Assessing the policy and access environment across European countries for SMA patients

Identifying key areas for improvement

AN EVIDENCE-BASED STUDY

Written by CRA Charles River Associates

in collaboration with SMA Europe

Funded by Biogen

Table of contents

Abbreviations

ABMM	Association Belge contre les Maladies neuro-Musculaires (Belgian Association against Neuromuscular Diseases)
ATU	Autorisations temporaires d'utilisation (temporary authorisation for use)
BeNeLuxA	Belgium, Netherlands, Luxembourg, Austria
CoE	Centre of excellence
CRA	Charles River Associates (authors)
CUP	Compassionate use programme
EMA	European Medicines Agency
ERN	European Reference Network
EU	European Union
EURODIS	European Organisation for Rare Diseases
EURO-NMD	European Reference Network for Neuromuscular Diseases
FINOSE	Finland, Norway, Sweden
FNDA	Finnish Neuromuscular Disorders Association
FSMA	Fundacja SMA (SMA Foundation)
FundAME	Fundación Atrofia Muscular Espinal España (Spinal Muscular Atrophy Foundation of Spain)
HTA	Health technology assessment
MA	Marketing authorisation
MHRA	Medicines and Healthcare products Regulatory Agency
MoH	Ministry of Health
NBS	Newborn screening
NMD	Neuromuscular diseases
OD	Orphan drug
RD	Rare disease
SMA	Spinal muscular atrophy

Introduction

Biogen and SMA Europe have asked Charles River Associates (CRA) to conduct a comparative assessment of the policy and access landscape for spinal muscular atrophy (SMA) patients across a selection of 23 European countries. The focus for the comparative assessment has been to characterise several key policy and access areas that impact the management of SMA patients. This includes the current status of access to innovative pharmacological treatments (termed 'treatments') and access to broader multidisciplinary care and patient support (termed 'care'). For the purposes of this assessment, the focus has been placed on selected care provisions (physiotherapy services, support for home adaptation and financial support) due to the complexity of the broader multidisciplinary care and support that is recommended for SMA patients.

The main objectives of this comparative assessment have been to (a) identify areas for improvement both within and across countries and (b) develop country-by-country summaries of the policy and access landscape for SMA patients. These findings have been used to develop a consolidated set of policy recommendations that can be used to advocate for improvements at the national and European level.

Context

SPINAL MUSCULAR ATROPHY (SMA)

Spinal muscular atrophy is a rare, genetic, neuromuscular disease affecting approximately 1 in 10,000 live births globally, with an estimated incidence in Europe ranging from 1 in 3,900–16,000 live births.[1] It is caused by homozygous mutations in survival of motor neuron 1 gene (SMN1) resulting in SMN protein deficiency. Characterised by degeneration of motor neurons, SMA leads to progressive muscle weakness and muscle wasting (atrophy), loss of lung function and difficulty swallowing.[2] At diagnosis, the broad spectrum of SMA phenotypes are classified into clinical types based on age of onset and maximum motor function ever achieved: type 0 (usually fatal at birth); type 1 (unable to sit independently); type 2 (able to sit independently but not walk); type 3 (independent walking) and type 4 (independent walking and adult onset).[3] However, variations in disease progression and disease heterogeneity regardless of type have been evidenced by natural history studies; therefore, SMA management recommendations in the rehabilitation phase are based on the current mobility level of patients – that is, whether the patient is a non-sitter, sitter or walker.[4] Without treatment, and depending on the severity of the condition, life expectancy in the severe forms may be less than two years and the ability to breathe (without respiratory support), swallow, sit and walk may be substantially impaired.[5] In addition, the lives and independence of individuals with SMA and also their caregivers are heavily impacted.

SMA patients usually require the support of multidisciplinary teams, and this is an important factor in why SMA is challenging for healthcare systems to manage.[6,7] The necessary elements to consider in the

1) Verhaart et al. (2017). "A multi-source approach to determine SMA incidence and research ready population". Available at: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5502065/#!po=27.7778

2) SMA Europe (2021). "What is Spinal Muscular Atrophy?" Available at: https://www.sma-europe.eu/essentials/spinal-muscular-atrophy-sma/what-is-spinal-muscular-atrophy/

3) National Organization for Rare Disorders (NORD) (2021). "Rare Disease Database: Spinal Muscular Atrophy". Available at https://rarediseases.org/rare-diseases/spinal-muscular-atrophy/

4) Mercuri et al. (2017). Neuromuscul Disord, "Diagnosis and management of spinal muscular atrophy: Part 1". Available at https://pubmed.ncbi.nlm.nih.gov/29290580/

5) SMA NBS Alliance (2021). "Spinal muscular atrophy: Screen at birth, save lives". Available at https://www.sma-screening-alliance.org/wp-content/uploads/2021/03/Spinal_muscular_atrophy_Screen_at_birth_save_lives_Whitepaper_SMA_NBS_Alliance_v1_26March21.pdf

6) Mercuri et al. (2017). Neuromuscul Disord, "Diagnosis and management of spinal muscular atrophy: Part 1". Available at https://pubmed.ncbi.nlm.nih.gov/29290580/

7) Finkel et al. (2018). Neuromuscul Disord, "Diagnosis and management of spinal muscular atrophy: Part 2". Available at https://www.sciencedirect.com/science/article/pii/S0960896617312907?via%3Dihub

optimal management of an SMA patient, as recommended in the guidelines, include comprehensive genetic diagnoses and counselling, regular physical therapy and rehabilitation, orthopaedic care, growth and bone health care, nutritional support, pulmonary care, acute care, management of other organ system involvement, medication and considerations for palliative care.[8] In addition to the necessary multidisciplinary management of patients, innovative pharmacological medicines for SMA are also crucial to improve the health outcomes of SMA patients. In this area there has been significant progress in recent years: Spinraza was the first medicine to treat SMA approved by the European Medicines Agency (EMA), in 2017.[9] It is now broadly available across European countries; however, access barriers remain, particularly for adult patients, in many countries. In addition, two other treatments have been approved more recently by the EMA: Zolgensma[10] (2020) and Evrysdi[11] (2021).

THE IDEAL POLICY AND ACCESS ENVIRONMENT FOR SMA PATIENTS

The complexity of SMA patient management (considering both the necessary care and available treatments) continues to present challenges for a number of European countries. Overall, these challenges are preventing SMA patients from accessing equal and in many cases optimal treatment and care. In order for optimal treatment and care to be provided to all SMA patients, the policy and access environment across countries needs to consider the unique elements that impact SMA patient outcomes.

First, the political environment should consider rare diseases (RD) and SMA a public health priority. Only with a strong political commitment to address the needs of SMA patients is it possible to guarantee SMA patients' access to timely and adequate treatment and care. Moreover, to ensure quality in the provision of treatment and care, patients and their carers should have a systematic and sustainable opportunity to be involved in healthcare and policy decision-making processes, either through patient experts or by providing their own experiences directly.

Second, the healthcare system should be prepared to provide reimbursed access to the three available treatment options and necessary care (as defined in guidelines). This requires the collection of epidemiological and clinical data to accurately assess the SMA population, to support the development and delivery of treatment and care, and to facilitate the efforts of international collaborations advancing support for SMA patients through increased registry data sharing and the development of shared best practices. In addition, for the provision of specialist treatments and management of patients with complex diseases it is important that patients have access to specialised centres of excellence (CoEs). Ultimately, the healthcare infrastructure should enable fast access to optimal treatment and care to patients at the time of their diagnosis.

Third, to maximise the benefits from treatments, it is necessary to have **prompt diagnosis of SMA**. Given the importance of treatment provision early in a patient's life, it is necessary for all the countries to adopt effective newborn screening (NBS) programmes. Until NBS is fully deployed across markets, it is also important to raise awareness amongst physicians and parents firstly of the early signs of SMA but also of the need to perform diagnostic tests systematically in children with early symptoms or familial history of SMA.

Fourth, SMA treatments should be made available to patients as soon as they are authorised. Ideally, national governmental programmes should identify funding solutions to provide patient access to treatments while the reimbursement decision is being made. Similarly, to ensure that SMA patients

8) Mercuri et al. (2017). Neuromuscul Disord, "Diagnosis and management of spinal muscular atrophy: Part 1". Available at https://pubmed.ncbi.nlm.nih.gov/29290580/

9) EMA (2017). "Summary of Opinion: Spinraza". Available at: https://www.ema.europa.eu/en/documents/smop-initial/chmp-summary-positive-opinion-spinraza_en.pdf

10) EMA (2020). "Summary of Opinion: Zolgensma". Available at: https://www.ema.europa.eu/en/documents/smop-initial/chmp-summary-positive-opinion-zolgensma_en.pdf

11) EMA (2021). "Summary of Opinion: Evrysdi". Available at: https://www.ema.europa.eu/en/documents/smop-initial/chmp-summary-positive-opinion-evrysdi_en.pdf

are able to access the available therapeutic treatments, standard reimbursement processes need to be adapted for orphan drugs: in particular to fully recognise the value these treatments provide to RD patients and to involve patients and/or caregivers in decision-making to ensure their voices are heard.

Finally, countries should allow equal access to treatment and care for all SMA patients in line with clinical evidence, and there should be no barriers for patients to access the available provisions to meet their individual needs. To this end it is also critical that the appropriate financial and social support is available to patients and caregivers as required.

In this comparative study, we assess how different European countries are performing in several key areas, to characterise their performance with regards to the policy and access environment for SMA patients. Due to the extensive and multidisciplinary management required by patients, this paper focuses on elements impacting access to treatments and selected elements of SMA patient care. From this assessment, we have identified several key areas for improvement, and have provided recommendations to key decision makers on the necessary changes that will improve European SMA patients' access to treatment and care.

Methodology

RESEARCH AND ANALYSIS METHODS

The findings of this white paper build on a secondary research exercise conducted between November 2020 and January 2021. The latest update on the metric 6 ('efficiency of the diagnostic pathway') and metric 10 ('treatment availability') was conducted on 8 August 2021, to reflect the constantly evolving status of NBS programmes and access to the available treatments. Analysis from the desk research has been validated by Biogen and SMA Europe and their national affiliates/member organisations. Further details of the research, analysis and drafting process are provided in the Appendix.

COUNTRY SCOPE

Twenty-three European countries were included in this study. The country selection was based on whether there was a currently active or prospective SMA Europe member organisation in that country, supporting advocacy activities (**Table 1**).

Table 1: Countries[12] in scope with current or prospective SMA Europe member organisations

ASSESSMENT FRAMEWORK: POLICY AND ACCESS LANDSCAPE

A framework to guide analysis of the policy and access situation in each country was developed. For this framework, or policy and access landscape, it was agreed that five key policy and access 'areas' should be covered to ensure that the ideal policy and access environment presented above was analysed with sufficient breadth and depth. The insights from this analysis fed into the area-level policy recommendations that are given in this white paper. The five areas included are:

1. Political leadership and policy
2. Healthcare system preparedness
3. Diagnosis
4. Access pathways
5. Access to treatment and care

12) Countries in scope: AT – Austria; BE – Belgium; CZ – Czech Republic; DK – Denmark; FI – Finland; FR – France; DE – Germany; GR – Greece; HU – Hungary; IS – Iceland; IE – Ireland; IT – Italy; MK – North Macedonia; NL – The Netherlands; PL – Poland; RO – Romania; RU – Russia; RS – Serbia; ES – Spain; SE – Sweden; CH – Switzerland; UK – United Kingdom; UA – Ukraine

Across the five areas, 11 specific metrics were identified and detailed analysis conducted in each country. Each of the 11 metrics selected for inclusion within the policy and access tracker covers one of the issues that most greatly impact SMA patient access to treatment and care. The rationale for the inclusion of each metric is provided in Table 2.

Table 2: Metrics used for comparative assessment of policy and access environment for SMA patients

1: POLITICAL LEADERSHIP AND POLICY	1. National strategies for rare/ genetic disorders	Ensures national priority placed on finding solutions for patients with rare diseases, including SMA patients.
	2. Patient organisations and advocacy	Patient organisations play an important role in ensuring the patient voice is heard amongst policymakers and other decision makers.
2: HEALTHCARE SYSTEM PREPAREDNESS	3. Epidemiology estimate	Provides basis for short- and long-term economic planning.
	4. National SMA patient registry	Ensures healthcare systems have visibility on number of patients with SMA.
	5. Infrastructure	Ensures all patients have good physical access to treatment centres.
3: DIAGNOSIS	6. Efficiency of diagnostic pathway	SMA patients should be treated before symptom onset for best results. Early and efficient diagnosis is critical to accessing the best treatment and care.
4: ACCESS PATHWAYS	7. Post-MA early access pathways	Ensures patient access to treatments as soon as regulatory approval is granted and product is deemed safe to use.
	8. Specialised reimbursement / HTA pathways	Ensures the value of products for rare diseases is recognised in national assessments.
5: ACCESS TO TREATMENT AND CARE	9. Treatment and care guideline recommendations	Ensures national recognition of internationally accepted treatment and care standards.
	10. Treatment availability	There are three potential treatments for SMA which between them can be used across almost all patients with SMA (from pre-symptomatic to adult patients). Ensuring unrestricted access to therapies is critical.
	11. Selected care provisions	SMA patients require complex multidisciplinary care[13] to optimise patient health outcomes. Financial support is also critical to help families adapt to the complications caused by the disease.

13) For the purposes of this assessment, selected care provisions have been explored.

Executive summary and policy recommendations

The SMA Tracker shines a light on existing gaps affecting SMA patients and highlights actions decision-makers can take to address them. While people living with SMA can now benefit from different care options, a number of challenges to access these options or connected care continue to exist in various European countries.

