number		Y/N	Y/N	Y/N	Y/N
Day 6		Y/N	Y/N	Y/N	Y/N	Number	Y/N	Number	Y/N	Number	Y/N	ST/Oscillation etc	Number		Y/N	Y/N	Y/N	Y/N
Day 7		Y/N	Y/N	Y/N	Y/N	Number	Y/N	Number	Y/N	Number	Y/N	ST/Oscillation etc	Number		Y/N	Y/N	Y/N	Y/N

Did the child have a bronchoscopy	Yes/No/DK		
Bronchoscopy (Yes): What day(s) was this performed	(D1 = First day of PICU admission)		
Did the child receive DNase (nebulised or with bronchoscopy)	Yes/No/DK		
DNase (yes): For how many days of treatment?	Drop down Day 1 to 28		
If invasive ventilation >7 days, what was the total duration of ventilation?	(D1 = First day of PICU admission)		

Discharge health status (impact of NFA)	Choice of one: Recovered Recovered with sequelae Died Unknown Unknown as transferred	<i>clerking history or hospital medical records</i>	
Discharge health status (impact of NFA) – Recovered with sequelae	Neurological Other - Free text -	<i>clerking history or hospital medical records</i>	
Duration of emergency oral steroids prescribed at discharge.	(Days)	<i>clerking history or hospital medical records</i>	Risk reduction

Level of regular asthma treatment at time of discharge	None This will be drop down lists for medicine, dose, frequency (including prn for combination inhalers) * include adrenaline auto-injector.	<i>clerking history or hospital medical records</i>	Risk reduction of future event in relation to prior asthma status
Documented evidence of asthma action plan provided during this admission	Yes/No	<i>clerking history or hospital medical records</i>	Risk reduction of future event
Clinical review and timescale planned at discharge	Column One (1) Yes/No (tick all that apply) Column Two (and Three) (2) General practitioner (and timescale XX days, XX weeks) (3) Asthma Nurse Specialist (and timescale XX days, XX weeks) (4) General Paediatrician (and timescale XX days, XX weeks) (5) General Paediatrician with respiratory interest (and timescale XX days, XX weeks) (6) Specialist Respiratory Paediatrician (and	<i>clerking history or hospital medical records</i>	Risk reduction of future event

	timescale XX days, XX weeks)		

Section 3

Pre NFA asthma baseline

Item	Field options (all have 'not known' option)	Data location	Relevance to outputs
Age (years) at first episode of wheeze	Number (0-16)	<i>clerking history or hospital medical records</i>	risk related to lifetime familiarity
Diagnosis of asthma by a clinician prior to this admission	Yes/No	<i>clerking history or hospital medical records</i>	Exploratory: how common is unrecognised/underdiagnosed asthma in such events/de novo NFA as primary wheeze event
Level of asthma treatment at time of admission	None This will be drop down lists for medicine, dose, frequency (including prn for combination inhalers) * include adrenaline auto-injector.	<i>clerking history or hospital medical records</i>	Risk in relation to prior asthma status
Number of asthma admissions to hospital in preceding 12 months	Number (1-25)	<i>clerking history or hospital medical records</i>	Red flag risk factor

Number of courses of oral glucocorticoids for asthma in preceding 12 months	Number (1-25)	<i>clerking history or hospital medical records</i>	Red flag risk factor
Asthma care by hospital consultant in preceding 12 months	Yes/No/DK	<i>clerking history or hospital medical records</i>	
Any previous PICU admission requiring ventilatory support (mechanical/non-invasive)	Yes/No/DK	<i>clerking history or hospital medical records</i>	Red flag risk factor
Current food allergy	Yes/No/DK	<i>clerking history or hospital medical records</i>	Red flag risk factor
Current food allergy (Yes)	Which food? Multiple options + free text Peanut Tree nut Sesame Milk Other	<i>clerking history or hospital medical records</i>	Red flag risk factor
Current food allergy (Yes)	Adrenaline auto-injector (Yes/No)		
Exposure to smoking within the family home	Yes/No/DK		
Have mental health/psychological issues been identified in the child	Yes/No/DK		Red flag risk factor
Have mental health/psychological issues been identified in the parents	Yes/No/DK		Red flag risk factor

Asthma action plan available prior to NFA event?	Yes/No/DK		

Appendix 13: 12 Month Follow Up Questionnaire

Near Fatal Asthma in Children and Young People
Version 1.0
01 March 2022

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One Year Review

Item	Field options	Data location	Relevance to outputs
Is the child alive or dead	Choice of one: Alive Dead Don't know	<i>hospital medical records</i>	
Response 'dead' – Death related to asthma?	Yes/No/DK	<i>hospital medical records</i>	
Response 'dead' – Death related to asthma? Yes	Date of death		
Response 'dead'	End of questionnaire		
Is the child still under review by your hospital	Choice of one: Yes (if yes, continue below) No – discharged to GP No - due to paediatric patient care transfer No - due to transition to adult services Don't know		Risk reduction of future event
Is this child still considered to have a diagnosis of asthma	Choice of one: Yes No Don't know	<i>hospital medical records</i>	Confirmation that event was NFA
If 'diagnosis' 'no' – 'If the diagnosis of near fatal asthma attack triggering this surveillance is no longer	Free text	<i>hospital medical records</i>	Confirmation that event was NFA

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correct, please provide the diagnosis for that event			
In the 12 months since the NFA has the child had a further admission to hospital with asthma	Choice of one: Yes No Don't know	<i>hospital medical records</i>	Risk reduction of future event
In the 12 months since the NFA has the child had a further admission to hospital with asthma: Yes	How many admissions? Number (1-25)	<i>hospital medical records</i>	Risk reduction of future event
In the 12 months since the NFA has the child had a further admission to hospital with asthma: Yes	Have any of these required PICU/HDU Choice of one: Yes No Don't know	<i>hospital medical records</i>	Risk reduction of future event
What clinical services were offered to the child with NFA in the past 12 months	Tick all that apply General paediatric clinic General paediatrician with a respiratory interest clinic Asthma nurse specialist review Respiratory Physiology service Specialist Respiratory Paediatrician clinic Psychology Physiotherapy Social work Other: please state	<i>hospital medical records</i>	Risk reduction of future event

What clinical services were offered to the child with NFA in the past 12 months were attended (i.e. at least one appointment attended in this period)	Tick all that apply General paediatric clinic General paediatrician with a respiratory interest clinic Asthma nurse specialist review Respiratory Physiology service Specialist Respiratory Paediatrician clinic Psychology Physiotherapy Other: please state	<i>hospital medical records</i>	Risk reduction of future event
What clinical services attended by the child with NFA in the past 12 months have future follow up planned	Tick all that apply General paediatric clinic General paediatrician with a respiratory interest clinic Asthma nurse specialist review Respiratory Physiology service Specialist Respiratory Paediatrician clinic Psychology Physiotherapy Other: please state	<i>hospital medical records</i>	Risk reduction of future event
In the 12 months since the NFA has the child had spirometry measured	Choice of one: Yes No Don't know		Risk reduction of future event
In the 12 months since the NFA has the child had spirometry measured: Yes	Please provide lowest recorded FEV 1 at routine clinic appointment		Risk reduction of future event

	FEV1 X.XX Litres (YY % predicted) FVC X.XX Litres (YY % predicted) Height XXX .Xcm Weight YYY.Ykg		
Asthma treatment at a clinic review closest to 12 months since NFA attack	None This will be drop down lists for medicine, dose, frequency (including prn for combination inhalers) * include adrenaline auto-injector.	<i>clerking history or hospital medical records</i>	Risk in relation to prior asthma status

