Overview of the sickle cell disease environment in select European countries
Contents

Introduction
Sickle cell disease: one of the most prevalent genetic diseases in Europe 4
About sickle cell disease 5
Purpose and scope of this document 6
About Global Blood Therapeutics 6
Methodology 6

1 The EU and the UK

1 Sickle cell disease in the EU and the UK 7
Sickle cell disease prevalence 7
Burden of sickle cell disease 7
Current assessment of sickle cell disease treatments 9

2 Activities in the field of sickle cell disease in the EU and the UK 11
Policy landscape 11
Advocacy landscape 13

INTERVIEW with Simone Boselli, Public Affairs Director at Eurordis 15

2 France

1 Sickle cell disease in France 17
Sickle cell disease prevalence 17
Burden of sickle cell disease 18
Current assessment of sickle cell disease treatments 19

2 Activities in the field of sickle cell disease in France 22
Policy landscape 22
Advocacy landscape 24

3 Germany

1 Sickle cell disease in Germany 27
Sickle cell disease prevalence 27
Burden of sickle cell disease 28
Current assessment of sickle cell disease treatments 29

2 Activities in the field of sickle cell disease in Germany 33
Policy landscape 33
Advocacy landscape 36
4 Italy

1 Sickle cell disease in Italy
   Sickle cell disease prevalence 40
   Burden of sickle cell disease 41
   Current assessment of sickle cell disease treatments 42

2 Activity in the field of sickle cell disease in Italy
   Policy landscape 46
   Advocacy landscape 47

   INTERVIEW with Professor Gian Luca Forni, President of SITE 49

   CASE STUDY
   Sickle cell disease patients in the EU have been disproportionately
   affected by the COVID-19 pandemic 50

5 Spain

1 Sickle cell disease in Spain
   Sickle cell disease prevalence 51
   Burden of sickle cell disease 52
   Current assessment of sickle cell disease treatments 53

2 Activities in the field of sickle cell disease in Spain
   Policy landscape 56
   Advocacy landscape 58

6 United Kingdom

1 Sickle cell disease in the UK
   Sickle cell disease prevalence 61
   Burden of sickle cell disease 63
   Current assessment of sickle cell disease treatments 68

2 Activities in the field of sickle cell disease in the UK
   Policy landscape 69
   Advocacy landscape 69

Conclusion 71
References 73
Introduction

Sickle cell disease: one of the most prevalent genetic diseases in Europe

Sickle cell disease (SCD) is a rare, inherited disorder, affecting more than 52,000 people in Europe. The condition, which carries a life expectancy of approximately 25 to 30 years below the general population, predominantly affects people of African, Mediterranean and South Asian descent.

The World Health Organisation recognised SCD as a global public health problem in 2006 and adopted a resolution on the prevention and management of birth defects at the 63rd World Health Assembly in 2010. Yet, levels of SCD awareness amongst the general public remain low. In countries with high prevalence, efforts are underway to improve the detection and management of the disease, but more needs to be done to ensure all SCD patients receive the care they need.

The following report is the result of research conducted in five European countries – France, Germany, Italy, Spain and the UK – and at European Union (EU) level to better understand the burden of the disease on patients, their families and healthcare systems. In addition, the report examines existing public policy efforts to address and alleviate the challenges faced by those living with SCD.
About sickle cell disease

SCD is a genetic condition that affects haemoglobin, a protein carried by the red blood cells that delivers oxygen throughout the body. It is caused by a genetic mutation and leads to the development of abnormally formed haemoglobin (haemoglobin S), which distorts red blood cells from a round to sickle (or crescent) shape. The sickling process causes the premature breakdown of red blood cells, leading to haemolytic anaemia; and inhibits red blood cells from passing through the small blood vessels, impeding the flow of oxygen. This leads to a blockage of red blood cells, causing vaso-occlusive crises and ischaemia (an inadequate supply of blood to vital organs such as the heart).

Due to the high levels of foetal haemoglobin, signs and symptoms of sickle cell disease generally do not appear until four to five months after birth.

Most SCD patients experience significant lifelong morbidities, although the severity of the disease varies considerably from person to person. In addition to leading to anaemia, which can cause shortness of breath, fatigue and delayed growth and development in children, over time, the sickling process can also damage major organs including the liver, kidneys, lungs, heart and spleen. In addition, SCD puts patients at higher risk of stroke, acute chest syndrome, blindness and bone damage.

Pain crises are the hallmark clinical presentation of sickle cell disease. The frequency of vaso-occlusive crises varies considerably, with some people having up to six crises per year, and others rarely experiencing them. People with SCD usually also live with underlying chronic pain.

Current SCD treatments centre around managing pain and treating complications such as cardiovascular effects and infections. While stem cell transplantation can be curative, there is a clear unmet need for new innovative treatments that improve patient outcomes.

It is notable that SCD affects particularly vulnerable groups in society who tend to have difficulties in accessing healthcare and that these groups have been made even more vulnerable by the COVID-19 pandemic.
Purpose and scope of this document

This report has been commissioned by Global Blood Therapeutics and aims to shine an informative light on the care pathways for SCD patients, as well as the key policies that affect them in France, Germany, Italy, Spain, the UK as well as at EU level.

About Global Blood Therapeutics

Global Blood Therapeutics (GBT) is a biopharmaceutical company dedicated to the discovery, development and delivery of life-changing treatments that provide hope to underserved patient communities. Founded in 2011, GBT is delivering on its goal to transform the treatment and care of sickle cell disease (SCD), a lifelong, devastating inherited blood disorder.

Methodology

This report is a combination of desk research and expert interviews with specialist medical practitioners, patient group representatives and policymakers, undertaken between July and September 2020. A thorough mapping of the key organisations involved in sickle cell disease in each European country considered was developed, to gain a clear understanding of the actors involved in shaping the SCD landscape, and to complement the research with structured telephone interviews. Each interviewed stakeholder was asked to provide insights on the prevalence of the disease, the current level of awareness in their respective countries, the policy agenda and other relevant information stakeholders wished to share. Two interviews are reported in this document.

Desk research was solely based on official resources, including position papers, official clinical guidelines, patient group information and available educational information. The full list of references is available at the end of this report.
1 The EU and the UK

Sickle cell disease in the EU and the UK

1.1 Sickle cell disease prevalence

In Europe, Sickle Cell Disease is one of the most frequent rare diseases. It is the most prevalent genetic disease in France, and in the United Kingdom (UK), and its prevalence is increasing in many other European countries. SCD primarily affects socio-economically vulnerable groups in the population.

According to figures from the European Medicines Agency (EMA), in 2019 approximately 1 in 10,000 people lived with SCD in the EU/ European Economic Area (EEA). This is equivalent to a total of around 52,000 people, which is considered below the ceiling for orphan designation (set at 5 people in 10,000). Similarly, 2020 figures from Orphanet (the European information resource for rare diseases) estimate that the prevalence of SCD in Europe is 10 per 100,000 people.

However, figures on the prevalence of SCD and other haemoglobin disorders are thought to be underestimated due to the lack of national registries and relatively poor access to care and diagnostic services. Introducing integrated care pathways across the EU and an EU-level registry of SCD patients would therefore help to better understand the burden of disease.

1.2 Burden of sickle cell disease

Vulnerable populations

The burden of SCD in Europe has been increasing over recent years and is likely to continue to do so. According to a 2018 consensus statement on newborn screening for SCD (see below for more detail), this increase can be explained by a combination of factors, including an increase in the number of newborns, an increase in SCD life expectancy, and an increase in migration from areas of high prevalence. Free movement of people and future migratory patterns may add to the strain healthcare systems currently face, and so will need to adapt to the needs of vulnerable SCD populations.
SCD patients across Europe face a number of challenges and barriers, including fragmentation of data across healthcare units, stigma towards Black, Asian and Minority Ethnicities (BAME) patients, lack of 360° care plans covering all medical issues, difficulty keeping track of medical checks and ensuring coordination amongst specialists, and differences in practice between doctors.

Patient registries

The establishment of the European Reference Networks (ERNs) by the European Commission in 2017 was a key step in the care of people with rare diseases, including SCD. The ERNs are virtual networks that involve healthcare workers across Europe, allowing them to share knowledge and resources on rare diseases.\(^{23}\) There are 24 ERNs working on different thematic areas.\(^{24}\)

EuroBloodNet is the ERN for haematological (blood) diseases, which builds on the work of the European Haematology Association (EHA) and the EU-funded European Network for Rare and Congenital Anaemias (ENERCA).\(^{25}\)

The European Rare Blood Disorders Platform (ENROL), which was launched in June 2020 and runs for 30 months, aims to provide EU-wide data on rare blood diseases across the Union.\(^{26}\) ENROL was developed by EuroBloodNet as an umbrella for both new and already existing registries on rare haematological disorders.\(^{27}\) Its aim is to avoid fragmentation of data by promoting the standards for patient registries’ interoperability released by the European Platform on Rare Diseases. It will map demographics, survival rates, diagnostic methods, genetic information, main clinical manifestations and treatments in order to obtain epidemiological figures and identify trial cohorts for basic and clinical research for rare blood diseases.\(^{28}\)

The Rare Anaemia Disorders European Epidemiological Platform (RADeep) is an initiative conceived by EuroBloodNet, which contributes to the ENROL Platform. It specifically pools data of patients affected by a rare anaemia, including sickle cell anaemia. The aims of the RADeep platform include promoting cost-effective allocation of resources, providing high-quality epidemiological data to aid decision-making, promoting best practices, generating knowledge and evidence through clinical trials and research projects, all the while for the benefit of patients and healthcare professionals.\(^{29}\)

These are very welcome developments in the monitoring of rare blood disorders, including sickle cell disease, in the EU and the UK. However, to fully understand the burden of SCD in Europe, an EU-wide patient registry is needed, which brings together data from all countries in a standardised manner. As with all rare diseases, it is difficult to make evidence-based decisions for SCD due to the small patient populations in each country. Therefore, EU-wide pooling of data would help toward better understanding of the disease mechanisms, disease course and for the sharing of best practices.
1.3 Current assessment of sickle cell disease treatments

*Treatment guidelines*

Overall, the currently available treatment options for SCD aim to manage the associated symptoms and pain crises.\(^{30}\) EuroBloodNet, the ERN for rare blood disorders, has reportedly developed 25 guidelines for red blood cell diseases based on the experience and good practice of the EU-funded European Network for Rare and Congenital Anaemias (ENERCA) and the European Haematology Association (EHA).\(^{31}\)

ENERCA published *clinical recommendations for SCD management in children* in 2011.\(^{32}\) For the treatment of SCD in children, the guidelines recommend prevention of infections with penicillin and pneumococcal vaccination; prevention of stroke through annual transcranial Doppler examination and regular blood transfusions in children with abnormal results; education and psychological support; yearly check-ups to check for early development or organ damage; and pre-operative preparation to prevent perioperative complications.\(^{33}\)

To treat disease complications, the guidelines contain specific indications for the various complications including pain, acute chest syndrome, infections and stroke.

For severe disease, the guidelines recommend three treatment options: hydroxyurea, chronic blood transfusion, or hematopoietic stem cell transplant in the case of HLA-identical siblings.\(^{34}\)

The European Haematology Association (EHA) has also announced on its website that it will publish guidelines on the management of pregnancy in patients with rare inherited anaemias.\(^{35}\) However, there is an unmet need for more recent European guidelines to guide standardised management of SCD patients across Europe.

*Newborn screening for SCD in the EU and the UK*

Screening programmes in the EU are determined at national level, and therefore there are wide variations and disparities in practice between countries. A *pan-European consensus conference on newborn screening for SCD* took place in 2017, and the conclusions were published the following year. The conference brought together over 50 experts in SCD from 13 European countries to discuss newborn screening for SCD in Europe and develop consensus-based statements.\(^{36}\) The report outlines the different NBS policies across Europe, and found that national screening policies are heterogenous across European countries, with no standardised approach to defining the population to be screened, the screening methodology or the flow of samples and patient reports.\(^{37}\)
In 2017, there were 5 countries with established NBS programmes for SCD in Europe: Belgium, France, the Netherlands, Spain and the UK. These programmes are universal, except in France where screening is universal only in overseas territories.

However, even amongst countries where universal screening is offered, differences exist for instance in the modality of screening used, and reporting of carrier status. The panel of the 2017 consensus conference agreed that in order to be successful, a newborn screening programme must be accompanied by a comprehensive care programme for affected infants. In line with this, the European Haematology Association (EHA) also states that newborn screening programmes should only be implemented with a disease management programme.

In terms of implementing a newborn screening for SCD, one of the main conclusions of the consensus statement is that newborn screening for SCD should be universal (i.e. offered to all children). This is because universal screening identifies more affected children and prevents more deaths, while targeted screening can miss cases and could lead to discrimination of at-risk groups. However, this raises cost-effectiveness issues, as countries often depend on evidence of cost-effectiveness in order to implement policies. If the disease prevalence is very low, it may not be cost-effective to screen all newborns.

This was taken into account by the panel and is highlighted in the consensus statement. There is evidence showing that newborn screening for SCD is cost-effective if the prevalence is above 1 in 6,000 births, however other factors such as the design of the screening programme also come into play.