– DAVID NESTOR, Head of Neuromuscular Disease, Europe, Canada and Partner Markets at Biogen

Executive summary and policy recommendations

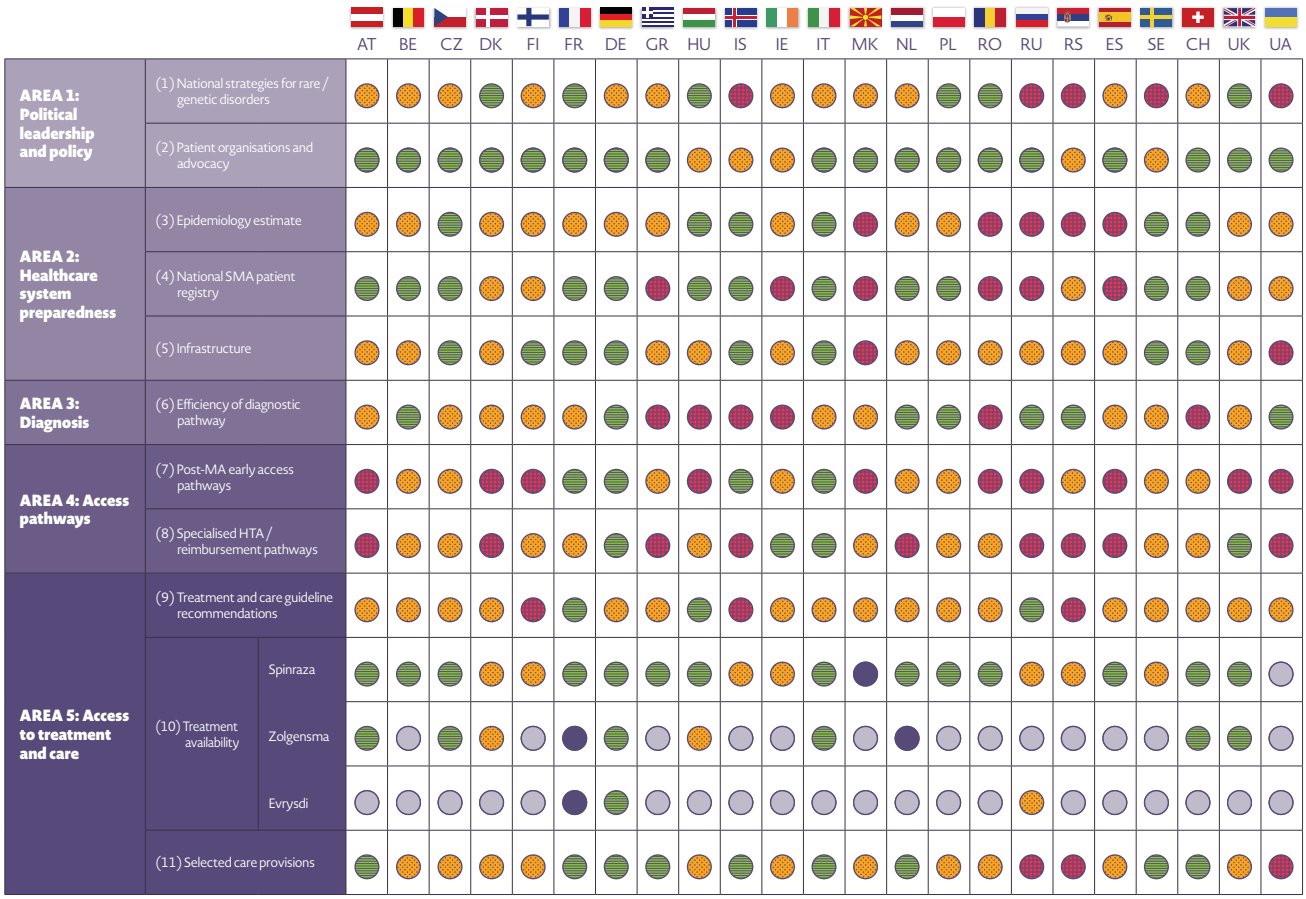
There is considerable variability in terms of performance among the different European countries within each area (**Figure 1**). In particular, the two areas noted as most needing improvement are Area 3: Diagnosis and Area 4: Access pathways. In addition, these two areas are also the most impactful for treatment access, and differences in the landscapes across European countries have resulted in significant variation in the lives of SMA patients across Europe. In order to make improvements in these areas, it is paramount that the foundation to influence SMA policy and healthcare support is as robust as possible, as indicated by the first and second policy areas. Political leadership and policy has historically been strong, with most countries having national rare-disease strategies and influential patient organisations. However, there is still a need to update these strategies and improve the healthcare system preparedness in some countries to ensure availability of patient-level data and access to centres of excellence.

It should also be noted that the picture captured in the current analysis (**Figure 1**) is significantly more progressed than the policy and access environment from several years ago. Achieving the status of the policy and access environment that we see across the European countries in scope has taken significant efforts from a range of stakeholders. For instance, while the treatment availability is generally showing a positive picture today, the current level of access to these treatments is the result of the strong commitment and engagement of many stakeholders, including national organisations, patient organisations and manufacturers. This strong commitment and collaboration from many stakeholders must remain, if the picture is to continue to improve. Further to this, the policy and access environment is continuously evolving, some areas more quickly than others, particularly due to the recent approval of two new treatments and other parallel efforts to improve areas such as registries (led by TREAT-NMD) and SMA's inclusion in NBS programmes (led by the European Alliance for Newborn Screening in Spinal Muscular Atrophy (SMA NBS Alliance)).

To address the existing challenges across the different policy areas and to ensure that all European SMA patients can be given the same opportunities to access SMA treatment and care, a number of specific policy recommendations, directed at both national and European policymakers, have been defined for each area (**Table 3**, **Table 4**, **Table 5**, **Table 6**, **Table 7**). A successful approach to achieve these improvements requires strong commitment and cooperation between the many stakeholders at both the national and international level.

Figure 1: Summary of metric status for each country

Refer to Table 19 in appendix for a fuller explanation of red, yellow and green assessment criteria for each metric



Key: Good · Room for improvement · Not good enough · Provisionally good, final status pending · Not applicable

AT – Austria; BE – Belgium; CZ – Czech Republic; DK – Denmark; FI – Finland; FR – France; DE – Germany; GR – Greece; HU – Hungary; IS – Iceland; IE – Ireland; IT – Italy; MK – North Macedonia; NL – The Netherlands; PL – Poland; RO – Romania; RU – Russia; RS – Serbia; ES – Spain; SE – Sweden; CH – Switzerland; UK – United Kingdom; UA – Ukraine

Area 1: Political leadership and policy

In our analysis, the political leadership and policy environment of a country is assessed in terms of its adoption of national rare disease strategies and the opportunities for political advocacy by patient organisations. The existence of currently valid national strategies can indicate a prioritisation of treatment and care for RD patients in the context of the wider health system policy agenda. Patient organisations with a strong advocacy platform can bring the patient voice to policymakers and shape policies directed to support patient access to treatment and care.

In terms of performance, although the majority of countries analysed have developed national strategies for RD, many of these plans have since expired or can be considered out of date due to the rapidly changing RD landscape. In addition, many countries have not reported on the outcomes of their strategies, limiting potential learnings for new RD plans. In terms of political advocacy of patient organisations, in almost all the countries there have been strong efforts by patient organisations to support positive reimbursement decisions for innovative treatments through the channels that are available to them (e.g. advocacy, awareness raising). However, in some countries there are limited channels for the inclusion of patient associations in policy-making, resulting in limited opportunities for effective advocacy.

POLICY RECOMMENDATIONS

Table 3: Policy recommendations for key improvements regarding political leadership and policy

Rare diseases should be high in the political agenda, and effective strategies to fight RD should be implemented so no patient is left behind
• We call on **European policymakers** to put in place a European policy framework guiding the implementation of consistent national plans for rare diseases, monitored and assessed by a multistakeholder body on a regular basis. • We call on **national governments** to prioritise rare diseases, including SMA, with dedicated and appropriately funded national plans that incorporate the key learnings from the rapid changes seen in RD communities in recent years. • **National decision makers** (including ministries of health (MoHs), payers, health technology assessment (HTA) bodies) should adopt a sustainable approach to systematically involve the relevant patient organisations in decision-making processes that affect the patients and caregivers they represent.

Area 2: Healthcare system preparedness

To ensure access to optimal treatment and care for SMA patients, the healthcare system must be adequately prepared to provide consistent high-quality specialist management of all SMA patients. The availability of infrastructure and CoEs for SMA therefore impacts patient access to treatment and care. Moreover, to adequately assess the level of resources required, and to ensure that patient management protocols are up to date, it is important to hold accurate epidemiological and clinical data on patients, allowing for accurate and informed decision-making. This can occur through dedicated epidemiological studies, or through the presence of a patient registry with a high coverage of the patient population.

In many of the countries assessed, detailed epidemiology studies are limited, and it can be difficult for key stakeholders to adequately allocate resources without a full understanding of the SMA population in their countries. This could also result in inadequate infrastructure or inconsistent management of patients. This situation is ameliorated where patient registries are well established and provide complete data on the patient population and clinical outcomes that help to identify areas of need and improvement within the system. In particular, data on disease progression can help to identify unmet needs and aid the development of standardised treatment and care provisions.

POLICY RECOMMENDATIONS

Table 4: Policy recommendations for key improvements regarding healthcare system preparedness

Healthcare systems should ensure that information about the needs of the SMA patient population is always up to date and that the infrastructure system for the provision of SMA treatment and care is adequately aligned with these needs
• We call for **national and regional authorities** to support the development and maintenance of comprehensive disease registries that report the epidemiology, clinical status and current outcomes for SMA patients. • We ask **patient registry owners** for aggregated, anonymised data to be regularly reported publicly to be used nationally and internationally to improve treatment and care for SMA patients. In particular, data collection and analysis should be harmonised in line with the TREAT-NMD core dataset.[14] • We call for **national ministries of health and other healthcare planners at national and regional level** to ensure that collaborative infrastructures (e.g. hospitals, specialised centres of excellence) are accessible for all patients and provide uniform treatment and care across countries.

14) TREAT-NMD (2021). "Spinal Muscular Atrophy (SMA) Core Dataset". Available at https://treat-nmd.org/patient-registries/treat-nmd-core-datasets/sma-core-dataset/#1583940679192-7000266f-ef8e

Area 3: Diagnosis

To achieve maximum impact in SMA disease management, treatment should begin before symptom onset: early and efficient diagnosis is critical to ensuring the best outcomes for patients as it enables access to treatment and care from an early stage of the disease. Reimbursed access to diagnostic services (with genetic testing now typically used) for suspected SMA patients is available in all countries; however, the need for early diagnosis has made the implementation of NBS a key priority for patient organisations, and it is the key metric when considering the diagnostic landscape.

However, SMA is not yet a part of routine NBS programmes in many of the countries analysed, which leads to diagnostic delays and likely reduces the impact of treatment outcomes due to delayed intervention. While there are increasing calls for SMA to be included in standard NBS programmes, several barriers continue to exist. In some cases, there are legal requirements for detailed consultations with a specialist prior to genetic testing, which in practice can delay or represent a hurdle for testing. In addition, even in countries which have formally approved the inclusion of SMA in their national NBS programmes, infrastructural and technical barriers were identified, which delay or limit the implementation of screening.

POLICY RECOMMENDATIONS

Table 5: Policy recommendations for key improvements regarding diagnosis

Nationwide SMA newborn screening and rapid access to diagnostic procedures should be the routine approach to ensure early disease detection and timely patient access to treatment and care
• Based on the strong evidence available, we call on national competent authorities urgently to include SMA in standard NBS programmes at the national level as quickly as possible. We call on national governments and parliaments to ensure sufficient funding to support appropriate, fast and sustainable implementation of SMA in these NBS programmes. • We call on the support of the European Commission to facilitate the gathering and exchange of data from pilot programmes to favour a harmonised approach across Europe. We ask that national screening committees utilise the existing evidence base from international pilot programmes to reduce the need for further country specific pilots which further delay the implementation of NBS. • As interim measures, we call on ministries of health and healthcare providers to address the diagnostic gap created by the lack of inclusion of SMA in NBS programmes by raising public awareness of early disease symptoms and ensuring adequate training of physicians and specialists to promptly prescribe the necessary SMA tests in case of symptoms or familial history of the disease.

Area 4: Access pathways

In countries where treatments for SMA have been approved at the regulatory level but not reimbursed, patients diagnosed with SMA can face long delays before gaining access to treatments that may be available in other European countries. Therefore, it is important that treatments are made available to patients during the national reimbursement process and the national process considers the specifics of RD to ensure rapid and equitable access.

Only a small number of countries have well-established and funded early access programmes[15] for large groups of patients, allowing for reimbursed early access to treatments prior to a formal reimbursement decision. Moreover, very few countries provide specialised health technology assessment (HTA) procedures for orphan drugs that take into account the often limited data available due to the small patient population; or utilise an accelerated version of the standard HTA procedure to reach a rapid access decision for products used in high unmet need areas such as SMA. These flexible approaches often require particular agreements with the manufacturers (e.g. coverage with evidence development agreements that allow patients to have reimbursed access to medicines while additional evidence to address payers' requests is collected). Where these programmes and flexibilities are not available, patients can potentially face long waits before a positive reimbursement decision is reached and before they can access treatments, and hence can lose motor functions that may never be regained.

Ultimately, without optimised access pathways specifically tailored for orphan medicines, patient access may rely on individual funding decisions, leading to limited, delayed and inconsistent access to innovative therapies.

POLICY RECOMMENDATIONS

Table 6: Policy recommendations for key improvements regarding access pathways

Access provisions should be available to support fast patient access to SMA treatment, and reimbursement pathways should consider the specifics of rare disease products to fully capture the value they deliver to rare disease patients and their carers
• We call for **national ministries of health and payers** to develop, implement and fund innovative early access provisions that enable patients to receive the treatments they need immediately after regulatory approval and while the reimbursement process is still ongoing. • We ask **HTA bodies** to ensure that the value assessment and reimbursement process fully considers the patient perspective (and the value that medicines bring to both their caregivers and society as a whole) by formally including disease-specific clinical specialists and patient experts in decision-making processes. • We ask that **payers and HTA bodies** implement specialised reimbursement/HTA pathways that take into consideration the characteristics of medicines for rare diseases such as SMA and the challenges associated with evidence generation.

15) Manufacturer-funded early access programmes (compassionate use programmes (CUPs)) are available prior to regulatory approval under European law. The focus of this assessment is on the availability of early access programmes that are funded by national healthcare systems/governments between the period of marketing authorisation and national reimbursement.