Appendix 14: 24 Month Follow Up Questionnaire

Near Fatal Asthma in Children and Young People
Version 1.0
01 March 2022

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Two year review

Item	Field options	Data location	Relevance to outputs
Is the child alive or dead	Choice of one: Alive Dead Don't know	<i>hospital medical records</i>	
Response 'dead' – Death related to asthma?	Yes/No/DK	<i>hospital medical records</i>	
Response 'dead' – Death related to asthma? Yes	Date of death		
Response 'dead'	End of questionnaire		
Is the child still under review by your hospital	Choice of one: Yes (if yes, continue below) No - discharged No - due to patient care transfer Don't know	<i>hospital medical records</i>	Risk reduction of future event
In the past 12 months has the child had a further admission to hospital with asthma	Choice of one: Yes No Don't know	<i>hospital medical records</i>	Risk reduction of future event
In the past 12 months has the child had a further admission to hospital with asthma: Yes	How many admissions? Number (1-25)	<i>hospital medical records</i>	Risk reduction of future event
In the past 12 months has the child had a further admission to hospital with asthma: Yes	Have any of these required PICU/HDU Choice of one: Yes	<i>hospital medical records</i>	Risk reduction of future event

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	No Don't know		
What clinical services were offered to the child with NFA in the past 12 months	Tick all that apply General paediatric clinic General paediatrician with a respiratory interest clinic Asthma nurse specialist review Respiratory Physiology service Specialist Respiratory Paediatrician clinic Psychology Physiotherapy Other: please state	<i>hospital medical records</i>	Risk reduction of future event

Appendix 15: BPSU Monthly Email

BPSU member,

Please return your BPSU orange reporting card for **December 2023** by clicking on the link **BPSU E-card** at the end of this email. If you are unable to please let the office know.

Emails from noreply@dundee.ac.uk are also from the BPSU but for the new platform. You must complete both reporting cards so if you have not done so already please respond.

To read more click the links within the notices at the top of the eReporting card.

Please open the card and enter the number of cases seen this month in the appropriate box(es) - if you have not seen any cases of any conditions on the card, tick **NOTHING TO REPORT**.

Please read the reporting instructions ([December 2023 reporting instructions](#)) and refer to the study protocols if necessary. If you wish to report a case please **NOTE** the patient's name(s), NHS number or other identification for easy reference when you are contacted by the investigator.

Best wishes,

BPSU team (email BPSU@rcpch.ac.uk)

You may open the survey in your web browser by clicking the link below:

[BPSU December 2023 Reporting Card](#)

If the link above does not work, try copying the link below into your web browser:

<https://redcap.slms.ucl.ac.uk/surveys/?s=fugYPIQGivHHWpGv>

This link is unique to you and should not be forwarded to others.

Notice

With your contribution to the British Paediatric Surveillance Unit (BPSU) 'reporting scheme' the BPSU continues to have a major impact on child health. The BPSU securely holds your email and hospital contact details. Once a case is reported to BPSU, your contact details are shared with the relevant study teams who will then send through a clinical questionnaire. Alongside the BPSU electronic reporting card, the BPSU sends out a quarterly e-newsletter and bi-annual evidence of contribution certificate to clinicians on its 'reporting scheme'. For further information, please contact the BPSU office (email BPSU@rcpch.ac.uk).

To view a copy of the BPSU's privacy notice please [click here](#)

This link is unique to you and should not be forwarded to others.

Appendix 16: BPSU Reporting Card BPSU reporting card



Orange E-Reporting Card

BPSU December 2023 Reporting Card

Please complete the E-card below to indicate whether or not you have seen cases for December 2023.

The reporting instructions for December 2023 are available to download by clicking [here](#)

Submitting cases seen earlier this year

As we are approaching the end of the year, if you have any unreported cases of any conditions the BPSU has conducted surveillance on this year please do highlight them to us in the free-text box at the end of the survey. Alternatively, please email us at bpsu@rcpch.ac.uk

BPSU is currently collecting data through two systems

The BPSU is collecting data through this current system and a new system which has studies on Near Fatal Asthma and Congenital and Hospitalised Neonatal Varicella. We require clinicians to provide a response to both systems. If you receive an email from noreply@dundee.ac.uk this is from the new BPSU data collection platform. No response does not mean that you have nothing to report. Please indicate this response on each card.

An FAQ page and walkthrough is available here. If you have any issues email bpsu@rcpch.ac.uk

E-card

Have you seen any cases in the month December 2023?

* must provide value

☐ Yes
☐ No

reset

Cases to report

Please specify in the appropriate box the number of cases seen:

To access the study/surveillance information page on our Web site, click on the condition name.

[1. Progressive Intellectual & Neurological Deterioration \(excluding Republic of Ireland\)](#)

[2. Near Fatal Asthma](#)

If you have a case of Near Fatal Asthma please report by logging into new data collection platform at this link or using the December reporting card email from noreply@dundee.ac.uk :

<https://hicservices.dundee.ac.uk/bpsu>

If you have any issues email the BPSU office.

[3. Congenital and Hospitalised Neonatal Varicella](#)

If you have a case of Congenital and Hospitalised Neonatal Varicella please report by logging into new data collection platform at this link or using the December reporting card email from noreply@dundee.ac.uk :

<https://hicservices.dundee.ac.uk/bpsu>

If you have any issues email the BPSU office.

Thank you for reporting a case

Please make a note of the case details for future reference.

Please keep a record of the report as an aide memoir. The study investigator/surveillance team will contact you shortly with a questionnaire/access to online data collection forms.

Change of details

Please inform us if you have retired or no longer have clinical work.

If you have moved, or would prefer emails to be sent to an alternative address, please include your new contact details here.

Expand

Notice

With your contribution to the British Paediatric Surveillance Unit (BPSU) 'reporting scheme' the BPSU continues to have a major impact on child health.

The BPSU Privacy Notice is available to view at <https://www.rcpch.ac.uk/bpsu-privacy-notice>

Submit

Save & Return Later

Appendix 17: Near Fatal Asthma in Children and Young People, Study Protocol

NFA surveillance study
Version 3.0, 20th September 2023
IRAS ID **310881**

Non-CTIMP Study Protocol

Near Fatal Asthma in Children and Young People

	The University of Edinburgh and/or Lothian Health Board ACCORD The Queen's Medical Research Institute 47 Little France Crescent Edinburgh EH16 4TJ
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Funder	Chief Scientists Office (Scotland)
Funding Reference Number	HIPS/20/21
Chief Investigator	Professor Steve Cunningham
Sponsor number	AC22026
REC Number	22/SS/0030
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Version Number and Date	2.0 23 rd September 2022



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LIST OF ABBREVIATIONS

ACCORD	Academic and Clinical Central Office for Research & Development - Joint office for The University of Edinburgh and Lothian Health Board
BPSU	British Paediatric Surveillance Unit
CI	Chief Investigator
CRF	Case Report Form
CYP	Children and Young People
ED	Emergency Department
GCP	Good Clinical Practice
HIC	Health Informatics Centre
ICH	International Conference on Harmonisation
NFA	Near Fatal Asthma
PCCS	Paediatric Critical Care Society
PERUKI	Paediatric Emergency Research United Kingdom and Ireland
PPI	Patient and Public Involvement
PI	Principal Investigator
PICU	Paediatric Intensive Care Unit
QA	Quality Assurance
REC	Research Ethics Committee
RDMP	Research Data Management Platform
SOP	Standard Operating Procedure