The main objective of newborn screening for SCD is to improve outcomes for patients by detecting the disease early and allowing early intervention, thus contributing to reducing childhood mortality from SCD, in particular because SCD tends to affect vulnerable groups with more difficulties accessing care (and thus increased risk of poorer outcomes with disease progression). Screening also allows the possibility of offering genetic counselling to parents of affected children. In addition, newborn screening can offer wider benefits by providing clear estimates of the disease burden and has been recognised as a tool to tackle the lack of awareness of this disease. This is a clear unmet need in the care of sickle cell disease patients across the EU.
The EMA and treatments for SCD

The European Medicines Agency (EMA) is responsible for the evaluation and regulation of drugs in the EU. One of the only SCD medicines currently authorised in the EU is hydroxycarbamide, otherwise known as hydroxyurea, which is used to prevent recurring pain episodes.49

The EMA is also responsible for reviewing applications for ‘orphan designation’ for drugs. To achieve orphan designation, a drug must be:50

• Designed to treat a rare disease, the prevalence of which is below 5 in 10,000 (for instance, the prevalence of SCD is estimated to be 1 in 10,000)

• The disease must be life-threatening or chronically debilitating

• And there must be no currently approved satisfactory treatment; otherwise, the medicine must provide significant benefit to people affected

2 Activities in the field of sickle cell disease in the EU and the UK

2.1 Policy landscape – Legislative initiatives and parliamentary activity

Rare diseases, cross-border healthcare and newborn screening

Over recent years, rare diseases have been one of the focus areas of the EU institutions in the health domain. This activity was initiated when, in 2009, the Council of the EU adopted a Recommendation on an action in the field of rare diseases.52 Among others, it calls on EU Member States to gather national expertise in order to develop European guidelines for screening and diagnosis of rare diseases.52

The European Reference Networks (ERNs), which started their activity in 2017, have been one of the biggest achievements in this area. They were established by the 2011 Directive on cross-border healthcare, with the aim of tackling complex or rare diseases that require highly specialised treatment and concentration of knowledge.53 Due to the low prevalence or complexity of these diseases, patients affected by them often struggle to access the adequate care in their country. The ERNs aim to tackle this by allowing healthcare professionals from different countries to share knowledge, including advice on specific cases, or for patients to travel to centres of expertise in other countries where specific treatments can be carried out.54 The basis of the ERNs is the cross-border healthcare directive as it allows the exchange of health information across borders, without which the ERNs would not
be possible. Similarly, they also depend on the digitalisation of health as this allows the transfer of health data within these virtual networks. As outlined above, the ERN for rare blood disorders (including SCD) is EuroBloodNet, which brings together 66 multidisciplinary healthcare teams in 15 Member States and is highly active in advocating for SCD patients.

In terms of research and innovation into rare diseases, under Horizon Europe, the EU’s flagship research funding programme which will start in 2021, the European Commission has identified non-communicable and rare diseases as part of the six priorities for health research and innovation. In 2019, the European Joint Programme on Rare Diseases (EJP RD) was launched, with the aim of creating an ecosystem for research, care and innovation for rare diseases. The project has a total of €100 million investment, €55 million of which are contributed by the EU. It includes projects on translational research for rare disease (translating pre-clinical research to clinical) among others.

Newborn screening for rare diseases has also been one of the areas of activity in recent years in the EU. In 2020, a Call to Action for newborn screening for rare diseases was signed by numerous Members of the European Parliament (MEPs) and health stakeholders. MEP signatories were from political groups from the far-left to the centre-right, including representatives from the European People’s Party (EPP), Socialists and Democrats (S&D), Renew Europe, the Greens/European Free Alliance, and the Confederal Group of the European United Left – Nordic Green Left (GUE/NGL).

EuroBloodNet and the European Haematology Association (EHA) are strong advocates for the development of a European registry for SCD, as well as for EU-wide screening of SCD. In line with this, the EHA calls for common screening tools and guidance to ensure comparability across Member States and is developing an ‘SCD curriculum’, which will outline minimum requirements for screening, among others.

In terms of treatments for rare diseases, the EU Regulation on Orphan Medicinal Products (OMPs) was adopted in 1999 and puts in place the incentives for orphan drugs outlined above. This regulation is important for rare diseases as it has stimulated research into them and has increased the number of treatments available for patients with rare diseases in Europe.
2.2 Advocacy landscape

Stakeholders

Patient groups and SCD advocacy

Thalassemia International Federation (TIF) is an NGO that was established in 1986 and is made up of 232 member associations in 62 different countries. It represents the voice of patients living with thalassemia and other haemoglobin disorders, including SCD. It is an important player in ensuring that the voice of SCD patients are heard and has been active in raising awareness for SCD.

EURORDIS is an umbrella organisation representing patients with rare diseases in Europe. In parallel to the establishment of the ERNs, EURORDIS initiated the development of European Patient Advocacy Groups (ePAG) for each ERN, to bring together patients who are affected by the diseases covered by that ERN. The European Patient Advocacy Group in Haematology includes a representative of the Thalassemia International Federation (TIF), representing patients with haemoglobin disorders.

At the end of 2019, it was announced that the European Network of Sickle Cell Disease Patient Organisations was being set up by EuroBloodNet and EURORDIS. The aim is that it will provide a centralised point of contact for local and national patient groups representing SCD patients, allowing collaboration between groups and ensuring that their voice is heard in the debate. It also aims to ensure that rare disease policies are adequately implemented and to make the patient voice front and centre.

Medical societies

The European Haematology Association (EHA) brings together blood disorders specialists from across Europe. It ‘advocates the interests of haematology and haematologists in Europe’ and carries out education and awareness-raising activities.

As outlined above, EuroBloodNet is the ERN for rare blood disorders, and has been highly active in advocating for rare haematological conditions since its creation in 2017. EuroBloodNet states that a patient-centred approach is central to its work, highlighting the importance of patient involvement to empower patients.

The EU-funded European Network for Rare and Congenital Anaemias (ENERCA) was founded in 2002 with the aim of improving care for rare anaemias, including SCD, by promoting collaboration between experts. The fourth phase of the ENERCA project, e-ENERCA, started in 2013 and aimed to enhance the use of digital technologies to improve care for patients with rare anaemias, ensuring the same access to rare anaemia services across Europe.
Advocacy and non-legislative initiatives

Due to the low prevalence of SCD across the EU, awareness levels and knowledge tend to be low, in particular among policymakers.

One of the EHA’s main goals is to raise awareness for haematological conditions, including SCD. It does this through educational activities for a range of audiences, including patients, the public, healthcare professionals and policymakers. In terms of awareness-raising activities, the EHA developed the ‘Topics-in-Focus’ programme, which aims to raise awareness for specific haematological diseases and stimulate activity and research on them. SCD was the EHA’s Topic-in-Focus for 2018-2019, with a dedicated web portal, SickleCellNet, to act as a central point of information for these awareness-raising activities.

EuroBloodNet also carries out educational activities and continuing medical education for healthcare professionals, as well as developing best practice guidelines, building on the work done by ENERCA. For instance, EuroBloodNet published best practice guidelines for healthcare professionals as well as organising interactive education sessions such as their Thursday webinars to provide education on specific topics.

The last phase of the ENERCA network ran from 2013 to 2016 and was entitled e-ENERCA. It was focussed on the implementation of digital tools to improve the care of rare anaemias. Its goal was to provide healthcare professionals and patients with digital health tools to ensure equal care for patients with rare anaemias across the EU. Digital tools are key for the care of patients with SCD and other rare diseases as they allow sharing of information across borders, pooling knowledge and increasing the knowledge base.

Despite growing advocacy on the need to provide better care for SCD patients by scientific societies and patient advocacy groups, awareness amongst policymakers remain low.
Interview with Simone Boselli
Public Affairs Director at EURORDIS

The impact of COVID on rare disease patients

In 2020, EURORDIS carried out a survey on the impact of COVID-19 on people with rare diseases. The survey results showed that the pandemic had led to a global disruption of care for these patients. Asked out the survey, Simone Boselli commented that ‘the results showed both the negative and positive (to a lesser extent) effects of the pandemic. The positive effects included an increase in virtual consultations and telemedicine.’ Simone added that ‘sometimes, a crisis is needed to take up safe and effective methods such as telemedicine.’ Regarding telemedicine, Simone Boselli added that ‘virtual consultation is the backbone of the European Reference Networks (ERNs), especially when it comes to sharing data and solving difficult cases. Although the infrastructure is there to make greater use of telemedicine, it remains to be seen how Member States will apply the recommendations made by EURORDIS on telemedicine and making sure the necessary safety requirements are applied in post-COVID.’

Asked about the main challenges that rare disease patients, and SCD patients in particular, face in the EU, Simone Boselli responded that ‘Some of the main challenges for SCD patients are the stigma and the misunderstanding of the disease, as well long times to diagnosis. These are very common amongst most rare diseases. In addition, SCD is primarily diagnosed in minority groups, which makes this social stigma even more important. Difficulties arise for patients in managing their disease, the number of HCPs they need to see and the difficulty of transporting their data between countries (especially for migrant populations). Making data interoperable is a common challenge that all people living with rare diseases face, not only when they travel across borders but also between different regions. It is very important to solve these social issues when it comes to SCD.’

Simone Boselli’s views on the impact of COVID-19 were that COVID-19 disproportionately affected patients who have to follow strict shielding rules, as they were not able to attend visits. According to him, ‘whilst there is no evidence on the direct impact of COVID-19 on SCD
patients in the EU as they fall under the shielding category, it is possible to infer that they too have been disproportionately affected. Putting in place safe corridors to access hospitals could help solve this problem.’

**Policy opportunities for rare disease patients and SCD patients**

On the topic of screening, Simone Boselli explained that ‘here is an opportunity to harmonise policy across the EU for newborn screening. Newborn screening is not only important for diseases where there are more therapies available but also because most of the diseases screened for are genetic. Screening allows parents to know the genetic information as well as what it means.’ He added that ‘in the context of the European Commission’s pharmaceutical strategy public consultation, EURORDIS has published a position paper which included a number of points relevant to SCD. Within this, the gap in the time taken for therapies to be made available in different countries is highlighted. For a debilitating condition like SCD, more needs to be done. EURORDIS are pushing for the ERNs to improve the overall eco-system from diagnosis to treatment.’

In their response to the European Commission’s consultation on the roadmap for a pharmaceutical strategy for Europe, EURORDIS called for reinforcement of ERNs at various levels including integration at national level and the creation of Clinical Research Network.

Although many EU policy commentators observed that the proposed health budget (EU4Health) had significantly been reduced, Simone Boselli observed that ‘the budget remains 3-4 times bigger than the previous budget allocated. Through it, there is a possibility to look at pilot projects, including tackling the social aspects of conditions such as SCD. It is therefore important to clearly highlight the economic and social impact of the disease in advocacy work.’
With more than 26,000 patients diagnosed with SCD in 2018, the country has the highest prevalence of SCD in Europe, followed by the UK. This high prevalence has been constantly increasing at a rate of 5–7% per year since the early 2000s. However, it vastly fluctuates from one region to another, depending on the distribution of at-risk communities – for instance, 1 in 16,000 cases are recorded in Lille in the North of France, while 1 in 550 are recorded in Saint-Denis in the Paris region.

SCD was recognised for the first time as one of the priorities in France in the public health law of 2004. The ambition of this law is to improve the health of the population by reducing health inequalities and acting on the modifiable determinants of premature mortality. The SCD-related objectives are to improve the care and quality of life of those affected by the disease.

In recent years, medical care for SCD has considerably improved, with the creation in 2005 of the reference centre for sickle cell syndromes. This reference centre brings together highly specialised medical teams with proven expertise in SCD care, research and training. In the overseas departments, a reference centre for SCD was established in 2006 in Antilles-Guyana and two competence centres were established in 2008, one in Guadeloupe and the other in Réunion-Mayotte.

There have been significant efforts in the past 10 years to increase awareness among the general public in France, including through TV spots broadcasting documentaries and information on SCD. For example, a TV spot shines a light every year alongside the Association for Information and Prevention of SCD (APIPD) on the need for continued action in support of SCD patients.
1.2 Burden of sickle cell disease

Studies on the mortality associated with SCD from the 1980s in France show a gradual improvement in the lifespan of those affected, measured by a decline in the median age at death and a decrease in the proportion of deaths in children.77

A 2015 study by Gomes E et al confirms that there is a decrease in the death rate linked to SCD among young children in France, and that the proportion of infections has decreased. These findings are encouraging as they suggest that early detection combined with better management of the disease in childhood has had an impact on the infectious complications of SCD and on mortality at an early age.78

In 2013, the High Authority of Health (Haute Autorité de Santé, HAS) in France developed an orientation report on newborn screening for SCD in France and the relevance of generalising screening to all newborns. According to this report, complications of SCD can arise as early as three months of age and can be life threatening. The child is usually protected before this age by the presence of fetal haemoglobin (HbF).

Knowing that the frequency and severity of clinical manifestations is highly variable over the life of the same patient and between different patients with the same genotype, the prognosis of sickle cell patients is difficult to predict. Death can, for instance, be precipitated by severe vaso-occlusive disease or organ failure. There is no validated model that predicts the clinical course of a person with sickle cell disease.79

Although the HAS states that there is no evidence to conclude on the relevance of a systematic screening strategy in terms of effectiveness and efficiency, the report still provides extensive research on the disease, including on the screening of SCD. Moreover, the report mentions that, in France, the observed average age at death declined steadily between the period 1981-1985 and the period 2001-2005, and it was estimated at 40 years for the period 2005-2008.80
1.3 Current assessment of sickle cell disease treatments

The French Newborn Screening (NBS) programme

A national NBS programme was established in France in 1978 and was entrusted to the French Association for the Screening and Prevention of Childhood Disabilities (AFDPHE), under the supervision of the General Directorate of Health (DGOS) and the National Health Insurance Fund for Salaried Workers (CNAMTS) which provides its funding. The NBS programme covers the entire national territory, including mainland France, the overseas departments (Réunion, Martinique, Guadeloupe, Mayotte and Guyana) and the overseas communities (Wallis-et-Futuna, Saint-Pierre-et-Miquelon, French Polynesia and New Caledonia).81

SCD was included in the NBS programme in 2000. The programme targets newborns identified as at risk in mainland France and all newborns in the French overseas territories. The at-risk population is qualified as newborns from parents originating from a country where SCD is endemic, based on an official list, when there is a family history of SCD, or when there is uncertainty with regards to both previous issues. This official list of regions has been published by the AFDPHE and includes the following regions: some French overseas departments (Antilles, Guyana, Réunion, Mayotte); all the countries of sub-Saharan Africa and Cape Verde; Brazil; black people from North America; India, Indian Ocean, Madagascar, Mauritius, Comoros; some countries in North Africa (Algeria, Tunisia, Morocco); Southern Italy, Sicily, Greece, Turkey; and some Middle Eastern countries (Lebanon, Syria, Saudi Arabia, Yemen, Oman).82

When the diagnosis of SCD is confirmed, patients have access to medical care that is free of charge for all aspects related to specific prophylactic and therapeutic measures for SCD, including treatment, as well as consultations and hospitalisation.83

SCD Care Network in France

For children with SCD, treatment is organised around a multidisciplinary care network made up of a paediatrician, a general practitioner, a hospital doctor specialising in SCD, mother and child health doctors and nurses, social workers, etc.

