# The Severe Heterogeneous Asthma Research collaboration, Patient-centred (SHARP) ERS Clinical Research Collaboration: a new dawn in asthma research

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**SHARP (Severe Heterogeneous Asthma Research collaboration, Patient-centred) is set up to harmonise severe asthma management across Europe and unravel the heterogeneity of severe asthma in a patient-centred way** http://ow.ly/s1x730mwLpk

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## Introduction

The past 30 years have seen major advances in the understanding of asthma mechanisms and the clinical introduction of effective medicines based on these pathways. The first major step-change occurred in the 1980s with the development of bronchial challenge as a research tool to dissect the airways inflammatory responses [1, 2]. The advent of bronchoscopy and sputum induction in the early 1990s, to study asthma

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pathology *in vivo*, enabled the description of characteristic features of airways inflammation and remodelling [3–6], while epidemiological and challenge studies showed viruses to be the main cause of asthma exacerbations [7, 8]. One of the greatest discoveries was the central role of Type-2 cytokines driven by the interleukin (IL)-4/IL-13 and IL-5 pathways, for which simple biomarkers, like sputum eosinophils and exhaled nitric oxide, were discovered [9, 10]. However, it was not until early 2000s that the basic science translated into fundamentally novel treatments, beginning the "era of biological treatments" with the anti-IgE antibody, omalizumab [11]. It took almost 15 years for the next biologics to arrive, targeting the pro-eosinophilic cytokine IL-5, showing how difficult drug development can be [12, 13].

We now find ourselves in a fortunate, yet challenging, situation: we have several biologics to offer to people with asthma, yet we do not have clinical algorithms to identify the "right drug for the right patient at the right time". Moreover, these biologics are constrained to Type-2 high asthma and we lack effective treatments for other phenotypes, such as neutrophil-variant and paucigranulocytic asthma. These issues of key importance to people with asthma, their clinicians, the laboratory scientists, the pharmaceutical industry, regulators and payers, gain even more importance with the recognition that severe asthma is heterogeneous both in clinical and pathological terms [14]. In Europe, the effort to stratify asthma was led by the Innovative Medicines Initiative (IMI)-funded consortium U-BIOPRED (Unbiased BIOmarkers for the Prediction of REspiratory Disease outcomes) resulting in major discoveries that, together with those from the US consortium, SARP (Severe Asthma Research Program), have transformed our understanding of asthma mechanisms and provided new clinical asthma phenotypes [15–17]. They open up the possibility of discovering the underlying driving molecular endotypes behind these variants. It is clear, however, that only large integrated data strategies will succeed in realising this ambition. At the same time, these programmes clearly demonstrated the value of working collectively, bringing together key stakeholders, especially people with asthma, to transform the research landscape [18, 19]. Following the conclusions and recommendations of the European Union (EU)-funded European Asthma Research and Innovation Partnership that "a more comprehensive and integrated partnership to tackle asthma is needed to share expertise, improve co-ordination, remove duplication, agree on the priority research needed" [20], an application for a Clinical Research Collaboration (CRC) on severe asthma was submitted to the European Respiratory Society (ERS). This article outlines the vision of SHARP and the complementary aspirations of the stakeholders for a new dawn in asthma research.

## The SHARP vision

The ERS CRC on severe asthma is named SHARP (Severe Heterogeneous Asthma Research collaboration, Patient-centred), to highlight the heterogeneity of severe asthma and to underline the key role of people with severe asthma in the consortium. SHARP's ambition is to transform the lives of people with severe asthma, initially relying on close interaction between patients, clinicians, scientists and the pharmaceutical industry, and gradually involving any other stakeholders, including policy-makers. Working as an integrated team, our four major aims are to: 1) end dependency on systemic corticosteroids for asthma control, 2) enable access to severe asthma specialists for all people with severe asthma, 3) improve understanding of the heterogeneity of severe asthma mechanisms, and 4) seek to prevent the development of severe forms of asthma.

By delivering our first aim, we will largely reduce severe exacerbations and the need for systemic corticosteroids, a treatment that carries substantial risk of iatrogenic harm and morbidity. Under our second aim, we will help optimise treatment pathways across Europe so that no one is left wanting of the best possible care. As our third aim, we all want to understand better what mechanisms drive the various asthma phenotypes, so that we can develop better treatments and biomarkers to improve management. Finally, we have set ourselves a very bold challenge to, if not yet to completely cure asthma, prevent its progression to the very severe forms that cause so much distress. We firmly believe these goals to be within our reach, but recognise that, in order to achieve our aims, a change in culture whereby such ambitious research is delivered is needed.