Area 5: Access to treatment and care

As noted above, treatment availability is closely linked to the access pathway available in a country and is often an evolutionary process, with treatments being made available for reimbursement in European countries at different times and achieving different levels of initial access. Although Spinraza, the first innovative treatment option for SMA, is now widely available across most countries analysed, the process has required significant advances in the overall policy and access areas to achieve reimbursement. Despite such progress, there remains inconsistency in the access across different European countries, with many adult patients still facing significant barriers to receiving treatment, indicating that further improvements are still necessary to optimise access for all patients. It is paramount that lessons learned and advances gained for treatment access are maintained and built upon to improve and accelerate access to existing and new treatment options.

In addition to achieving reimbursement, in order to also ensure equal access to SMA treatment and care both across and within countries, national adoption of clinical guidelines based on the most up-to-date clinical evidence ensures that available treatments are used in the right patients based on clinical value and that there is appropriate provision of multidisciplinary care. Most of the countries in scope recognised the 2017 international standards of care for SMA; however, the utilisation of these guidelines in practice can vary between hospitals. Further, the recommendations on available treatments provided by the latest international standards of care are limited, due to developments in the therapeutic area since their publication in 2017. Only a small number of countries have developed guidelines that include recommendations for the use of recently available treatments based on the latest clinical evidence and provide a national framework for standardised patient management across the country.

Subsequently, access to care – characterised in this assessment by the reimbursement of physiotherapy, home adaptation services and additional financial support for patients/caregivers – is often unequal within a single country. The reimbursement and financial support that SMA patients from the same country are eligible to receive can often depend on their location and disease progression, which itself may be assessed differently depending on region. On the other hand, a number of countries provide clear benefits and payment exemptions to SMA patients regardless of disease progression, highlighting a clear disparity across countries as well.

POLICY RECOMMENDATIONS

Table 7: Policy recommendations for key improvements regarding access to treatment and care

Treatment and care approaches should ensure equal access for all SMA patients and their carers
• We call for **national reimbursement bodies** to support access to all authorised SMA treatments in line with the approved labels (e.g. to include adult patients), allowing physicians the freedom to prescribe the treatment(s) deemed most appropriate for patients based on their clinical needs and wishes through collaborative decision-making. • We call for **national reimbursement bodies and healthcare providers** to facilitate reimbursed and efficient access to care services and financial support as recommended in international clinical guidelines. All affected patients should be eligible for services according to their needs and regardless of their location within the country. • We call on **national and regional healthcare providers** to reflect the latest international clinical guidelines in their clinical guidance, including the support of shared decision-making between patients and their multidisciplinary care team. We call on **individual centres of excellence** to ensure that these guidelines are consistently applied throughout the country.

POLICY AND ACCESS LANDSCAPE FINDINGS

Area 1: Political leadership and policy

Metric 1: National strategies for rare / genetic disorders

OVERVIEW

POLITICAL LEADERSHIP AND POLICY: National strategies for rare/genetic disorders

Rationale for inclusion of metric

The existence of currently valid national strategies can indicate the relative priority given to improving rare disease – and thus SMA – treatment and care in the context of the wider health system policy agenda. Patient groups can use national rare disease strategies to identify leverage points where governments are willing to deploy resources and support which can ultimately improve patients' level of access to the treatment and care they need.

Following a recommendation from the European Union (EU) in 2009 that all countries should establish and implement rare disease (RD) strategies by 2013,[16] most countries have had at least an initial RD strategy in place since 2013. In addition, many non-EU countries (e.g. Switzerland, North Macedonia) also developed RD strategies. However, given most plans were written to cover a period of 3–5 years (e.g. 2013–2018), most are now expired, indicating that continued commitment in this area from national and international policymakers is not consistent across European countries (**Table 8**).

Table 8: Metric status – National strategies for rare / genetic disorders

Comparative assessment

Six out of 23 countries have currently **valid national RD strategies** (**Table 8**). In many cases, these are extensions of plans launched over five years ago that have been **renewed based on the level of progress seen through monitoring efforts**, indicating a commitment to continue to improve the policy environment for RD patients. For example, in **Denmark (DK)** the working group responsible for the national RD strategy evaluated its status in 2018 once the initial plan had ended.

This evaluation resulted in recommendations to continue implementation efforts under the same plan and monitor them (**Figure 2**).[17]

16) Official Journal of the European Union (2009). COUNCIL RECOMMENDATION of 8 June 2009 on an action in the field of rare diseases. Available at http://www.europlanproject.eu/Resources/docs/CouncilRecommendation_2009-C%20151-02.pdf

17) Danish Health Authority (2018). "National strategy for rare diseases: Status evaluation and recommendations for future efforts". Available at http://download2.eurordis.org/rdpolicy/National%20Plans/Denmark/2.Denmark_RD%20National%20Strategy_Evaluation%26Recommendations_2018_Danish.pdf

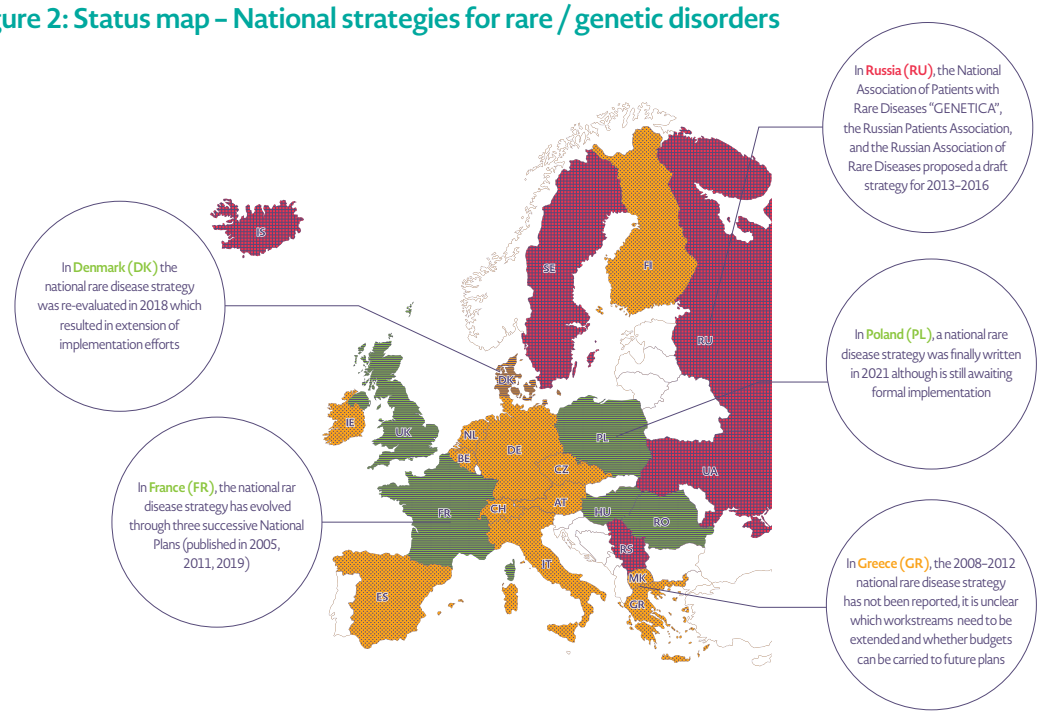
The overall success of current strategies will rely on the effectiveness of their implementation and monitoring of impact. For example, in January 2021, the **United Kingdom (UK)** published a new Rare Disease Framework to build on key priorities. While the drafting and publication of this strategy is a key step to promote RD within the health policy agenda, **success** of the new framework will be **determined by the quality of implementation** and by the extent of adoption in the devolved nations (England, Scotland, Wales and Northern Ireland).

Twelve out of 23 countries have expired or outdated national RD strategies (**Table 8**). Although a large proportion of the assessed countries have not renewed their initial RD strategies, many have reported significant progress under their original RD plans. For example, in **Finland (FI)**, the 2014–2017 national RD strategy established an RD unit in every Finnish university hospital.[18] Patient advocacy groups are currently leveraging this progress to persuade the government to make further updates to this plan.

In contrast, many countries have **not reported RD strategy outcomes**, which is likely to have contributed to the lack of their extension: without an understanding of implementation progress it is **difficult for policymakers to determine whether RD plans need to be extended**. Further, it may show a lack of transparency and commitment to improving the policy and access environment for patients with rare diseases.

Five countries have no established RD strategies (**Table 8**). In **Sweden (SE)** and **Serbia (RS)**, governments have **drafted policy frameworks** for RD strategies, but **they do not yet have active implementation workstreams**.[19,20] In **Russia (RU)**, the National Association of Patients with Rare Diseases "GENETICA", the Russian Patients Association, and the Russian Association of Rare Diseases **proposed a draft strategy for 2013–2016** (**Figure 2**).[21] Despite this significant effort and investment from patient associations, the government did not express support for the strategy.

Figure 2: Status map – National strategies for rare / genetic disorders



18) Ministry of Social Affairs and Health (2014). "THE FINNISH NATIONAL PROGRAMME FOR RARE DISEASES 2014–2017". Available at http://www.europlanproject.eu/DocumentationAttachment/The%20finnish%20national%20programme%20for%20rare%20diseases_%20eng%20(en)%20%20[unofficial%20version%20by%20EUROPLAN].pdf

19) EURORDIS (2012). "Swedish National Conference Report". Available at https://www.eurordis.org/nationalplans/sweden

20) Ministry of Health, Serbia (2020). "The Program for Rare Diseases in the Republic of Serbia for 2020-2022". Available at http://download2.eurordis.org.s3.amazonaws.com/rdpolicy/National%20Plans/1.%20European%20Countries%20Outside%20EU/Serbia/1.National_programme_for_rare_diseases_2020-2023_serbian.pdf

21) All-Russian Society of Rare (Orphan) Diseases (2020). "Strategy for the development of the patient care system with rare (orphan) diseases in the Russian Federation for a short-term planning period 2013–2016". Available at: http://www.rare-diseases.ru/component/content/article?id=259:l-.html

Metric 2: Patient organisations and advocacy

OVERVIEW

POLITICAL LEADERSHIP AND POLICY: Patient organisations and advocacy

Rationale for inclusion of metric

Patient organisations and advocacy groups leverage collective experiences of living with SMA to engage with decision makers to raise awareness and advocate for patient perspectives to be incorporated into decision-making and shape policies accordingly. To differentiate between the consistently high levels of patient group engagement across all countries, ratings have focused on assessing the extent to which patient groups have an explicitly political mandate and thus have the capacity to engage with national decision makers to advocate for the patient voice.

Each country included in this study has a patient organisation that is active in supporting patients directly, and in some cases also through political advocacy to support improved access to treatment and care (**Table 9**).

Table 9: Metric status – Patient organisations and advocacy

Comparative assessment

Political advocacy by patient groups ensures that the **patient perspective is shared with national decision makers** in order that they make more informed decisions on health policy and access to SMA treatment and care. National decision makers include political stakeholders responsible for development of health policy agendas as well as reimbursement decision makers at the national level. **In 17 of the countries in scope, patient groups have engaged with political stakeholders through advocacy activities**. The most common mode of political advocacy has been to coordinate public campaigns to raise awareness of the burden of SMA (**Table 9**).

The extent to which healthcare systems accommodate patient perspectives in national policy decision-making processes varies between countries. Policies that embed patient perspectives in national processes can empower patient groups to play a larger role in shaping the treatment landscape of their respective countries. For example, in **France (FR)** representatives of patient associations have voting rights when the national health technology assessment (HTA) body (Haute Autorité de Santé) makes its final recommendations for the reimbursement of treatments.[22]

22) HAS website (2021). "HAS transparency committee". Available at https://www.has-sante.fr/jcms/c_1729421/en/transparency-committee

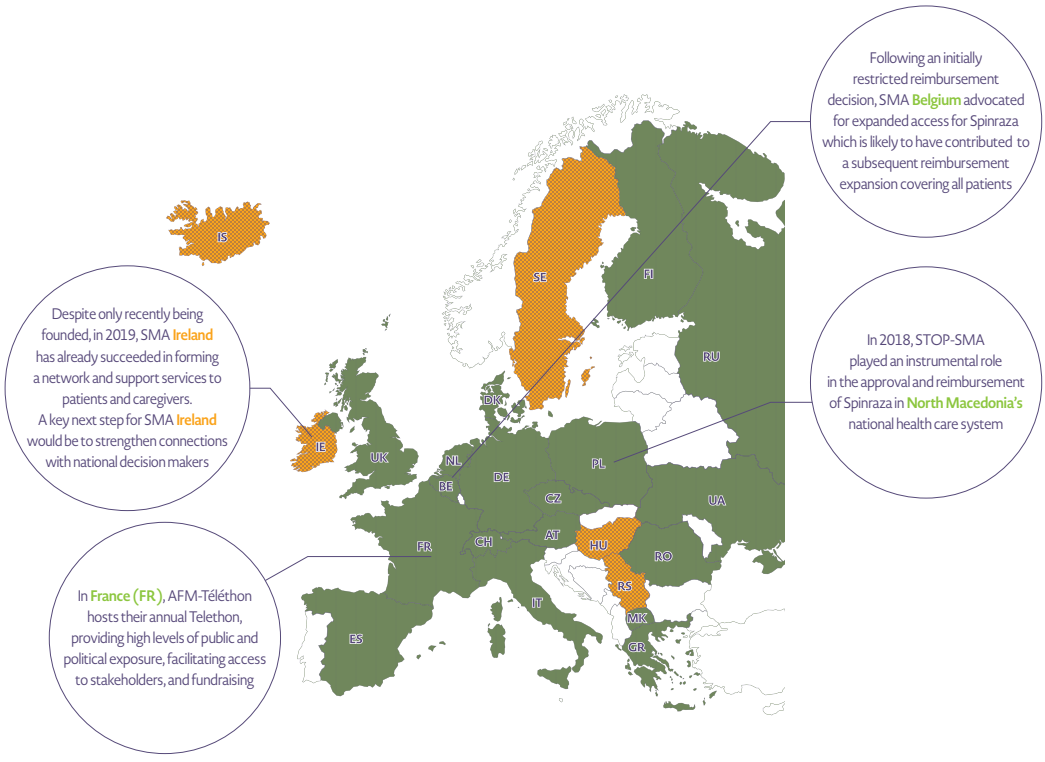
Other countries target political stakeholders through high-impact advocacy campaigns such as:

- STOP-SMA, **North Macedonia (MK)**, conducted a campaign to advocate for funding for Spinraza (**Figure 3**).[23] The campaign was formally recognised by the Prime Minister, and contributed to the allocation of state funds for reimbursement.
- Association Belge contre les Maladies neuro-Musculaires (Belgian Association against Neuromuscular Diseases) (ABMM) Wallonia, Belgium (BE), assisted in the launch and funding of a region-wide newborn screening (NBS) pilot for SMA (**Figure 3**).[24]
- Fundacja SMA (SMA Foundation) (FSMA), **Poland (PL)**, campaigned successfully for access to Spinraza through an early access program, and later full reimbursement to all SMA types.[25]

The focus of many patient groups is to support patients directly through financial and educational activities. This especially seems to be the case in newer patient associations (e.g. **Ireland (IE)** and **Iceland (IS)**) that do not appear to have existing and strong links with national decision makers. These associations have prioritised the need to provide direct support to patient and families (**Figure 3**).