To improve the coordination of care of patients with SCD, an ‘emergency and healthcare card’ is given to parents and patients. The purpose of the card is to facilitate the flow of information between patients, carers and healthcare professionals, while respecting medical confidentiality.
This card consists of two parts:

- A care section that provides contact details for doctors and people to be contacted in case of emergency, contact details for sites and organisations from which to find information, as well as useful personal data in case of emergency
- An *information and advice* section intended to provide patients and families with practical information on the disease and management advice in the form of ‘golden rules’ (when to urgently consult, how to better prevent and rapidly take charge of any complications, etc)

**SCD detection and management in France**

In 2011, the HAS in France developed a Medical Guide for long-term condition (ALD) on SCD entitled *Major SCD syndromes in children and adolescents*. The aim of this national diagnostic and care protocol (PNDS) is to explain to healthcare professionals the current optimal management and the course of care for patients with SCD. Healthcare professionals can refer to it to establish the most appropriate treatment protocol. The protocol was drawn up by a steering group coordinated by the reference centres for sickle cell syndromes in France, with the methodological support of the HAS.84

Overall, the medical management of SCD in France consists of monitoring anaemia, preventing and treating vaso-occlusive crises and infections, and quickly detecting complications in order to treat them as soon as possible. This medical care has considerably improved since the majority of diagnoses are made at birth since the inclusion of SCD in the NBS programme in 2000.85

Thanks to screening at birth, it is possible to manage children with the disease from an early stage: around the age of two months, medical follow-up for the patient is set up, as well as the care network that parents can rely on.

Specific measures include:

- Vaccinating the child according to the 11 compulsory vaccinations set up in 2018,86 with the addition of vaccinations against influenza, BCG against tuberculosis, as well as vaccination against hepatitis A and typhoid (in case of travel)
- Taking an antibiotic (penicillin) continuously for at least five years
- Taking vitamin B9 supplementation (folate)
- Monitoring every two to three months with blood tests, ultrasounds, x-rays, and transcranial doppler (TCD) ultrasounds from the age of 12 to 18 months
- Educating parents on the warning signs that require an emergency consultation
- Educating parents on the hygiene measures to adopt (regular hydration, prevention of colds, oral and personal hygiene, etc)
Other important aspects of SCD management in France include:87,88

- **The management of painful vaso-occlusive crises:** Patients or parents of children with SCD are trained in the management of a possible painful vaso-occlusive crisis. They always have a prescription for analgesics (paracetamol or ibuprofen, with or without codeine), and are trained to, in case of a crisis, take these medications and drink more than usual. In case this independent management at home is not enough to relieve the crisis, more powerful analgesics can be prescribed. Hospitalisation may be necessary (especially for children). This hospitalisation can allow intravenous hyperhydration and the administration of analgesics such as nitrous oxide, a sedative gas treatment by inhalation.

- **The management of fever episodes:** During a fever episode, which is more common in children, it is necessary to look for an infectious cause and, if necessary, prescribe an appropriate antibiotic treatment.

- **The management of acute chest syndrome:** Treatment of acute chest syndrome is most often done with intravenous hydration, prescription of antibiotics and pain relievers, and possibly with oxygenation and blood transfusions.

- **The management of acute anaemia:** Whether due to splenic sequestration or an aplastic crisis, acute anaemia requires blood transfusions to provide functional haemoglobin and restore optimal organ oxygenation.

French guidelines also include information on Haematopoietic Stem Cell Transplantation (HSCT), the transplant of haematopoietic stem cells, and on the future gene therapy which would consist of inserting the gene encoding normal haemoglobin into a patient’s bone marrow cells to have this gene become functional over time.

Recent media coverage has highlighted the hope for the latter to become reality. In fact, a press release from the Imagine Institute (Institute of genetic diseases) has opened up a new avenue for the treatment of SCD with a new approach to gene therapy. The aim of this new therapy is to activate a replacement gene that is already available, the globin-γ produced during fetal development. To come to this lead, the researchers observed people who carried the mutation that caused SCD but who did not develop the disease because globin-γ was still produced following a second genetic mutation, which cancelled out the disease effect of the first. However, these results will need to be confirmed by further clinical studies.89

A sickle cell information and screening centre (CIDD) was also created in December 2006 in Paris, where a multidisciplinary team welcomes SCD patients to help them cope with their disease.
2 Activities in the field of sickle cell disease in France

2.1 Policy landscape

SCD is still considered a rare disease, and is included in the Filière de santé maladies constitutionnelles rares du globule rouge et de l’érythropoïèse (MCGRE) network – the French National Rare Disease Network – which deals with research and education on rare diseases, in collaboration with the Ministry of Health.

France was among the first countries in Europe to promote bloodspot testing through the Guthrie test. The test currently allows for the detection of five rare diseases: phenylketonuria, congenital adrenal hyperplasia, hypothyroidism, cystic fibrosis and, for newborns with risk factors, sickle cell anaemia.90

Even though SCD is often described as the most common genetic disease in France, neonatal screening is still only targeted to newborns at risk based on the country of origin of their parents.91 Since 1989, SCD neonatal screening has covered all French overseas territories. In 2014, the HAS published a report showing the rationale for generalising neonatal screening for SCD to all newborns in France. However, this study did not explicitly recommend extending screening for sickle cell anaemia to all newborns.92

Legislative and governmental initiatives

Newborn screening is undoubtedly the most debated issue amongst all identified key opinion leaders, particularly the National Assembly and Senate. Numerous Members of the Parliament from overseas territories have led the debate, focusing on the importance of systematic neonatal screening to detect SCD.

Access to treatment and care

On 5 March 2020, a written question related to this topic was put forward, raising the issue of the unmet needs of SCD patients in the Guadeloupe archipelago. In their response on 3 September 2020, the Minister of Health and Solidarity detailed the various measures and initiatives put in place to ensure the equal access to treatment for Guadeloupe residents.93

The role of University Hospitals in the provision of care has also been discussed. The debate highlighted on the structural limits of University Hospital Centres in France, such as regular budget deficits and important differences between the Centres in metropolitan France and those operating in overseas departments.
Access to SCD screening in France

Access to SCD screening has been put forward numerous times at a Parliamentary level in France. Members have advocated on the importance of systematic neonatal screening and for an amendment aimed at launching a €5 million budget for research on SCD in the 2020 Budget Law. However, the recommendations and amendments put forward have neither been followed nor adopted by the French Parliament.

Recent conversations on the law of bioethics

In 2019, the French Parliament discussed the report on the revision of the law on bioethics. The report highlights that the diagnosis of sickle cell anaemia is based on genetic tests and that the regulatory framework on genetic testing should therefore be applied to SCD. During the discussion of the Bioethics Bill in the National Assembly, Members of Parliament in favour of the inclusion of genetic tests in newborn screening programmes were not supported by the Government.94

In January 2020, the Senate discussed genetic tests for newborn screening for the second time. During this debate, the Government suggested rejecting the article aimed at prioritising first-line genetic tests as part of newborn screening for early detection of genetic anomalies, including SCD.

At the time of preparing this report, the draft law on bioethics was still in progress (second reading at the French Parliament) and was being evaluated by the Special Committee in charge of the Bill on Bioethics. The potential systematic implementation of genetic tests and screenings for diseases of genetic origin continues to be a lively political debate due to the ethical and practical implications of systematic genetic tests for rare diseases, including sickle cell anaemia.

On Monday 27 July 2020, the National Assembly debated the Bioethics Bill again. Debate on the topic of pre-implantation genetic diagnosis (PGD) was politically charged. After much discussion, the National Assembly voted against the expansion of PGD to search for chromosomal abnormalities.

The National Plans for Rare Diseases

The Ministry of Health is responsible for producing National Plans for Rare Diseases. The national plan for rare diseases (2018–2022) aims to improve neo-natal and pre-natal diagnosis (PND) as well as pre-implantation genetic diagnosis (PGD) to enable earlier diagnosis, in accordance with the objectives set in the National Health Strategy (2018–2022) such as encouraging pre and neo-natal screening, especially for sickle cell anaemia.
The plan for rare diseases also aims to tackle the ethical and regulatory issues raised by PND and PGD and the performance of post-natal screening in the general population, in the context of the revision of the bioethics law.

2.2 Advocacy landscape

Stakeholders and non-legislative initiatives

There are several influential opinion leaders who are active in the field of SCD education and awareness in France. Patient associations are particularly active around 19 June, World Sickle Cell Day.

The MCGRE network on red blood cell diseases is comprised of healthcare professionals and patient representatives. This network ensures optimal coordination at a national level between the key actors involved in red blood cell genetic diseases. The network implements projects and awareness campaigns in key areas such as therapeutic patient education, child/adult transition, medical-social care and emergency care. It also aims to improve the harmonisation of quality and access to care throughout France, comprising the standardisation of databases, their interoperability and connection with the National Bank of Rare Disease Data. MCGRE participates in the ERN EuroBloodNet, a collaborative platform dedicated to sharing clinical information on haematological diseases.
Medical societies

Institute Imagine brings together researchers, doctors and patients to maximise access to clinical innovations and new treatments for rare genetic diseases. The institute works together with Necker-Enfants Hospital and INSERM/University of Paris to share knowledge and equipment, and to accelerate research. Imagine researchers study the genetic defects of haemoglobin in two forms of severe anaemia: sickle cell anaemia and thalassaemia.

Other medical societies are active at a local level via university hospitals where some high-profile SCD advocates work. These hospitals include:

- **CHU Henri Mondor** in Paris with their Red Blood Cell Genetic Diseases Unit. Two specialists and high profile SCD advocates, Professor Frédéric Galacteros – who contributed to the publication of the article ‘Gene Therapy in a Patient with Sickle Cell Disease’95 – and Professor Paolo Bartolucci, work in this unit.

- **Centre de la drépanocytose, Hôpital Tenon** in Paris. The Sickle Cell Disease Centre at Tenon Hospital coordinates the multidisciplinary management of a cohort of more than 1,000 adult patients. Tenon Hospital is one of the two largest centres monitoring adults with SCD in Metropolitan France together with Henri-Mondor hospital in Créteil.

- **Hôpital Necker Enfants** is the reference centre for sickle cell syndrome. It supports more than 1,300 patients with red blood cell pathologies and erythropoiesis from birth to adulthood. The centre works closely with community medical organisations, medical schools and patient associations. The biotherapy department takes care of adult patients, especially those receiving regular transfusions, and is a reference centre for the care of pregnant women with SCD. It also acts as an information centre on national diagnostic and treatment protocols for rare diseases and offers therapeutic trainings on pain management and sport activities for SCD patients. It is also a knowledge hub for research on early prognostic factors of SCD severity, the role of innate immunity in SCD and gene therapy for haemoglobin diseases.
Patient organisations

SOS Globi Federation brings together 16 patient organisations fighting against SCD and thalassemia in France. Their mission is to promote the creation of local associations and to represent patients at a national level. They actively advocate for better management and recognition of SCD and thalassemia.

In June 2020, SOS Globi launched the DRE Patient survey, the first national survey led by the MCGRE network to assess the impact of SCD on quality of life, education and socio-professional integration of adult patients and parents of sick children living in France.

Association Pour l’Information et la Prévention de la Drépanocytose (APIPD) regularly carries out awareness-raising campaigns across schools, and businesses and for different age groups to support children and adults impacted by SCD. It also helps patients complete administrative procedures and campaigns for the development of SCD services in hospitals, especially in emergency departments. APIPD was one of the first stakeholders to call for the generalisation of SCD screening for all newborns with the aim of freeing patients from the stigma of the disease.

Association Guadeloupe Espoir Drépanocytose seeks to raise awareness about SCD in Guadeloupe, campaign for financial resources, and influence the creation of paediatric intensive care services.

DREPAVIE’s mission consists of raising awareness of SCD, fighting against the isolation faced by sickle cell patients and their families, and promoting access to care for sickle cell patients in France and in the Southern countries. In 2011, DREPAVIE organised a series of events and artistic projects, in partnership with various artists and the photo agency D.E.E.P. to raise awareness of SCD. A notable output from this campaign was the music video ‘Juste un regard’ aiming to outline the often invisible challenges faced by SCD patients and the prevalence of the disease.
3 Germany

1 Sickle cell disease in Germany

1.1 Sickle cell disease prevalence

There are an estimated 3,000 children and adults living with SCD in Germany.\(^\text{96}\) The country does not offer newborn screening for SCD, making it difficult to reliably track the prevalence and the number of children born with the disease. According to a 2017 study by Kunz et al, the epidemiology of SCD in Germany is continuously changing due to ongoing immigration.

Data relating to admissions and diagnoses provide an estimate of the increasing prevalence of SCD and its complications in Germany.\(^\text{97}\) However, more detailed epidemiological data is required to assess the burden of disease, identify shortcomings in patient management and improve patient care. Additionally, health policy decision-making, for example regarding the implementation of a newborn screening programme for SCD, needs to be supported by robust evidence. This is why a registry for patients with SCD was established by the German Society of Paediatric Oncology and Haematology (GPOH).

Based on annual births, it is estimated that 230,000 children (0.74% of births) are born with SCD in sub-Saharan Africa, whilst only a total of 1,300 children are born with the disease across Europe.\(^\text{98}\) Extrapolated to Germany, this corresponds to around 200 children per year.\(^\text{99}\) In the GPOH registry, around two thirds (69%) of the 327 paediatric patients currently evaluated come from sub-Saharan Africa (Ghana, Nigeria, Togo) or the Middle East (Lebanon, Turkey, Syria).\(^\text{100}\)

Based on the research conducted, it is apparent that SCD has only recently been identified as a challenge in Germany, with only very recent actions taken by the government to combat this disease. However, based on the positive outcomes of a 2019 survey on screening for SCD in newborns, conducted by the Institute for Quality and Efficiency in Health Care (IQWiG),\(^\text{101}\) a newborn screening programme is expected to be introduced in Germany in 2021.

The rapidly increasing number of inpatient treatments and deaths of young children from SCD clearly indicates the need for a general newborn screening
programme and highlights the importance of increasing awareness of this disease among medical practitioners.

