REVIEW
ASTHMA

SHARP: enabling generation of real-world evidence on a pan-European scale to improve the lives of individuals with severe asthma

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ABSTRACT Real-world evidence is important to help unravel unanswered problems in severe asthma and is valuable to better understand the patient experience and common clinical practice.

The Severe Heterogeneous Asthma Registry, Patient-centred (SHARP) Clinical Research Collaboration is created as a network of national registries and severe asthma centres that work together to perform registry based real-world research and clinical studies on a pan-European scale.

Such collaboration requires a new, innovative design to overcome the many issues that arise with large-scale data collection across national borders. SHARP has developed a platform that offers a federated analysis approach where national registry data are transformed and integrated into a common data model (CDM). The CDM then allows a local analysis of de-identified patient data and subsequent aggregate (meta-)analysis. To facilitate an easily accessible way to set up new registries, SHARP enables new registries to take part in a central database, based on already proven technology. Next to being economical, this linkage ensures data from different SHARP central members to be comparable.

Technological advancements lead to an ever-expanding rate of patient data that will be collected; with the collective effort of the pan-European severe asthma research community SHARP hopes to ensure that they are well equipped to enter a new era of medical research, with the ultimate goal to positively impact the lives of patients with severe asthma.

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SHARP brings together national asthma registries in Europe and enables generation of real-world evidence on severe asthma by using a common data model that aligns data from existing registries and by facilitating the development of new asthma registries https://bit.ly/3a1E42D

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Introduction

Although individuals with severe asthma make up only a small percentage of the entire asthma population, they account for a disproportionate amount of the disease burden, with nearly 50% of all asthma related health costs being incurred in their management [1]. Accordingly, there has been and continues to be intense interest in finding new therapies for severe asthma. A number of new and effective therapies (Anti-immunoglobulin (Ig)E, -interleukin (IL)5, -IL-5 receptor (R), and -IL4R monoclonal antibodies) have been developed for certain (pheno)types of severe asthma. These biologic therapies reduce asthma exacerbations by up to 50%, and improve lung function and quality of life [2]. However, a number of challenges and questions remain. Oral corticosteroids are still widely used to achieve control in many individuals with severe asthma, despite major side-effects that can lead to significant co-morbidity [3, 4]. Furthermore, biologics are mainly effective in individuals with asthma categorised as being driven by type 2 (T2) cytokines (IL-4, IL-5, IL-13), the so-called type-2 high, eosinophil-driven, asthma phenotypes. Non type-2 high (or T2 low) asthma phenotypes, *e.g.*, neutrophilic and pauci-granulocytic, are largely lacking treatment options [5].

Many questions about severe asthma remain unanswered. When should treatment be switched between different biologic therapies? What should happen with inhaled corticosteroids or reliever medications? How should biologic therapy be handled in the setting of increased infectious disease risk, such as a viral pandemic? To what degree do biologic therapies reduce the burden of severe asthma in practice? Are there symptoms that patients care about the most that remain even after a good clinical response to biologic therapy? The answers to these questions are not readily available because access to long-term real-world data on severe asthma is limited, although there is a growing general interest in real world evidence [6, 7]. Recent studies have confirmed that mepolizumab in the real world had effects similar to the randomised control trials (RCTs) leading up to its approval [8, 9]. Such studies reflect an increasing interest in the ability to quantify the impact of new and often costly therapies. In many European countries, there is an obligation to enter patient data into a registry before patients become eligible to start biologic medication. However, while real-world data is being generated, it is not translated into real-world evidence on a pan-European scale.

Real-world evidence is also important for gaining a better understanding of the patient experience and clinical practice. There is a rising sentiment that classical clinical measurements of the signs, as well as currently used patient reported outcomes (PROs), do not reflect symptoms and outcomes that patients care about the most. In addition, there is a perception that there are differences in the management of severe asthma across Europe [4], but there is only minimal evidence to support such perceptions. It is a well-stated goal to deliver the highest quality and patient centred care to all individuals with severe asthma. For this and the reasons outlined above, the European Respiratory Society (ERS) Clinical Research Collaboration (CRC) Severe Heterogeneous Asthma Registry Patient-centred (SHARP) was formed. More specifically the SHARP CRC has four major aims [10]: 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, 4) prevent the development of severe forms of asthma.