## A central role for people with asthma: a step-change in asthma research

From its inception, the SHARP chairs committed to embedding the perspectives and needs of patients with severe asthma. This ethos has placed patients centrally in the project as equal partners in establishing research, governance and collaboration structures.

As the first ERS CRC with patient co-chairs, SHARP emphasises the real-world challenges and aspirations of severe asthma patients. The patient co-chairs are supported by the patient advisory group, formed of 13 people from across Europe with severe asthma and two representatives from asthma patient organisations, with a strong commitment to grow further national patient engagement. The European Lung Foundation

coordinates the patient advisory group, which supports several ERS CRCs and Task Forces in severe asthma.

The patient chairs and patient advisory group have already played an influential role on SHARP's plans and approaches, ensuring the following key aspects.

- Third party patient data, data privacy, patient-important outcomes and patient involvement have been incorporated in SHARP's vision and plans.
- Research priorities for severe asthma patients were highlighted to the other stakeholders, resulting in a research agenda that includes several questions directly proposed by the patient advisory group.
- Patient input and collaboration is embedded into every level of SHARP, from the research working groups to the project management team, the steering committee and chair positions.

## The research aims of SHARP

The vision, ambitions and specific aims of SHARP were agreed on April 25, 2018 at the first meeting where all the elements of our CRC worked together to forge our immediate and longer-term research programme. Prior to the meeting, the four stakeholder groups (patients; national leads (clinicians) from 23 countries; basic and translational scientists; and pharmaceutical company (clinical) scientists) had discussions as individual stakeholder groups. They discussed the challenges and ambitions from their stakeholder perspective. Each group then narrowed down a broad list of research questions to their top three priority questions. They then outlined for each question: Why is it important? What will be done to answer the question? How will it be answered? The combined stakeholder groups identified a total of eleven key questions (table 1). During a subsequent face-to-face meeting, the attendees were grouped into mixed stakeholder groups to ensure diversity of views. The result was a vibrant meeting, full of enthusiasm and a spirit of joint purpose, and three main questions were selected as priorities on which SHARP will focus.

1) Is there a high level of variance in the characteristics and treatment of severe asthma across Europe?
2) What are the mechanisms of severe asthma, including the causes and consequences of asthma exacerbations and their treatment?
3) What is the best way to measure patient outcomes in severe asthma?

In order to deliver the research addressing the agreed questions, seven working groups were established.

## The need for more knowledge of mechanisms

Basic research into asthma mechanisms has provided a wealth of knowledge about this complex disease. Efforts focused on severe forms of asthma through large programmes, like U-BIOPRED and SARP [21, 22], are providing additional insight into underlying the pathobiological mechanisms possible only through such large collaborative efforts. For this reason, SHARP will remain closely associated with the U-BIOPRED Alliance established in 2017 after completion of the IMI-funded U-BIOPRED programme.

TABLE 1 Questions proposed by stakeholder groups of the Severe Heterogeneous Asthma Research collaboration, Patient-centred (SHARP) consortium as being of key interest to them as well as to the whole consortium

| Research question | Stakeholder group submitting the proposal |
|---|---|
| Is there a high level of variation in the characteristics and treatment of severe asthma across Europe? | Patients |
| How beneficial are digital services for patients in managing their asthma? | Patients |
| Are the real-life effectiveness and long-term safety with biologics different from that in clinical trials? | Patients |
| Who benefits most from biologics? | Pharmaceutical company (clinical) scientists |
| What is the health economic burden of severe asthma? | Pharmaceutical company (clinical) scientists |
| What biomarkers identify different phenotypes in severe asthma? | National leads (clinicians) |
| What can we learn from a patient in the database about the onset of their disease? | Basic and translational scientists |
| What are the mechanisms of severe asthma, and what are the consequences of an exacerbation and the subsequent patient care and the patient perception? | Basic and translational scientists |
| Does airways remodelling matter? | Basic and translational scientists |
| What baseline characteristics are captured in the registries? | National leads (clinicians) |
| What is the real-life economic impact and disease burden of severe asthma? | National leads (clinicians) |
| What is the best way to measure patient outcomes in severe asthma? | National leads (clinicians) |

The use of unbiased approaches has "thrown up" some novel endotypes, *i.e.* subsets of asthma defined by molecular mechanisms rather than clinical or simple biomarker variables. This has been particularly true for forms of asthma with evidence of Type-2 cytokines being central to the disease, so called T2-high asthma, but there is increasing interest in T2-low forms, which may involve cytokines like IL-17 [23] or as yet unrecognised processes like mitochondrial stress [24] and defects in innate immunity leading to an altered lung metagenome [25].