1.2 Burden of sickle cell disease
As raised above, there is practically no epidemiological data on SCD in Germany. SCD was not perceived as a significant problem in the German healthcare system until 2018, when the Federal Joint Committee (G-BA) commissioned the IQWiG to evaluate screening for SCD in newborns.\textsuperscript{102}

Based on an unselected cohort of 34,084 Berlin newborns that were tested for SCD between 1 September 2011 and 30 November 2012, the study indicated a 95% probability that the incidence of SCD in Berlin was at least 2.5/10,000. In fact, the results showed that 14 newborns were affected by SCD and 265 newborns were identified as haemoglobin S (Hb S) carriers. It was also noted that, at the time of registration, more than two thirds of patients had previously experienced at least one pain crisis requiring hospitalisation, and over one quarter of the patients had already suffered from acute chest syndrome.\textsuperscript{103}

SCD is not a target disease of the general newborn screening programme in Germany. This is often why SCD patients are diagnosed after the first year of life when symptoms of SCD have already occurred.\textsuperscript{104} A 2019 study, based on a retrospective registry, tried to assess whether early diagnosis and follow-up treatment leads to fewer complications. Two groups of patients were defined as part of the study. Group one, labelled as ‘diagnosed early’, consisted of patients diagnosed within the first six months of life before the onset of symptoms either due to newborn screening, positive family history, or an incidental finding. Group two, labelled as ‘diagnosed late,’ had already been affected by symptoms of
SCD or were diagnosed after six months of life. Results showed that the number of patients with a history of symptoms, such as pain crises, was higher in the late diagnoses group as opposed to the early one, with a ratio of 69.6% to 53.7% respectively.105

In terms of prevention of deaths of affected children, the 2019 IQWiG study showed that there is a slight benefit in favour of newborn screening for SCD, particularly if a positive test is followed by further interventions such as educating family members on the signs of serious complications and how best to manage them.

1.3 Current assessment of sickle cell disease treatments

The 2014 SCD guidelines developed by the Association of the Scientific Medical Societies in Germany (AWMF), with the GPOH as the leading professional society, recommend preventive behavioural measures for SCD treatment (e.g. education and instructions) as well as methods of long-term monitoring and treatment of SCD patients.106

**Long-term therapies recommended in Germany**

All recommendations are based on the 2014 SCD guidelines developed by the Association of the Scientific Medical Societies in Germany, with the GPOH functioning as the leading professional society. The guidelines have not been updated for over 5 years and are currently being revised, it is however still unclear when the new guidelines will be published107 Their current long-term recommended therapies include the following:

- Treatment with hydroxycarbamide is recommended for all patients that have ever experienced painful vaso-occlusive crises (including mild ones) or acute chest syndrome. The treatment is recommended to be started as early as possible. The recommendation is based on the National Heart, Lung, and Blood Institute guidelines, developed after the ‘BABY HUG’ clinical trial, a randomised, double-blind, placebo-controlled clinical trial of hydroxyurea in infants (beginning at 9–18 months) with SCD108

- The transfusion of red cell concentrates is recommended as an important pillar in the treatment of patients with SCD. This is recommended to treat certain cutaneous complications but can also be part of a long-term therapy programme

- Stem cell transplantation (SCT) is recommended for adult patients. The implementation of a registry study on stem cell transplantation in SCD patients is ongoing. As mentioned in the guidelines, the improvement of supportive therapy and the introduction of hydroxycarbamide have significantly reduced the morbidity and mortality in SCD patients, particularly in children. Yet adults
still have a high morbidity rate, which significantly limits their life span and quality of life. The only curative therapy strategy currently used for SCD is stem cell transplantation.

**The GPOH-registry of sickle cell disease**

The GPOH-registry of SCD, established in January 2013, aims to describe the epidemiology of SCD in Germany. Patients with SCD are characterised clinically and genetically, and treatments are documented, with the aim of identifying predictors of the course of the disease. Additionally, the results of the registry seek to provide solid evidence to support the incorporation of SCD into routine newborn screening and to update the national guidelines for the management of SCD patients in Germany. A group of five university hospitals (Berlin, Frankfurt, Hamburg, Heidelberg and Ulm) have been mandated to implement the GPOH registry. Centres that deal with either paediatric or adult patients with SCD are encouraged to support the registry.

The GPOH-registry analyses various aspects of SCD:

- **What are the most common forms of SCD in Germany?** Several genetic factors influence the clinical course of SCD, including (but not limited to) mutations in haemoglobin genes. The GPOH-registry aims to define which genetic forms of disease characterise sickle cell patients in Germany.

- **What complications occur in sickle cell patients?** Patients with SCD can suffer from diverse complications. Many factors influence the clinical course of the disease, for instance age at initial diagnosis and the type of treatment received. As the situation of patients living in central Europe differs from that of patients living in other countries – owing to the fact that countries have different screening practices and treatments – the GPOH-registry wants to collect more information about the typical complications of patients living in central Europe to better understand the disease and to define appropriate therapeutic strategies.

- **How can the clinical course of sickle cell disease be predicted?** The clinical course of SCD varies from patient to patient. The GPOH-registry aims to define some disease characteristics which can help predict the course of the disease for both individuals and groups.

- **How are patients with sickle cell disease treated?** In order to treat patients with SCD uniformly, the coordinators of the GPOH-registry published national guidelines for therapy. The GPOH-registry will provide information on the number of patients treated according to these set guidelines.
• What consequences does sickle cell disease have on patients’ lives?
SCD is rare and largely unknown in central Europe. Patients are frequently misunderstood, e.g. limitations at school or at work may not be attributed to SCD but wrongly misinterpreted as laziness. With the help of appropriate questionnaires, the GPOH-registry will investigate how much SCD restricts patients’ everyday lives.

General preventive care and screening
Paediatric screenings and preventive medical check-ups were established and included in the benefits package in Germany in 1970. The scope of this package continues to expand. Recurring developmental check-ups (Untersuchungen) mostly carried out by paediatricians, are offered to infants (U-check-ups 1-6), children (U-check-ups 7-11) and adolescents (U-check-ups 12-13). The screenings are paid for by the statutory health insurance funds.

In the course of the second to third day of life (36 to 72 hours after birth – possibly during the second U-check-up), a laboratory screening to test for inborn disorders of metabolism is performed. The blood will be tested for 11 diseases.* However, a urinary screening, for example for proteinuria, haematuria, and leukocyturia is not regularly performed.² Nor is this type of screening mentioned in the guidelines on prevention of diseases for children up to 6 years of age (Kinder-Richtlinien), which outline the details of newborn screening in appendices 2 to 4.¹¹

The German Newborn Screening (NBS) programme
The NBS programme was established in 1969 and the number of targeted diseases in the programme has now reached 16, including all diseases associated with endocrine or metabolic disorders such as phenylketonuria, a rare genetic condition entailing decreased metabolism of the amino acid phenylalanine. These newborn screenings are promoted to new parents but are not obligatory. Despite this, the test uptake is very close to 100%.¹²

SCD is not included in the targeted diseases of the NBS programme. This is mainly due to the disease not being previously seen as endemic. The first systematic attempt to identify SCD in newborns was made in 2008 by Genzel et al, in their report on Haemoglobinopathies and newborn haemoglobinopathy screening in Germany. The report was conducted by the Department of Obstetrics in Munich and is based on a targeted pilot project including 306 neonates born to African mothers in Munich.¹³

* Congenital adrenal hyperplasia (CAH), Maple syrup urine disease (MSUD), Biotinidase deficiency, Carnitine inborn errors of metabolism, Fatty-acid metabolism disorder, Galactosmia, Glutaric acidemia type 1, Hyperphenylalaninemia, Hypothyroidism, Isovaleric acidemia, Phenylketonuria (PKU), Severe combined immunodeficiency (SCID), Tyrosinemia type 1.
The establishment of the GPOH-registry has drastically improved awareness and care of SCD. So far, the members of the registry have completed four regional pilot studies on NBS for SCD. Two have been done in the Berlin NBS laboratory and one each in the Hamburg and Heidelberg NBS laboratories.114

**Newborn screening for SCD in 2021**

The aim of newborn screening for SCD is early identification and treatment for affected children. It is thought that the life expectancy of children with SCD increases with earlier diagnosis in conjunction with family training and infection-prevention measures from the third month of life.

As mentioned, SCD is not currently one of the targeted diseases of the newborn screening programme carried out in Germany according to the G-BA’s guidelines on children, for which blood from the heel is dripped onto filter paper cards in the 36th to 72nd hour of life. This is in contrast to other countries, such as the United States and, in Europe (Belgium, France, the Netherlands, Spain and the UK) where newborn screening for SCD is well established.

In order to assess whether testing newborns in Germany for SCD would be valuable, IQWiG used a retrospective, historically comparative screening study from Jamaica. Between 1995 and 2007, a total of 150,803 newborns were screened for SCD in Jamaica and treated early, if positively diagnosed. This means that children were given penicillin prophylaxis from the fourth month of life and were examined regularly. In addition, parents were informed comprehensively about the disease and doctors showed them how to feel changes in their child’s spleen. As part of the screening, 435 newborns were diagnosed with SCD, and 395 of them were subsequently part of the intervention programme. The Jamaican scientists compared the development of these 395 children with the development of 105 children who had also been diagnosed, using newborn screening, between 1973 and 1981 but who were not – due to a lack of treatment options – treated in the first years of life.

The outcome showed that the mortality rate dropped by a factor of 10. The effect of the early diagnosis of SCD in connection with early intervention measures is very clear: 0.01% died in the group of children treated early whilst in the group of untreated children 0.1% died. There are consistent effects for the evaluations up to the age of five.115

On the basis of these results, the IQWiG observes a benefit in favour of newborn screening for SCD in combination with earlier diagnosis and other intervention measures such as education of family members, to improve outcomes for children with SCD.
2 Activities in the field of sickle cell disease in Germany

2.1 Policy landscape

The child health care system in Germany

Regarding the coordination of care, training of paediatricians, improvement of clinical care, as well as the empowerment of children and their families, the German health care system has gone through an intense period of change.\textsuperscript{116}

The increasing number of so-called ‘new morbidities’ (e.g. obesity, attention deficit disorder, dyslexia, speech delay and psychosomatic symptoms), has given rise to a set of new challenges for clinicians. In response to this, Germany has created 145 social paediatric centres (Sozialpädiatrische Zentren) across the country since the late 1960s. These centres are designed to focus on the treatment of these morbidities, along with the treatment of children with long-term conditions and children with disabilities.\textsuperscript{117}

The rise of rare diseases in Germany has also led to the introduction of multiple paediatric subspecialties, including among others cardiology, neonatology and intensive care, haemato-oncology, nephrology, endocrinology, neuropaediatric, and diabetology. These subspecialties are generally located at universities and larger regional hospitals across the country.

A key issue identified by Ehrich et al in their study of the child healthcare system in Germany is training caregivers in multidisciplinary teamwork. A modular teaching programme (Modulares Schulungsprogramm) has been put into practice to improve the health education of children and families. These programmes are put in place by the Competence network patient training e.V, and can be requested by patients and trainers. In parallel, a training network (Kompetenznetz Patientenschulung im Kindes- und Jugendalter e.V.) for caregivers is also expanding.

Embryonic and fetal bioethics

Debates on embryonic and foetal bioethics matters have been part of an ongoing discussion within social groups for many years in Germany. Political parties, such as the Social Democrats (SPD) and the Green Party, advocate for children’s well-being.
Recently, at the end of 2019, the G-BA approved non-invasive prenatal tests (NIPTs) to become a benefit provided and reimbursed by the statutory health insurance scheme (under strict conditions).\textsuperscript{118} NIPTs can detect certain genetic variations of the foetus in the maternal blood, such as trisomy 13, 18 or 21.\textsuperscript{119}

**Nine national health goals: ‘health around childbirth’**

Since 2000, the Federal Ministry of Health, together with the federal states, statutory health and pension insurance, private health insurance, doctors and other health care providers as well as patient representatives and self-help groups, initiated the development and implementation of nine national health goals. These goals act as supplementary control instruments in the healthcare system. They strive to improve the health of individuals or certain groups in defined areas and are also committed to strengthening health-promoting structures.

The following national health goals have been agreed upon:

- **2003** Diabetes mellitus Type 2: lower the risk of disease, diagnose and treat sufferers earlier; breast cancer: lower mortality, improve quality of life; reduce tobacco consumption; grow up healthy: life competence, physical activity, nutrition; increase health competence, strengthen patient sovereignty

- **2005** Depressive diseases: prevent, diagnose early, treat effectively

- **2012** Healthy ageing

- **2015** Reduce alcohol consumption

- **2017** Health around childbirth

The latest goal, ‘Health around childbirth’, includes information on the recommended vaccinations for infants and children as well as the prevention of fatal infections in pregnancy. It also focuses on neonatal health. The aim of this health goal is better cooperation between professional groups in order to identify existing risks as early as possible and ensure optimal help to mothers and their newborns. However, the goal does not include any information on SCD.

Based on a dialogue forum that took place at the end of November 2019, the cooperative network gesundheitsziel.de, is planning to develop a strategy paper for the further implementation of the health goal ‘Health around childbirth’. This cooperative network is in charge of further development of the national health goal process, which more than 120 organisations in the German health care system have been involved in for almost 20 years. So far, nothing further has been announced, but it will be important to monitor any developments.
Stakeholders

Governmental stakeholders

The Federal Joint Committee (Gemeinsamer Bundesausschuss, G-BA) is a public legal entity comprising of the four leading umbrella organisations of the self-governing German healthcare system. It is an assembly of the National Associations of Statutory Health Insurance Physicians and Dentists, the German Hospital Federation, and the Central Federation Association of Health Insurance Funds. The G-BA is responsible for the regulation of services and their reimbursement within the SHI scheme. It is involved in raising awareness and stimulating action on SCD. For example, the G-BA commissioned the IQWiG to conduct the study assessing the evolution of screening for SCD in newborns.120

The Institute for Quality and Efficiency in Health Care (IQWiG) objectively examines the advantages and disadvantages of medical interventions for patients. The Institute produces independent, evidence-based reports on drugs, non-drug interventions, clinical practice guidelines, disease management programmes, and diagnostic tests and screening tests. The study assessing the evolution of screening for SCD in newborns was developed in 2019 by the Department of Non-Drug Interventions at IQWiG.
Legislative and governmental initiatives

The 2019 IQWiG study sought to assess the benefit of newborn screening for SCD. The research question set was to assess whether newborn screening for SCD, which consequently reduces the time until diagnosis and treatment, is beneficial in comparison with no screening. The study analysed the following patient-relevant outcomes:

- Mortality (both overall survival and disease-specific survival)
- Morbidity (e.g., fatigue, breathing difficulties, impaired performance due to anaemia, hospital stays, infections, developmental disorders and growth retardation, organ damage, and pain)
- Adverse events
- Health-related quality of life of the child

The study showed that, under certain conditions, SCD screening was beneficial.