Regional fragmentation of countries and decentralised approaches to the running of healthcare systems can act as a key hurdle for patient groups. With multiple political stakeholders allowing for different levels of engagement, a patient group's ability to engage in political advocacy can be affected by external factors such as regional and national policy environment.

Figure 3: Status map – Patient organisation and advocacy



23) TreatSMA website (2021). "Macedonia will fund Spinraza Treatment". Available at https://www.treatsma.uk/2018/04/macedonia-will-fund-spinraza-treatment/#:~:text=The%20government%20of%20Macedonia%20has,those%20with%20spinal%20muscular%20atrophy.&text=Its%20GDP%20per%20capita%20is,times%20lower%20in%20absolute%20terms.

24) SMA NBS Alliance (2021). "Newborn screening in Belgium". Available at https://www.sma-screening-alliance.org/newborn-screening-in-belgium/

25) FSMA (2017). "A joint announcement by the Children's Health Centre and the SMA Foundation on the administration of nusinersen". Available at: https://www.fsma.pl/2017/02/wspolny-komunikat-centrum-zdrowia-dziecka-i-fundacji-sma-w-sprawie-podawania-nusinersenu/

Area 2: Healthcare system preparedness

Metric 3: Epidemiology estimate

OVERVIEW

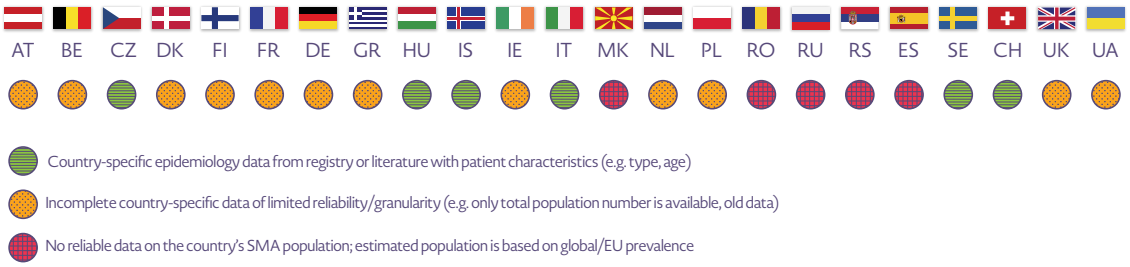
HEALTHCARE SYSTEM PREPAREDNESS: Epidemiology estimate

Rationale for inclusion of metric

Publicly available epidemiological data can complement epidemiology estimates of national bodies for decision-making about provision of SMA treatment and care. For instance, a deep understanding of the patient population characteristics allows policymakers and healthcare systems to identify the services required for children vs adult populations. Moreover, the availability of public information on epidemiology can help in raising national and international awareness of the burden of the disease. It can help policymakers and other key stakeholders within the industry to prioritise SMA with clear supporting data and support international collaborations in areas where data are scarce due to patient population size.

Published epidemiology data are available in the majority of countries; however, there is variation in the granularity and scope of data captured (**Table 10**). Though there are multiple potential sources for epidemiology data, there is a correlation between the completeness of a country's epidemiology data and the existence of a national SMA registry which allows for a continuously updated record estimate of the epidemiology in that country.

Table 10: Metric status – Epidemiology estimate



Comparative assessment

Across countries, published epidemiology studies are sparse, with the most recent pan-national study conducted in 2017 using data from available TREAT-NMD registries.[26] This pan-national study reports national epidemiology figures for 19 of the 23 countries in scope. Of the remaining four countries, the most recent data available is from literature studies now significantly older.

In Iceland, however, the 1999 epidemiological study was re-analysed in 2017, and it was concluded that **figures are still likely to be accurate** given the country's small population.[27,28]

26) Verhaart, I. E. C. et al. (2017). "A multi-source approach to determine SMA incidence and research ready population". Available at https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5502065/

27) Ludvigsson, P., Olafsson, E. and Hauser, W. A. (1999). "Spinal muscular atrophy. Incidence in Iceland". Available at https://pubmed.ncbi.nlm.nih.gov/10461052/

28) Verhaart, I. E. C. et al. (2017). "Prevalence, incidence and carrier frequency of 5q–linked spinal muscular atrophy – a literature review". Available at https://ojrd.biomedcentral.com/articles/10.1186/s13023-017-0671-8

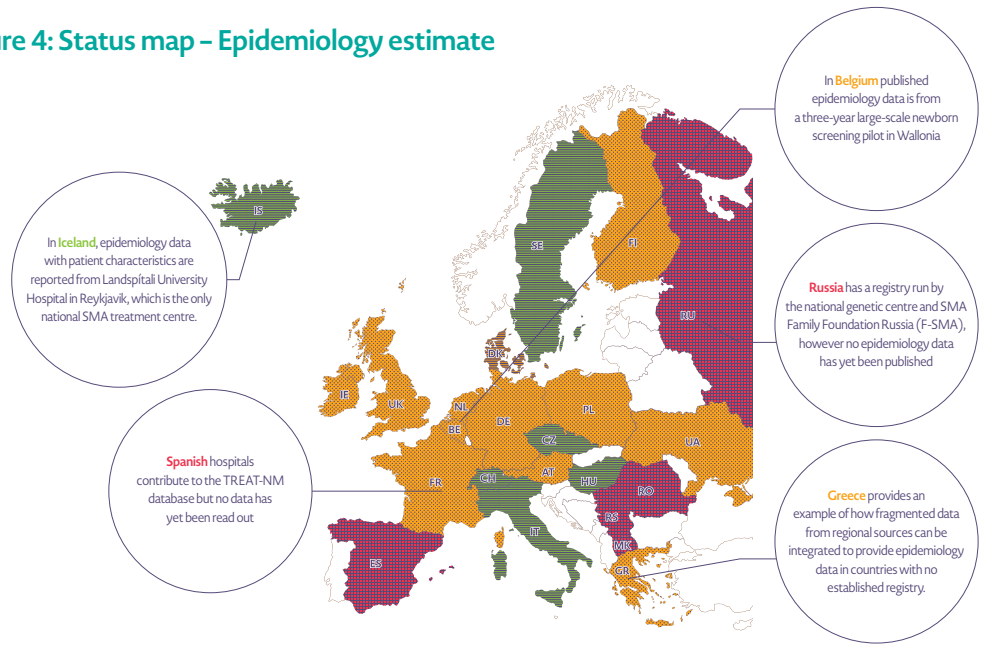
Epidemiology data from national registries often serves as the most recent and reliable epidemiological estimate. This is supplemented by TREAT-NMD's efforts to harmonise registry datasets and support the collection of patient characteristics such as SMA type and age within registries, resulting in more detailed epidemiology estimates being provided.[29] For example, the **Czech Republic (CZ)** neuromuscular disease registry is harmonised with the internationally agreed core dataset set out by TREAT-NMD and therefore collects patient characteristics data. The data are made available online through a 'registry status' page and regular publication outputs, which allow for a breakdown of the epidemiology estimate to be seen.[30] **Five out of the six** countries with published **'high-quality' epidemiology estimates** have obtained these from their national registries which are harmonised with TREAT-NMD's core dataset.[31]

However, the presence of a national registry harmonised with TREAT-NMD's dataset is not always sufficient for providing a reliable published epidemiology estimate. Many countries do not regularly publish epidemiological data from their registries. For example, **10 out of the 12 countries ranked with room for improvement** have existing national registries; however, these data are not publicly available. Instead, publicly available epidemiological estimates come from older studies or studies in aggregate that do not provide the same breakdown – for example, in **Belgium (BE)**, the most recent epidemiological estimate is extrapolated from a recent regional NBS pilot.

Although regional fragmentation of registries, governments or studies can prevent reliable epidemiological estimates from being provided, **Greece (GR)** offers an example of how fragmented data from regional genetic services can be integrated to provide a national epidemiology estimate, **even if there is no established registry** (**Table 10**).[32] This was achieved by an analysis of genetic and clinical data from SMA patients referred to the public-sector provider of genetic services for SMA across regions.

Countries with no reliable published epidemiology data generally lack established national SMA registries – for example, in **Spain (ES)**, regional registries have only recently been consolidated into a national registry and harmonised with TREAT-NMD resulting in a no recent estimation on national epidemiology. Similarly in **Serbia (RS)** a national registry has been more recently established, data from this has not yet been made public and no supplementary literature exists with an alternative source of epidemiology data.

Figure 4: Status map – Epidemiology estimate



29) TREAT-NMD (2021). "Spinal Muscular Atrophy". Available at https://treat-nmd.org/patient-registries/list-of-registries-by-disease/spinal-muscular-atrophy/

30) REaDY (2020). "Introduction". Available at: https://ready.registry.cz/

31) Czech Republic, Italy, Hungary, Sweden, Switzerland

32) Kekou et al. (2020). J Neuromuscul Dis, "Evaluation of Genotypes and Epidemiology of Spinal Muscular Atrophy in Greece: A Nationwide Study Spanning 24 Years". Available at https://content.iospress.com/articles/journal-of-neuromuscular-diseases/jnd190466

Metric 4: National SMA patient registry

OVERVIEW

HEALTHCARE SYSTEM PREPAREDNESS: National SMA patient registry

Rationale for inclusion of metric
In addition to providing a basis to understand the epidemiology and health economic impact of SMA, registries can provide a foundation for assessing the quality of SMA services in each country. Registries that capture clinical information can provide evidence on current efficiency of treatment and care provision with regards to health outcomes. Assessment criteria has focused on the type of data collected in national registries.

Most countries have or plan to establish a national SMA registry. Organisations contributing to the set-up and maintenance of national/sub-national registries include SMA patient organisations, governments and individual hospitals. Many of the SMA registries have been harmonised through efforts made by TREAT-NMD. However, there is still variation across countries in the data that these registries collect and the way in which they operate (**Table 11**).

Table 11: Metric status – National SMA patient registry

Comparative assessment

Currently, in 13 countries there is a national registry that collects both clinical and epidemiological data. (**Table 11**). Clinical registry data can be leveraged to bring access to investigational therapies. For example, in the **Czech Republic (CZ)**, the capture of clinical data is used to incentivise inclusion of Czech patients in clinical trials.[33] Some registries have gone further to capture the broader burden of disease. For example, the **French (FR)** SMA patient registry captures both **patient and caregiver quality of life**.[34] Evolution of registries to capture such **disease burden data**, could provide additional evidence for the reimbursement of new SMA therapies. **Figure 5** provides additional examples of best practices.

Of the five countries whose registries collect only epidemiological data, three have registries hosted or sponsored by patient groups.[35] Government support of patient-group-hosted databases could reduce the workload of starting national SMA registries from scratch. All countries needing further improvement in the scope of data captured **collect epidemiological data** only and do not capture clinical progression over time. Although epidemiological data can feed into assessments of cost-effectiveness; **clinical data** can help **identify unmet needs**, aid **guideline development** and provide **evidence needed to broaden treatment labels** of existing therapies.

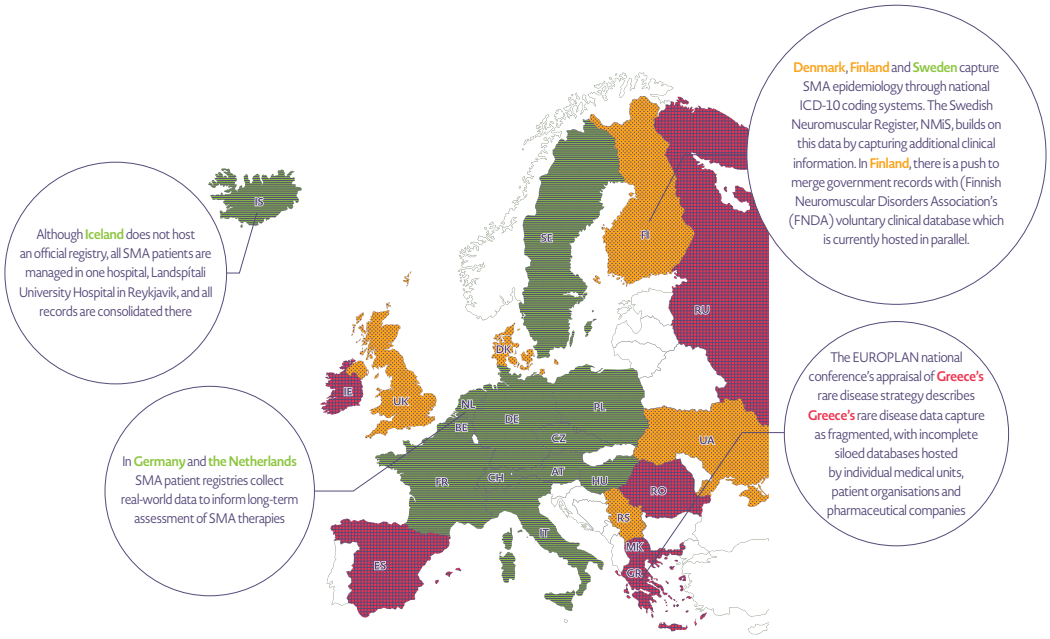
33) REaDY (2020). "Introduction". Available at https://ready.registry.cz/

34) The UMD Website (2018). "Welcome". Available at http://www.umd.be/

35) Finland (https://lihastautiliitto.fi/lihastaudit/tutkimus/lihastautirekisteri/), United Kingdom (https://www.treat-nmd.org.uk/registry/general/index.en.html), Ukraine (https://csma.org.ua/украинский-реестр-сма/)