Changes to Protocol

Version 2.0

Section	Change
Protocol authors	Addition Deepa Varghese
2	REDCap will only operate in parallel in England, Wales, Northern Ireland and Republic of Ireland
4.1	REDCap will only operate in parallel in England, Wales, Northern Ireland and Republic of Ireland
4.1	The study team will use HIC platform messaging system to contact responding clinicians.
4.2.1	Additional opt –out of study by contacting study team.
5.1	Addition of contacting clinicians for 12 and 24 month follow up by HIC messaging system.
6.2	Study's NHS email will be used
6.2	A NHS Lothian computer will be used
6.2	The use of registered post will not be used for NHS Scotland data.
7.1.1	Notification of duplicates will be from HIC Dundee. Secure data transfer and use of laboratory numbers not required within HIC system for duplicate identification.
7.1.1	Age in days will be used by Northern Ireland
7.1.1	Ethnicity will only be available in summary form for analysis
7.1.1	Sex will only be available in summary form for analysis
7.1.1	Partial postcode will be used for patients reported for Northern Ireland
7.1.2	Anonymised data will be held on NHS Lothian computers
Appendix 1	Change in graphics, REDCap excluding Scotland

Version 3.0

Section	Change
7.1.1	Remove Dundee, replaced with organisation
7.1.2	Removal of University of Dundee
7.1.2	Removal of University of Dundee
7.1.3	Wording change to reflect location of data storage

1 INTRODUCTION

1.1 BACKGROUND

In the UK, 1 in 10-12 children and young people have asthma. The UK has higher rates of asthma deaths than any other country in Europe and North America(1), with UK deaths twice as high as the next EU country rate. Children who have had an asthma attack severe enough to need admission to intensive care are re-admitted to hospital sooner with their next asthma attack(2), have a higher rate of re-admission to intensive care(3) and are also at a high risk of death from asthma(4). In adolescents and adults, one in six people who have a severe Near Fatal Asthma attack will die within the next 10 years(5). Follow up appointments for children after a severe asthma attack is often provided by a confusing range of people(6), that can include doctors without the right level of specialist skills(7), even after an admission to intensive care(8). Children and adolescents (5 to 24 years of age) have an enhanced risk of severe asthma attacks and death because of evolving self-care roles and risk-taking behaviours across this age range(9).

Factors limiting progress to reduce severe asthma attacks and asthma deaths include: (i) lack of a common case definition for near fatal asthma attacks to enable the frequency of events to be identified, (ii) a better understanding of risk factors in these individuals, (iii) variations in care and its potential impact for both acute outcomes and future asthma health, and (iv) no agreed standard of care to apply.

Case definition: Status asthmaticus is used within Medical Subject Headings (MeSH) and ICD-11, but lacks definition. SIGN/BTS (2019) and Global Initiative for Asthma (GINA) (2020) provide a category of severe/life threatening asthma, however these have wide interpretation. In a scoping review (Pubmed, CINAHL, Embase, Web of science) we identified that severe asthma events have different terminologies and varied, often vague definitions. We resolved this with an international Delphi consensus of clinicians across specialties and ages (paediatric and adult healthcare providers). We determined an agreed name (Near Fatal Asthma, NFA) and case definition (see below). The frequency of such asthma events in UK children and young people has no published data, but interrogation of PICAnet (UK Paediatric Intensive Care Database) suggest c200-250 admissions per year (aged 5-16 years) have invasive or non-invasive ventilatory support. We consider that our NFA definition would incorporate some from this population (not all asthma in PICU is consistent with NFA), together with a smaller number who are not ventilated following initial intervention (3 of 11 cases of Delphi defined NFA interviewed in preceding work were managed outside a PICU setting).

Risk factors have been described for children experiencing severe asthma attacks(10). However, these descriptions are not within a defined population and have been sufficiently recent to incorporate more granular data available from a prospective survey with follow up, or for a number of environmental exposures, in particular pollution.

Higher levels of ambient air pollution (PM2.5) is associated with lower lung function(11). In children, acute increases in air pollution are associated with increased airway inflammation and reduced lung function(12, 13). Acute changes in ambient air pollution are associated with change in lung function in adults with asthma(14). Higher levels of pollution (PM10 and SO₂) are associated with more frequent asthma hospital admissions in children and are postulated to be associated with risk of lower respiratory tract infection(15). Chronic exposure to ambient air pollution has been (NO₂) has been associated with asthma mortality both in adult and children(16), with short term exposures to PM2.5 and NO₂ associated with an increase in asthma deaths(17). There is no data to understand the impact of ambient air pollution on episodes of near fatal asthma.

In those dying from asthma, there appear to be two groups, where the time from onset to death is sudden or slow. A sudden asthma death has been associated with neutrophilic dominance within the airway (eosinophilic for longer onset to death) and greater smooth muscle shortening which appears resistant to bronchodilator(18, 19). In children, sudden onset asthma death has been identified as high as 50%(20). In all age groups sudden onset represents approximately one third of asthma deaths and often has no or mild prior asthma. Slow onset asthma death represents two thirds and is often in those with known asthma and a history of exacerbations.

Asthma attacks have also been observed as sudden or slow onset. Sudden onset has been identified from 30 minutes to 6 hours (21-23). In those admitted to hospital with an asthma attack, sudden onset episodes represented 6% of events (3% in those aged 6-17 years), tended to present overnight (midnight to 0800) and were older (population age range 2-54 years), who need more frequent intensive care but a shorter overall hospital length of stay(24).

The role of anaphylaxis causing severe asthma attacks in children has been estimated at 4%, but may be as high as 18%(25).

There is wide variance in the emergency care of children presenting with acute asthma(26, 27). The variance of acute clinical care in CYP presenting with near fatal asthma is unknown.

We will be able to explore time of onset and relative resistance to therapy in relation to acute care interventions, environmental and subsequent risk. Phenotyping NFA may help develop specific interventions and reduce variance in care.

There is increasing concern of the role of excessive use of bronchodilator in those who experience severe asthma attacks, and overuse has been associated with death in asthma death reviews(28). Guidelines and practice advice documents now recommend the use of a single corticosteroid bronchodilator inhaler, particularly in those who have over-reliance on bronchodilator as a principal therapy (<https://ginasthma.org/gina-reports/>). This recommendation is not embedded for CYP given a lack of supporting evidence, however we will aim to consider in how many CYP with evidence of overuse of bronchodilator there is a transition to single combined inhaler management practice.

In preceding work (now completed), we also interviewed children and their parents who have experienced a near fatal asthma attack to understand factors from a patient perspective that may help reduce near fatal asthma attacks. Patients and parents vocalised significant variation in the subsequent provision, location and experience of those who provide care (something also noted by others(6)). We also therefore wish to understand the services CYP and their families are provided with and access in the year following a NFA attack, and the asthma related health outcomes of such children in the 24 months following a NFA attack.