2.2 Advocacy landscape

Stakeholders and non-legislative initiatives

The Association of the Scientific Medical Societies in Germany (AWMF), founded in 1962, is the umbrella organisation for 179 German medical societies. The Association provides advice on fundamental and interdisciplinary questions in scientific medicine, promotes the cooperation of its member companies in the performance of their scientific-medical tasks and goals, and transfers scientific knowledge into medical practice. Additionally, in cooperation with other medical organisations, it represents the interests of scientific medicine vis-à-vis the responsible political bodies and the public and strives for close cooperation with comparable organisations. It thus represents an important pillar in the medical organisation in Germany.

With regards to SCD, the AWMF has developed a detailed guideline on the disease with the GPOH as the leading professional society.

Medical societies

There is no specific medical society for SCD, but the German Society of Paediatric Oncology and Haematology (GPOH) is regarded as the society most engaged with the disease. The society performs a variety of tasks in relation to the immediate treatment of patients, in researching diseases, in advancing training and in cooperating with other specialist societies. The medical society’s main focus areas are:
• Research, diagnosis and therapy of tumours, such as blood diseases in children and adolescents
• Promotion of further medical education with a focus on children’s haematology and oncology
• Cooperation with other children’s medical societies and specialist self-help groups and patient organisations
• Development of national and international studies on the diagnosis and therapy of oncology and haematology disorders in children and adolescents

The Society for Thrombosis and Haemostasis Research (GTH) is clinically and scientifically engaged with the prevention, diagnosis and therapy of disorders of blood coagulation, as well as thrombotic clinical pictures. In terms of SCID, they have supported the kinderblutkranheiten.de in the creation of a patient text with general information and recommendations on SCID.

Patient organisations and foundations
The German Childhood Cancer Foundation offers help to children with malignant diseases and their families. The Foundation also raises funds for intensive medical research on childhood cancers to provide optimal treatment. For instance, they support clinical studies of the GPOH as well as the GPOH-registry. Since November 2016, the SCID registry has been mainly funded by the German Childhood Cancer Foundation.

The Sickle Cell Disease interest group (IST e.V.) is a self-help group for patients and relatives affected by SCID. They provide extensive information on the disease, medical supplies and tips for those affected. The group is, among others, annually funded by the ÖKV-Community Funding Self-Help at Federal Level. Private individuals, companies, doctors, and others also fund the interest group.
The Competence Network for Patient Education in Childhood and Adolescence e.V. (KomPaS) is an association dedicated to patients, patient trainers, treatment teams and cost bearers, providing training content on various diseases. They have recently published a modular training programme for chronically ill children and adolescents, and their families (Volume 1: Modular patient training and Volume 2: Quality management and trainer training). The training programme was developed and tested by medical specialists, including specialists in psychology, pedagogy, nursing, nutritional science and sports therapy. It consists of cross-indication modules that can be used equally for all diseases, as well as disease-specific modules for understanding diseases, therapy and emergency management. Although there is no mention of SCD in this programme, the project announcement report, published in 2013, mentions that further research in the indications of celiac disease, primary ciliary dyskinesia and sickle cell anaemia are being undertaken.

The Alliance of Chronic Rare Diseases e.V. – ACHSE for short – was founded in 2004. It is the umbrella organisation of and for people with chronic rare diseases and their relatives in Germany. ACHSE pools expertise and knowledge in the field of rare diseases and represents the interests of all those affected in politics and society, in medicine, science and research.

There is also a range of information portals which acknowledge SCD, including:

- **Children’s Blood Diseases** (Kinderblutkrankheiten), which shares up-to-date information on blood disorders in children and adolescents, including a dedicated page and detailed patient text – as mentioned above – on SCD. It is aimed at patients, families, healthcare professionals, scientists and other professionals working in paediatrics

- **Onkopedia**, which is part of the German Society for Haematology and Medical Oncology and offers detailed information on oncology, including SCD

- **Amboss**, an expert portal for doctors and students, which offers detailed medical information on SCD

**Education and awareness**

The Sickle Cell Disease interest group (IST e.V.) has perhaps been the most active group since 2008, in trying to raise awareness of SCD through their website, flyers and information brochures in different languages. They are also members of the ACHSE, through which they raise awareness on SCD in the context of rare diseases. However, as mentioned on their website, there is still an important need to attract more members, to enable the creation of a stronger voice in the public sphere.
The lack of newborn screening, limited examinations in at-risk groups, and low levels of in-depth information about the disease, reflects a general lack of awareness about SCD in Germany. According to the interest group, this situation could be improved by teaching doctors about the disease (general information, pain therapy, prognosis, etc.) in medical school.

With the recent COVID-19 pandemic, the German Society of Paediatric Oncology and Haematology (GPOH) has been very active in raising awareness of COVID-19 and the associated risks for patients with SCD, advocating that patients ‘should not underestimate the situation’. On 26 March 2020, they published a detailed guide on what SCD patients and their carers should know about COVID-19, including contact details in case of emergency. The guide has been made available in several languages and was followed by a guide in case of emergency, written by Dr Regine Grosse and published on 1 April 2020.
Sickle cell disease in Italy

1. Sickle cell disease in Italy

1.1 Sickle cell disease prevalence

In Italy, according to 2019 data from the National Registry of Thalassemia and Haemoglobinopathies, there are approximately 1,275 patients living with SCD. The epidemiology of SCD has changed considerably in the country over recent years, in particular in response to changes in migratory patterns and migration from countries with high SCD prevalence.

The highest frequency of SCD has historically been reported in Sicily. Chromosomal analysis suggests that SCD in Sicily originated from Northern Africa. However, although prevalence was historically high in Sicily, migratory patterns have caused diffusion across the country, in particular to the industrialised areas in the north of Italy in the last 15 years. Correspondingly, the number of SCD patients has been increasing in Italian regions with historically low disease prevalence, such as the region of Veneto.

A survey was carried out in 1998 by researchers at the Department of Haematology and Paediatric Oncology of the University of Catania and distributed to all Italian centres of Paediatrics and Haematology. It found that, of the 673 SCD cases in people with a known place of residence, 60% lived in Sicily, 20% in Southern Italy, 6% in Central Italy and 13% in Northern Italy. In an update of the survey in 2003, the proportion of SCD patients in Northern Italy had increased to 20% and the proportion in Sicily had decreased to 53%.

As can be seen in 2019 data from the National Registry of Thalassemia and Haemoglobinopathies, while SCD began as a regional issue in Italy, it has now become national, with cases spread across the country.
1.2 Burden of sickle cell disease

**SCD registries**

The National Registry of Thalassemia and Haemoglobinopathies (*Registro nazionale della talassemia e delle emoglobinopatie*) was established in 2018 following the 2017 proposal made by Senator Paola Boldrini, head of the centre-left delegation in the Senate Public Health Committee. The Decree of the President of the Council of Ministers on 3 March 2017 recommended the implementation of a national register to monitor SCD in Italy and to respond to patients’ needs through the **essential levels of assistance (LEA)**, which are health services that must be provided for free through the national health system. On 23 July 2020, the privacy guarantor and the Italian Ministry of Health approved, by Ministerial Decree, the regulation thus establishing this register.

The registry is coordinated by the **Italian National Institute of Health (ISS)**. In order to fulfil the legal obligations of the registry, the **National Blood Centre (CNS)** of the ISS set up a Steering Committee and Technical-Scientific Committee, which involved representatives of:

- **Scientific societies**: the Italian Society of Thalassemia and Haemoglobinopathies (**SITE**), the Italian Society of Transfusion Medicine and Immunohaematology (**SIMTI**), and the Italian Association of Paediatric Haematology and Oncology (**AIEOP**).
- **The Heads of the Coordination Structures of the transfusion activities in Sardinia and Sicily**, the regions with the highest number of patients affected by haemoglobinopathies.
- **Patient groups**: **United Onlus** (the national federation of groups representing patients affected by thalassemia, SCD and rare anaemias) and the **Giambrone Foundation**.
- **Dr Deborah Mascalzoni**, a European expert on bioethics.
- **The National Centre for Rare Diseases** of the ISS.

The aim of the registry is to provide an accurate census of the patients affected by haemoglobinopathies, which was previously based on estimated prevalence (given that some regions did not have registers) and to improve the care for these patients.

**Burden on patients**

The background knowledge accumulated by the reference centres caring for SCD patients, and their distribution throughout Italy, highlights Italy as an example of a successful network of expert physicians on haemoglobinopathies that optimises patient clinical management. This network has been built since the 1960s, together with national programmes on prevention and screening.
Having a network of expert physicians has enabled patients throughout Italy to access SCD treatments, developing a thorough knowledge of their disease and receiving a good level of financial assistance from the National Health System (SSN). The SSN covers all expenses related to SCD patients within the national framework of financial assistance. Additionally, the National Institute for Social Welfare (INPS) provides workers suffering from thalassaemia major or from SCD, who have paid contributions for more than 10 years, with an annual pension. Depending on the severity of their disease and complications, children with SCD also have the right to an ‘accompanying allowance’, which is granted when the child is not able to carry out daily activities independently. Moreover, the region of Sicily also offers an annual pension to all SCD patients at the time of their diagnosis.

The burden on Italian SCD patients may be heightened due to disparities in practices and treatments across the country. However, the new National Network aims to remedy this lack of standardisation with the potential inclusion of SCD treatments in the Essential Levels of Assistance (LEA) (i.e. healthcare services that the SSN has to provide to all Italian citizens, for free or upon payment of a participation fee). Whilst there are no major differences across regions in access to SCD treatments, delays are more likely in some regions causing inequity in care. Despite these disparities, during the COVID-19 pandemic, access to treatment and check-up of blood quality has been guaranteed in all regions.

As previously mentioned, unlike in other countries, thalassaemia and haemoglobin disorders are not strictly a ‘disease of migrants’ in Italy. However, despite a well-established treatment network, follow up issues do arise especially for the most vulnerable groups. In 2019, SITE coordinated a study looking at the identification of SCD in refugees by analysing their first admission to an emergency department. The study identified 67 patients with SCD between 2014 and 2017, 48% of which were children. The main reasons for presentation to the emergency department were vaso-occlusive crisis, anaemia and fever. Only 60% of the patients identified were then followed in reference centres for haemoglobinopathies.

1.2 Current assessment of sickle cell disease treatments

**National network for haemoglobinopathies**

As with the national register, in 2017, the Italian government approved a law supporting the establishment of a National Network of Thalassemia and Haemoglobinopathies. However, it took over three years to implement the Ministerial Decree for the establishment of this network, which was finally implemented on 23 July 2020, by Minister for Health Roberto Speranza.
The network aims to ensure equal access for all citizens to SCD prevention, diagnosis and treatment services as well as the integration of acute and post-acute hospital activities with initiatives available at a local level. The network combines the existing centres for thalassemia, SCD, haemoglobinopathies and rare red blood cell defects and operates through regional networks based on the hub and spoke model.\textsuperscript{144} The model is organised in ‘first level centres’, which ensure prevention, diagnosis and treatment in day hospitals; centres providing transfusions and multi-disciplinary care; and centres providing only transfusion therapy.\textsuperscript{145} The Ministerial Decree also allows the nomination of a Coordination Centre in each region of the country, which will be responsible for ensuring coordination between individual districts and specialised services for patients, thus streamlining care.\textsuperscript{146} This network was established with the involvement of the patient group United Onlus and the SITE medical society.

\textit{Clinical guidelines}

Guidelines for the management of SCD have been published at various levels in Italy. For instance, at a regional level, guidelines have been developed by the Regional Health System in \underline{Puglia} and \underline{Sicily}.

As per the Ministerial Decree signed by the Minister of Health in July 2020, the National Network for Thalassemias and Haemoglobinopathies will develop guidelines for the correct application of therapeutic protocols and pathways
for the treatment of patients with haemoglobinopathies. The newly-launched National Network will also rely on an ‘institutional web-community’ led by the Ministry of Health. This web community will act as a repository for official medical recommendations and guidelines whilst also collecting evidence substantiating any future regulatory updates or legislative proposals.147

In the past 10 years, the medical societies involved in the care of adult and young SCD patients (SITE and AIEOP) have made significant efforts to develop guidelines for the treatment of adult and paediatric SCD patients. Based on international recommendations, tailored to the Italian healthcare system, their work includes:148

- AIEOP published guidelines for the management of children with SCD in 2011. These were updated in 2012, and then most recently in 2018. The guidelines were developed in response to an increased need for comprehensive care for SCD patients, due to the spread of the disease throughout the country. They are designed to be a tool to aid HCPs in decision-making in their care for children with SCD, however they are not intended as a set of inflexible rules to follow.149 The guidelines cover all stages of the disease, from diagnosis to potential complications. The Italian National Institute of Health (ISS) refers to these guidelines for the management of children with SCD150

- SITE published recommendations for the management of adult SCD patients in 2014. In cases of diffuse cerebral vasculopathy, there is general consensus among experts that transfusion programmes should be continued even in adulthood. In adolescent patients, stroke is considered an indication for bone marrow transplantation with an HLA-identical blood donor. These guidelines also recommend genetic counselling to inform patients and prevent SCD for carriers and members of their family networks. Genetic counselling should be done prospectively for both men and / or women suffering from SCD, and for HbS carriers151

- In 2014, SITE coordinated a panel including AIEOP, SIMTI and SIMEU and a representative from the nursing community to develop an interactive, easy-to-use algorithm for the clinical management of acute SCD events in emergency departments. The algorithm aimed to respond to the need for improved disease awareness in clinical settings. For patients with confirmed or suspected SCD, the algorithm identifies four priority groups, based on the severity of their clinical presentation, and outlines treatment pathways for each group
Treatments available in Italy

The main treatment options available for SCD in Italy are hydroxyurea and blood transfusions.

A national survey was carried out recently by the SITE, SIMTI and AIHEOP to collect information on the different therapeutic approaches used to treat SCD patients in Italy, the preliminary results of which were published in 2018. The results show that out of 1,579 SCD patients:

- 23% did not receive any therapy
- 12% received hydroxyurea alone
- 10% received acute transfusion regimens alone
- 14% received chronic transfusion regimens alone
- 40% received a combination of transfusions and hydroxyurea

A sub-analysis of paediatric data from another nationwide study published in 2018, found a tendency to treat children with lower doses than is recommended. In addition, although guidelines recommend commencing hydroxyurea treatment during the first few months of life, in the cohort of children studied, this treatment was not administered before 11 months of age. The results of the survey indicate relatively good adherence to the guidelines.