Romania (RO) does not have an SMA patient registry and has no plans to implement one.[36,37] **North Macedonia (MK)** plans to establish a TREAT-NMD registry to capture epidemiological data.[38] In **Russia (RU)**, SMA Family Foundation Russia (F-SMA) has established a registry with the national genetic centre which captures over 1,000 patients.[39] However, this is not yet officially recognised as the national patient registry. In **Greece (GR)** reports have concluded that the rare disease data captured within the country is fragmented with incomplete databases hosted across different organisations and companies (**Figure 5**).[40,41]

Figure 5: Status map – National SMA patient registry



36) Orphanet (2020). "Rare Disease Registries in Europe". Available at https://www.orpha.net/orphacom/cahiers/docs/GB/Registries.pdf

37) RD Action (2017). "State of the Art of Rare Diseases – Activities in EU Member States and Other European Countries: Romania Report". Available at http://www.rd-action.eu/wp-content/uploads/2017/10/Romania-Report-15.12.2017.pdf

38) Treat-NMD Website (2021). "SMA Registry – Macedonia". Available at https://treat-nmd.org/patient-registry/sma-registry-macedonia/

39) RT (2021). "'Good, but not enough'": what the year 2020 was like for patients with spinal muscular atrophy". Available at: https://russian.rt.com/russia/article/818035-sma-lechenie-itogi-goda

40) Ministry of Health, Social Services and Equality (2015). "Royal Decree 1091/2015, of December 4, which creates and regulates the State Registry of Rare Diseases." Available at https://www.boe.es/diario_boe/txt.php?id=BOE-A-2015-14083

41) EUROPLAN (2012) "Greece - EUROPLAN National Conference Final Report". Available at http://download2.eurordis.org/rdpolicy/National%20Plans/Greece/3.EUROPLAN_2012_Greece%20National%20Conference_Report_English.pdf

Metric 5: Infrastructure

OVERVIEW

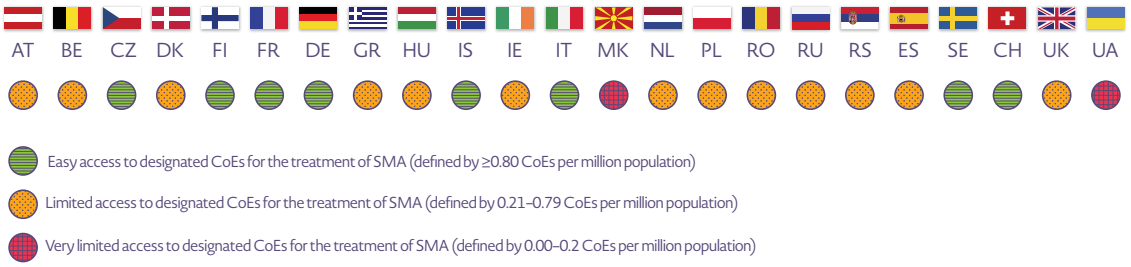
HEALTHCARE SYSTEM PREPAREDNESS: Infrastructure

Rationale for inclusion of metric

Due to the multiple medical needs of SMA patients, a coordinated multidisciplinary approach is required to ensure patients receive high-quality and consistent care, regardless of patient age or area of residence. Therefore, it is important that all patients have good physical access to treatment centres and all centres apply a similar standard of treatment and care.

Each country included in this study was assessed quantitatively based on the number of centres of excellence (CoEs) present per million people. Countries were then subdivided into the three ratings based on this outcome. Several countries with a low number of CoEs per million, due to being small countries and therefore not requiring a large number of centres for geographic coverage, received a better status than their quantitative score would suggest (e.g. **Iceland (IS)**[42], **Denmark (DK)**[43]). All countries examined have at least one designated CoE, with the exception of **North Macedonia (MK)**[44] (**Table 12**).

Table 12: Metric status – Infrastructure



Comparative assessment

Overall, countries rated as 'green' are defined as having a high number of CoEs per capita, facilitating easy access to specialists regardless of patient location. Countries rated as 'red' have a low number of CoEs per capita (e.g. one was identified in Ukraine (UA) and none in North Macedonia (MK)); this results in limited access to specialist management.

Of the centres identified in many countries, the majority provide both adult and paediatric treatment and care; however, in several countries (e.g. **Czech Republic (CZ)**[45], **Poland (PL)**[46], **Romania (RO)**[47], **Russia (RU)**[48]) **the management of adult and paediatric patients takes place at separate**

42) Landpitali (2021). "Practical Information". Available at https://www.landspitali.is/um-landspitala/languages/landspitali-the-national-university-hospital-of-iceland/

43) Rigshospitalet (2021). "Copenhagen Neuromuscular Center". Available at http://neuromuscular.dk/

44) Tasic et al. (2016), The Journal of Pediatrics, "The Child Health Care System of Macedonia". Available at https://www.jpeds.com/article/S0022-3476(16)30152-4/pdf

45) Neuromuscular Diseases Section of the Czech Neurological Society (2021). "List of Neuromuscular Centers in the Czech Republic". Available at: https://www.neuromuskularni-sekce.cz/index.php?pg=neuromuskularni-sekce-kontakty-zapisy--neuromuskularni-centra

46) FSMA (2021). "Hospital units running a drug program". Available at https://www.fsma.pl/leki/spinraza/szpitale/

47) National Alliance for Rare Diseases (2017). "Centres of Excellence". Available at: https://www.bolirareromania.ro/node/210

48) Society of Specialists in Neuromuscular Diseases (2021). https://neuromuscular.ru/patient/

centres. Although this may not change the patient's difficulty in travelling to visit a specialist as they transition to adulthood (for example, both CoEs in Ireland are located in Dublin), it may result in having an entirely new multidisciplinary team that is unfamiliar with the patient. Moreover, services can vary significantly between regions. For example, in **Russia (RU)**, SMA CoEs are limited to a few hospitals in Moscow with other centres in St Petersburg and Yekaterinburg.[49]

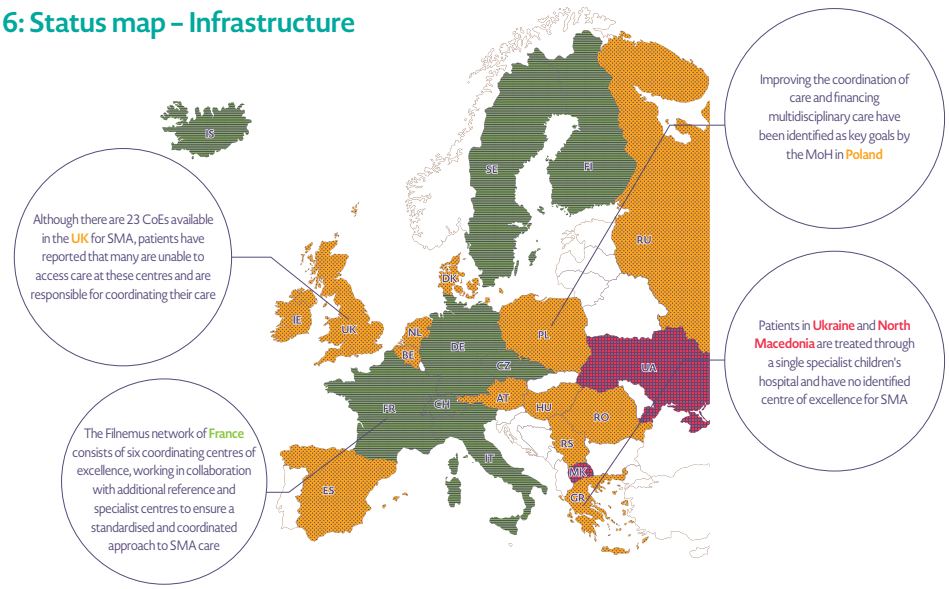
In the majority of countries examined, **there is no official definition of a CoE; therefore, treatment and care standards are likely to vary both between countries and even within countries**. Due to the multiple needs of SMA patients, a coordinated multidisciplinary approach is required to ensure patients receive high-quality management; however, in practice, coordination of treatment and care may be limited and has been identified as a key goal of countries in RD strategies (e.g. **UK**[50], **Poland (PL)**[51]). For example, a recent report from the **UK** stated that 71% of patients have been responsible for coordinating their own care,[52] adding an additional burden to patients which may limit the multidisciplinary approach required in SMA.

Utilisation of national/international care networks

In addition to relying on CoEs, several countries **utilise formal networks allowing for increased standardisation in treatment and care received across a country**; this includes **Germany (DE)**, **France (FR)** and the **Netherlands (NL)**. Notably in France (FR), the RD neuromuscular network Filnemus consists of six coordinating centres working in collaboration with reference centres and patient associations to ensure coordination of multidisciplinary care and further developing existing patient management protocols.

Further, programmes such as the European Reference Network's (ERN) Neuromuscular Diseases programme (EURO-NMD) (currently with members in 21 EU member states and 13 of the countries examined in this report) and TREAT-NMD provide important opportunities for international collaboration between clinicians and researchers in diagnosis, treatment and care, including the recent 2017 international standards of care for SMA patients. While some centres are part of these international-level networks, it is not uncommon that only a small percentage of the designated CoEs in a country are part of this.

Figure 6: Status map – Infrastructure



49) F-SMA (2021). https://project.f-sma.ru/

50) Department of Health and Social Care (2021). "The UK Rare Diseases Framework". https://assets.publishing.service.gov.uk/government/uploads/system/uploads/attachment_data/file/950651/the-UK-rare-diseases-framework.pdf

51) Health Challenges Congress (2021). "Coordinated Medical Care – A Goal or a Trendy Topic?". Available at: https://www.hccongress.pl/2017/pl/news/koordynowana-opieka-medyczna-cel-czy-modny-temat,138.html

52) Genetic Alliance UK (2020). "RARE EXPERIENCE 2020: The lived experiences of people affected by genetic, rare and undiagnosed conditions". Available at https://rareexperience2020.geneticalliance.org.uk/wp-content/uploads/2020/12/Rare-Experience-2020-Report-.pdf

Area 3: Diagnosis

Metric 6: Efficiency of diagnostic pathway

OVERVIEW

DIAGNOSIS: Efficiency of diagnostic pathway (as of 08 August, 2021)

Rationale for inclusion of metric

Due to the early onset of SMA types I, II and III, in order to achieve maximum impact in SMA disease management, treatment should be begun before symptom onset; therefore, early and efficient diagnosis is critical to accessing the best treatment and care. It is critical that legislation allows for the implementation of genetic newborn screening and that countries commit to incorporating SMA in existing screening programmes either following a pilot scheme or using data that has been generated internationally.

Each country included in this study currently has reimbursed access to genetic testing for SMA if requested by a physician because of patient symptoms or family history. In some countries, barriers to efficiently accessing these genetic services are reported; however, this metric predominantly focuses on the rapidly changing environment of NBS that identifies SMA patients pre-symptomatically (**Table 13**). Further details on the implementation status of SMA in NBS programmes across Europe can be found on both the SMA NBS Alliance website and Novartis's recent review on NBS.[53,54]

Table 13: Metric status – Efficiency of diagnostic pathway (as of 08 August, 2021)

Comparative assessment

All countries examined have reimbursed access to diagnostic tests for SMA, with seven countries (**Belgium (BE)**, **Germany (DE)**, **the Netherlands (NL)**, **Poland (PL)**, **Russia (RU)**, **Serbia (RS)** and **Ukraine (UA)**) now having announced the inclusion of SMA as part of their national NBS programmes.[49] In **the Netherlands (NL)**[55], **Poland (PL)**[56], **Serbia (RS)**[57] and **Ukraine (UA)**[58] local pilot programmes were not a prerequisite for inclusion of NBS in their national programmes, with decisions being based on the recent evidence from other countries demonstrating the value of early treatment of SMA patients. In other countries, the decision to include SMA on the NBS panel has followed a successful pilot (e.g. in

53) SMA NBS Alliance (2021). "Map". Available at https://www.sma-screening-alliance.org/map/

54) Novartis (2021). "Newborn Screening for Spinal Muscular Atrophy". Available at https://www.novartis.com/our-company/novartis-pharmaceuticals/novartis-gene-therapies/newborn-screening-spinal-muscular-atrophy-sma

55) RIVM (2020). "Spierziekte SMA in hielprikscreening". Available at https://www.pns.nl/nieuws/spierziekte-sma-in-hielprikscreening

56) AOTMiT (2021). "Opinion of the president". Available at https://bipold.aotm.gov.pl/assets/files/oopz/2021/OP-0008-2021.pdf

57) Novartis Website (2021), "Newborn Screening for Spinal Muscular Atrophy (SMA)", Available at https://www.novartis.com/our-company/novartis-pharmaceuticals/novartis-gene-therapies/newborn-screening-spinal-muscular-atrophy-sma

58) SMA NBS Alliance (2021). "Map". Available at https://www.sma-screening-alliance.org/map/

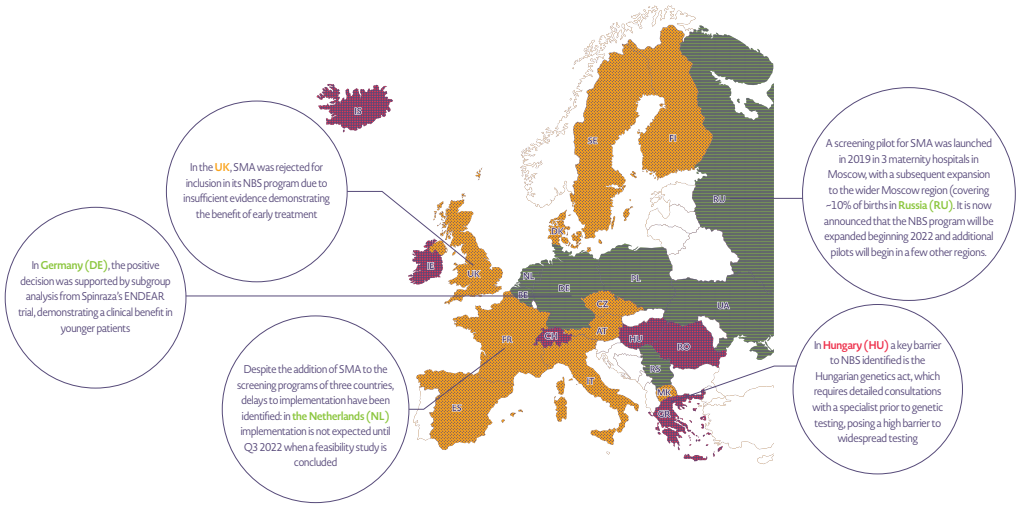
Germany (DE)[59] and in Russia (RU)[60]). While these countries have announced expansion of their programs, rollout and implementation is expected to vary: expected national implementation across the countries ranges from Q3 2021 (Germany (DE))[61] to Q3 2022 (Netherlands (NL))[55] and in other countries implementation dates are still unknown.

