

Severe asthma:

the unmet need and the global challenge



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Foreword

It is easy to take for granted the simplicity and ease of breathing but for people with severe asthma the struggle for breath is something they contend with all too often, overshadowing much of their daily lives and often affecting their ability to carry out the simplest of tasks. Severe asthma is a specific type of asthma that does not respond to current readily available treatments, rather than simply an extreme form of the condition, and affects around 200,000-250,000 people in the UK. Despite high dose treatments the underlying asthma is difficult to control, leading to a greater burden of symptoms and attacks, often resulting in admission to hospital and even death. Attacks are terrifying and difficult to predict. They can be triggered by the simplest of activities, such as walking down the road. However, due to the failure of current treatments to control and mitigate the effects of cold weather, pollution or pollen, this is the reality for people living with severe asthma.

The fact that we do not know exactly how many people are living with this condition in the UK is symptomatic of our inability to treat them effectively. There has been little incentive to find out when there is little that we could do to treat them. We can and must do better than this.

The standard treatment option for people living with severe asthma is the corticosteroid tablet. Whilst

these are usually effective, they are extremely toxic when taken over the long term, which for many people is the pay-off; live better today and deal with the consequences tomorrow. Oral steroids can cause debilitating side effects such as mood swings, weight gain, osteoporosis and diabetes. Eventually, treating the side effects can become more expensive than treating the asthma symptoms. This perverse reliance on a treatment that is cheap and effective in the short term, but costly and often damaging on a personal and health system level, must end.

Our acceptance of this situation for many years has been largely due to our limited understanding of the mechanisms driving asthma, which has meant that alternative treatment approaches have not been developed. Now, however, we are on the cusp of new discoveries that could bring us a step closer to a cure if we are strategic in our thinking and our efforts. This is because for years 'asthma' has been regarded as the same condition independent of severity and pattern of symptoms, but it is becoming increasingly clear from painstaking research (largely led by UK scientists) that 'asthma' is not one condition but many, and that there are several sub-types of severe asthma. Although research is still in its early days, it would be difficult to overstate how transformational a better understanding of these different types of asthma would be.

“The best example of precision medicine in my opinion does not come from cancer, it comes from asthma. For this condition we have gone more than 20 years without a new drug, because the disease was not defined very well.”

Professor Sir John Bell, Royal Society of Medicine's 2015 Darwin lecture.

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Asthma has been described by some experts as the best example of precision medicine. However, in practice we have only begun to scratch the surface. With further investment in new diagnostics and new treatments, we could see severe asthma leading a new era of personalised medicine in the NHS.

Although there is a healthy pipeline of innovative new treatments (including monoclonal antibodies) that have been shown to be effective in a specific sub-type of asthma (called eosinophilic asthma), this will only help the estimated 40% of people with that type of severe asthma. Even this assumes that all those who would benefit will be able to access the treatments, but the reality is that it takes years for these treatments to reach all those who need them. And even being optimistic, the remaining treatment gap will leave approximately 60% of people with severe asthma reliant on oral steroids. This is our challenge to address.

We urgently need research into the mechanisms that drive other forms of severe asthma so that new treatments can be developed. This requires pooling our efforts, reducing risk of failure through collaborations and driving global investment by pharmaceutical companies as well as public investment in research. It will require large trials in people with different types of asthma, recognising that the pool of people to recruit from gets smaller and

smaller within individual communities and countries as further sub-types are identified. And it will require international multi-sector, multi-disciplinary collaboration and significant financial investment as trials are increasingly expensive, a challenge that the international asthma community needs to rise to.

The UK, with its strong international track record in severe asthma research, is well placed to spearhead much of this work and use the assets at our disposal working with people with severe asthma to create new public-private partnerships. The UK has led the way in identifying and publishing the most important research priorities in asthma R&D¹ to guide focus and investment, which are now being adopted internationally. This includes understanding what causes and triggers different types of severe asthma, and creating new ways of identifying them. Our vision is that this focus on a small number of key areas, namely understanding what causes and triggers different types of severe asthma, and creating new ways of identifying them, will lead to a new generation of treatments for severe asthma – transforming the lives of people with severe asthma in the years to come.

Dr Samantha Walker

Director of Research and Policy and Deputy Chief Executive

Although there is a healthy pipeline of innovative new treatments (including monoclonal antibodies) that have been shown to be effective in a specific sub-type of asthma (called eosinophilic asthma), this will only help the estimated 40% of people with that type of severe asthma.

Executive summary

The impact of severe asthma and the need for new treatments

Severe asthma affects all age groups

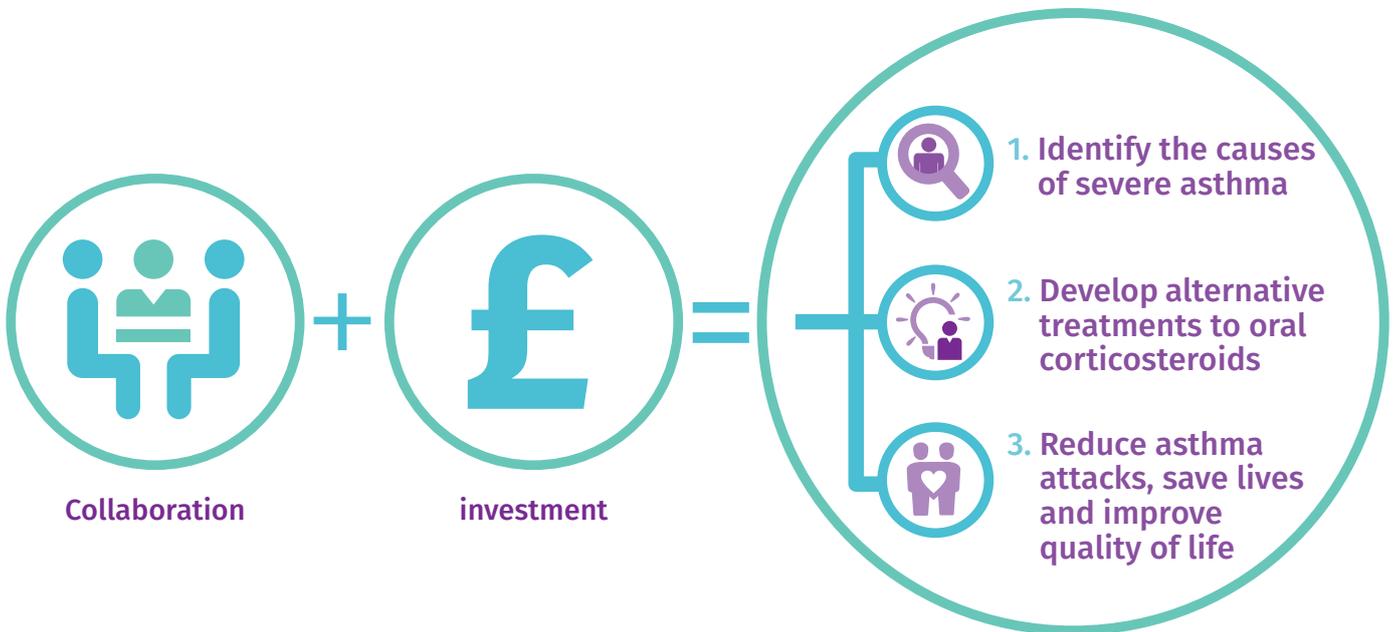
- It causes breathlessness, shortness of breath, disturbed sleep, cough and wheeze
- It's associated with frequent, unpredictable and devastating attacks
- Treatment relies on oral corticosteroids