Screening for SCD in Italy

Pre-conceptual and pre-natal screening

In contrast to other European countries, pre-natal screening and prevention appears to be preferred over newborn screening in Italy. Specifically, mothers are usually screened before conceiving or during their pregnancy to detect whether they are carriers. In this context, medical specialists have been trained to play a pivotal role in informing and guiding mothers. As per Italian law, a universal screening programme for haemoglobinopathies is available to couples before or after conception, which includes the possibility for voluntary pregnancy termination up to the 22nd week of pregnancy.

Screening programmes initiated in the 1970s in Italy have attained remarkable results in raising public awareness of SCD and other haemoglobinopathies. For instance, systematic preconception screening in the 1970s achieved outstanding outcomes in Emilia-Romagna and Sardinia, and ensured early diagnosis of SCD. Until the 1980s, SITE led prevention campaigns which screened the oldest students in high schools, particularly those whose parents came from at-risk regions or countries.
Newborn screening

The Italian healthcare system is organised regionally, meaning that certain healthcare services, such as new-born screening programmes, are organised at the regional level. Following joint efforts by the medical societies AIEOP and SITE in advocating for national screening for SCD, six pilot programmes were developed in recent years at regional and local levels, two universal and four targeted ones.158

According to experts, the practice of new-born screening may be redundant in the face of effective pre-conceptual or pre-natal screening, particularly because these services are available for free in the Italian National Health System. However, new-born screening is essential for individuals from high-risk groups who are not aware of their carrier status and who may not have been screened in their country of origin or who did not previously have access to the usual care pathways for screening.159

2 Activity in the field of sickle cell disease in Italy

2.1 Policy landscape

Stakeholders

The decree of the President of the Council of Ministers of 3 March 2017 (published in the Official Gazette no. 109 of 12 May 2017), established the National Register of thalassaemia and of other haemoglobinopathies, aimed at proposing adequate care models and essential levels of assistance (LEA) to meet the needs of all patients.

In July 2020, the Minister of Health, Roberto Speranza, signed the proposal for a Ministerial Decree for the establishment of the National Network of Thalassemia and Haemoglobinopathies.

At a regional level, Sicily and Emilia-Romagna issued sectorial laws on rare diseases and, since 2000, have created welfare networks based on the hub and spoke model. Since 1990, Sicily has held a regional register for research on thalassemia and haemoglobinopathies (RESTE) and is the only region that has reliable epidemiological data, registering patients into a mandatory regional registry.
2.2 Advocacy landscape

**Stakeholders**

*Medical societies*

There are several medical societies who are active on SCD in Italy, from developing guidelines to being involved in legislative changes and advocacy activity.

**SITE** is the Italian Society for Thalassemia and Haemoglobinopathies, which was formed in 1997 in Sicily (originally under the name SOSTE). It brings together different healthcare professionals involved in the care of people with thalassemia and other haemoglobinopathies, including haematologists, paediatricians, transfusionists, hepatologists and cardiologists. SITE’s original objective, which they have already achieved, was to move from a regional to a national society for haemoglobinopathies. Its activities include developing clinical guidelines, advocating for policy change and delivering educational activities. They were heavily involved in the development of the National Register of Thalassemias and Haemoglobinopathies.

**AIEOP** is the Italian Association for Paediatric Haematology and Oncology. It brings together paediatricians, haematologists, oncologists, surgeons, biologists and other disciplines involved in the care of children with haematological, oncological and immunological disorders. Its main purpose is to improve the care of children affected by these diseases, including through developing guidelines, raising awareness and advocating for change.

**SIMTI** is the Italian Society of Transfusional Medicine and Immunohaematology. SIMTI brings together healthcare professionals involved in transfusional medicine across Italy, with the aim of improving practice in the country.

**SIMEU** is the Italian Society for Emergency Medicine. Given the fact that SCD patients often present to emergency departments, SIMEU was involved in the development of an algorithm for the best management of SCD in emergency rooms.

*Patient groups*

**United Onlus** is a patient group established in 2012, which was formed to bring together regional and local patient groups representing patients with haemoglobinopathies in order to make their voice heard. Their aim is to provide patients and their families with global assistance, protecting their right to health, access to care, social equality and job opportunities. They pursue these aims through proposals for legislative change and advocacy campaigns. United Onlus’ ambition is to fill the gap in patient advocacy that previously existed in Italy, by providing a national-level united patient voice. They have been highly active in the establishment of the new Register for haemoglobinopathies, as outlined above.
The Fondazione Giambrone is a not-for-profit organisation in Italy that aims to improve care for people affected by thalassemia and SCD. It was founded in 1992 with the objective of promoting the ‘Healing Project’ by funding research projects to identify and test treatments for thalassemia.

**Non-legislative initiatives**

**Education and awareness**

The creation and implementation of the National Registry and the National Network of Thalassemia and Haemoglobinopathies aims to contribute to improving levels of education and awareness of SCD in Italy. As per the Ministerial Decree establishing the National Network, €100,000 per year is allocated to create informative tools, implement awareness-raising activities and gather data to monitor the effectiveness of the services offered through the National Network. Given the high prevalence of the disease and the well-established treatment networks as well as strong levels of advocacy, there is a generally high level of awareness of SCD in Italy.

Clinical societies involved in the care of people with SCD have carried out numerous awareness raising activities, from advocacy campaigns to publishing educational material. In addition, SITE and AIEOP are both active in training clinicians on SCD and haemoglobinopathies. For instance, SITE offers a Masterclass in the Management of Haemoglobinopathies, which is available for 20 young medical graduates who wish to increase their knowledge of the disease.

Overall, given the high prevalence of the disease and the well-established treatment networks as well as strong levels of advocacy, there is a generally high level of awareness of SCD in Italy.
Interview with Professor Gian Luca Forni
President of SITE

Main challenges and opportunities for patient access to SCD diagnosis and treatment

According to Professor Forni, ‘the approval of the National Network for Thalassemia and Haemoglobinopathies marks an important step in the care of patients with thalassemia and haemoglobinopathies. The Ministerial Decree will allow for the identification of regional Coordination Centres (1 per region) responsible for ensuring optimal coordination of care across specialised services for patients. This would cover centres for prevention, monitoring, diagnosis and therapy.’

Dr Forni acknowledged the importance of this achievement, as a regional network of centres had operated without official recognition for 50 years in regions where SCD was traditionally more prevalent (e.g. Sicily and Lombardy). Dr Forni shared that ‘in 2017 already, the Italian Society of Thalassemia and Haemoglobinopathies (SITE), together patient organisations, had called for the official recognition of the network at the national level.’ Dr Forni added, ‘today, 10% of the Italian population carries a haemoglobin anomaly. The approval of the Network shows that SCD is not regarded as a regional issue anymore.’

Asked about how the network would operate, Dr Forni shared that ‘the National Network will rely on a newly launched ‘institutional web-community’ led by the Ministry of Health. This web community will act as a repository of official recommendations and guidelines and, at the same time, will collect evidence substantiating any future regulatory updates or legislative proposals.’

Highlights on the situation of SCD in Italy

Unlike other countries, centres for treating haemoglobinopathies in Italy have been working on both thalassemia and SCD. When asked, Dr Forni responded: ‘this is one of the strengths of the Italian approach. Although there may be an incomplete harmonisation of practices and treatments proposed across the various regions, the quality of treatment that SCD patients receive in Italy is one of the highest in the world.’
COVID-19 has increased the fragility of vulnerable patients, impacting their access to care and treatment. However, this impact has not been solely physical. In fact, whilst 90% of rare disease patients have experienced interruptions to care due to COVID-19, the virus has also generated other problems in addition to delays in medical consultations or treatments. The results of a recent Italian survey found that COVID-19 also had a psychological impact on SCD patients, including worries related to the risk of infection.

The lack of literature on the effects of COVID for people living with SCD created enormous difficulties for SCD patients, who, especially at the beginning of the pandemic, had no meaningful tools to understand the outcomes for patients admitted to hospital compared to the prognosis for those staying home and delaying treatment.

This gap led to a call for more data and information sharing amongst the community at European level. As an example, the German Society of Paediatric Oncology and Haematology (GPOH) has been very active in raising awareness on COVID-19 and the associated risks for patients with SCD.

In March 2020, the GPOH published a detailed guide on what patients with SCD or their carers should know about COVID-19, including contact details in case of emergency. In addition, the GPOH SCD consortium is participating in an international research project of the European Reference Network (ERN) EuroBloodNet, in which COVID-19 infections in people with SCD are recorded and their progression is evaluated with the aim of providing timely and reasonable recommendations for action.

At an EU level, efforts to support SCD patients during the pandemic have been consolidated into the creation of a Collaborative Platform on Red Blood Cell and COVID-19 aiming to pool information that may be useful in assessing the impact of COVID-19 risk factors on SCD patients.

Although these initiatives may have come in too late to support SCD patients during the first wave of COVID-19, the increased availability of data regarding sickle cell disorders and the virus may make them useful in addressing potential future pandemics.
1 Sickle cell disease in Spain

1.1 Sickle cell disease prevalence

The accurate prevalence of haemoglobinopathies in Spain is unknown. According to data in the Spanish Registry of Haemoglobinopathies (REHem), there were 826 SCD patients in the country as of 31 December 2017. SCD is a fairly new challenge to Spain and its incidence has greatly increased over the past years due primarily to immigration from endemic areas. In 2014, as many as 33% of births in Spain were from a parent who had immigrated. Out of the 826 SCD patients recorded in the REHem in 2017, 63.3% were born in Spain, 26.8% were born in Africa, and 8.1% were born in America. Carriers can also be found amongst the autochthonous population in the south of Spain, particularly in the area of Cádiz within the Autonomous Community of Andalusia.

In 2014, the incidence of SCD was estimated at 14 cases among 426,303 live births (0.03 per 1,000 live births). Diagnoses of SCD reached a maximum of 42 per year in 2006–2010 and declined to 24 in the following 5 years. Prenatal counselling and a decrease in immigration from half a million in 2008 to a quarter of a million in 2014 are thought to have driven this change.

There is an overall estimation, based on migratory flows, which classifies Spain in the group of countries with low risk of incidence of sickle cell anaemia. However, the distribution of immigrants varies greatly throughout the country’s regions (called Autonomous Communities). The prevalence of SCD is much higher in Madrid and Catalonia for example, when compared to other Autonomous Communities. Out of the 826 SCD patients recorded in the Spanish Registry of Haemoglobinopathies in 2017, 38.3% were in the Community of Madrid, 35.6% in Catalonia, and 8.1% in Valencia.

The first report of an increase in infants with sickle trait appeared in 2003 and led to the implementation of universal newborn screening programmes in specific regions. At national level, the Inter-territorial Council of the National Health System (SNS) approved the inclusion of a universal newborn screening programme for SCD in the common basic portfolio of SNS services in 2013.
In November 2014, Order SSI/2065/2014 was published, officially establishing newborn screening for SCD in the common basic portfolio of SNS services.

1.2. Burden of sickle cell disease

In Spain, SCD mainly affects the immigrant population, who often face economic and social challenges in addition to the challenges already inherent to dealing with a chronic disease. Health education and psychological support for these patients are, therefore, very important for the prevention and early treatment of many of the complications of SCD. Such support should include educating patients and their families about avoiding factors that may precipitate a vaso-occlusive crisis, such as exposure to cold, dehydration, and fever. In addition, patients should also learn how to treat mild pain crises with increased water intake, rest and pain relievers and be taught to recognise the warning signs that require immediate attention in an emergency department, such as pallor, fatigue, high fever, respiratory distress, or the appearance of a focal neurological deficit.180

In its 2019 Clinical Practice Guidelines for SCD, states that it is important to investigate the socioeconomic situation of the family of the patient, as the disease is often associated with very precarious socio-economic situations, which may influence compliance with monitoring and medication due to lack of resources or difficulties with work. For this reason, it is recommended that the local social services should be involved.181

In addition, psychological support for the patient and family members is essential and acceptance of the disease varies. SCD is a chronic disease, associated with acute pain crises and sometimes chronic pain, hospital admissions and serious complications that can be fatal. All these factors can lead to school absenteeism and the need for tutoring, while some patients also experience cognitive disorders due to ‘silent’ strokes. Adolescence is an especially difficult time for these chronic patients, who frequently have a pubertal delay in terms of sexual development and height.182 The 2019 SEHOP guidelines provide an information guide for relatives of children with SCD as well as information for teachers regarding when to seek medical attention for a child with SCD.183

Patient registries

The lack of sound epidemiological data in Spain led to the 2014 implementation of a national registry of haemoglobinopathies (REHem) under the auspices of the Spanish Society of Paediatric Haematology and Oncology (SEHOP).185 The objective of the registry is to develop a database of patients of all ages affected by haemoglobinopathies and rare anaemias from centres throughout Spain.
The registry provides epidemiological data on the prevalence of these diseases in Spain, which has shown to be vital in the designing of strategies for diagnosis, treatment, and follow-up care for patients. The current research team behind the registry is SEHOP’s Erythropathology Group.\textsuperscript{185}

The former Spanish Society of Paediatric Haematology (SEHP) began to maintain a registry of SCD patients in the year 2000.\textsuperscript{186} However, the organisation no longer exists under that name and the SEHOP’s REHem is currently the only registry used in Spain.

In 2002, the Spanish Ministry of Health implemented a national Rare Disease Registry. Declaration in the registry is voluntary for patients and gives them access to specific information on their disease, and participation in online studies regarding issues such as medication, quality of life, dependency analysis, health resources and donation of samples. The registry records a very low number of patients with SCD (8) and is evidently not as widely used as the SEHOP registry, which recorded 826 in 2017, as mentioned above.

1.3 Current assessment of sickle cell disease treatments

Clinical guidelines

The leading professional organisation is the Spanish Society of Paediatric Haematology and Oncology (SEHOP). SEHOP published its third Clinical Practice Guidelines for SCD in 2019,\textsuperscript{187} following those published in 2002 and 2010. The guidelines are widely used by clinicians in Spain and aim to offer a clinical practice guide for the comprehensive care of children, adolescents and young adults with SCD to ensure low morbidity rates and long-life expectancies.