1.2 RATIONALE FOR STUDY

Our aim is to describe the frequency, risks factors, clinical care and future asthma risk of children and young people (aged 5-15 years) experiencing a Delphi defined near fatal asthma attacks in the UK and ROI. A greater understanding of the frequency and risk factors associated with NFA could help support CYP, parents and clinicians to identify and modify risk, both independently and through a resulting clinical care pathway and also develop future research to improve effectiveness of interventions. We will explore both commonly identified clinical factors, but also for the first time describe in detail the variance in medical management (acute and intensive care) that could lead to future clinical trials and guideline development to standardise care. The study will also describe, through data-linkage, socio-demographic factors associated with NFA, to include pollution, pollen, weather, viral prevalence that could lead to better care for higher risk CYP.

To encourage more consistent, less fragmented care following a near fatal asthma attack, the study team will consider how care is provided subsequent to an NFA attack using BPSU surveillance at 12 and 24 month follow up.

STUDY OBJECTIVES

1.3 OBJECTIVES

1.3.1 Primary Objective

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To describe the frequency of Near Fatal Asthma attacks each year in children and young people (aged 5-15 years inclusive).

1.3.2 Secondary Objectives

To describe the clinical, social and environmental characteristics of those who experience NFA.

To describe the care provided to CYP who experience NFA at the time of the event, during emergency, in patient and critical care.

To describe changes in therapeutic approach by clinicians to CYP who experience NFA.

To describe for the 24 months following an episode of NFA, the future risk of a health-related asthma event and the healthcare that is provided to those experiencing NFA.

1.4 ENDPOINTS

1.4.1 Primary Endpoint

The annualised frequency of near fatal asthma attacks in children and young people aged 5-15 years in the UK and ROI.

1.4.2 Secondary Endpoints

- (1) Epidemiology
 - a. The clinical characteristics of CYP experiencing NFA (i.e. ethnicity, past asthma history, current medication, initial vital signs/physiological measures)
 - b. The environmental exposures of CYP at the time of experiencing NFA (environmental pollution, pollen, viral, weather)
 - c. The sociodemographic status of CYP affected by NFA
- (2) Acute Treatment
 - a. Pre-hospital recognition and treatment
 - b. Initial assessment and treatment on arrival in ED or a PAU
 - c. The care (support/treatment) provided to children with NFA in paediatric critical care
- (3) Subsequent Care
 - a. Changes in asthma treatment following NFA
 - b. The frequency of follow up in a hospital clinic in the 12 months following a NFA attack (to include attendance and non-attendance rates)
 - c. The level of specialist training of the clinicians who provide follow up care in a hospital clinic in the 12 months following a NFA attack
 - d. To describe what clinical services are offered to and attended by children and their families following a NFA attack
- (4) Longer term risk
 - a. The frequency of subsequent acute asthma related hospital attendances in the 24 months following a NFA attack
 - b. The frequency of asthma death in children within this cohort in the 24 months of the survey (when compared with 10-year average)?

2 STUDY DESIGN

An observational surveillance study. The study will perform surveillance across the UK and ROI using the platform and methodology of the British Paediatric Surveillance Unit (BPSU, <https://www.rcpch.ac.uk/work-we-do/bpsu>).

- BPSU provides surveillance by monthly email contact with clinically active paediatric doctors across the UK and ROI. Doctors respond to the monthly email if they have seen a case consistent with the case definition. Research teams then contact the doctor to request that they complete structured questionnaires to an online database (BPSU survey tool hosted by Health Informatics Centre, University of Dundee).
- Paediatric Emergency Medicine and some Paediatric Intensive Care doctors do not have sufficient engagement with BPSU surveys and so we will run a parallel notification system (Redcap, University of Bristol, Mark Lyttle) for reporting clinicians in England, Wales, Northern Ireland and Republic of Ireland. Study information within Paediatric ED and Paediatric ICU will contain a QR code, that when accessed will direct clinicians to (1) enter minimal data of the case (hospital, clinician name, clinician email, date of event), (2) the BPSU notification system. The research team will follow up RedCap submissions by contacting clinicians to support their BPSU HIC access for data submission.
- The NFA surveillance will be open for 18 months for active registration of cases. Each case will be followed up for 24 months.
- In the surveillance study, there will be contact with the submitting doctor to request information at baseline, and subsequently at two further time points (12 and 24 months after the date of the Near Fatal Asthma event). If a doctor does not submit a return, then a reminder is sent on two occasions.
- Schematic diagram of the study design (Appendix)

Patient and public involvement (PPI)

There has been PPI within this study from the Asthma UK Centre for Applied Research (AUKCAR), where the original concept for these studies came from discussions with the PPI team. AUKCAR PPI have reviewed and provided useful feedback for patient facing documents. AUKCAR PPI members have also provided a letter providing support to the proposed methodologies, including the use of personal data analysis via safe haven. There will be ongoing integration with AUKCAR PPI to add to the interpretation and distribution of results. Asthma UK (AUK), as the lead UK patient organisation for people with asthma have also provided a letter of support for this study and its proposed methodology.

3 STUDY POPULATION

3.1 NUMBER OF PARTICIPANTS

- The number of children and young people identified who experience NFA within the 18-month surveillance period is not known, but is estimated to be c400 (from paediatric intensive care admission data). All UK and ROI hospitals where children may attend with acute asthma could be potential contributing sites. Each case will be followed up for 24 months following the near fatal asthma event.

3.2 INCLUSION CRITERIA

A child/young person is considered to have experienced an episode of near fatal asthma if they meeting any one of the following:

- (1) Any child aged 5-15 years surviving* an acute episode of asthma, who when presenting self-ventilating with severe dyspnoea (e.g. inability to speak) and all the following features:
 - a. Pulse oxygen saturation below 92% despite maximal oxygen therapy (i.e. 10-15l/min oxygen flow via non-rebreather mask) during acute presentation
 - b. pH $\leq$ 7.2 and/or pCO₂ $\geq$ 60mmHg or 8kPa
 - c. Escalation to use of intravenous bronchodilator infusion
- (2) Any child aged 5-15 years surviving* an acute episode of asthma, who had a respiratory arrest and/or required cardiopulmonary resuscitation as part of their presentation.
- (3) Any child age 5-15 years surviving* an acute episode of asthma for which he/she was invasively ventilated.

*surviving to hospital discharge.

3.3 EXCLUSION CRITERIA

CYP not meeting the case definition will be excluded. An expert panel (consisting of three clinicians) will adjudicate borderline cases.

3.4 CO-ENROLMENT

There will be no restriction on co-enrolment for participants in this study.

4 PARTICIPANT SELECTION AND ENROLMENT

4.1 IDENTIFYING PARTICIPANTS

BPSU Anonymised notifications are provided to the BPSU office predominantly by members of the Royal College of Paediatrics and Child Health (RCPCH) using the BPSU 'Orange Card' which is sent out to all BPSU respondents every month via email. This card has a list of disorders currently being studied and the clinicians ticks a box if they have seen a case or ticks 'nothing to report' if not. This is called 'active surveillance' as the email is sent out on a monthly basis and a response is expected. BPSU/HIC Dundee receives the notification automatically sends the respondent details of how to register/login to the HIC Dundee secure database and in parallel informs the study team that a case has been reported. The contact details of the notifying clinician are available to the study team within the HIC Dundee database. We will also enable paediatric ED doctors in England, Wales, Northern Ireland and Republic of Ireland to notify cases via a PERUKI Redcap process which ED clinicians access via a QR code on study materials within their department. These notifications are sent to the BPSU/HIC system in the same way that a BPSU email would. The study team will use a messaging system within the HIC questionnaire platform to contact responding clinicians and follow up at 12 and 24 months.