Severe asthma has a devastating impact on approximately 200,000-250,000 people in the UK², of whom around 50,000 are on the highest level of treatment³. Severe asthma affects all age groups and is markedly different from mild or moderate asthma in terms of reduced quality of life and impact on healthcare costs. Severe asthma can destroy daily lives, severely limiting activities and causing long periods of time away from school and work, particularly during severe flare ups. Treatments are extremely limited and rely in the main on oral corticosteroids to control symptoms, which cause toxic and debilitating side effects, especially if taken for long periods. These treatments are loathed by patients and are a significant factor in low adherence rates.

Despite time and effort, treatment options for severe asthma have not developed at the pace and scale required to meet unmet treatment demand. However, thanks to careful and sustained research to try and understand the mechanisms that underpin it, it is increasingly clear that severe asthma is a complex condition that includes a range of different types or 'phenotypes' that may respond differently to different treatments. These discoveries have opened the door to the development of new and more effective treatments that could transform the lives of people with severe asthma. New treatments are urgently needed to enable people with severe asthma to be less reliant on oral corticosteroids or replace them completely.

“Asthma has stopped me from doing the things I love – I can no longer do my job, flying is not possible so travelling is restricted and I have never been able to play sport.”

Lehanne, 46



Identifying different types of severe asthma

Our scientific understanding of asthma is changing as it is researched more, with asthma being increasingly seen as having distinct phenotypes with different biological markers. Though there are significant challenges, severe asthma is ripe for the development of more targeted diagnostic tools and new targeted treatments to help address the treatment gap for people with the condition.

Efficient ways of pairing people up with the treatment that will be most effective for them are vital. Diagnostic tests that can stratify treatments according to someone's phenotype are the next logical step and are urgently required, so that the right treatment can be given to the right person without delay and thus avoid potentially fatal asthma attacks.

A step towards precision medicine in asthma

As our knowledge about the mechanisms involved in severe asthma has developed, companion diagnostic tests based on specific biological markers ('biomarkers') are becoming increasingly important in order to identify the type of asthma and tailor the treatment accordingly. There is a significant diagnostic gap in severe asthma, with no test able to accurately determine what type of severe asthma a person has.

The challenge is to identify biomarkers that are easy to collect and measure in primary care settings as that is where people will be initially treated and potentially monitored. Tests need to be easy to carry out and minimally invasive; this is a particular priority for children who may not cope with invasive tests that are physically draining or involve needles. Current tests such as induced sputum or even blood eosinophil counts do not meet this challenge.

The most established biomarker is eosinophil count. A number of new innovative treatments targeted at severe eosinophilic asthma are on the verge of becoming available to patients.

There are a number of other biomarkers identified and with further research the full potential for each of them can be established. All biomarkers need to be tested, validated and adopted in the development of diagnostic tests that will enable personalised medicine to become a reality in the treatment of severe asthma.

Focusing research

Whilst there is a good pipeline of effective treatments for severe eosinophilic asthma, the non-eosinophilic asthma pipeline is extremely limited and urgently needs focus and investment. In order to ensure that there is consistent progress towards comprehensive and effective treatment, focused funding calls for research into mechanisms, targets and treatments to address the unmet need will be required.

National and international collaboration across different academic disciplines that bring the best scientists together to learn from other disciplines and disease areas are needed. New partnerships would have the potential to build capability and capacity in severe asthma research, develop the UK's life sciences capability and international stature, identify a new generation of leading scientists and speed up discoveries that will transform the lives of people with severe asthma.

Leading the global challenge on severe asthma

There is a substantial treatment gap for people with severe asthma, but there are a number of promising research developments to be built on.

UK industry and researchers can lead the global challenge to develop accurate diagnostics and treatments for the global population of people with severe asthma.

In addition, a strategic approach to research needs to take place that builds on the developing biomarkers to place severe asthma at the centre of personalised medicine.

Without significant research investment, the substantial gaps in treatment will remain and new treatments will be decades away.

Recommendations

Challenge 1 Test and validate biomarkers that identify each different phenotype of severe asthma and how it changes over time.

Challenge 2 Develop simple, inexpensive, non-invasive tests that can accurately identify different types of severe asthma.

Challenge 3 Replace oral steroids with new, preferably inexpensive and non-invasive targeted treatments for severe asthma with better side effect profiles.

Challenge 4 Develop specific treatments for types of severe asthma that do not respond to existing treatments.

Challenge 5 Build understanding of the different phenotypes of severe asthma, the opportunities for new targeted treatments and companion diagnostics.

Challenge 6 Demonstrate the cost-benefit of new treatments as well as efficacy for regulators, payers

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and clinicians to ensure treatments are positively appraised in health technology assessments and reach the people who would benefit from them.

Challenge 7 Establish a comprehensive, sustainably resourced national registry of people with severe asthma (or build on an existing one) that will allow ongoing data collection to measure the long term impact of treatments.

Challenge 8 Funders to specifically call for cross-disciplinary research bids.

Challenge 9 To refine our understanding of asthma biomarkers and their clinical use, form international, public-private and cross-disciplinary research collaborations to identify, understand and

better classify the different forms of asthma, their progression, and effect on airway inflammation and the immune system.

Challenge 10 Make the commercial case for the pharmaceutical industry to work within large research collaborations, focusing on developing new treatments for non-eosinophilic asthma.

Challenge 11 Build on the European Asthma Research Innovation Partnership research priorities to develop novel treatments targeted at non-eosinophilic asthma.

Challenge 12 Develop national and international research funding calls based on new trial designs that allow different treatments to be tested and biomarkers to be refined in large populations.

Actions for researchers, funders and industry:

- Adopt the European Asthma Research & Innovation Partnership research priorities to inform their funding calls and funding to proposals that seek to address these priority areas.
- Establish new funding calls for international collaborations to develop adaptive trials researching into non-eosinophilic treatments.
- Explicitly state in funding calls that research proposals involving researchers from different countries and disciplines are encouraged.
- Explore international and cross-disciplinary collaborations focused on research to identify, understand and better classify the different forms of asthma, their progression, and effect on airway inflammation and the immune system in order to further refine our understanding of asthma biomarkers and their use in clinical practice.
- Target research to enhance understanding into potential non-eosinophilic asthma treatments in order to reduce the unmet treatment need through new treatment development.
- Design and deliver research to develop accurate tests to identify people who are steroid responsive vs non-steroid responsive.
- Using data from the UK registry, analyse and build a robust evidence base of the long-term impact of sustained oral corticosteroid use for people with severe asthma and the cost of treating the long-term side effects.
- Identify new trial designs that allow multiple treatment comparisons within the same trial that are acceptable to industry (considering commercial pressures and issues of

confidentiality in drug development) to inform the clinical trials of the future.