Standard treatments are as follows:

- Baseline treatments: infection prophylaxis with penicillin starting from age two months and maintained indefinitely, or at least until age 5; Vitamin D; folic acid supplements if a deficiency in serum folate levels is found
- Hydroxyurea (cytostatic ribonucleotide reductase inhibitor): to reduce vaso-occlusive crises, acute chest syndrome, admissions and transfusions
- Blood transfusions: to treat the anaemia as well as to treat or prevent acute or chronic complications of the disease
- Vascular access: for patients with multiple complications or with chronic transfusions, a permanent central device can be implanted
- Pre-surgical preparation
- Iron overload: in case of iron overload, different chelation therapies are recommended depending on the patient’s age
• Haematopoietic stem cell transplantation: all patients or families with a child with SCD should have the opportunity to discuss transplantation as a therapeutic option regardless of whether the family has a suitable donor at that time. Every young patient with symptomatic SCD and a suitable donor should have the option to have a transplant as soon as possible, preferably before school age (6 years).

Further treatments are also recommended for the following complications: musculoskeletal, infectious, gastrointestinal, spleen, neurological, aplasia and transient anaemia, renal and urological, ocular, developmental delays and, cardiovascular and lung complications.

The following additional vaccines are also recommended, as well as those that are in the vaccine schedule for the general population: Pneumococcus conjugate 13-valent, Pneumococcus polysaccharide, Haemophilus influenzae b, Meningococcus ACWY, Meningococcus B, Inactivated flu, Varicella, Hepatitis A and B, Typhoid fever, Yellow fever or Regional Encephalitides.

Newborn screening

The optimal care for children with SCD starts with new-born screening (NBS), which allows for a diagnosis to be established before the onset of symptoms thus permitting early interventions. NBS followed by adequate comprehensive care reduces morbidity, mortality, and healthcare costs while improving the quality of life for patients. A national universal new-born screening programme has been available in Spain since 1978. Although screening works on a voluntary basis, it has nearly 100% coverage. Universal screening for haemoglobinopathies started in the Madrid region in 2003, in the Basque country in 2011, in Valencia in 2012, and was extended nationwide in 2015. In November 2014, Order SSI/2065/2014 was published, officially including universal new-born screening for SCD in the common basic portfolio of SNS services.

The heel test is usually carried out systematically 48 hours after birth in the hospital where the delivery took place or in a corresponding Health Centre. High Performance Liquid Chromatography (HPLC) is the first test used in most of the regions. Confirmatory testing is done with HPLC on the same dried blood spot and on a new capillary sample before the age of three months.

The objective of the new-born screening programme for SCD is the detection of the disease in a pre-symptomatic stage, allowing the establishment of early treatment in order to reduce morbidity and mortality in childhood. The proposed early treatment is based on two pillars: prevention of pneumococcal infection (with antibiotic prophylaxis and pneumococcal vaccination) and educating parents to identify acute complications in their initial phase.
Many healthy children with sickle cell trait are detected during SCD screening, which can be considered either a fortuitous or adverse finding given some of these children do not directly benefit from early diagnosis. In some countries, the communication of these results is not allowed, but in Spain families are informed for genetic counselling and general recommendations for carriers of sickle cell trait.

**Comprehensive patient care**

The 2019 SEHOP guidelines recommended that patients diagnosed with SCD should have access to comprehensive care. In case of emergency, they should have access to a local hospital close to their home with specific guidelines for the treatment of acute presentations, and there should be the possibility of transferring seriously ill patients to a centre with a Paediatric Intensive Care Unit and Paediatric Surgery. In case of hospitalisation, patients should be seen by a specialised paediatrician or haematologist and must have access to a specialist nurse, as well as other paediatric specialists (e.g. orthopaedics, neurologists, etc) and obstetricians. In addition, there should be a direct connection with adult Haematology Units. During out-patient consultations, patients should be able to address chronic complications with specialists, be seen by a specialist nurse, psychologist, geneticist or social worker, and receive the support of educators in case of cognitive difficulties. There should also be inputs from a primary care paediatrician and support groups (e.g. patient associations).

The follow up of SCD patients by specialised units in Spain has significantly improved prognosis. A multidisciplinary and coordinated approach is very important for the correct management of children with the disease. A primary care
paediatrician plays a central role in patient follow-up and is often the one who will be contacted when a complication first occurs and who will make a referral to an emergency service when required.194

**A Catalan network for diagnosis and follow-up**

In the Autonomous Community of Catalonia, there is a dedicated network for diagnosis and follow-up of haemoglobinopathies and thalassaemias, called **CATGLOBALIN**. Coordinated by the Barcelona Hospital Clinic and the Sant Pau Hospital in Barcelona, CATGLOBALIN’s main objective is to create a multicentre network made up of a multidisciplinary team of paediatricians, haematologists, biologists and other specialists with the common objective of guaranteeing the correct diagnosis, prevention and clinical management of SCD, thalassaemic syndromes and other haemoglobinopathies associated with chronic anaemia. The network has 9 different working groups, covering issues related to diagnosis and prevention, clinical follow-up and treatment, epidemiological and clinical records, and education.

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**2 Activities in the field of sickle cell disease in Spain**

**2.1 Policy landscape**

**Stakeholders**

**Legislative measures**

In November 2014, Order SSI/2065/2014 was published, modifying the Royal Decree 1030/2006 of the 15th of September and, by law, adding SCD to the newborn screening programme for endocrine-metabolic diseases within the common basic portfolio of SNS services. Services included within the common basic portfolio of SNS services must be guaranteed to all users of the health service.

**Rare diseases**

**Rare disease strategies**

Haemoglobinopathies are addressed under the policy framework for rare diseases in Spain. Spain has had a **National Rare Disease Strategy** since 2009 (Estrategia en Enfermedades Raras del Sistema Nacional de Salud), which was subsequently updated in 2014.195 The strategy aims to improve services provided for those affected by a rare disease and their families, based on the principles of quality, equal access, and cohesion. The strategy is based around seven strategic lines, which are expanded on with specific objectives. These are: information on rare
diseases; prevention and early detection; health care; treatment; research; and training. SCD is mentioned once in the strategy in the context of screening, where it is listed as one of the diseases included in the new-born screening programme for endocrine–metabolic diseases. However, aside from this mention, there is no specific focus on SCD, nor on haemoglobinopathies more broadly.

Although the 2014 Strategy states that the next evaluation is planned for four years after its publication, with a partial evaluation after two years, the Ministry of Health is yet to announce any rework. This negligence is despite pressure from stakeholder organisations, including the Spanish Federation of Rare Diseases (FEDER, highlighting the need to revisit and re-evaluate the document. The Community of Madrid – with the highest number of SCD cases of any Autonomous Community (see section 2.1 above) – has its own regional plan, spanning 2016–2020, to improve health care for people with rare diseases in the city. The plan aims to contribute to the reduction of morbidity and mortality and improve the quality of life of those affected by rare diseases through comprehensive health care. It does not include any specific focus on, or mention of, haemoglobinopathies.

Madrid is one of only five Autonomous Communities which has its own regional plan for rare diseases, the others being Andalusia, Extremadura, Murcia and Navarra. Although the Basque Country, Catalonia and the Community of Valencia do not have dedicated regional rare disease plans, they do have other initiatives to address such diseases.

In Catalonia – with the second highest number of SCD cases of any Autonomous Community (see section 2.1 above) – rare diseases are covered by the Health Plan for Catalonia 2016–2020. The Health Plan proposes ten priority areas requiring particular attention, including rare diseases where the objective is to deploy the care model for rare diseases of the Catalan Health Service (CatSalut). This model is considered pioneering in Europe. Deemed to be comprehensive, equitable, high-quality, and patient centric, the model considers rare disease care from the perspectives of both clinicians, and their experiences, and the needs of patients and their families.

Similar to Catalonia, the Basque Country addresses rare diseases in its Health Plan 2013–2020, which includes specific actions related to rare diseases. In the Community of Valencia, a ‘Decalogue’ for improving care for people with rare diseases, which includes a number of measures to be taken, was developed in 2017 in collaboration with the Spanish Federation of Rare Diseases (FEDER). The rest of Spain’s Autonomous Communities do not have specific rare disease plans nor measures at a regional level, and therefore rely solely on the national strategy.
While it is encouraging to see action being taken on rare diseases more broadly at a national level and in certain regions, all of the above-mentioned plans lack a focus on haemoglobinopathies. To truly address the needs of patients with haemoglobinopathies, more specific focus in future national and regional plans and initiatives must be ensured.

**State Reference Centre for Care for People with Rare Diseases and their Families**

In 2009, a State Reference Centre for Care for People with Rare Diseases and their Families (CREER) was established with the strategic objective of achieving better care for people with rare diseases. The Centre performs two main tasks – Reference Services and Direct Care Services. The Reference Services are specialised resources in the research, study and knowledge of rare diseases, and in the training of professionals who care for patients and their families or who work in this sector. They also serve as expert resources in knowledge management, and the generation and dissemination of good practices and technical advice. They were created with the purpose of promoting the improvement of the quality of life and social participation of people with rare diseases and their families.

The purpose of Direct Care Services is to make multidisciplinary teams available to people affected by a rare disease and their families and caregivers so that they can receive specialised health, psychological and social care, as well as education. This care aims to ensure that people impacted by a rare disease can achieve the highest possible levels of development, personal fulfilment, autonomy and social participation, to ultimately improve their quality of life as well as their support network.

**Parliamentary activity**

There has been very little parliamentary activity on SCD and awareness among policymakers appears to be low. For example, there have been no parliamentary questions asked regarding SCD in either the Spanish Congress or the Senate.

**2.2 Advocacy landscape**

**Stakeholders and non-legislative initiatives**

**Medical societies**

The Spanish Society of Paediatric Haematology and Oncology (SEHOP) is the most active medical organisation on SCD. As mentioned above, SEHOP has published three sets of clinical practice guidelines on SCD, in 2002, 2010, and most recently in 2019. It is also the organisation which set up and coordinates the national registry of haemoglobinopathies (REHem).
The Spanish Society of Haematology and Haemotherapy (SEHH) is a scientific organisation that brings together more than 2,500 haematologists and professionals from related specialties. Its mission is to ensure the adequate development of haematology and haemotherapy in Spain. It aims to improve the professional, teaching and research levels of specialists, enabling them to provide better care.

The Spanish Group of Erythropathology (GEE) is a scientific association promoted by health professionals involved in the study, diagnosis, treatment and research of red blood cell-related diseases, including SCD. Its activities include disseminating knowledge of red blood cell diseases to general physicians and specialists in order to improve disease management. In addition, the GEE organise meetings, working groups, courses and symposia to ensure that scientific advances in the field reach all those who work in this area, and also participates in research projects in order to forge new scientific advances for disease management. GEE also collaborates with patient organisations, particularly in an educational capacity such as by flagging SCD focused diagnostic and treatment centres.

The Spanish Society of Out-of-hospital Paediatrics and Primary Care (SEPEAP) has an Immigrant Patient Care Manual intended to provide a reference point for healthcare professionals attending to immigrant patients. The manual provides information on SCD, including clinical information and treatment options. SEPEAP has also published articles about SCD treatments on its website.

The Spanish Association of Paroxysmal Nocturnal Haemoglobinuria, the Rare Diseases Platform of the Autonomous University of Barcelona’s Doctor Robert Foundation, and the European Network for Rare and Congenital Anaemias (ENERCA), co-organised the First National Congress of Rare Anaemias and Related Syndromes in 2013. The Congress was aimed at all those affected by a rare anaemia (including SCD) and their families, as well as physicians and health professionals involved in the diagnosis and follow-up treatment of rare anaemias. The aim of the meeting was to provide information on the latest advances in the diagnosis and specialised clinical follow-up of rare anaemias. While the event was called the First National Congress of Rare Anaemias and Related Syndromes, no follow up event has occurred.

Patient organisations

The main patient group for SCD is the Spanish Association Against Haemoglobinopathies and Thalassaemias (ALHETA). ALHETA was created with the intention of helping and improving the day-to-day life of patients affected by haemoglobinopathies and thalassaemia. They aim to inform, guide, support and listen to patients as well as raise awareness about the diseases. ALHETA has run an
information campaign for patients with thalassaemia and haemoglobinopathies and their family members in all hospitals in Spain. In 2010, ALHETA created a children’s comic on SCD in collaboration with the Spanish Federation of Rare Diseases (FEDER), the European Network for Rare and Congenital Anaemias (ENERCA) and Fundación Inocente Inocente (a private welfare foundation which supports entities dedicated to improving the quality of life of children who are sick, disabled or at risk of social exclusion). Despite this progress, it seems that patients have difficulty accessing the most recent materials.

The Spanish Federation of Rare Diseases (FEDER) is the most active and influential patient organisation for rare disease patients in Spain. In 2018, FEDER signed an agreement with the Catalan Bioengineering Institute (IBEC) to connect IBEC’s work with patient organisations and boost research into rare diseases, including SCD. Along with the development of new research projects, the two organisations agreed to participate in, and mutually promote, events and initiatives focused on raising awareness about these pathologies and giving visibility to the research that is being developed.

In June 2020, an online information portal, Anemiatalciforme.es, was launched to provide information and support to people affected by SCD. It includes national data, as well as information on genetics, the impact on red blood cells, pain crises, common myths and realities, the impact of SCD on the body, and recommendations for avoiding and managing pain crises. It also covers the emotional and social impact of SCD.
United Kingdom

1 Sickle cell disease in the UK

1.1 Sickle cell disease prevalence

Despite being a rare disease, SCD is the UK’s most prevalent genetic disorder with the numbers affected increasing faster than any other genetic disease. There are an estimated 15,000 people in England living with SCD, with 350 babies in England born with the condition each year. Stigma and prejudicial judgements are often associated with SCD due to the nature of the disease and its episodic pain that requires recurrent use of strong opioid-based analgesics. In addition, the condition remains largely unknown to the general public. A UK-wide survey conducted by the Picker Institute and published in 2016 concluded that information provision and lack of public awareness of the condition were some of the biggest issues affecting patient experience and the care they receive.

The condition is significantly more prevalent in communities with African or Caribbean heritage, with an estimated one in seven (145 per 1,000) babies born as carriers of the condition, as compared to 1 in 540 babies.

Figure 1 overleaf highlights the geographic concentration of SCD in the UK and shows finished hospital admission episodes with a primary or secondary diagnosis of SCD by NHS England region of residence in the latest year for which figures are available (2017/18).