Driven by countries' national RD plans calling for expanding NBS, and the approval of the first treatments for SMA, there has been additional pressure on decision makers to establish pilot screening programmes. Further to this, the recent formation of the SMA NBS Alliance and publication of a comprehensive white paper on the topic has amplified the pressure on policymakers and healthcare providers.[62] Ten countries studied in this assessment currently have ongoing NBS pilots for SMA. In many countries, pilots have begun in selected hospitals before a subsequent expansion to one or more regions (e.g. Italy (IT)[63], and Spain (ES)[64]), with the goal of demonstrating the value of NBS for SMA at the national level. This same approach has been successful in other countries that have now announced expansion of their NBS programs (e.g. in Germany (DE)[65] and in Russia (RU)[66]).

There has been significant progress in 2021 with several countries making submissions or establishing new pilots to support future inclusion in national NBS programs. The UK have previously rejected the submission for SMA's inclusion in the national NBS program, citing insufficient evidence on available therapies and diagnostic techniques.[67] However work is now ongoing by the UK NBS Alliance to make a further submission and planning for a pilot screening program is underway.[68]

Despite the significant recent program made across Europe, six countries have no publicly identifiable plans to develop an SMA NBS pilot or to include SMA in their national NBS programmes. In Ireland (IE), a national screening advisory committee was only established in 2020 with a formal process for submitting applications still being drawn up.In addition, legislative barriers (in the form of bioethics laws in Hungary (HU)[69]) and budgetary pressures have also been identified as an obstacles to widespread genetic testing; however, some countries have successfully amended legislation (e.g. France (FR)) or announced additional budget (e.g. Ukraine (UA)[70]) to remove potential barriers in advance of launching pilot screening programmes.[71]

Figure 7: Status map – Efficiency of diagnostic pathway (as of 08 August, 2021)



59) Vill, K., et al. (2019). "One Year of Newborn Screening for SMA – Results of a German Pilot Project". Available at https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6918901/

60) SMA Screening Alliance (2021). "Status of Newborn Screening for SMA". Available at: https://www.sma-screening-alliance.org/map/

61) G-BA (2020). "G-BA erweitert Früherkennungsuntersuchung bei Neugeborenen auf spinale Muskelatrophie". Available at https://www.g-ba.de/presse/pressemitteilungen-meldungen/919/

62) SMA NBS Alliance (2021). "About". Available at https://www.sma-screening-alliance.org/about/

63) Regione Toscana (2021). "Newborn Screening for SMA". Available at https://www.regione.toscana.it/-/sceening-neonatale-per-la-sma-atrofia-muscolare-spinale

64) SMA NBS Alliance (2021). "Status of Newborn Screening for Spinal Muscular Atrophy". Available at https://www.sma-screening-alliance.org/map/

65) Vill, K., et al. (2019). "One Year of Newborn Screening for SMA – Results of a German Pilot Project". Available at https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6918901/

66) SMA Screening Alliance (2021). "Status of Newborn Screening for SMA". Available at: https://www.sma-screening-alliance.org/map/

67) Legacy Screening (2021). "UK NSC recommendation on Spinal Muscular Atrophy". Available at https://legacyscreening.phe.org.uk/sma

68) SMA Screening Alliance (2021). "Status of Newborn Screening for SMA". Available at: https://www.sma-screening-alliance.org/map/

69) SMA Hungary (2020). "Newborn Screening for SMA". Available at https://smahun.hu/hasznos/SMA_ujszulottszures_tajekoztato.pdf

70) SMA NBS Alliance (2021). "Map". Available at https://www.sma-screening-alliance.org/map/

71) AFM Telethon (2020). "Neonatal genetic screening permitted by bioethics law: a victory for life!". Available at https://www.afm-telethon.fr/actualites/depistage-genetique-neo-natal-permis-par-loi-bioethique-victoire-pour-vie-140504

Area 4: Access pathways

Metric 7: Post-MA early access pathways

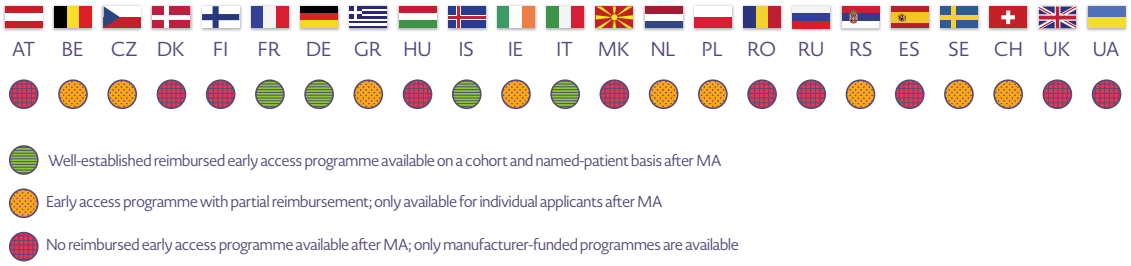
OVERVIEW

ACCESS PATHWAYS: Post-MA early access pathways

Rationale for inclusion of metric
Although a medicine can have regulatory approval / marketing authorisation for use in a country, patients can face long delays between marketing authorisation and reimbursed access. The presence of early access programmes after authorisation ensures patients gain access to treatments as soon as regulatory approval is granted and the product is deemed safe to use, or soon after.

In Europe, due to the requirement in most countries for national reimbursement assessments and decisions, there is often a 'gap' to access between regulatory approval / marketing authorisation (MA) and confirmed reimbursement. The use of compassionate use programmes (CUP) helps to address the need to access treatments that have not yet received regulatory approval (and, in particular circumstances, this access is prolonged when MA is granted but the treatment is not yet reimbursed). However, CUP are not sufficient to provide patient access while an authorised treatment is still under evaluation for reimbursement. This metric therefore looks for countries that enable reimbursed early access (on a cohort or individual basis) for high-unmet-need treatments after the regulatory approval is granted and prior to a reimbursement decision. (**Table 14**)

Table 14: Metric status – Post-MA early access pathways



Comparative assessment

Currently three countries are assessed as having **well-established cohort access programmes** that allow for reimbursed access after MA. In addition, due to the rapid approval of its nominative program,[72] combined with the low population, **Iceland (IS)** is assessed as providing a similar level of early access.[73]

72) An early access programme that is available for individual patients rather than a broad approval for a group of patients, with reimbursement request typically being made by a patient's physician to the relevant authority

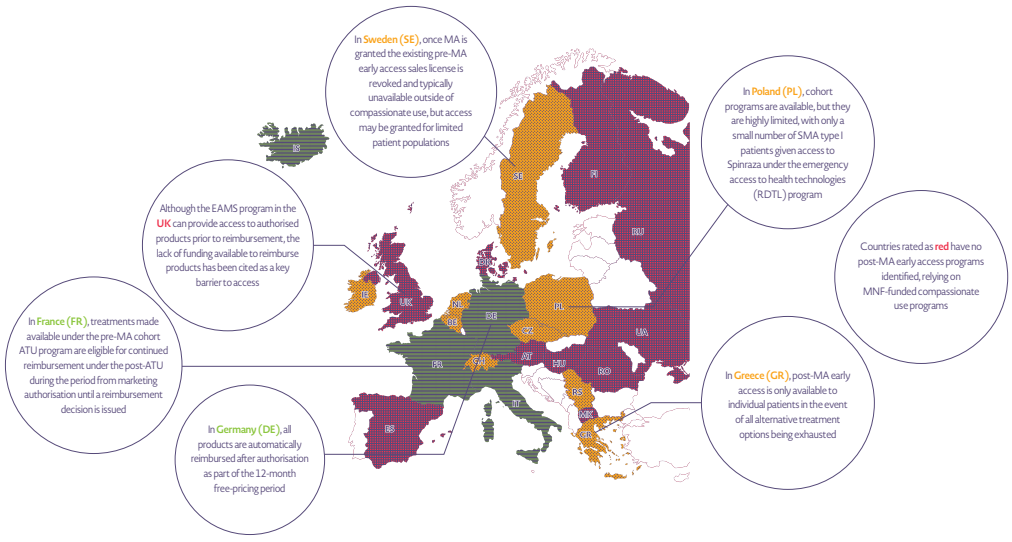
73) Icelandic Medicines Agency (2021). "FAQs: Compassionate use/exemption to use an unauthorised product". Available at https://www.ima.is/ima/faqs#Compassionate_use

Both **Italy (IT)**[74,75] and **France (FR)** have well-funded and accessible cohort programmes,[76] with France continuing pre-MA access until a reimbursement decision is made through its post-ATU (temporary authorisation for use) programme.[77] Uniquely in Europe, in **Germany (DE)** all products are automatically reimbursed at the time of the MA. The existence of this process means no additional early access programmes after MA are required, and it provides a gold standard example to other countries.[78] The existence of early access programmes/systems in some European countries **facilitates access** between MA and national reimbursement, thus **addressing a key gap in the patient access pathway**.

Nine countries were identified as providing post-MA early access but with limited reimbursement or on an individual basis. Of these, **Belgium (BE)**[79], **Poland (PL)**[80], **the Netherlands (NL)**[81], and **Sweden (SE)**[82] do have the programmes in place to provide early access on a cohort basis, but in practice these cohort programmes are limited. Restrictions identified include the **requirement for no therapeutic alternatives** (which now excludes conditions such as SMA given the availability of Spinraza), and **restriction to small patient cohorts**. Further, the programme in Belgium only provides financial support for the program's infrastructure and administration, rather than reimbursement for the product itself. In the case of SMA, early access is often restricted to just a small number of newly diagnosed SMA type I patients, **with limited opportunities for individual reimbursement for type II and type III patients**.

All 10 countries rated as '**red**' have no reimbursed early access programmes available after MA. The **lack of funding** available through post-MA early access schemes has been identified as a key barrier to patient access in the lead up to a national reimbursement decision. For example, the lack of funding available through the Early Access to Medicines Scheme (EAMS) in the **UK** was reported to result in limited access to high-cost innovative therapies due to the **requirements of manufacturer funding**.[83]

Figure 8: Status map – Post-MA early access pathways



74) AIFA (1996). "Legge 648/96". Available at https://www.normattiva.it/uri-res/N2Ls?urn:nir:stato:legge:1996-12-23;648!vig=

75) AIFA (2021). "AIFA National Fund (5% fund)". Available at https://www.aifa.gov.it/en/fondo-nazionale-aifa

76) An early access programme that provides reimbursement to a group of patients (for example all SMA patients under a certain age or all type I and type II patients in the country), allowing for reimbursed access without an application per individual patient

77) ANSM (2020). "Temporary user authorizations (ATU)". Available at https://www.ansm.sante.fr/Activites/Autorisations-temporaires-d-utilisation-ATU/Qu-est-ce-qu-une-autorisation-temporaire-d-utilisation/(offset)/1

78) Federal law SGBV 35a (2011). Available at http://www.sozialgesetzbuch-sgb.de/sgbv/35a.html

79) INAMI (2020). "Unmet Medical Need". Available at: https://www.inami.fgov.be/fr/themes/cout-remboursement/par-mutualite/medicament-produits-sante/remboursement/Pages/unmet-medical-need.aspx#.Vqt3sSlitFQ

80) AOTMiT (2021). "RDTL". Available at: https://www.aotm.gov.pl/produkty-lecznicze/rdtl/

81) ZIN (2020). "Second parallel procedure MEB Healthcare Institute: medicines available to patients more quickly". Available at https://www.zorginstituutnederland.nl/actueel/nieuws/2020/12/23/tweede-parallelle-procedure-cbg-zorginstituut-geneesmiddelen-sneller-beschikbaar-voor-patient

82) Eriksson, I. et al. (2017). "The Early Awareness and Alert System in Sweden: History and Current Status". Available at https://www.frontiersin.org/articles/10.3389/fphar.2017.00674/full

83) Lyons, G. (2018). "What next for the Early Access to Medicines Scheme?". Available at https://www.politicshome.com/members/article/what-next-for-the-early-access-to-medicines-scheme

Metric 8: Specialised reimbursement/HTA pathways

OVERVIEW

ACCESS PATHWAYS: Specialised reimbursement/HTA pathways

Rationale for inclusion of metric

Once products have been authorised for use they usually must undergo reimbursement and HTA at an individual country level. Specialised HTA procedures that consider the specifics of RD within the evaluation process can be used to ensure broad and efficient patient access to treatment. The use of standard HTA processes and pathways (i.e. without considering the specificities of RD) is likely to lead to negative access outcomes in terms of restrictions, fairness and efficiency.

Across countries there is a wide range of provisions made by national bodies with regards to specialised assessments for orphan products; however, very few result in consistently faster or similar times to access for products. Many countries use the same HTA methods as for non-orphan products but with accelerated timelines applied; in reality, the extent to which these timelines are met is not consistent. On the other hand, nearly half of the countries assessed in this study had no specialised provisions for orphan products, or they apply additional hurdles for orphan drug submissions. (**Table 15**)

Table 15: Metric status – Specialised reimbursement/ HTA pathways

Comparative assessment

Currently, four countries have formal specialised reimbursement/HTA pathways for orphan drugs. These pathways have **greater flexibility than the standard national HTA pathways, with reduced clinical or economic data requirements to accommodate the challenges of evidence generation in orphan populations**. The use of these specialised assessment pathways allows for fairer, and often more efficient, access to treatment. This can provide significant value in countries typically requiring comparative assessments, for example in **Germany (DE)**, where orphan drugs receive, at a minimum, an 'unquantifiable benefit' rating through an orphan drug (OD) exemption provided annual sales do not exceed €50M.[84]

Currently, many countries assessed use standard HTA pathways to assess ODs; however, **there are mechanisms in place to accelerate access**, either through an accelerated assessment timeline (**Finland (FI)**[85], **France (FR)**[86], **Switzerland (CH)**[87], **North Macedonia (MK)**[88]) or the possibility of temporary reimbursement (the **Czech Republic (CZ)**[89], **Sweden (SE)**[90]) (**Figure 9**).