## The need for better management

The advent of monoclonal antibodies supressing aspects of T2 immunity has given asthma drug development the much-needed energy, optimism and investment, leading to major advances and improved quality of life for so many people with difficult asthma with antibodies against IgE and Type-2 cytokines (IL-5, IL-4/13) [11–13, 26, 27]. However, we recognise that not all patients benefit and many only partially benefit from these treatments. Thus, understanding of the mechanisms of exacerbations in these non- or partial-responders is an unmet need of high priority. To meet the aims of personalised medicine, we also need to understand better how to predict who will respond to which biologic. The SHARP registry will serve this need well through long-term follow-up of patients on biological treatment, aiming to optimise

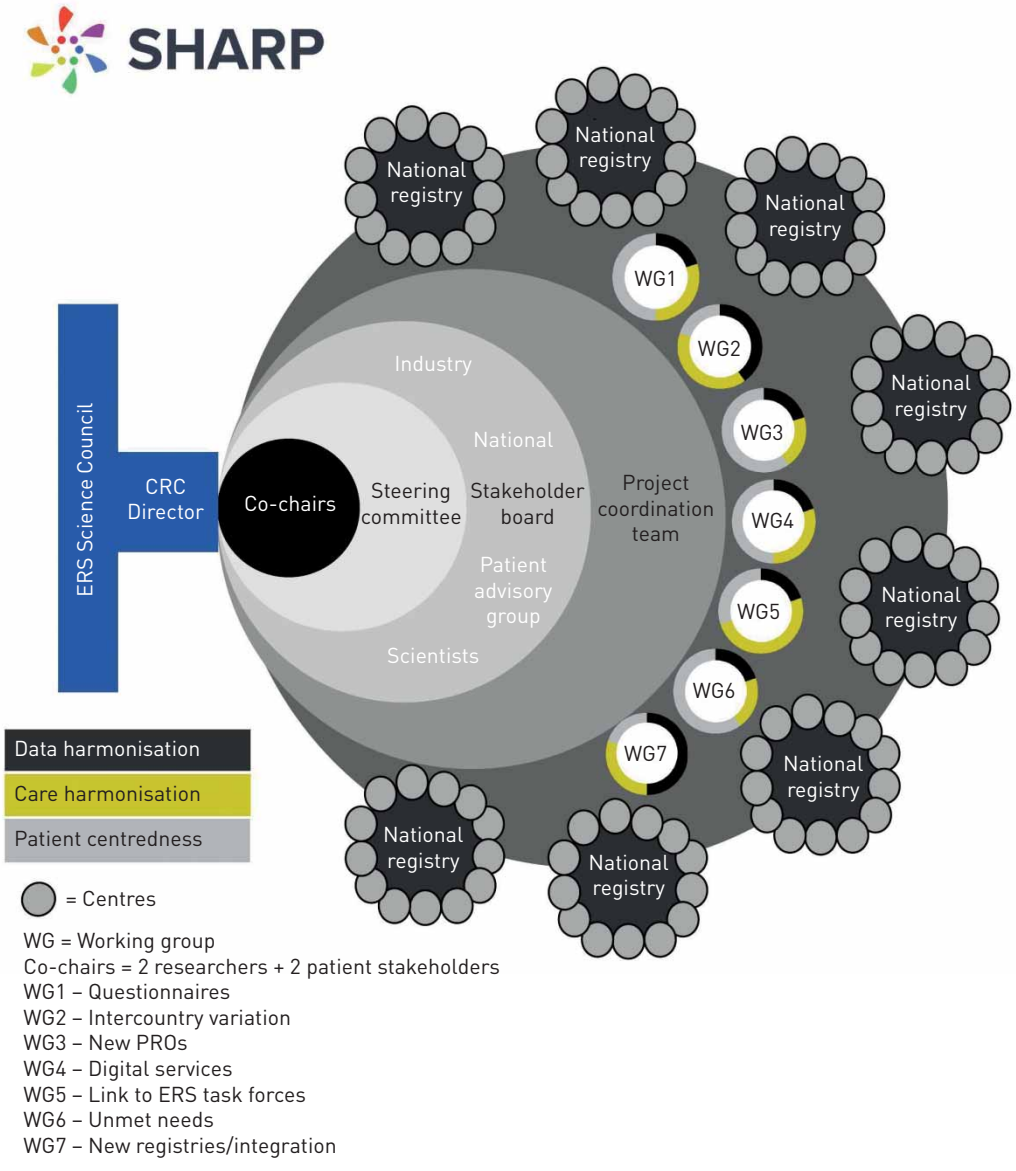


FIGURE 1 Organisational chart for the Severe Heterogeneous Asthma Research collaboration, Patient-centred (SHARP) Clinical Research Collaboration (CRC). ERS: European Respiratory Society; PRO: patient-reported outcome.