4.2 CONSENTING PARTICIPANTS

BPSU methodology does not require consent. The BPSU reporting methodology has received Confidential Advisory Group approval to allow its facilitated studies to collect unconsented

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patient information. It was accepted that to do so would reduce and bias case ascertainment, i.e. certain groups or types of individual might be more likely to refuse consent. In a study of a rare disorder, such as near fatal asthma, in which the number of cases is small, refusal to contribute data by one or two individuals will result in under-ascertainment of cases and incorrect conclusions on frequency and associations. If all the refusals occurred in a single region or were from children who had a less severe disorder, then this would 'bias' the results. To avoid bias, a BPSU surveillance study is undertaken without seeking individual consent and uses limited identifiable data via Safe Haven to protect confidentiality.

4.2.1 Withdrawal of Study Participants

Information on how to opt-out is available on the BPSU website (including study-specific website) and public information leaflet. Opt-out can be done by directly contacting their local clinician or the study team (contact information on website and public information leaflet).

5 STUDY ASSESSMENTS

5.1 STUDY ASSESSMENTS

BPSU active surveillance is performed each month by email to paediatricians across the UK and ROI. We will also promote the surveillance each month to Emergency Medicine clinicians and Intensive Care clinicians who care for CYP with acute asthma through the relevant organisations (PERUKI via Dr Mark Lyttle, Consultant Paediatric Emergency Medicine and PCCS Network, via Dr Peter Davis, Consultant Paediatric Intensive Care,) who will also receive active surveillance messages to contribute cases through the same BPSU/HIC Dundee database.

When BPSU/HIC receive notification of a case by a clinician, the clinician is provided with information on the study and login details for the BPSU/HIC database. The research team are notified that a case has been notified and can access clinician details via the BPSU/HIC database. Once logged into the BPSU/HIC database the clinician can directly complete the baseline questionnaire. The clinician is then contacted again at 12 and 24 months to complete follow up questionnaires via HIC messaging system. Lack of response to a questionnaire request will have two reminders at each time point.

The 24 month questionnaire is the end of the study.

Each clinician has a unique user name and password, and each study participant will be given a unique study number by the BPSU HIC database.

Assessment	Notification of a case	Baseline Questionnaire	12 month Questionnaire	24 month Questionnaire
Part 1				
BPSU/HIC Notification	☒			
BPSU/HIC notify research team	☒			
Clinician contact by BPSU (HIC)		☒	☒	☒

5.2 LONG TERM FOLLOW UP ASSESSMENTS

The protocol should describe the long term follow up period including the frequency of follow up visits, duration of follow up period and any assessments that will be carried out.

There will be a 12 and 24 month online questionnaire follow up by clinicians notifying cases. There are no other longer term follow up assessments.

5.3 STORAGE AND ANALYSIS OF SAMPLES

This study does not collect, store or analyse biological samples.

6 DATA COLLECTION

The study time points (baseline, 12 and 24 months) are described in section 6.1

Data input will be made by clinicians who provide care for CYP with asthma.

The data collection questionnaires are standardised and are provided as appendices.

Members of the study team will contact clinicians who fail to complete data time point questionnaires, providing two reminders at each time point.

6.1 Source Data Documentation

The source documents will be data entry to the BPSU survey tool hosted by the Health Informatics Centre at the University of Dundee (<https://www.dundee.ac.uk/hic>).

6.2 Case Report Forms

We will utilise a BPSU survey tool hosted by the Health Informatics Centre at the University of Dundee (<https://www.dundee.ac.uk/hic>). Clinicians receive a monthly email from the BPSU listing the current surveillance study conditions. If a clinician has observed a case of NFA they click within the email to identify to BPSU/HIC that they have observed a case. BPSU/HIC then send an email with details of how to access the baseline questionnaire, including registration (username and password) for the BPSU/HIC database if this is first access. Emails will ask notifying clinicians to login to the BPSU/HIC database to fill case report forms (questionnaires) at baseline, 12 and 24 month follow up.

In the very unlikely event if clinicians are unable to use the online system, questionnaires will be sent out in an electronic document format to the reporting clinicians via the study's secure nhs email account which is ISO 9001 Standards certified. As a very last resort, a paper questionnaire form will be sent. It will be marked confidential and double enveloped for data collection with self-addressed envelope to be returned to the chief investigator's office in the University of Edinburgh. This will be sent by registered mail. In the unlikely event of email or paper questionnaires being completed, the study team will immediately transcribe the information onto the UoD - HIC data platform from a UoE computer (ISO 27001 certified with standard UoE theme, secure remote access and automatic upgrade of firewall and antivirus software) on behalf of the reporting clinicians and the questionnaires destroyed thereafter. Questionnaires sent electronically or paper will contain hospital number (to assess duplication of cases) and ethnicity, but date of birth only by month and year, and only partial postcode so that researchers have limited access to personal identifiable information. The use of registered post will not be used for NHS Scotland data.

7 DATA MANAGEMENT

7.1.1 Personal Data

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The following personal data will be collected as part of the research:

Personal data will be directly submitted online and stored within the HIC organisation which is ISO 27001 certified secure environment in compliance with Data Protection legislation. Identifiable data is received by HIC in encrypted form and is stored and processed in secure areas on the NHS network, accessible only to HIC technical staff.

Personal data will be stored for a maximum 3 years after the end of the study.

Data collection cannot be completely anonymous as it would not be possible to determine if two clinicians, or two sources, had reported the same child. Minimal identifiers are required to match duplicate cases reported to the study. A hospital reference number is required for the study investigator to refer to if they have a query for the notifying paediatrician. Date of birth is required to calculate age at time of NFA event.

We will request that the following personal information is submitted to the online questionnaires. This information will be available to contributing clinicians within the BPSU HIC database and accessed by their login. Approved and trained HIC technical staff will run anonymising codes against identifying data prior to release, this process could give HIC staff potential access to identifiable data as part of Safe Haven operations, but they would have no need to. Personal data will be visible to/accessed by the research team as set out below.

CHI/NHS/ROI Hospital number.

This data will be held securely within the BPSU HIC database. It will be visible to contributing clinicians when logging into the BPSU HIC database. This data will be utilised to determine duplicate submissions in two ways (a) The BPSU HIC database will perform searches to identify potential duplicate case submission, once confirmed as duplicate, case data can be amalgamated within the BPSU HIC database, (b) The research team will be notified of the potential duplicate case submission by HIC Dundee and can liaise with the relevant submitting clinicians to confirm or refute a duplicate case.

Date of birth:

This data will be held securely within the BPSU HIC database. It will be visible to contributing clinicians only and to them when logging into the BPSU HIC database. This data will be utilised to determine duplicate submissions. This will allow us to determine age at the time of NFA event (which will be summarised as years and months of age or decimal age to one decimal point). Age in days will be collected for Northern Ireland.

Ethnicity:

This data will be held securely within the BPSU HIC database. It will be visible to contributing clinicians only and to them when logging into the BPSU HIC database. Ethnicity will be a characteristic available within the safe haven for analysis in relation to other risk factors, i.e. deprivation or pollution exposure. Ethnicity will only be reported in summary form (no less than five rule).

Sex: This data will be held securely within the BPSU HIC database. It will be visible to contributing clinicians only and to them when logging into the BPSU HIC database. Sex will be a characteristic available within the safe haven for analysis in relation to other risk factors, i.e. deprivation or pollution exposure. Sex will only be reported in summary form (no less than five rule).