- Work in partnership to explore the repurposing of existing treatments and previously abandoned compounds through new trial designs.
- Work in partnership to develop companion diagnostics to enhance precision medicine.

Main actions for government and decision makers:

- Work with industry, researchers and funders to capitalise and build on the UK's world class respiratory research infrastructure.
- Work with healthcare organisations to build on the existing severe asthma registry infrastructure to make the UK an attractive trial location.

Main actions for healthcare organisations and clinicians:

- Agree a minimum dataset to be collected by all clinicians in all specialist centres and ensure the data collection is resourced appropriately and sustainably.
- Expand and sustain the pan-UK registry of people with severe asthma to ensure all people with severe asthma are included in the registry.
- Use the registry to enable everyone with severe asthma to participate in trials, creating an internationally attractive pool of trial participants.
- Streamline NHS systems and processes to allow recruitment of sufficient people with severe asthma into the large clinical trials required to test new treatments.

The impact of severe asthma

Severe asthma¹ has a devastating impact on approximately 200,000-250,000 people in the UK², of whom around 50,000 are on the highest level of treatment³. Despite recommendations for people to be referred to specialist care when on high dose treatment or continued oral corticosteroids⁴, many are not under specialist care. Severe asthma affects all age groups and is markedly different from mild or moderate asthma in terms of reduced quality of life and impact on healthcare costs. It is associated with daily symptoms of breathlessness, shortness of breath, disturbed sleep, cough and wheeze, compounded by frequent 'attacks' (sudden, unpredictable and often devastating worsening of symptoms)⁵. Severe asthma can destroy daily lives, severely limiting activities and causing long periods of time away from school and work, particularly during severe flare-ups. Treatments are extremely limited and rely in the main on oral corticosteroids to mitigate symptoms that cause toxic and debilitating side effects, especially if taken for long periods⁶.

In 2014, the National Review of Asthma Deaths reported on the circumstances surrounding and leading up to 195 asthma deaths between February 2012 and January 2013 (14% of 1374 asthma deaths reported in 2012⁸). Whilst severe asthma accounts for a small proportion of people with asthma, 39% of the people who died and were included in the review had severe asthma⁹.

People with severe asthma have more frequent severe attacks, which are not only life-threatening in the short term but also damaging in the medium term. People with severe asthma report that the impact of a severe attack can take weeks to get over¹⁰, and this extended recovery time is often overlooked and misunderstood by employers. Whilst hospital stays may be limited to two or three days, normal health levels are unlikely to be regained for weeks¹¹. Having more frequent severe attacks also impacts on people's employment and education and people with severe asthma are less likely to be in full-time employment, particularly those on oral corticosteroids. A study found that 26% of participants were not working due to their severe asthma, 73% of whom were on sustained oral corticosteroids¹².

People with severe asthma may also experience depression; however, the research evidence is mixed¹³. The impact of severe asthma is broad, affecting work and family life, and also people's quality of life. People experience discrimination at work, social isolation, financial difficulties and loss of independence¹⁴. For children, there are additional impacts including missed days of school, bullying and being excluded from activities because the schools are not set up to cope with their condition¹⁵.

Despite time and effort, treatment options for severe asthma have not developed at the pace and scale required to meet unmet treatment demand. However, thanks to careful and sustained research to try and understand the mechanisms that underpin it, it is increasingly clear that severe asthma is a complex condition that includes a range of different types or 'phenotypes' that may respond differently to different treatments¹⁶. These discoveries have opened the door to the development of new and more effective treatments that could transform the lives of people with severe asthma. The development of new treatments that target distinct types of asthma and enable people to stay well, manage their condition and remain socially active and in work, are within our reach with the right focus and financial investment.

Side effects of high doses of corticosteroids

- Increased appetite
- Lower resistance to infection
- A puffy face and swollen ankles
- High blood pressure
- Mood swings
- Adrenal insufficiency, causing weight loss and fatigue
- Diabetes
- Osteoporosis

¹Severe asthma is defined as asthma that requires treatment with high-dose inhaled corticosteroids plus a second controller and/or systemic corticosteroids to prevent it from becoming 'uncontrolled' or that remains 'uncontrolled' despite this therapy. This would normally be treated at what was previously referred to as steps 4 or 5 of the BTS/SIGN guidelines on asthma management. See: Chung KF et al, 2014.

Case study 1 – Kaitey, 27

Since 2011, my day-to-day life has changed drastically. All of a sudden at 21 I would have periods of time where I couldn't breathe. My GP asked me to breathe in and out, listened, and declared me asthmatic on the spot.

I was given a plethora of medications and went through the usual process of trial and error to land on three tablets and two inhalers. Only one of my tablets was directly associated with my lungs – the others focused on allergy and reflux issues which arose at the same time and seemed to mutually exacerbate one another. I was using an entire reliever inhaler every week. But the improvement was minimal. It felt like trying to stick a limb back on with Blu-Tack.

My job – and every job I've had since, including my current role – was at risk. Too much time off sick, absences with certification are all well and good but “the needs of the business” have to come first beyond a point. I was off for about a third of my working hours. Before long, my usual 37 hours a week dropped to 12 as my boss “couldn't rely on me being there”. When you have scary health problems going on, further uncertainty, stress, and financial loss really weakens your resolve. I often go in to work when I am unwell because I'm afraid I'll lose my job and despite that I end up in out of the HR office to discuss my absence. I am unsure of whether I'll have my job for much longer, even though the income is essential to us.

I am now on a newly available treatment that seems to be working, it has made a difference in my life that I'll never be able to fully explain, but for which I will always be grateful. Whilst my day-to-day wellbeing is improved now, winter in particular is still a time where I'm very vulnerable.

The reality is that I am surrounded by things that trigger attacks. Some things I know to avoid but that's by no means the whole list, and I often have an attack which I don't know the cause of.

I can track it as much as I like, and attend all my injections on time and take my medicines religiously, but asthma dictates my entire day. It shapes where I go, how I get there (if I get there at all), what I eat, how many pillows I have on my bed, what washing powder I use... the list feels endless. Every day I am consciously controlling something which should be automatic, and one day I hope to have the freedom I took for granted back.



All of a sudden at 21 I would have periods of time where I couldn't breathe. My GP asked me to breathe in and out, listened, and declared me asthmatic on the spot.

Why we need new treatments

As established, the mainstay of treatment for severe asthma is oral corticosteroid tablets. This is because inhaled corticosteroids, which work for many, often do not control their symptoms or prevent attacks.

Oral corticosteroids are very effective but extremely powerful drugs that over the long term have toxic and debilitating side effects. In a study including 808 people with severe asthma, it was found that 93% of them had one or more condition linked to oral corticosteroid use¹⁷. However, this is just a snapshot of those with severe asthma and wider data collated through a registry of all people with severe asthma is needed to evidence the full picture.