To achieve these aims, SHARP set out to facilitate the generation of more real-world data and evidence on severe asthma by bringing together existing asthma registries across Europe and facilitating the development of new asthma registries in countries that lacked such a registry. While SHARP was in development, it became clear that the two biggest challenges would be the integration of existing registries and making it easy to set up new registries. On the one hand, existing registries contain personal data that need to be protected by the rules laid out in the General Data Protection Regulation (GDPR) while, on the other, creating new registries is costly and logistically complex. Therefore, the SHARP CRC was envisioned from the outset as a network of national registries and severe asthma centres that could work together to perform registry based real-world research and clinical studies.

Building a network of registries and centres

To build a network of registries, ERS reached out to national respiratory societies to identify National Leads for each European country. In order to reflect the perspectives of multiple different stakeholders, SHARP assembled patient, pharmaceutical industry and basic scientist stakeholder groups alongside the group of national registry leads, representing the clinicians caring for people with severe asthma. These four different stakeholder groups first met individually to define, from their perspective, the most important research questions that SHARP could address. Then, in a face-to-face meeting, smaller groups of mixed stakeholders reviewed and prioritised the list of research questions. This was again discussed in a joint session combining members of all the individual stakeholder groups and a set of focus areas or task forces were defined. All research questions were reviewed and reframed to make them fully patient centred

through engagement of the SHARP Patient Advisory Group (PAG) and the SHARP patient stakeholder co-chairs. The results of these discussions and the resulting list of research questions were then used to design three programmes of work: 1) Integrating existing registries and setting up new registries, 2) Collaborative research question workflows, and 3) Clinical studies focussed on validating more patient-centred outcomes and the use of digital endpoints.

Subsequently, SHARP added another stakeholder group comprised of "rising star" investigators, loosely defined as anyone working on severe asthma research who does not have a full professor appointment and is motivated to engage and work on delivering SHARP programmes. In response to the COVID-19 pandemic, a fourth programme has been added recently, focussing on the patients' and their doctors' experience during the first peak of the coronavirus disease 2019 (COVID-19) pandemic.

Beyond the integration of patient-level data

Integration of data from national registries in a central database is challenging because personal data have to remain in the country where they are collected. Initial reviews of datasets also revealed that the data models used in the different national registries, including the types of variables and the variable names, are heterogeneous. To overcome these challenges, it was decided to build a federated analysis platform (FAP).

The growing interest in real world evidence has led to the development of federated analysis approaches. One of the first of these types of approaches was the Food and Drug Administration's (FDA) Sentinel Program [7] in which real-world adverse events are monitored through a system of summary data reports from individual data centres sent to the FDA. Perhaps the biggest federated analysis effort is that of the Observational Health Data Sciences and Informatics (OHDSI) [11] consortium, which has developed a common data model and software tools to support the deployment of federated analysis approaches. OHDSI has datasets representing more than 500 million patient records under its common data model (OMOP) [12]. More recently, the Innovative Medicines Initiative (IMI) has launched a project (European Health Data and Evidence Network (EHDEN)), which is developing a network of service providers that will work to support the conversion of datasets into the OMOP common data model.

SHARP adopted an approach similar to OHDSI. A SHARP common data model was developed by selecting the existing severe asthma registry (Register of Adult Patients with Severe Asthma for Optimal DIsease management (RAPSODI), www.rapsodiregister.nl) from the Netherlands, based on a comparison with other registries to assure that the RAPSODI data model was adequate to capture the types of data that most registries were using. The RAPSODI protocol requires a baseline recording of patient data followed by yearly follow-up entries to record the variation from baseline parameters. This capability is an advantage over most national registries which are either cross sectional or require only occasional follow up. Such an expedient choice allowed SHARP to focus efforts on the legal and technical aspects of creating a FAP instead of investing substantial effort in building a new variable list and data model. The list of variables captured in the SHARP data model is as follows:

- Name of the hospital where the patients receives asthma treatment
- Year/month of birth
- Sex
- Ethnicity (Caucasian/non-Caucasian)
- Height and weight
- Smoking status
- Age of asthma diagnosis
- (Asthma) questionnaire scores (Asthma Control Questionnaire, quality of life, health care use, work productivity and activity impairment)
- Routine lung function tests results
- Blood tests results
- Sputum test results
- Chest radiography and/or chest computed tomography scan results
- Dual-energy X-ray absorptiometry scan
- Bronchoscopy results
- Number of exacerbations in the past year
- Number of hospitalisations for asthma in past year
- Number of intubations past year
- Current and previous asthma medication
- Adherence
- Inhalation technique
- Previous participation in rehabilitation programs
- Previous bronchial thermoplasty