Full post code:

This data will be held securely within the BPSU HIC database. It will be visible to contributing clinicians only and to them when logging into the BPSU HIC database. Full post code will allow us to determine both sociodemographic status and external pollution exposure (at 1km x 1km level), and within London and Glasgow a more detailed (100mx100m) determination of pollution exposure. Data linkage for these outcomes will be made within the HIC Safe Haven. Post code district (i.e. EH52) will be made available to researchers for summarising location of cases, analysing events by weather and pollen exposure, and virus prevalence in the community. Cases reported for Northern Ireland will only record partial postcode.

7.1.2 Data Information Flow

The study will use the Research Data Management Platform within HIC,. The system allows researcher access to data with anonymisation, security and audit.

The study design with data flow is in Figure 1. Use of personal data is in Table 1 below.

Pseudo-anonymised data held by HIC will be destroyed following publication at the end of the project.

Patient study number and hospital number will be held on password protected encrypted NHS Lothian network drive and will be destroyed following publication at the end of the project.

Anonymised data held by the study team will continue to be held on password secured NHS Lothian computers

Table 1. Personal identifiers and stages of identification/deidentification

Personal Identifiers	Local clinician via encrypted HIC database	HIC database stored encrypted	Researcher use via encrypted HIC safe haven access	Researchers on NHS Lothian network computers for analysis	Publication/public domain
Hospital number	Identifiable	Identifiable	Identifiable	Identifiable	Not identifiable
Date of birth	Identifiable	Identifiable	Identifiable	As age to one decimal point	Summary to group no less than five
Ethnicity	Identifiable	Identifiable	Identifiable	Identifiable	Summary to group no less than five
Sex	Identifiable	Identifiable	Identifiable	Identifiable	Summary to group no less than five
Full postcode	Identifiable	Identifiable	Identifiable	Summary to group no less than five	Summary to group no less than five
District postcode	Identifiable	Identifiable	Identifiable	Identifiable	Summary to group no less than five

7.1.3 Transfer of Data

Data for the study will be directly submitted online, hosted and managed by the Health Information Centre (HIC) affiliated with the University of Dundee. Services provided by HIC Dundee are delivered within an ISO 27001 certified secure environment and in compliance with Data Protection legislation. Identifiable data is received by HIC in encrypted form and is stored and processed in secure areas on the NHS network, accessible only to HIC technical staff. The research team will access the data via the HIC Safe Haven (<https://www.dundee.ac.uk/hic/hicsafehaven/>). Researchers accessing the HIC Safe Haven will complete the MRC e course 'Research Data and Confidentiality' and comply with HIC Dundee standard operating procedures (<https://www.dundee.ac.uk/hic/datasecurityconfidentiality/standardoperatingprocedures/#!/faq-0>).

Clinicians who notify a case of NFA, will (at first notification) be asked to register with a user name and password. This password protected secure area will contain the relevant questionnaires for their case. Details of all cases they have submitted will be available for them to see, including identifiers. Identifiers will not be visible to any other users, including the BPSU/HIC team, nor the study team.

The study CI and delegated members of the research team will be able to access data for cases submitted. Hospital number will be visible to the research team as set out in 7.1.1, other identifiers (date of birth, postcode) will not be visible or accessible to research team members. Aggregate case data will be downloadable by the study team for storage on password protected NHS Lothian or University of Edinburgh computers.

7.1.4 Data Controller

The University of Edinburgh and NHS Lothian are joint data controllers along with any other entities involved in delivering the study that may be a data controller in accordance with applicable laws (e.g. the site)

7.1.5 Data Breaches

Any data breaches will be reported to the University of Edinburgh and NHS Lothian Data Protection Officers who will onward report to the relevant authority according to the appropriate timelines if required.

The HIC, University of Dundee SOP for handling data breaches is subject to an HIC Security policy SOP (<https://www.dundee.ac.uk/hic/datasecurityconfidentiality/standardoperatingprocedures/#!/faq-0>)

8 STATISTICS AND DATA ANALYSIS

8.1 SAMPLE SIZE CALCULATION

Not applicable.

The frequency of such asthma events in UK children and young people has no published data, but interrogation of PICAnet (UK Paediatric Intensive Care Database) suggest c200-250 admissions per year (aged 5-16 years) have invasive or non-invasive ventilatory support. We consider that our NFA definition would incorporate some from this population (not all asthma in PICU is consistent with NFA), together with a smaller number who are not ventilated following initial intervention (3 of 11 cases of Delphi defined NFA interviewed in preceding work were managed outside a PICU setting). Over 18 months we estimate a maximum 300-375 cases in the UK and on a population basis an additional 50 cases from the Republic of Ireland. We estimate the maximum UK sample size will be 375, making a total 425 when including Republic of Ireland cases over the 18 month surveillance period.

8.2 PROPOSED ANALYSES

Descriptive data will be provided (mean, median, standard deviation, interquartile range, minimum, maximum as appropriate). We will describe NFA events and by exploration of the data whether any groups appear separate and their characteristics (i.e. fast/slow onset NFA).

There will be no imputation of missing data. We will work to resolve spurious data with local clinicians, but remove this data from summary statistics if unresolved.

The trial is observation of a convenience sample and there will be no intention to treat analysis.

Pre-defined sub-group analyses:

Any summary data to be made available in a public arena will be limited to a minimum of five within a description (i.e. rather than one case in Edinburgh, two in Glasgow, one in Livingston and one in Wishaw, we would report five cases were observed in the central belt of Scotland).

We will explore associations (as in Endpoints) between disease onset, severity and response to treatment in relation to prior asthma and health status (i.e. prior allergy).

Data Linkage

We will investigate whether we are able to utilise date of event and full postcode (held in a pseudo-anonymised database) for data linkage to

(a) **Indices of deprivation** (by UK nation). We will utilise country level measures of deprivation searched by postcode and also date of NFA event (or most recent available data for that postcode). The following sources will be accessed:

England: English Indices of Deprivation (<https://www.gov.uk/government/statistics/english-indices-of-deprivation-2015>)

Scotland: Scottish Index of Multiple Deprivation (<https://www.gov.scot/collections/scottish-index-of-multiple-deprivation-2020/>)

Wales: Welsh Index of Multiple Deprivation (<https://gov.wales/welsh-index-multiple-deprivation?lang=en>)

Northern Ireland: Northern Ireland Multiple Deprivation Measure (<https://www.nisra.gov.uk/statistics/deprivation/northern-ireland-multiple-deprivation-measure-2017-nimdm2017>)

ROI: <https://maps.pobal.ie/WebApps/DeprivationIndices/index.html>

(b) **pollen counts** (Met Office Library and Archive team under an Open Government License (OGL) <https://www.metoffice.gov.uk/binaries/content/assets/metofficegovuk/pdf/data/pollen-count-datasheet.pdf>),

ROI: <https://www.met.ie/forecasts/pollen>

(c) **respiratory virus community positivity** (linking to weekly Respiratory DataMart viral surveillance output),

We will use publicly available data to investigate the inter-relationship of NFA attacks and population viral test positivity for common respiratory viruses (to include Influenza A, Influenza B, Respiratory Syncytial Virus, Rhinovirus, Parainfluenza, Adenovirus). Weekly data reports are available. We will analyse by date of NFA attack and virus positivity on that date in that country.

The following sources will be accessed:

England and Wales: Public Health England (PHE) and NHS laboratories voluntary surveillance database (Second Generation Surveillance System, SGSS) (<https://www.gov.uk/government/publications/respiratory-virus-circulation-england-and-wales>).