Side effects not only impact on quality of life but also increase healthcare use and costs due to the comorbidities they can cause¹⁸. People with severe asthma hate taking corticosteroids, partly because of the immediate effects (sleeplessness, anxiety, euphoria, increased appetite) but also because they fear the long-term impact.

It is estimated that 45% of people are non-adherent to oral corticosteroids¹⁹. People with severe asthma have

a high use of healthcare systems²⁰ as they are not able to control their asthma symptoms and are at risk of potentially life-threatening asthma attacks.

We urgently need new treatments to replace oral corticosteroids. It is time to invest in research that enables us to understand the different sub-types of asthma and develop treatments for those types for which there are no alternatives to oral corticosteroids.

“I’ve come to realise that even though I’m getting side effects from taking steroids, my asthma medicines are keeping me out of hospital so it’s worth it. The side effects don’t outweigh the benefits quite yet and there are ways to get them under control.”

Nichola, 39

Identifying different types of severe asthma

As mentioned previously, it is becoming clear that asthma is not one disease but many. Distinct phenotypes with different biological markers (biomarkers) and more targeted treatments are emerging. After many years of effort, a new pipeline of treatments for severe eosinophilic asthma is about to become available. Eosinophilic asthma is one of the more established phenotypes of asthma where patients have higher levels of eosinophils in bronchial biopsies or sputum despite correctly adhering to their treatment²¹. This is an exciting development for this cohort who previously relied on oral corticosteroids and had a low quality of life with frequent attacks²². This adds to the other treatment for severe allergic asthma, omalizumab, which targets the immunoglobulin E (IgE) antibody involved in the

allergic response. But for those whose asthma is not driven by eosinophils or IgE (up to 60% of people), there are still no alternatives to oral steroids²³. Further research is needed to identify additional phenotypes so that ultimately they can be confidently treated much like eosinophilic asthma can be now.

To ensure that those who will and will not benefit are identified and given the right treatment, diagnostic tests for relevant biomarkers are needed. Both additional treatments and diagnostics represent significant unmet need which should be addressed by the development of targeted new medicines and diagnostic tools. This will be explored further in the next section: **‘A step towards precision medicine in asthma’**.

Severe asthma: the unmet need and the global challenge

The work funded through the Innovative Medicines Initiative and the European Union – U-BIOPRED (Unbiased Biomarkers for the Prediction of Respiratory Disease Outcomes) – is one of a number of projects that have attempted to identify the differences in symptoms, mechanisms and personal characteristics between people with severe asthma and then cluster them into categories (or phenotypes). The emerging clusters have already allowed the identification of distinct asthma handprints, which will allow research to be better targeted at identifying new therapeutic targets within each cluster. Although the project is now finished (in terms of recruiting sufficient people with asthma to participate), huge biobanks of data have been established which remain open and accessible and, with additional funding, will be used to provide the evidence of ‘asthas’ as opposed to one homogenous condition.

Efficient ways of pairing people up with the treatment that will be most effective for them are vital. Diagnostic tests that can stratify treatments according to someone’s phenotype are the next logical step and are urgently required so that the right treatment can be given to the right person without delay and avoid potentially fatal asthma attacks.

Challenges

- Challenge 1** Test and validate biomarkers that identify each different phenotype of severe asthma and how it changes over time.
- Challenge 2** Develop simple, inexpensive, non-invasive tests that can accurately identify different types of severe asthma.
- Challenge 3** Replace oral steroids with new, preferably inexpensive and non-invasive targeted treatments for severe asthma with better side effect profiles.
- Challenge 4** Develop specific treatments for types of severe asthma that do not respond to existing treatments.

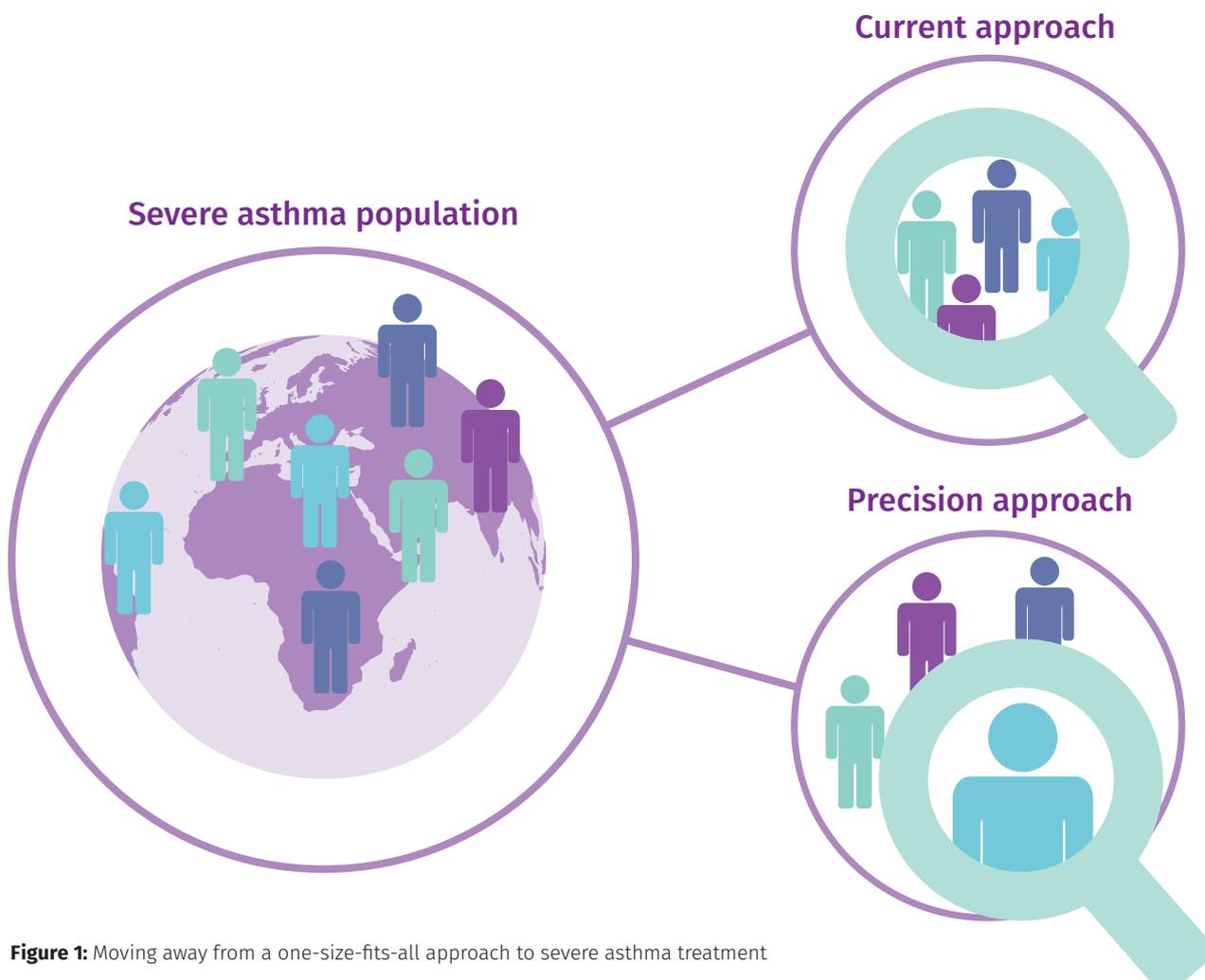


Figure 1: Moving away from a one-size-fits-all approach to severe asthma treatment