- Steroid-induced adverse effects
- Comorbidities

The first step in creating the FAP was to create the SHARP Common Data Model by transforming the RAPSODI data model into a data model based on OHDSI's OMOP common data model. This effort was conducted by a group of service providers (ITTM solutions, Esch-sur-Alzette, Luxemburg; MetaSeq, Birmingham, UK; Biomeris, Milan, Italy) that work together in the eTRIKS Data Science Network (eDSN), two members of which received the training on transforming datasets into the OMOP common data model from the EHDEN project. Data from other existing registries are also transformed into the SHARP common data model for use in individual analyses as part of defined projects. Each registry hosts a version of their dataset that has been transformed into the SHARP Common Data model alongside the existing national registry dataset. OHDSI provides a suite of software tools to support federated analyses. On a study-by-study basis, using the ATLAS tool from OHDSI, statistical analysis scripts can be composed and distributed throughout a network of federated registries that have an instance of the SHARP common data model. The ATLAS software allows for a National registry to approve or reject a request to include their data in a given analysis. If approved, the analysis script is then run on the SHARP common data model version of the national registry. Then, only a summary analysis report is delivered to the SHARP FAP and only on review and approval by the National Registry. Thus, patient level data (personal data) never leave the national registry, thereby protecting the privacy of the individuals whose data are in a national registry. Figure 1 shows a graphic representation of the SHARP FAP.

Scientifically the biggest challenge is that federated analyses requires its own set of statistical approaches. For example, to have descriptive statistics that combine multiple national registries the analysis approach is as follows:

$$\bar{x}_* = \frac{(\bar{x}_1 N_1) + (\bar{x}_2 N_2)}{(N_1 + N_2)}$$

$$s_* = \sqrt{\frac{\sum x_1^2 + \sum x_2^2 - (N_1 + N_2)\bar{x}_*^2}{N_1 + N_2 - 1}}$$

where N_1 is number of matching records in registry 1, $\bar{x}_1$ is mean of matching records in registry 1, $\bar{x}_*$ is mean of combined cohort and s_*: standard deviation of combined cohort.

Similar approaches can be undertaken to conduct correlation analysis, predictive modelling, and even artificial intelligence-based deep learning [13–15].

In respect of administration, the biggest challenge is building up an understanding of what it means to conduct a federated analysis. To accelerate the process, SHARP held meetings to explain the concept. However, even when investigators had a clear understanding of the approach, they often met administrative and legal resistance within their organisation. To further accelerate the process, SHARP created a collaboration agreement that clearly explained how data will be used, explicitly stating that there would not be any protected intellectual property arising out of the combined analyses. The agreement, made between ERS and the national registries has helped tremendously to move the platform forward, so SHARP is now close to having agreements in place to cover registry data in 27 European countries.

Building new registries

To facilitate an efficient, fast-track route for starting up new severe asthma registries in European countries, the SHARP CRC offers the possibility for countries to participate in a centralised registry called SHARP Central that evolved out of the RAPSODI registry that has been operating for three years in the Netherlands, collecting data from 15 hospitals. Unlike existing registries with legacy data, new registries can obtain informed consent prospectively, clearly explaining how data will be used in a centralised database.

At present, SHARP Central acts as a multi-national registry with data from eight European countries. Data are stored in a central server hosted by a charity located in The Netherlands. All SHARP central members use the same electronic data capture system (Castor EDC, Amsterdam, the Netherlands) and an electronic case report form (eCRF) built around the SHARP data model. Castor EDC is a secure, cloud-based data solution, enabling researchers to easily capture and integrate data from any source. Data entry is menu-driven *via* a user-friendly electronic case report form (eCRF). Each participating centre manages its own data in their own private section of the central server. The documentation needed to run a local registry (*e.g.*, patient information leaflets, informed consent forms, *etc.*) is based on the already existing RAPSODI documentation, translated into the languages of the national registries. A data sharing and