Scotland: Public Health Scotland (PHS). Produces corresponding data for Scotland (<https://publichealthscotland.scot/publications/weekly-national-seasonal-respiratory-report/weekly-national-seasonal-respiratory-report-week-41-2021/>)

Northern Ireland: A surveillance and reporting system for Influenza (A and B) is available (<https://www.publichealth.hscni.net/sites/default/files/2021-10/Flu%20Bulletin%20Week40-41.pdf>), but not other respiratory viruses.

Republic of Ireland: A surveillance and reporting system for Influenza (A and B) is available from October to May each year (<https://www.hpsc.ie/a-z/respiratory/influenza/seasonalinfluenza/surveillance/influenzasurveillance-reports/>), but not other respiratory viruses.

For NI and ROI, we will investigate the potential to align surveillance for Influenza positivity across the four sources, and infer relative positivity for other respiratory viruses for each period.

(d) **Ambient Air Pollution** (link with Edinburgh University, School of Geosciences, Dr Tom Clemens).

We will use two sources of data, both provided by the Department for Environment, Food and Rural Affairs (DEFRA) and both available on an open access basis. The first is the Automatic Urban and Rural Network (AURN). This consists of approximately 171 spatially dispersed static monitors located across the UK which collect hourly measurements of 8 key pollutants including particulates (sizes 10 and 2.5 micrograms), Nitrogen Dioxide (NO₂) and Sulphur Dioxide (SO₂). This data are made available in near real-time (<https://uk-air.defra.gov.uk/networks/find-sites?view=region>) and provide temporal detail for assessing exposure. The second are published concentration maps (<https://uk-air.defra.gov.uk/data/pcm-data>) that have been derived from atmospheric chemistry transport models and are mapped to a 1x1 km regular grid across the UK for the period 2001-2020. This data consist of annual average concentrations for the same 8 pollutants in each of the 1x1 km grid squares across the UK. This data complements the temporal data by providing detailed spatial information for exposure assessment and have been widely used for studying the health effects of long-term exposure to air pollution in the UK(29, 30). Air quality data is also available in the ROI (<https://airquality.ie/>) and we will explore integration of this into the dataset.

As there are no controls to this study, we will use WHO recommended safe levels for 24 hours and annual levels (page 4,

<https://apps.who.int/iris/bitstream/handle/10665/345334/9789240034433-eng.pdf>.)

To observe whether a temporal change in pollution or variability of pollution exposure is associated with greater instability of asthma control resulting in NFA attacks, we will combine spatial and temporal data to investigate this. This data is most complete for the UK but we will also explore whether this data can provide similar granularity within the ROI.

We will also explore whether exposure data in younger children with acute wheeze/asthma from the PICNIC trial(15) provides comparator data.

Triangulation

PICU: We will triangulate the number of admissions to intensive care within our cohort with a time matched interrogation of PICANet (<https://www.picanet.org.uk>), the UK and Ireland Paediatric Intensive Care database network.

Dr Peter Davis provides a direct link to this resource to enable triangulation of admissions to intensive care with a diagnosis of asthma. We will place a request to PICANet for data to triangulate the number of children aged 5-15 years who were admitted to PICU and the frequency of mechanical invasive ventilation, CPAP, high flow oxygen therapy and no respiratory support over the duration of the BPSU survey.

Death from Asthma: During BPSU follow up of CYP experiencing NFA we will identify those who have died from a subsequent asthma attack. To place these deaths in context of all deaths from asthma in CYP during this period we will access registries of deaths. From National Child Mortality Databases, we will assess the number of deaths of children experiencing NFA during the follow up period and compare this to the 10-year average mortality rate for children with asthma. To understand missing child deaths, to we will use information on child age (in years), sex and location to make a match with triangulated sources, but no further details will be matched.

The following sources will be accessed:

England: National Child Mortality Databases (National Child Mortality Database for England): (<https://www.ncmd.info/data/>)

Scotland: National Records of Scotland (<https://www.nrscotland.gov.uk/statistics-and-data/statistics/statistics-by-theme/vital-events/deaths>)

Wales: Office for National Statistics for England and Wales (<https://www.ons.gov.uk/peoplepopulationandcommunity/birthsdeathsandmarriages/deaths/methodologies/mortalitystatisticsinenglandandwalesqmi>), and also the registry of deaths (and cause) kept by the Welsh Child Death Reviews (Rosalind Reilly, Public Health Wales).

Northern Ireland: Northern Ireland Statistics and Research Agency (<https://www.nisra.gov.uk>).

Republic of Ireland: National Paediatric Mortality Register (<https://www.noca.ie/audits/national-paediatric-mortality-register>)

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9 ADVERSE EVENTS

Not applicable

10 OVERSIGHT ARRANGEMENTS

10.1 INSPECTION OF RECORDS

Investigators and institutions involved in the study will permit trial related monitoring and audits on behalf of the sponsor, REC review, and regulatory inspection(s). In the event of audit or monitoring, the Investigator agrees to allow the representatives of the sponsor direct access to all study records and source documentation. In the event of regulatory inspection, the Investigator agrees to allow inspectors direct access to all study records and source documentation.

10.2 STUDY MONITORING AND AUDIT

The ACCORD Sponsor Representative will assess the study to determine if an independent risk assessment is required. If required, the independent risk assessment will be carried out by the ACCORD Quality Assurance Group to determine if an audit should be performed before/during/after the study and, if so, at what frequency.

Risk assessment, if required, will determine if audit by the ACCORD QA group is required. Should audit be required, details will be captured in an audit plan. Audit of Investigator sites, study management activities and study collaborative units, facilities and 3rd parties may be performed.

11 GOOD CLINICAL PRACTICE

11.1 ETHICAL CONDUCT

The study will be conducted in accordance with the principles of the International Conference on Harmonisation Tripartite Guideline for Good Clinical Practice (ICH GCP).

Before the study can commence, all required approvals will be obtained and any conditions of approvals will be met.

11.2 INVESTIGATOR RESPONSIBILITIES

The Investigator is responsible for the overall conduct of the study at the site and compliance with the protocol and any protocol amendments. In accordance with the principles of ICH GCP, the following areas listed in this section are also the responsibility of the Investigator. Responsibilities may be delegated to an appropriate member of study site staff.

11.2.1 Informed Consent

This study will not seek informed consent for the reasons set out in 4.2

11.2.2 Study Site Staff

The Investigator must be familiar with the protocol and the study requirements. It is the Investigator's responsibility to ensure that all staff assisting with the study are adequately informed about the protocol and their trial related duties.

11.2.3 Data Recording

The Principal Investigator is responsible for the quality of the data recorded in the CRF at each Investigator Site.

11.2.4 Investigator Documentation

- The Principal Investigator will ensure that the required documentation is available in local Investigator Site files ISFs.

11.2.5 GCP Training

For non-CTIMP (i.e. non-drug) studies all researchers are encouraged to undertake GCP training in order to understand the principles of GCP. However, this is not a mandatory requirement unless deemed so by the sponsor. GCP training status for all investigators should be indicated in their respective CVs.

11.2.6 Confidentiality

All laboratory specimens, evaluation forms, reports, and other records must be identified in a manner designed to maintain participant confidentiality. All records must be kept in a secure storage area with limited access. Clinical information will not be released without the written permission of the participant. The Investigator and study site staff involved with this study may not disclose or use for any purpose other than performance of the study, any data, record, or other unpublished information, which is confidential or identifiable, and has been disclosed to those individuals for the purpose of the study. Prior written agreement from the sponsor or its designee must be obtained for the disclosure of any said confidential information to other parties.