treatments so that we stop relying on systemic corticosteroids that cause much morbidity and add huge expense to our already stretched healthcare systems. The SHARP registry should also enable testing of established biomarkers, such as eosinophils and exhaled nitric oxide fraction, and further development and validation of emerging tools like breathomics [28] and urinary metabolomics [29]. Understanding the health economics of severe asthma will help healthcare systems and pharmaceutical companies plan allocation of resources better. This will be of particular benefit in countries where access to biologics is still difficult. To answer all the research questions of SHARP, it is also important to consider paediatric asthma. We will achieve this by linking with SPACE (Severe Paediatric Asthma Collaborative in Europe), the CRC focusing on severe paediatric asthma [30]. One of the valuable aspects of a pan-European registry integration effort is the potential for registries to drive practice, particularly when they are designed in a way that integrates well with clinical workflows. In this way, SHARP aims to be a driver for increased harmonisation of asthma care across Europe, and equally importantly, to achieve close coupling of research with clinical practice thereby speeding up the translation of research into clinical practice.

## Building the research base across Europe

The SHARP CRC offers an excellent opportunity to bring patients, healthcare workers and scientists from academia and the pharmaceutical industry to work together, and it also provides a means whereby research capabilities are raised in quality and quantity across Europe. The ambitions of the national leads and their country networks will ensure collection, comparison and harmonisation of national real-life data to provide new insights coming from both the "severe asthma big data" analysis and the fruitful national experiences and programmes. These achievements will shorten the application period of valid procedures into different national initiatives and will promote interactions with national regulatory authorities and healthcare systems to set up criteria of eligibility for novel and expensive treatments and sustainability of the costs. People with asthma, acting in partnership within the centres across the SHARP family, will have opportunities to promote dissemination of the culture of SHARP at national level in order to: 1) implement strategies for better adherence to treatment, *e.g.* by means of educational programmes; 2) promote patient referral to severe asthma centres; 3) make visible and advocate the ambition of our CRC and the needs of people with severe asthma through the media; and 4) make the existing and new treatments accessible to all eligible patients. The final aim of SHARP is to "speak the same language for severe asthma" throughout Europe and, consequently, to disseminate, at individual country level, the concept of "the right drug for the right patient at the right time".

## The operational model of SHARP

The operational model of SHARP is centred around a true collaborative partnership with all involved stakeholders (figure 1), based upon a set of core principles that include: distributed responsibility, open communication, maximising the value of data, and delivering the aspirations of all stakeholders. The oversight of SHARP comes from a group of chairs that includes two academic clinical scientists, and two patients. The operating principle is based upon design thinking, with an emphasis on early prototyping and iterative refinement. The centrepiece of this model is a research agenda based upon the integration of the priorities of a strong network composed of four stakeholder groups: patients, clinical researchers, translational researchers and pharmaceutical industry partners who, in addition to engaging intimately in all operations of SHARP, are at present the main funders. This stakeholder board is the driving force that ensures that all tasks are completed to a high standard and that barriers to progress are resolved.

## A look forward

The partners in SHARP intend to be a driving force for changing the culture of research on severe asthma. The aim is to move away from fragmented efforts and move towards a more harmonised approach to asthma registries that will allow for real world research on quality data at scale. Concrete deliverables in the first 3 years will consist of assembling a catalogue of existing European registries, building the SHARP registry integration platform, developing data capture plans, and completing the first collaborative "proof of concept" involving the data of more than 3000 patients from 10 European countries. This exciting first collaborative study will not only align the approach to severe asthma management across Europe but will also provide important input for future randomised controlled trials and real-world pragmatic studies [31]. Perhaps the biggest cultural change is SHARP's stakeholder centric approach with particular emphasis on the perspectives and needs of patient stakeholders. Patient stakeholders are active participants in the co-development of SHARP, a characteristic of SHARP that makes it highly likely that SHARP will generate new and unexpected knowledge about severe asthma that will have a direct impact.

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