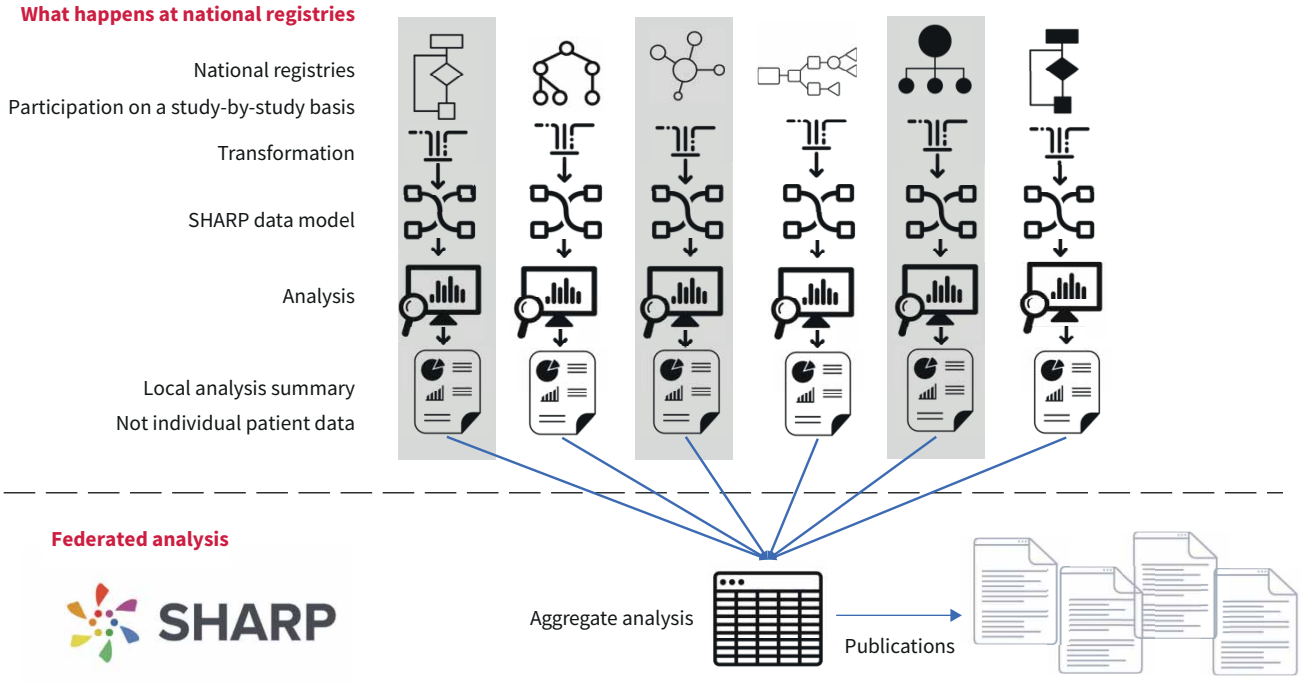

FIGURE 1 Graphic representation of the Severe Heterogeneous Asthma Registry, Patient-centred (SHARP) Federated Analysis Platform.

collaboration agreement has been concluded between participating registries and the charity. The SHARP Central Platform allows participating registries to send out invitations (*via* email or through a specially developed smartphone app) to periodically fill in several PRO questionnaires.

SHARP Central was intentionally designed to reduce the barriers to starting a severe asthma registry in countries that previously did not have one. Making use of the SHARP Central infrastructure based on the Castor CRF is economical and easy. The linkage to SHARP means that the data from SHARP Central countries is easily comparable to data from other European countries. This not only elevates the importance of the research that is possible, but also provides for a comparison of clinical practice across Europe, which helps drive the development of the processes to support best possible care for individuals with severe asthma.

The future

As research moves from an era of linear expansion of data and knowledge into an era of exponential data collection, driven by advancements in technology, the distinctions between different types of clinical research are dissolving. Accordingly, SHARP aims to conduct prospective clinical studies in addition to analysing registry data. This will start with a prospective study launched in 2021 that will validate the Severe Asthma Questionnaire (SAQ) within the SHARP network. The SAQ was developed with severe asthma patient stakeholder input and is, therefore, more patient-centred than the Asthma Control Questionnaire (ACQ) and more disease specific for severe asthma. In this study an online app, originally used within the RAPSODI registry, will be deployed, giving patients direct access to the questionnaires and facilitate the data collection. Future studies will incorporate measurements of mechanistic endpoints, through collaboration with other initiatives such as Unbiased BIOmarkers in PREDiction of respiratory disease outcomes (U-BIOPRED), Refractory Asthma Stratification Programme (RASP) and Study of Mechamisms of Action of Omalizumab in Severe Asthma (SAMOSA), as well as quantify the impacts of the environment.

Achievement of the ambitious major aims of SHARP requires more than what has been achieved so far. The severe asthma research community needs to pull together with patients to collect and organise as much relevant data as possible. It is only when a critical mass of data is achieved that research questions such as how to optimise therapies with biologics or other therapies and make the use of oral corticosteroids obsolete will be answered. Furthermore, it is only through pan-European efforts, such as SHARP, that we can gain an understanding of country to country variation in practice and the

organisation of the delivery of severe asthma care. Most important of all, initiatives such as SHARP are changing the doctor–patient relationship into a true partnership for research and management of severe asthma.

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