A step towards precision medicine in asthma

A number of studies have identified biomarkers that are specific to different sorts of severe asthma, but development is slow. This is due to the large number of mechanisms involved in severe asthma, the variation of biomarkers at different levels of inflammation and the level of invasive tests needed to collect these biomarkers which limits the applicability in clinical settings²⁴. In asthma, part of the challenge is to identify biomarkers that are easy to collect and measure in primary care settings as that is where people will be initially treated and potentially monitored. Tests need to be easy to carry out and minimally invasive; this is a particular priority for children who may not cope with invasive tests that are physically draining or involve needles. Current tests such as induced sputum or even blood eosinophil counts do not meet this challenge.

“The ideal biomarker would be easy to collect and measure, not invasive nor expensive, and can be used to identify either clinical or treatment response phenotypes, evaluate changes in disease activity, or confirm a diagnosis. This prospect provides the impetus for the research for reliable markers in severe asthma.”²⁵

To date we can confidently talk about some biomarkers including neutrophils, eosinophils, fractional exhaled nitric oxide, exhaled breath condensate, periostin galectins and IgE. The table below summarises how each of these biomarkers work.

Biomarker	Description
Neutrophils	The use of this biomarker is not yet clear but neutrophilic inflammation is common in severe asthma.
Eosinophils	Present in sputum and blood. Sputum eosinophils are a more reliable test but blood levels, whilst not as reliable, are increasingly used to indicate treatment need due to eosinophilic lung inflammation ²⁶ . This is due to the invasive procedure required to induce sputum which is difficult to collect.
Fractional exhaled nitric oxide (FeNO)	High levels of FeNO can be used as a predictor of Th2 cells/airway inflammation and allergy.
Exhaled breath condensate	Studies have been limited but a difference has been found between the chemicals in the breath of severe asthma patients and healthy patients and may offer future hope.
Periostin	Debate continues as to whether this is a reliable predictor of sputum eosinophilia.
Galectins	Believed to be a reliable biomarker to predict airway remodelling.
Immunoglobulin E (IgE)	This biomarker is produced when an allergen is present and is used to indicate allergic asthma.

Table 1: Promising biomarkers to stratify medicine²⁷

Severe asthma: the unmet need and the global challenge

With further research investment, the relevance of these biomarkers can be established and then tested, validated and adopted in the development of diagnostic tests that will enable personalised medicine to become a reality in the treatment of severe asthma. Not all of these biomarkers will ultimately be relevant or suitable for use in clinical settings. Additional ones will be identified, but with investment, there is significant potential to stratify and target medicines to individuals using diagnostic tools that measure levels of these biomarkers. There is also hope that old compounds previously abandoned and assumed to be ineffective might yield more promising results if targeted at different subgroups of the severe asthma

population. Whilst in the past these would have been tested on trial participants diagnosed with severe asthma, we now know that they would almost certainly have had different forms of severe asthma. It is possible that there are existing compounds that could provide the basis for new and effective treatments doing little more than 'gathering dust'.

Currently, severe asthma treatments are largely targeted at eosinophilic asthma. The knowledge of eosinophilic asthma is more established and for this group there is an emerging pipeline of treatments undergoing market authorisation and health technology appraisals.

Treatment	Company	Target population	Status (as of March 2017)
Omalizumab	Novartis	Severe allergic (IgE) asthma	Available through the NHS across the UK
Mepolizumab	GSK	Severe eosinophilic asthma	Approved for use on the NHS across the UK – available from April 2017
Reslizumab	Teva	Inadequately controlled eosinophilic asthma	Undergoing appraisal by NICE and the SMC
Benralizumab	AstraZeneca	Eosinophilic asthma (dependent on marketing authorisation)	EMA marketing authorisation expected in 2017
Tralokinumab	AstraZeneca	Severe asthma (specific population to be determined)	Phase III trial stage
Dupilumab	Regeneron/Sanofi	Eosinophilic asthma (dependent on marketing authorisation)	Phase III trial stage
Fevipirant	Novartis	Eosinophilic asthma (dependent on marketing application)	Phase III trial stage

Table 2: Treatment pipeline

Severe asthma: the unmet need and the global challenge

If the treatments outlined above are all given market authorisations and are positively appraised in the UK (through the National Institute for Health and Care Excellence, Scottish Medicines Consortium, and All Wales Medicines Strategy Group) then there will be a choice of treatments for people with eosinophilic asthma (40% of people with severe asthma²⁸). One of the major problems with these treatments is that we do not currently know who will benefit, and, to be cost effective, treatments will need to evidence unique or improved effect or be positioned as a more cost effective option. To date 56% of all single technology appraisals assessed by NICE have been passed and an additional 21% have been passed but for a smaller group of patients than the market authorisation allows²⁹. In order to ensure that NHS resources are used optimally and effectively, each treatment will need to be able to clearly identify its target population and prove to be clinically and cost effective. The pharmaceutical industry has a responsibility to be able to define and identify the population who will benefit from each treatment through companion diagnostics. Additionally, ongoing evidence of improved quality of life, reduced attacks, oral corticosteroid sparing and value for money will strengthen the case for each new treatment.

Focusing research

Whilst there is a good pipeline of effective treatments for severe eosinophilic asthma, the non-eosinophilic asthma pipeline is extremely limited. This massive area of unmet need is illustrated in the diagram below and urgently needs focus and investment. Asthma attacks are driven by different triggers and vary significantly from person to person. However, there are widely recognised triggers such as infections, exercise and allergens that provoke a rise in eosinophils – triggering asthma which, broadly speaking, has good treatment options through the eosinophilic pipeline. The areas of limited treatment options are largely where the triggers do not drive increased eosinophil levels. These drivers include smoking, hormones and obesity and are more common in adults than children.

In order to ensure that there is consistent progress towards comprehensive and effective treatment, focused funding calls for research into mechanisms, targets and treatments to address the unmet need will be required. The priorities for research have been established through the European Asthma Research and Innovation Partnership (EARIP) which through extensive consultation amongst patients, clinicians and industry has identified 15 research priorities,

Challenges

Challenge 5 Build understanding of the different phenotypes of severe asthma, the opportunities for new targeted treatments and companion diagnostics.

Challenge 6 Demonstrate the cost-benefit of new treatments as well as efficacy for regulators, payers and clinicians to ensure treatments are positively appraised in health technology assessments and reach the people who would benefit from them.