There is a very high concentration of SCD in London. 61% of all hospital admissions related to SCD in 2017/18 – nearly 29,000 admissions – occurred in London. Data from other sources reinforce this picture, and show that:

- Two-thirds of people with SCD in England live in London
- Four-fifths of all patients with SCD are managed in London healthcare settings even if they are not themselves resident in London, with many patients in the wider South East accessing services in the capital
- Almost half (25 out of 53) of listed Sickle Cell Centres in the UK are in London

Notwithstanding this, however, the geography of SCD is starting to change. People with SCD and their families are increasingly moving out of London – both to the wider South East, and to other urban areas. Figure 2 overleaf shows that there has been a relative decline in the number of babies born with SCD in London, and a slight rise or stagnation in SCD births in other regions of England.
Figure 1: Where sickle cell disease patients receive care and support

Finished admission episodes with a primary or secondary diagnosis of SCD by NHS England region of residence, 2017/18

Figure 2: Number of babies born with SCD in England

Babies born with a significant sickle cell condition by NHS England Commissioning Region, 2009/10 to 2016/17
Finally, Figure 3 above shows how the spending on SCD services has changed from 2015/16 to 2017/18. It shows that spending on services has increased markedly in recent years. Whilst the level of spending in London dwarfs that of other regions, spending has increased markedly in some other areas – most notably the East of England, where spending has more than doubled from £1.6 million to £3.3 million.

1.2 Burden of sickle cell disease

Patient population

The incidence of SCD in England is growing. As noted earlier, the patient population is overwhelmingly from Black African and Black Caribbean backgrounds and is concentrated in London, but the geography of the patient population is shifting to new urban areas and to surrounding areas outside the capital.
The majority of SCD patients who access NHS services are from relatively deprived backgrounds. Figure 4 illustrates the level of health inequity and shows finished admission episodes with a primary or secondary diagnosis of SCD by Index of Multiple Deprivation Decile in England in 2017/18. The English Indices of Multiple Deprivation are a relative measure of deprivation and split each area of England into one of ten deciles, from most deprived to least deprived.

As the data show:
- Almost a quarter (23%) of patients admitted with a primary or secondary diagnosis of SCD in England are from the most deprived 10% of the population
- Almost half (48%) are from the most deprived fifth of the population
- By contrast, just 5% are from the least deprived fifth of the population

**Figure 4: Health inequalities and sickle cell disease**

*Finished admission episodes with a primary or secondary diagnosis of SCD by Index of Multiple Deprivation decile, 2017/18*¹²⁴

**Service provision**

The NHS England directly commissions services for people with SCD, as part of a service specification which includes all people with haemoglobinopathies (the majority of which have SCD or thalassaemia²¹⁵). There is a separate policy framework for devolved nations, and Scotland is responsible for decisions on the reimbursement of its own treatments through the Scottish Medicine Consortium (SMC).
In 2018, NHSE set out plans to reorganise service provision for haemoglobinopathy patients, and this reorganisation was completed in early 2020.\textsuperscript{216} This reorganisation only covers specialised services which are commissioned directly by NHSE, and will not extend to non–specialist care of SCD patients access, such as primary care, social care or community services. Nor does it cover hospital appointments where haemoglobinopathy is not the main reason for being seen.\textsuperscript{217}

Figure 5 overleaf, sourced from NHSE, provides a structure for the new services. As a result of this reorganisation, the new service structure consists of:\textsuperscript{218}

- **A National Haemoglobinopathy Panel (NHP) and an NHS England Clinical Reference Group (CRG) for haemoglobinopathies.** The CRG existed under the previous structure, is comprised of clinicians and commissioners, and has a role in setting national policy and shaping how the commissioning hubs contract services. The NHP is a new entity, and is responsible for:
  - Providing specialist clinical advice to local Haemoglobinopathy Coordinating Centres (HCCs; see below) on the treatment of more complex patients
  - Coordinating efforts to reduce inequalities in care
  - Supporting the introduction of innovative new treatments for SCD, by “acting as a national panel to consider individual patients most able to benefit” and “enabling patients to have access to these therapies, irrespective of where they live”

- **10–14 local “Clinical Networks” led by Haemoglobinopathy Coordinating Centres (HCCs) in each area** to take responsibility to coordinate local provision in their areas. These centres will:
  - Lead local networks of centres which provide services for people with haemoglobinopathies
  - Provide specialist advice to local hospitals in areas which lack specialised haemoglobinopathy services, to ensure all patients have access to the advice required

- **Local haemoglobinopathy services managed by the HCCs.** A large number of acute NHS Trusts provide haemoglobinopathy service,\textsuperscript{219} with the Brent Sickle Cell & Thalassaemia Centre listing 53 Sickle Cell and Thalassaemia centres across the UK.\textsuperscript{220} However specialised haemoglobinopathy services are delivered in fewer than 20 centres in England.\textsuperscript{221} Each of these sit under one of the HCCs.

The review did not implement any major changes to existing specialist haemoglobinopathy centres, and NHSE has stated that “we fully expect all of them to continue providing care.”\textsuperscript{222}
They will however be renamed Specialist Haemoglobinopathy Teams (SHTs) and will have to provide 24/7 advice for other clinical teams. Local Haemoglobinopathy Teams (LHT) will report to them; and each SHT will report to the HCC in their Clinical Network.

NHSE’s stated aim of this reorganisation is to:

- Improve the standard of care across the country, as they recognise that despite improvements in care over the past decade, “some people still experience poor care”\(^\text{224}\)
- Address the variation in services between areas. NHSE acknowledges there are “inequities in both the quality and access to high quality care” for haemoglobinopathy patients, which it attributes to “the varied prevalence of haemoglobinopathies” and “difficulties in delivering care to minority groups”\(^\text{225}\)
• Prepare the NHS for the adoption of potential new treatments for people with haemoglobinopathies, to ensure patients are able to access them wherever they live in the UK, without inequalities in access

In response to written parliamentary questions, NHSE has further stated that an equality impact assessment which was carried out indicates that the reorganisation will reduce health inequalities by providing patients with “equitable access to high quality specialist care and support within specialised commissioned centres irrespective of where in the country they live.”

**Standard of care**

Whilst as noted earlier there have been improvements in the life expectancy and quality of care for people with SCD, NHS England continues to acknowledge that there are inequities in service provision for people with SCD.

There are a range of challenges in SCD care, including:

• **Inequalities in service provision.** NHS England has acknowledged that there are inequalities in SCD service provision, leading to differences in outcomes for patients and variation in the management of care between different areas.

• **Geographical challenges with accessing care.** With people living with SCD increasingly moving out of London, where the majority of specialist SCD centres are, patients have found it increasingly difficult to access services close to their home.

• **Wider disadvantage in the SCD community.** As Figure 4 earlier illustrates, many patients with SCD encounter a range of challenges in accessing appropriate care and support, including potential discrimination.

• **The availability of innovative treatments for SCD.** There are currently only a limited range of treatments available for patients, which include regular blood transfusions and the use of hydroxycarbamide for the treatment of painful episodes. It is possible that new and more innovative treatments could soon become available.

• **An ageing patient population.** Although the SCD patient population is relatively young, improvements in life expectancy in recent years have nonetheless created challenges as the NHS seeks to manage the comorbidities in older people with SCD.

• **Variations in specialist knowledge of care and support.** There can be limits to specialist knowledge of SCD within certain healthcare settings and in certain parts of the country – especially those where the population of people with SCD is smaller.

NHS England has acknowledged that there are inequalities in SCD service provision, leading to differences in outcomes for patients and variation in the management of care between different areas.
1.3 Current assessment of sickle cell disease treatments

In order to inform treatment and commissioning decisions, NICE has published guidelines for:

- Sickle cell disease in general (April 2014)\(^{234}\)
- Commissioning for acute painful episodes (April 2014)\(^{235}\)
- Managing acute painful episodes in hospital (June 2012)\(^{236}\)

At present, stem cell or bone marrow transplants are the only ‘cure’ for SCD, but due to the high risks of the procedure this is very rarely attempted\(^{237}\). Beyond this, the recommended treatments are focussed on managing SCD, and fail to tackle the underlying causes of the condition.

They include:

Treatments to manage pain crises, through:

- **Regular blood transfusions (10% of adult patients).** For patients who require them, these are usually administered every 6 weeks in one of two ways:
  
  - Using the standard method to deliver blood transfusions, in line with that used for other patients
  - Using a more specialist device (Spectra Optia) which can improve patients’ quality of life and is cheaper for the NHS, and which was approved by NICE for use for SCD patients in 2016\(^{238}\)

- **Hydroxycarbamide (hydroxyurea) (25% of adult patients),** which is used to treat pain if they experience painful episodes. Most children with SCD should also take this treatment

More basic advice, forms of medication and techniques to manage the condition, such as:\(^{239}\)

- Drinking plenty of fluids
- Avoiding sudden temperature changes and wrapping up warm
- Taking over the counter or prescribed painkillers to manage a crisis
- Taking dietary supplements like folic acid to help stimulate red blood cell production
- Taking antibiotics regularly in order to prevent the risk of infection, with most people with SCD expected to take daily doses of antibiotics for the rest of their lives
2 Activities in the field of sickle cell disease in the UK

2.1 Policy landscape

Ongoing changes to the access environment

There are three pillars which define access to SCD care in the NHS:

- **Pillar 1: SCD service provision**, consisting largely of NHSE stakeholders involved in the national commissioning of SCD services, but also some local stakeholders

- **Pillar 2: Access to medicines framework**. This sits under the responsibility of another Government Minister, and includes policymakers within NHS England, the Accelerated Access Collaborative and (in the event of an appraisal) the National Institute for Health and Care Excellence

- **Pillar 3: Public health / screening**. There have not been any significant policy developments in SCD screening in the UK in recent years, and screening coverage continues to be high following a Labour manifesto commitment in the 2001 General Election. Nevertheless, there have been some significant policy developments in the wider public health environment, which have been spurred on by the COVID-19 pandemic. A new National Institute of Health Protection is to be created, merging both Public Health England and the new COVID-19 Test and Trace infrastructure

2.2 Advocacy landscape

There are a large number of national and local patient organisations involved in campaigning on SCD, including:

- **The Sickle Cell Society**, which acts as the Secretariat for the All Party Parliamentary Group (APPG) on Sickle Cell and Thalassaemia (a role it fulfils jointly with the UK Thalassaemia Society). Working with the APPG, the Sickle Cell Society has carried out a number of campaigns:
  - In July 2019, the APPG launched a campaign to end prescription charges for people with sickle cell and thalassaemia, called “end the blood tax.” It published a report on the impact which prescription charges have on this community, informed by testimony from qualified nurses, doctors and other allied health professionals\textsuperscript{240}
In June 2020, the APPG shifted its focus towards campaigning on COVID-19 and has launched a survey trying to understand the experiences of those living with SCD or caring for someone during the pandemic. Given the impact of the pandemic, the outputs from this survey and campaigning will likely shape their policy asks well into the future.

- **Sickle Cell and Young Stroke Survivors**, which supports young people and families affected by SCD and strokes
- **The Great Angels Foundation**, a Manchester-based charity which provides a nationwide support service to SCD patients
- **Local sickle cell organisations**, such as the Sickle Cell and Thalassaemia Support Project in Wolverhampton

Finally, because of the high prevalence of the condition in the African and Caribbean community, a number of BAME campaigning organisations have carried out activities related to sickle cell disease. Notably, the National BAME Transplant Alliance (NBTA), an organisation dedicated to promoting awareness of organ and stem cell donation amongst BAME people, engages regularly with the Sickle Cell Society.
Conclusion

This report has taken a comprehensive look at various aspects of patient care, the policy environment and initiatives aimed at raising awareness of sickle cell disease in France, Germany, Italy, Spain, the UK, as well as at EU level.

Analysis shows that there is a need for greater prioritisation of SCD across these areas in order to achieve better outcomes for an under-served patient population suffering from one of the most prevalent rare genetic diseases in Europe. Some common threads have been identified across each of these countries in how SCD is treated and understood as well as the priority accorded to the condition by politicians, policymakers and payers.

In particular, the report highlights the following considerations:

• The incidence of SCD is increasing across Europe, yet the political and policy priority accorded to the condition is disproportionately low compared to other less prevalent conditions. SCD is the most prevalent genetic disease in the UK, yet it does not receive the same attention as other less prevalent conditions.

• The distribution of patients varies widely within European countries, creating challenges for patient care. For example, in France, Spain and the UK the SCD patient population is overwhelmingly concentrated, respectively in Paris and Overseas Territories, Madrid and Barcelona, and London. This situation has created challenges in patient care, with difficulties in accessing specialist care for patients living in areas of lower prevalence.

• Most European countries studied in this report have demonstrated positive efforts to improve SCD outcomes. France, for example, has created a reference centre for sickle cell syndromes; the UK has reorganised SCD services and established a National Haemoglobinopathy Panel; Germany has established a GPOH-registry of SCD; Italy has just created a National Network for Thalassaemia and Haemoglobinopathies; and Spain has a National Registry for Haemoglobinopathies. The new European Rare Blood Disorders Platform (ENROL) will also provide crucial data on SCD and other conditions on a pan-European level.

Yet, whilst patient outcomes in all countries have improved over the past few decades, more needs to be done to further improve life expectancy and quality of life, including avoiding cognitive deficit. Inequalities in care and wider disadvantages in the SCD patient community also exacerbate outcomes in many countries.
In this context, policymakers and campaigners across Europe are encouraged to explore the issues raised in this report and take concrete steps to improve the life expectancy of people living with SCD. In particular, they may wish to consider:

1. How to improve data collection on SCD patient outcomes and the patient population, in order to gain a full understanding of how people living with SCD across Europe are supported and to improve standards of care.

2. What steps should be taken to address inequalities in service provision for people living with SCD, and to ensure all SCD services are delivered to consistent and high national standards of care, wherever people live.

3. How patient organisations advocating for people with SCD can best be supported in order to effectively raise awareness of the condition.

4. How best to address inequalities and stigma in the SCD patient population, addressing access to care, particularly for the BAME population.

5. How to effectively support innovation and research to ensure SCD patients receive access to novel and innovative therapies.

During the period in which this report was produced, health systems across Europe have faced unprecedented challenges. The COVID-19 pandemic has placed considerable pressure on health services in every country studied, and the impact of this pandemic has often fallen heaviest on those from black and minority ethnic backgrounds – the same population where SCD is most prevalent.

This calls for a renewed focus on improving health outcomes for the entire population, addressing entrenched health inequalities and treating under-served patient populations. Improving SCD outcomes must necessarily be an integral part of this objective, and it is hoped that this report will lead to greater recognition of the imperative of further prioritising SCD and of the critical role in which SCD could play in helping to address these wider issues.
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