84) Federal law SGBV 35a (2011). Available at http://www.sozialgesetzbuch-sgb.de/sgbv/35a.html

85) Fimea (2018). "RAPID ASSESSMENT OF NEW HOSPITAL-ONLY MEDICINAL PRODUCTS. Available at https://www.fimea.fi/documents/160140/1454513/Sairaalal%C3%A4%C3%A4kkeiden+arviointiprosessi/73aa08fa-7136-54c2-111b-47e68b016c64

86) HAS (2020). "Innovative medicines assessment action plan". Available at https://www.has-sante.fr/upload/docs/application/pdf/2020-03/ innovative_medicine_action_plan_27.01.20.pdf

87) HSPM (2021). "Health Systems in Transition (HiT) profile of Switzerland". Available at https://www.hspm.org/countries/switzerland25062016/livinghit.aspx?Section=2.8%20Regulation&Type=Section

88) Gammie et al. (2015), PLOS ONE, "Access to Orphan Drugs: A Comprehensive Review of Legislations, Regulations and Policies in 35 Countries". Available at https://journals.plos.org/plosone/article?id=10.1371/journal.pone.0140002

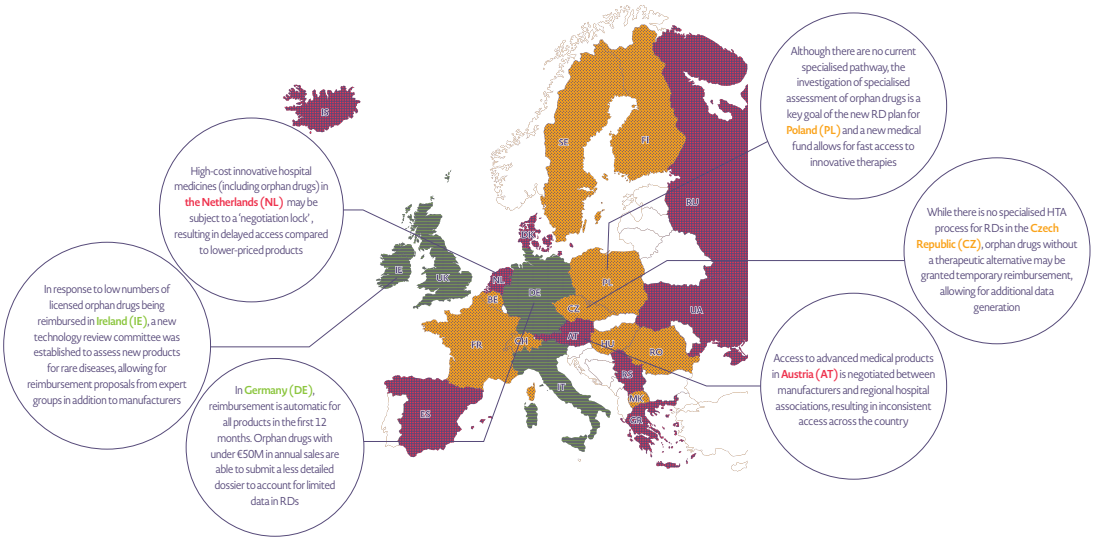
89) NZIP (2020). "Highli Innovative Medicines (VILP)." Available at https://www.nzip.cz/clanek/800-vysoce-inovativni-lecive-pripravky-vilp#:~:text=Jako%20vysoce%20inovativn%C3%AD%20je%20mo%C5%BEn%C3%A9,%C4%8Di%20podstatn%C4%9B%20sni%C5%BEuj%C3%AD%20%C3%BAmrtnost%2C%20pop%C5%99.

90) TLV (2019). "Types of Reimbursement". Available at https://www.tlv.se/in-english/medicines/pricing-and-reimbursement-of-medicines/types-of-reimbursement.html

Currently, 9 of the countries assessed have **no specialised reimbursement/HTA pathway for orphan drugs, with cost-saving measures in some countries potentially leading to delayed or no access to orphan drugs**. In **the Netherlands (NL)** high-cost therapies (including orphan drugs) are subject to a 'negotiation lock' on the typical automatic reimbursement of hospital products, resulting in access delays of up to nine months (**Figure 9**).[91] **Hungary (HU)** was identified as utilising a specialised HTA pathway for orphan drugs, with a higher ICER threshold than is typically used.[92] However, this is informally applied on a case-by-case basis, often leading to a prolonged assessment process.[93] In countries with regional assessment procedures for orphan drugs (such as **Austria (AT)** and **Spain (ES)**), this can result in variable access across the country, due to their high cost.[94,95] Both countries have proposed a centralised, standardised framework for orphan drugs to reduce geographic inequalities.

In addition to national HTA procedures, several countries have established **international joint HTA programmes**, most notably **FINOSE**, which conducted an HTA of the cell therapy Zynteglo on behalf of **Finland**, **Norway** and **Sweden**,[96] and **BeNeLuxA**, which conducted an assessment of Spinraza for **Belgium** and **the Netherlands**.[97] While both of these programmes have assessed orphan medicines, due to their limited experience it is unclear what the long-term impact of such collaborations will be.

Figure 9: Status map – Specialised reimbursement/HTA pathways



91) RARE IMPACT (2020). "A review of the challenges proposals for improving patient access to advanced therapeutic medicinal products in the Netherlands". Available at https://rareimpact.eu/site/wp-content/uploads/2020/04/RARE-IMPACT-Country-Assessments-Netherlands_v1_2020-04-28.pdf

92) Malinoswki et al. (2020). ""Health technology assessment and reimbursement policy for oncology orphan drugs in Central and Eastern Europe". Orphanet Journal of Rare Diseases 15:277. Available at https://ojrd.biomedcentral.com/articles/10.1186/s13023-020-01556-9#Tab4

93) Malinoswki et al. (2019). Front Pharmacol 10:487. Available at https://www.frontiersin.org/articles/10.3389/fphar.2019.00487/full#T7

94) RARE IMPACT (2020). "Improving patient access to gene and cell therapies for rare diseases in Europe". Available at https://rareimpact.eu/site/wp-content/uploads/2020/04/RARE-IMPACT-Country-Assessments-Austria_v1_2020-04-28.pdf

95) RARE Impact (2020). "A review of the challenges and proposals for improving patient access to advanced therapeutic medicinal products in Spain". Available at https://rareimpact.eu/site/wp-content/uploads/2020/04/RARE-IMPACT-Country-Assessment-Spain_v1_2020-04-28.pdf

96) TLV (2020). "FINOSE, a Nordic cooperation". Available at https://www.tlv.se/in-english/international-collaboration/finose---a-nordic-cooperation.html

97) Beneluxa (2020). "HTA". Available at https://beneluxa.org/hta

Area 5: Access to treatment and care

Metric 9: Treatment and care guideline availability

OVERVIEW

ACCESS TO TREATMENT AND CARE: Treatment and care guideline availability

Rationale for inclusion of metric

In order to set equal access standards both across and within countries, national publication of the latest and most up-to-date guidelines ensures that available treatments are used in the right patients based on clinical value and that treatment is provided alongside the best possible supportive care and management. Due to the complexity of a condition such as SMA, comprehensive treatment and care guidelines are required to ensure consistent patient management across and within countries.

An international consensus on the standards of care for SMA diagnosis and management was published in 2017.[98,99] This provides a comprehensive overview of the optimal care for SMA patients. However, as the standards were developed prior to broad treatment availability, they do not provide specific treatment recommendations in line with authorised indications. Many countries appear to have recognised and adopted these international standards of care, as evidenced through publication on national/hospital websites or translation into local language. However, it is rare that any adaptations or additions to these guidelines regarding the use of authorised treatments have been made (**Table 16**).

Table 16: Metric status – Treatment and care guideline availability

The country has adopted guidelines that provide recommendations on treatment and care, which reflect the most recent clinical consensus and evidence

The country has adopted guidelines that provide recommendations on care, which reflect the most recent clinical consensus and evidence, but not on treatment

The country has not adopted any guidelines and does not provide recommendations on treatment or care

Comparative assessment

The majority of countries (ranked in **green** and **yellow**) appear to have recognised and adopted the 2017 international standards of care, as noted above (Error! Reference source not found.). While this is beneficial to encourage standardised international provision of care, it is also worth noting that the extent to which these guidelines are applied and followed in reality can vary. For example, in **Italy (IT)** the availability of PDTAs[100] can vary across regions and are not always applied; this is due to inadequate organisational infrastructure, especially when it comes to RD.[101]

98) Mercuri et al. (2017). Neuromuscul Disord, "Diagnosis and management of spinal muscular atrophy: Part 1". Available at https://pubmed.ncbi.nlm.nih.gov/29290580/

99) Finkel et al. (2018). Neuromuscul Disord, "Diagnosis and management of spinal muscular atrophy: Part 2". Available at https://www.sciencedirect.com/science/article/pii/S0960896617312907?via%3Dihub

100) PDTAs are diagnostic, therapeutic and care pathway guidelines (Percorso Diagnostico, Terapeutico e Assistenziale) set at the regional level to provide guidance on recommended standard of care

101) National Monitoring of Organisational and Management Models of Care networks. Available at https://www.quotidianosanita.it/allegati/allegato792713.pdf

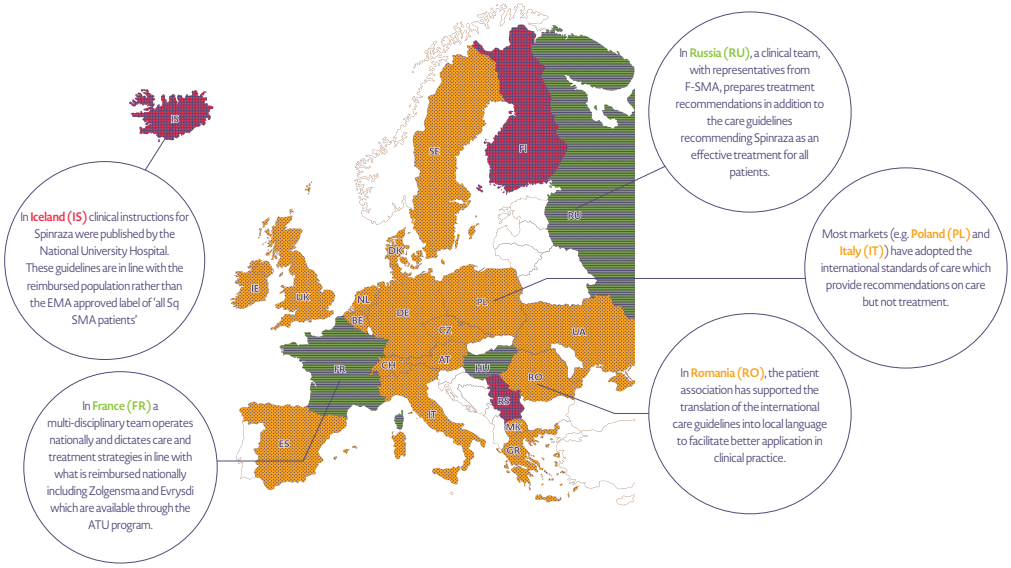
The countries performing the best on this metric are those which have adopted and expanded the available international guidelines to provide treatment recommendations in line with the relevant MA (e.g. Spinraza for the treatment of all 5q SMA patients) and availability. Indeed, in **France (FR)** and **Russia (RU)** national-level, multidisciplinary teams have dictated care and treatment strategies. In **France (FR)**, treatment recommendations in line with the reimbursement of Spinraza and availability of Zolgensma and Evrysdi through the ATU programme are provided, while **Russia (RU)** provides recommendations on both Spinraza and Evrysdi based on the available clinical data (**Figure 10**).[102]

Both **Hungary (HU)** and **Germany (DE)** are in the process of developing or reviewing national-level guidelines to include wider treatment recommendations given the evolving treatment landscape. **Hungary (HU)** already provides national treatment recommendations citing Spinraza as an effective treatment, but these were developed in 2018 before Zolgensma and Evrysdi had approved MA.[103] These guidelines are expected to be reviewed and amended in May 2021.[104] **Germany (DE)**, which has not previously provided national treatment recommendations, currently has guidelines for the treatment and diagnosis of SMA under review, although without a clear date on which they will be adopted officially.

On the other hand, most countries have not added any treatment recommendations to the international standards of care (e.g. **Poland (PL)**, **Spain (ES)**). In some countries (e.g. **United Kingdom (UK)**, **Romania (RO)**, **Denmark (DK)**, **Iceland (IS)**) only reimbursement recommendations are provided, which are often more restrictive than the approved regulatory label. Some countries, supported by patient organisations, have translated the international standards of care into local language to facilitate use. For instance, FundAME in **Spain (ES)** and SMACARE in **Romania (RO)** were responsible for funding the translation of the guidelines and ensuring clinical review by local specialists to facilitate more standard application across the country (**Figure 10**).

Three countries **do not appear to have adopted the international standards of care as evidenced by a lack of availability through national or hospital websites**, nor are national guidelines available (Error! Reference source not found.). In **Finland (FI)**, no clinical practice guidelines have been produced for SMA, although there have been unofficial discussions, and different centres tend to have the same types of treatment.[105]

Figure 10: Status map – Treatment and care guideline availability



102) Clinical Guidelines (2020). "Proximal spinal muscular atrophy 5q". Available at http://cr.rosminzdrav.ru/I/593_2

103) Professional College of Health (2021). "Professional Guidelines". Available at: https://kollegium.aeek.hu/Iranyelvek/Index

104) Professional College of Health (2021). "Healthcare Professional Guidelines -On spinal muscular atrophy, clinic, and treatment". Available at: https://kollegium.aeek.hu/Download/Download/3371?AspxAutoDetectCookieSupport=1

105) RD Action (2017). "State of the Art for Rare Diseases – Activities in EU Member States and Other European Countries, Finland Report". Available at http://www.rd-action.eu/wp-content/uploads/2017/10/Finland-Report-09.10.2017.pdf

Metric 10: Treatment availability

OVERVIEW

ACCESS TO TREATMENT AND CARE: Treatment availability (as of 08 August, 2021)

Rationale for inclusion of metric

There are three potential treatments for SMA patients: Spinraza (*nusinersen*, Biogen), Zolgensma (*onasemnogene abeparvovec*, Novartis) and Evrysdi (*risdiplam*, Roche), which between them can be used across all patients with SMA (from pre-symptomatic to adult patients). To ensure efficient patient access, it is critical for national payer authorities and healthcare systems to make every effort to ensure these products are accessible to authorised patients as soon after regulatory approval as possible with minimal restrictions.