Challenge 7 Establish a comprehensive, sustainably resourced national registry of people with severe asthma (or build on an existing one) that will allow ongoing data collection to measure the long term impact of treatments.

including developing new treatments³⁰. These priorities have been endorsed by the European Respiratory Society. The EARIP papers have identified the most promising areas of research and will provide the foundation for future focused research.

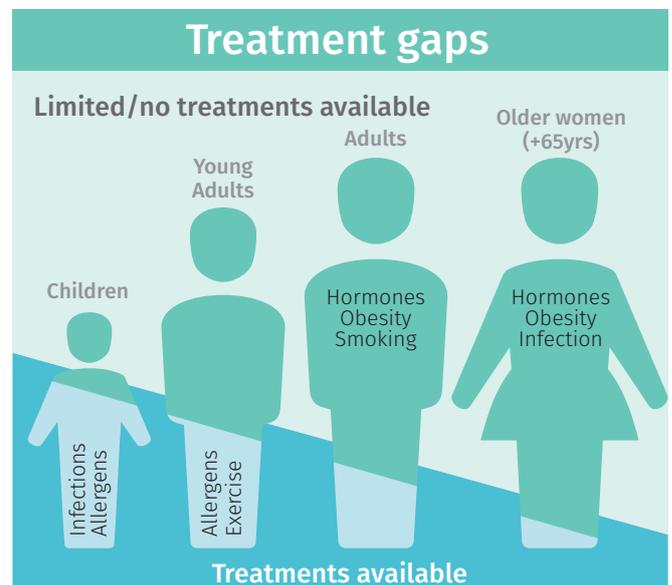


Figure 2: Triggers and unmet treatment need

Severe asthma: the unmet need and the global challenge

The top priority identified through the EARIP international prioritisation exercise was:

- Identify, understand and better classify the different forms of asthma, their progression, and effect on airway inflammation and the immune system.

Additionally:

- Develop new treatments for the different types of asthma: treatment-resistant and steroid-resistant asthma, severe asthma, allergic asthma, hyper-responsive asthma

Each of these priorities were broken down with supporting papers and PICOⁱⁱ questions developed. Now that these priorities have been agreed, there is a clear focus for international collaboration to fund, design and carry out research that is line with these priorities.

Whilst answering these research questions is a significant challenge, progress has already begun. Understanding of biomarkers is developing all the time and there is as much opportunity in revisiting studies and compounds previously deemed to have failed to see if they will work effectively in different populations.

National and international collaboration across different academic disciplines that bring the best scientists together to learn from other disciplines

and disease areas are needed to achieve this much-needed focus. Collaborations may develop organically but with increased funding these could be developed faster and yield results more quickly. These new partnerships would have the potential to build capability and capacity in severe asthma research, develop the UK's life sciences capability and international stature, identify a new generation of leading scientists and speed up discoveries that will transform the lives of people with severe asthma.

One of the ways that will speed up access to treatments is to adopt new, more efficient and less expensive trial designs. For example, adaptive trials effectively combine multiple trials into one so that there are modifiable parts, and participants are moved through the trial onto different branches if the treatment they are taking is found to be ineffective for them. This means that the trial participant pool is used to maximum effect. However, these are more complex trial designs and require larger numbers of trial participants to power the trials. With limited subpopulations of severe asthma with different phenotypes, it is likely that international partnerships will be required to recruit large enough pools of trial participants. One efficient way of learning more about severe asthma will be to involve all those diagnosed with severe asthma into a registry. Patient records and data can be used to help refine the understanding of severe asthma and ensure that people are aware of opportunities to participate in clinical trials.

RASP-UK – The Refractory Asthma Stratification Programme builds on the findings of U-BIOPRED and other biomarker-based research projects. This UK academic and industry collaboration aims to develop research and move away from the 'one size fits all' approach to treatment in severe asthmaⁱⁱⁱ. Rather than continuing to use the stepped approach to treatment, which is based heavily on oral corticosteroids, the project aims to stratify treatments to different cohorts to reduce the stages that people have to go through to find an effective treatment. By studying the biomarkers of people who respond to corticosteroids and people who do not the project aims to predict who will and will not respond to corticosteroids, therefore enabling stratification to appropriate treatment at the outset rather than a trial of treatments over time.

The research will ensure that adherence and steroid response is considered as part of identifying the people who do not respond to treatment. This will make sure that the use of corticosteroids is optimised and people are not unnecessarily taking steroids, which patients have long stated as having long-term negative effects on health and lifestyle. The research will be undertaken through workstreams at centres around the UK, but patients will be stratified into two strands, one for populations who respond to steroids, the other for those who do not respond to steroids. For steroid responsive severe asthma there are already a number of treatments in the pipeline, however we know less about non-steroid responsive asthma and we need to speed up the development of new biologic treatments for these patients, a key aim of RASP-UK.

ⁱⁱ PICO questions are a framework to ensure questions are asked and answered specific to:

P – patient, problem or population **I** – intervention **C** – comparison, control or comparator **O** – outcome