11.2.7 Data Protection

All Investigators and study site staff involved with this study must comply with the requirements of the appropriate data protection legislation (including the General Data Protection Regulation and Data Protection Act) with regard to the collection, storage, processing and disclosure of personal information.

Computers used to collate the data will have limited access measures via user names and passwords.

Published results will not contain any personal data and be of a form where individuals are not identified and re-identification is not likely to take place

STUDY CONDUCT RESPONSIBILITIES

11.3 PROTOCOL AMENDMENTS

Any changes in research activity, except those necessary to remove an apparent, immediate hazard to the participant in the case of an urgent safety measure, must be reviewed and approved by the Chief Investigator.

Amendments will be submitted to a sponsor representative for review and authorisation before being submitted in writing to the appropriate REC, and local R&D for approval prior to participants being enrolled into an amended protocol.

11.4 MANAGEMENT OF PROTOCOL NON COMPLIANCE

Prospective protocol deviations, i.e. protocol waivers, will not be approved by the sponsors and therefore will not be implemented, except where necessary to eliminate an immediate hazard to study participants. If this necessitates a subsequent protocol amendment, this should be submitted to the REC, and local R&D for review and approval if appropriate.

Protocol deviations will be recorded in a protocol deviation log and logs will be submitted to the sponsors every 3 months. Each protocol violation will be reported to the sponsor within 3 days of becoming aware of the violation. All protocol deviation logs and violation forms should be emailed to QA@accord.scot

Deviations and violations are non-compliance events discovered after the event has occurred. Deviation logs will be maintained for each site in multi-centre studies. An alternative frequency of deviation log submission to the sponsors may be agreed in writing with the sponsors.

11.5 SERIOUS BREACH REQUIREMENTS

A serious breach is a breach which is likely to effect to a significant degree:

- (a) the safety or physical or mental integrity of the participants of the trial; or
- (b) the scientific value of the trial.

If a potential serious breach is identified by the Chief investigator, Principal Investigator or delegates, the co-sponsors (seriousbreach@accord.scot) must be notified within 24 hours. It is the responsibility of the co-sponsors to assess the impact of the breach on the scientific value of the trial, to determine whether the incident constitutes a serious breach and report to research ethics committees as necessary.

11.6 STUDY RECORD 7.1.1

All study documentation will be kept for a minimum of 3 years from the protocol defined end of study point. When the minimum retention period has elapsed, study documentation will not be destroyed without permission from the sponsor.

11.7 END OF STUDY

The end of study is defined as the last participant's last visit.

The Investigators or the co-sponsor(s) have the right at any time to terminate the study for clinical or administrative reasons.

The end of the study will be reported to the REC, and R+D Office(s) and co-sponsors within 90 days, or 15 days if the study is terminated prematurely. The Investigators will inform participants of the premature study closure and ensure that the appropriate follow up is arranged for all participants involved. End of study notification will be reported to the co-sponsors via email to resgov@accord.scot

A summary report of the study will be provided to the REC within 1 year of the end of the study.

11.8 CONTINUATION OF TREATMENT FOLLOWING THE END OF STUDY

Detail if intervention will be continued to be provided following the end of the study. If not provide justification

11.9 INSURANCE AND INDEMNITY

The co-sponsors are responsible for ensuring proper provision has been made for insurance or indemnity to cover their liability and the liability of the Chief Investigator and staff.

The following arrangements are in place to fulfil the co-sponsors' responsibilities:

- The Protocol has been designed by the Chief Investigator and researchers employed by the University and collaborators. The University has insurance in place (which includes no-fault compensation) for negligent harm caused by poor protocol design by the Chief Investigator and researchers employed by the University.
- Sites participating in the study will be liable for clinical negligence and other negligent harm to individuals taking part in the study and covered by the duty of care owed to them by the sites concerned. The co-sponsors require individual sites participating in the study to arrange for their own insurance or indemnity in respect of these liabilities.
- Sites which are part of the United Kingdom's National Health Service will have the benefit of NHS Indemnity.
- Sites out with the United Kingdom will be responsible for arranging their own indemnity or insurance for their participation in the study, as well as for compliance with local law applicable to their participation in the study.

12 REPORTING, PUBLICATIONS AND NOTIFICATION OF RESULTS

12.1 AUTHORSHIP POLICY

Ownership of the data arising from this study resides with the study team.

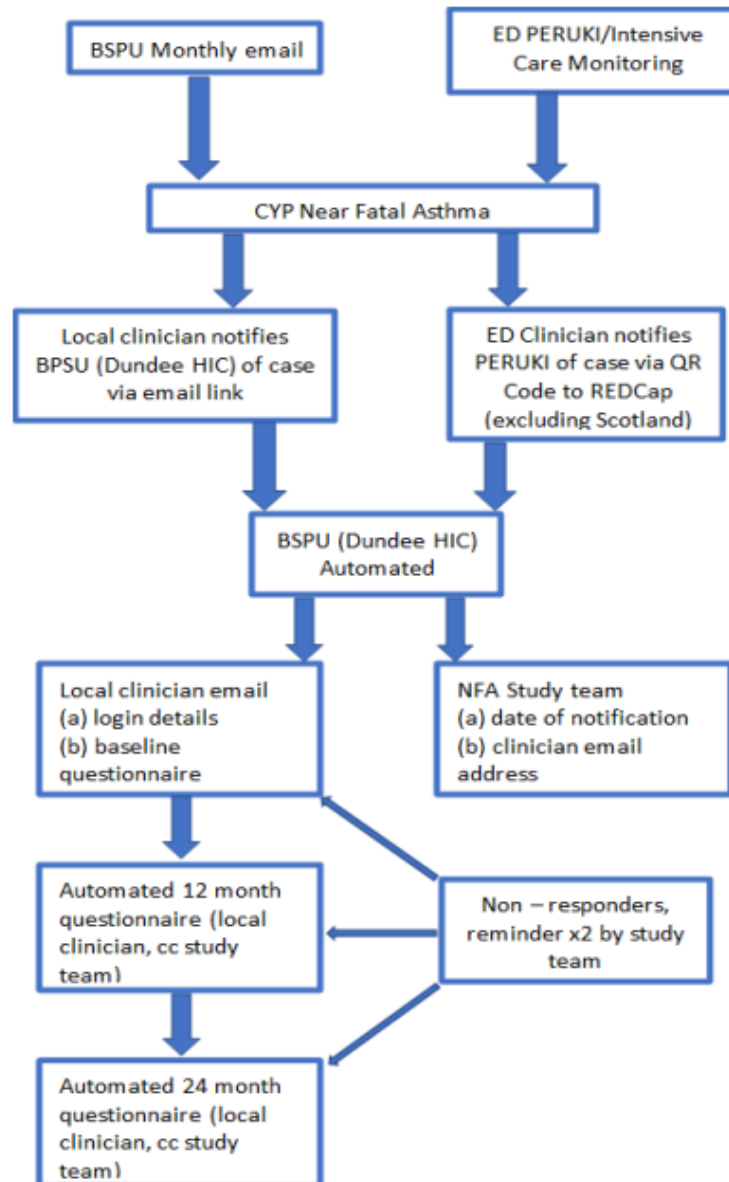
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Appendix 1 – Study Design



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