ⁱⁱⁱ www.rasp.org.uk

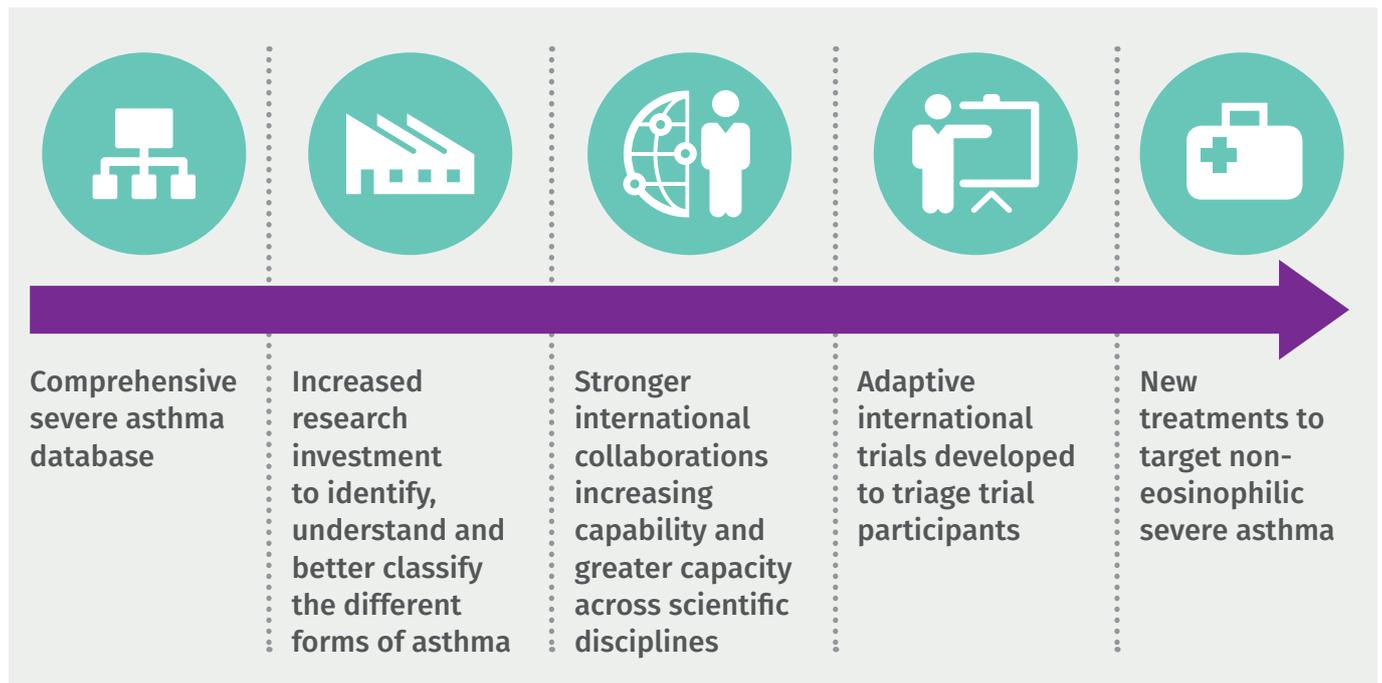


Figure 3: Steps to address the unmet need

Challenges

Challenge 8 Funders to specifically call for cross-disciplinary research bids.

Challenge 9 To refine our understanding of asthma biomarkers and their clinical use, form international, public-private and cross-disciplinary research collaborations, and identify, understand and better classify the different forms of asthma, their progression, and effect on airway inflammation and the immune system.

Challenge 10 Make the commercial case for the pharmaceutical industry to work within large research collaborations, focusing on developing new treatments for non-eosinophilic asthma.

Case Study 2 – Lehanne, 46

I was diagnosed with asthma as a child around age 3-4 and since my early teenage years my asthma has been severe. Every 4-6 weeks from about 13 years old I have had to be admitted to hospital. Despite having periods of very ill-health I have managed to complete my education and qualified as a chartered surveyor and have a successful career but at 40 years old I was medically retired. Asthma has stopped me from doing the things I love – the job I can no longer do, flying is not possible so travelling is restricted and I have never been able to play sport.

I am now on over 20 different medicines including high dose oral corticosteroids which I have been taking since I was 14. This has had serious impacts to my health. I have had to have a hip replacement and I now have diabetes, epilepsy, high blood pressure, high cholesterol, herniated discs and reflux in addition to weight gain and stretch marks.

Severe asthma has had a big impact on my life, I have been ventilated 13 times and have been very unwell on lots of other occasions; it has caused other health conditions, affected my career, friendships and relationships causing a lot of worry and stress.



Why the UK?

The UK is well placed to play a significant part in this field due to the established and vibrant life sciences sector across both public and private sectors and the universal healthcare system which could enable easier identification of trial participants. The UK's scientific community has established credibility and the potential to lead the world in the development of new treatments for severe asthma, companion diagnostics and, ultimately, a cure. The UK has a wealth of experience and expertise to be built upon, including a comprehensive network of severe asthma centres providing support to other non-specialist centres, a limited registry of severe asthma patients, a cohort of specialist centres participating in clinical trials, several longitudinal birth cohort studies and numerous academic centres with experience of participating in international projects such as U-BIOPRED. Many of these are unique to the UK due to our publicly-funded healthcare system and the development of a comprehensive registry of all people with severe asthma would give the UK a competitive edge in research partnerships due to the data, insights and potential trial participants that could be approached. With these assets the UK is uniquely placed to lead research into severe asthma. It is inevitable that the next generation of global asthma experts will emerge from this challenge.

In summary, the UK has the potential to capitalise on the existing mechanistic insights into severe asthma, and the established infrastructure, to lead international work in this area. Greater investment will generate new treatments and transform the lives of thousands of people living with severe asthma and the lives of generations to come.

Challenges

Challenge 11 Build on the European Asthma Research Innovation Partnership research priorities to develop novel treatments targeted at non-eosinophilic asthma.

Challenge 12 Develop national and international research funding calls based on new trial designs that allow different treatments to be tested and biomarkers to be refined in large populations.



The opportunity

We are on the cusp of significant discoveries that in the medium term will help to stratify asthma treatment in a way that has never been possible before and, in the long term, could abolish asthma symptoms and 'cure' asthma. But in order to reap these rewards, research needs to be accelerated now so that the gains are realised as soon as possible.

UK industry and researchers can lead the global challenge to develop accurate diagnostics and treatments for the global population of people with severe asthma. With a comprehensive understanding of the phenotypes of severe asthma and the

associated biomarkers clinicians will be able to use companion diagnostics in order to accurately treat people with precision medicine that is right for them. People with severe asthma will no longer have to endure unacceptably toxic treatments with long-term side effects but will have treatments that enable them to focus on their ambitions, education and employment and families.

This is a collective and international grand challenge involving people with asthma, industry, academia and research funders, which no party alone can resolve.

Case study 3 - Peter, 52

I was diagnosed with asthma aged three but it wasn't until I had a particularly bad asthma attack in 2010 that I got the diagnosis of severe asthma.

My employers have been very understanding recently – they know that I might have to take time out to use my inhalers, or get some air outside, and they're pretty accommodating when I need to go to medical appointments.

I've had asthma since I was three so it's all I've ever known, and I've been to hospital dozens of times. I started worrying about whether I'd be able to go back to work, and whether I'd have another attack – it was terrifying.

I remember being in hospital and knowing that the medicines weren't working, getting more and more terrified, then looking up and seeing a sign saying 'resuscitation'. I used to play squash in a competitive league, but I found that my asthma caught up with me and meant I couldn't improve. It's an extremely physical sport, in such a hot and enclosed space – if I hadn't had asthma I could have done a lot better.

The prednisolone tablets have severe side effects – I put on weight, and they make me feel anxious and depressed, but the GP has no choice but to prescribe them. They can make my mood really up and down, so I have to tell my employers that I'm taking them.

I'm on a good combination of medicines now – I have to use my reliever inhaler pretty regularly but I can still get to the gym around three times a week. It took a while to find the right combination of medicines to find out what worked with the minimum of side effects, but my current combination seems to be working. Relationships have also suffered – sometimes girlfriends don't understand, and it can be embarrassing to wheeze. When I was younger I felt under pressure to go to smoky pubs and clubs, and people would get quite agitated when I said I couldn't go because it would set off my asthma.

The NHS comes in for a lot of criticism but in general, the quality of service I've had is exceptional. I was seen by a consultant while I was in the hospital, but I'm mostly managed by my GP and asthma nurse now. They're pretty good – they send me reminders about my annual reviews, and check my medicines and weight.



Summary and recommendations

Challenge 1 Test and validate biomarkers that identify each different phenotype of severe asthma and how it changes over time.

Challenge 2 Develop simple, inexpensive, non-invasive tests that can accurately identify different types of severe asthma.

Challenge 3 Replace oral steroids with new, preferably inexpensive and non-invasive targeted treatments for severe asthma with better side effect profiles.

Challenge 4 Develop specific treatments for types of severe asthma that do not respond to existing treatments.

Challenge 5 Build understanding of the different phenotypes of severe asthma, the opportunities for new targeted treatments and companion diagnostics.

Challenge 6 Demonstrate the cost-benefit of new treatments as well as efficacy for regulators, payers and clinicians to ensure treatments are positively appraised in health technology assessments and reach the people who would benefit from them.

Challenge 7 Establish a comprehensive, sustainably resourced national registry of people with severe asthma (or build on an existing one) that will allow ongoing data collection to measure the long term impact of treatments.

Challenge 8 Funders to specifically call for cross-disciplinary research bids.

Challenge 9 To refine our understanding of asthma biomarkers and their clinical use, form international, public-private and cross-disciplinary research collaborations to identify, understand and better classify the different forms of asthma, their progression, and effect on airway inflammation and the immune system.

Challenge 10 Make the commercial case for the pharmaceutical industry to work within large research collaborations, focusing on developing new treatments for non-eosinophilic asthma.

Challenge 11 Build on the European Asthma Research Innovation Partnership research priorities to develop novel treatments targeted at non-eosinophilic asthma.

Challenge 12 Develop national and international research funding calls based on new trial designs that allow different treatments to be tested and biomarkers to be refined in large populations.

Actions for researchers, funders and industry:

- Adopt the European Asthma Research & Innovation Partnership research priorities to inform their funding calls and funding to proposals that seek to address these priority areas.
- Establish new funding calls for international collaborations to develop adaptive trials researching into non-eosinophilic treatments.
- Explicitly state in funding calls that research proposals involving researchers from different countries and disciplines are encouraged.
- Explore international and cross-disciplinary collaborations focused on research to identify, understand and better classify the different forms of asthma, their progression, and effect on airway inflammation and the immune system in order to further refine our understanding of asthma biomarkers and their use in clinical practice.
- Target research to enhance understanding into potential non-eosinophilic asthma treatments in order to reduce the unmet treatment need through new treatment development.
- Design and deliver research to develop accurate tests to identify people who are steroid responsive vs non-steroid responsive.
- Using data from the UK registry, analyse and build a robust evidence base of the long-term impact of sustained oral corticosteroid use for people with severe asthma and the cost of treating the long-term side effects.
- Identify new trial designs that allow multiple treatment comparisons within the same trial that are acceptable to industry (considering commercial pressures and issues of confidentiality in drug development) to inform the clinical trials of the future.
- Work in partnership to explore the repurposing of existing treatments and previously abandoned compounds through new trial designs.
- Work in partnership to develop companion diagnostics to enhance precision medicine.

Main actions for government and decision makers:

- Work with industry, researchers and funders to capitalise and build on the UK's world class respiratory research infrastructure.
- Work with healthcare organisations to build on the existing severe asthma registry infrastructure to make the UK an attractive trial location.

Main actions for healthcare organisations and clinicians:

- Agree a minimum dataset to be collected by all clinicians in all specialist centres and ensure the data collection is resourced appropriately and sustainably.
- Expand and sustain the pan-UK registry of people with severe asthma to ensure all people with severe asthma are included in the registry.
- Use the registry to enable everyone with severe asthma to participate in trials, creating an internationally attractive pool of trial participants.
- Streamline NHS systems and processes to allow recruitment of sufficient people with severe asthma into the large clinical trials required to test new treatments.

UK industry and researchers can lead the global challenge to develop accurate diagnostics and treatments for the global population of people with severe asthma.

Glossary

Allergic asthma

A type of asthma that is triggered by inhaled allergens (a substance that triggers an allergic reaction). Common allergens include pollen, pets, moulds and house dust mites.

Asthma attack

A sudden worsening of asthma symptoms caused by the tightening of muscles around the airways (bronchospasm). During the asthma attack, the lining of the airways also becomes swollen or inflamed and thicker mucus is produced.

Biomarker

Short for biological marker. It refers to a measurable indicator of some biological state or condition. Biomarkers can be found in blood, urine and breath. These can be linked to asthma phenotypes (see below).

Companion diagnostic

A companion diagnostic is a medical device which provides information that is essential for the safe and effective use of a corresponding drug or biological product.

Corticosteroids

Often known simply as steroids. Corticosteroids are an anti-inflammatory medicine prescribed for a wide range of conditions – commonly as inhaled or oral treatments. They are a man-made version of hormones normally produced by the adrenal glands (two small glands that sit on top of the kidneys).

Eosinophilic asthma

A type of asthma that is characterised by increased levels of eosinophils (see below) in the airways.

Eosinophils

A type of white blood cell and one of the immune system components. Along with other cells in the immune system, they control mechanisms associated with allergy and asthma. When activated, they release toxic proteins that attack parasites, viruses and some other infections, but if regularly activated they also cause tissue damage and dysfunction to the host.

FeNO

Fractional exhaled nitric oxide (FeNO) is a marker of eosinophilic airway inflammation. It is a good predictor of corticosteroid response.

Immunoglobulin

Also known as antibodies, they are protein molecules produced by a type of white blood cells, called B cells. They act as a critical part of the immune response by specifically recognising and binding to particular antigens, such as markers on bacteria or viruses and aiding in their destruction.

Mechanisms of asthma

The complex mix of genetic, allergic and environmental factors that cause asthma, its symptoms and asthma attacks. Currently, the mechanisms of asthma are not fully understood.

Phenotype

The observed characteristic of an organism that results from the interaction between the genotype (set of genes) and its environment.

Precision medicine

Precision medicine is an approach to the treatment and diagnosis of disease that takes into account variations in an individual's genes, environment and lifestyle (also known as personalised medicine or stratified medicine).

Public private partnerships

A contract between a private party and a public/charitable organisation, for providing a public asset or service.

Specialist care

Specialist centres treat people that are affected by rare conditions that frontline healthcare staff are unused to dealing with. They tend to be located in specialised hospital trusts that recruit a team of staff with the appropriate expertise.

Th2 cells

Type 2 T helper cells (Th2 cells) are a type of white blood cell and an important component of the immune system. They produce proteins called cytokines that activate eosinophils.

Treatment pipeline

Medicines for a specific condition that are being developed or are being assessed by regulators.

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Severe asthma: the unmet need and the global challenge

About Asthma UK

Every ten seconds someone in the UK has a potentially life-threatening asthma attack and three people die every day. Tragically two-thirds of these deaths could be prevented, whilst others still suffer with asthma so severe current treatments don't work.

This has to change. That's why Asthma UK exists. We work to stop asthma attacks and, ultimately, cure asthma by funding world-leading research and scientists, campaigning for change and supporting people with asthma to reduce their risk of a potentially life threatening asthma attack.

We fight asthma in three ways:

- We fund world-class asthma research.
- We campaign to improve the quality of care received by people with asthma.
- We help hundreds of thousands of people a year with our expert advice and support.

To find out more about Asthma UK's work:



Asthma UK Helpline:
0300 222 5800



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info@asthma.org.uk



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