Although products receive MA from regulatory authorities, the key next step for patients to gain access is an efficient national assessment leading to a positive unrestricted reimbursement decision. In the absence of an immediate reimbursement decision, innovative early access arrangements should be explored to ensure efficient patient access.

All three products now (as of 08 August, 2021) have MA in the majority of countries studied (through the European Medicines Agency (EMA), or national regulatory authorities such as the Ministry of Health (MoH) (RU), Swissmedic (CH) and the Medicines and Healthcare products Regulatory Agency (MHRA) (UK)). However, despite their approval from a regulatory perspective, the reimbursed treatment availability shows a more variable picture, with many countries applying restrictions to the regulatory label or with no routine reimbursement decision yet being made at the national level (**Table 17**).

Table 17: Metric status – Treatment availability for Spinraza (S), Zolgensma (Z) and Evrysdi (E) (as of 08 August, 2021)

*EMA in most countries; national regulatory agencies in CH, MK, RS, RU, UA, UK[106]

106) Following the United Kingdom's exit from the European Union, the MHRA is now responsible for granting marketing authorisation to Evrysdi. EMA marketing authorisation for Spinraza and Zolgensma is valid in the UK.

Comparative assessment

As of 08 August, countries **without MA** for a product or countries where a **national-level reimbursement decision has not commenced or is ongoing** have been marked in **lilac**. Countries that have established a **formal reimbursed early access programme** have been marked **purple**.[107]

Several European countries **have reimbursed Spinraza to the full indication**. In most cases the decision for full reimbursement was not granted immediately and there have been several different decision dates, allowing access to different patient groups at different time points. For example, in **Hungary (HU)** Spinraza was made available first to a subset of under-18s in 2018,[108] then to all patients up to the age of 18 in 2019;[109] access to adults was subsequently granted in February 2021.[110] Three countries have already reimbursed Zolgensma immediately (**Germany (DE)** as mandated by law) or shortly after EMA approval was granted (**Austria (AT)** and the **Czech Republic (CZ)**) (**Figure 11**).[111,112]

In **France (FR)** both Evrysdi and Zolgensma are reimbursed without restrictions through an **early access program**, Cohort ATU and continue to be available through a cohort post-ATU program.[113] Early access arrangements have also previously been made for Zolgensma in **Switzerland (CH)** (although now formally reimbursed) and continue in **the Netherlands (NL)**. These unique agreements have been made to provide access to patients before a formal reimbursement decision is made (**Figure 11**).

Despite Spinraza's approval over four years ago in April 2017, **some countries still have restrictions on Spinraza** further to the indicated label of all 5q SMA patients, which often results in exclusion of adult patients. Common restrictions include: limiting use to paediatric patients (e.g. in **Iceland (IS)**, where Spinraza is approved for use in type I–III patients under the age of 18); limiting use to the most severe patient types (e.g. in **Denmark (DK)**, where only type I and a subset of type II patients have reimbursed access[114]). In the **UK**, while both Spinraza and Zolgensma are reimbursed, access in England is through managed access agreements (MAAs) which apply very specific stopping criteria and for some patients access is conditional on a future assessment (e.g. reimbursement of Zolgensma for pre-symptomatic patients will be revisited in 2024).[115,116] Zolgensma is still not widely reimbursed across Europe but of the countries that have made a formal reimbursement decision, some countries have applied additional measures in terms of age or weight (e.g. **Denmark (DK)**)[117] or in terms of prior-authorisation required without clear criteria (e.g. **Hungary (HU)** where access is granted based on 'individual fairness requests').[118]

No countries in the scope of this project have assessed and completely denied any reimbursement to Spinraza/Zolgensma, which is likely testimony to the extreme unmet need faced by patients.

107) Reimbursed early access programmes do not include compassionate use programmes, named patient early access or access funded via charitable donations / private funding.

108) Biogen (2018). "Access to reimbursed treatment". Available at https://smauk.org.uk/files/files/Research/Biogen%20Community%20Update%20September%202018.pdf

109) Hungary Today (2019). "All SMA Patients Under 18 to Receive Free Treatment". Available at: https://hungarytoday.hu/all-sma-patients-under-18-to-receive-free-treatment/

110) Magyarorszag Kormanya (2021). "Treatment of adult patients with SMA with Spinraza may begin". Available at https://kormany.hu/hirek/megkezdodhet-a-felnott-sma-betegek-kezelese-a-spinraza-keszitmennyel?utm_source=mandiner&utm_medium=link&utm_campaign=mandiner_202102

111) "Stellungnahme der Arbeitsgruppe Neuropädiatrie und des ÖGKJ Präsidiums zur medikamentösen Therapie der Spinalen Muskelatrophie" (2019). Available at https://www.paediatrie.at/images/AGLeiter/Neuropaediatrie/stellungnahme-sma_therapie-mit-nusinersen_v0819.pdf

112) VZP (2020). "VZP will allow treatment for all children with SMA indicated for treatment with Zolgensma". Available at: https://www.vzp.cz/o-nas/aktuality/vzp-umozni-lecbu-vsem-detem-s-sma-indikovanym-k-lecbe-pripravkem-Zolgensma

113) ANSM (2021). "Risdiplam". Available at: https://ansm.sante.fr/tableau-atu-rtu/risdiplam-0-75-mg-ml-poudre-pour-solution-buvable

114) The Danish Medicines Council (2018). "Nusinersen (Spinraza)". Available at https://medicinraadet.dk/anbefalinger-og-vejledninger/laegemidler-og-indikationsudvidelser/m-p/nusinersen-spinraza-5q-spinal-muskelatrofi-revurdering

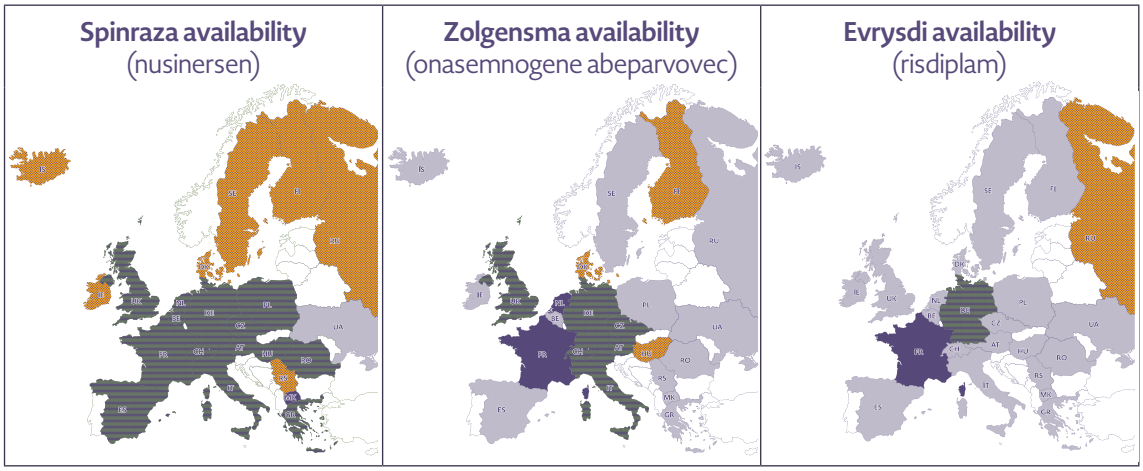
115) NICE (2020). "Managed Access Agreement Nusinersen (SPINRAZA®) for the treatment of 5q spinal muscular atrophy". Available at https://www.nice.org.uk/guidance/ta588/resources/managed-access-agreement-july-2019-pdf-6842812573

116) NICE (2021). "1 Recommendations". Available at https://www.nice.org.uk/guidance/hst15/chapter/1-Recommendations

117) The Danish Medicines Council (2021) "Onasemnogene abeparvovec (Zolgensma)". Available at https://medicinraadet.dk/anbefalinger-og-vejledninger/laegemidler-og-indikationsudvidelser/m-p/onasemnogene-abeparvovec-zolgensma-spinal-muskelatrofi

118) NEAK (2021). "Another six SMA sick children receive state-funded gene therapy treatment". Available at http://www.neak.gov.hu/friss_kozlemenyek/kozlemenyek_SMA.html?query=zolgensma

Figure 11: Status map – Treatment availability (as of 08 August, 2021)



Metric 11: Selected care provisions

OVERVIEW

ACCESS TO TREATMENT AND CARE: Selected care provisions[119]

Rationale for inclusion of metric

Beyond treatment, patients with SMA require support from a multidisciplinary care team to manage the range of complications which can result from the disease. Optimal care, as defined by the latest guidelines, includes many considerations, including genetic diagnoses and counselling, regular physical therapy and rehabilitation, orthopaedic care, growth and bone health care, nutritional support, pulmonary care, acute care, management of other organ system involvement, medication and considerations for palliative care.[120] In this assessment, access to this support has been characterised through an analysis of (1) the reimbursement of physiotherapy, (2) support provided for home adaptation and (3) additional financial support available to patients and caregivers.

Across all countries in scope, according to government policies, some form of financial support or reimbursed care services is provided by the state; but there are many countries where there are struggles to access this care or the level of reimbursement is limited or unclear.

Table 18: Metric status – Selected care provisions*

Note – significant clinical[121] and geographical[122] variation within countries as highlighted in comparative assessment

AT	BE	CZ	DK	FI	FR	DE	GR	HU	IS	IE	IT	MK	NL	PL	RO	RU	RS	ES	SE	CH	UK	UA
Green	Orange	Orange	Orange	Orange	Green	Green	Green	Orange	Green	Orange	Green	Orange	Green	Orange	Orange	Red	Red	Orange	Green	Green	Orange	Red

- (Green) Selected care provisions analysed are reimbursed for SMA patients and caregivers without major issues experienced in gaining access to these services
- (Orange) Selected care provisions analysed are reimbursed for SMA patients or caregivers, but there are issues for patients in accessing the necessary care
- (Red) Selected care provisions analysed are not reimbursed or are limited for SMA patients or caregivers

*Although optimal care is multidisciplinary and multifactorial, only three selected care provisions could be assessed in this metric: (1) physiotherapy and rehabilitation therapies, (2) home adaptation; and (3) financial support for patient/caregiver.

Comparative assessment

In almost all countries, the three categories of treatment-related care considered in this assessment* are reimbursed by the state. Very often these services are provided by local councils/regions or municipalities, which can result in a fragmented approach; however, **some countries have made efforts to harmonise the provision of services at the national level**.

119) The assessment of treatment-related care will focus specifically on: (1) physiotherapy and rehabilitation therapies, (2) home adaptation and (3) financial patient/caregiver support

120) Mercuri et al. (2017). Neuromuscul Disord. "Diagnosis and management of spinal muscular atrophy: Part 1". Available at https://pubmed.ncbi.nlm.nih.gov/29290580/

121) Clinical variation such as variation across patient type, age or disease severity is common given that many countries provide benefits based on disease severity or assessments of disability (Belgium, Czech Republic, Germany, Iceland, Ireland, Italy, Romania, UK)

122) Geographical variation across countries such as variation by region, municipality, city or hospital is common given that support services are rarely provided at a national level. Many countries therefore see discrepancies in this care geographically (Austria, Belgium, Denmark, Finland, Spain, UK)

For example, in **Sweden (SE)**, despite the provision of services from municipalities, **the support that must be provided is mandated at the national level** through several acts.[123] In addition, municipalities in **Sweden (SE)** also **employ 'family consultants' who can work with families to explain which support services they are able to access** (**Figure 12**).

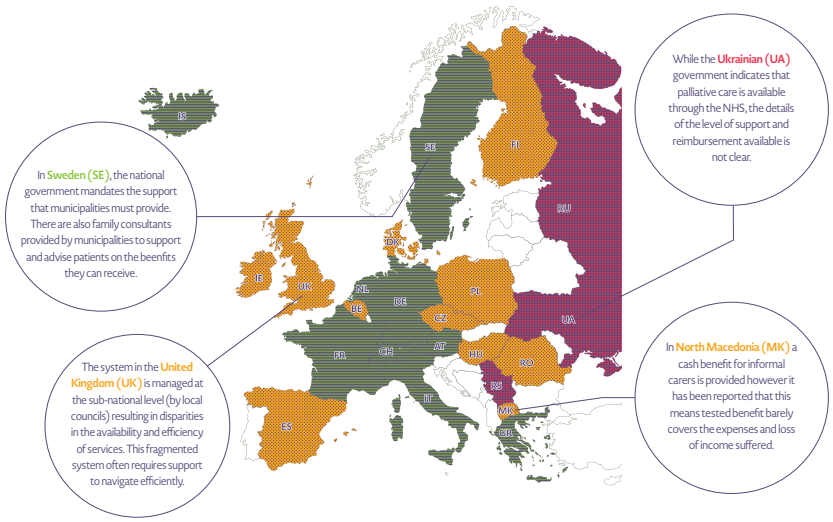
Equivalents of these 'family consultants' do exist in other countries where the complex nature of the system and the requirement for the submission and review of individual applications can make it difficult for patients to receive the care they need. However, there are reported shortages of these dedicated workers to support families, and hence this can result in delayed or unequal access to care, and often patient associations are required to provide this advice and support to patients and caregivers to navigate the system.

In addition, most countries provide reimbursed access to treatment-related care, and the level of reimbursement or the quality of services often varies by 'disability level' or 'severity level'. In **Iceland (IS)** for example, only patients with a classified 75% disability level are entitled to reimbursement. This is calculated using a disability assessment, which must be renewed every two years.[124] The same is true in other countries (for example in **Spain (ES)**). Given the approach and criteria set in many countries, this review of individual applications can result in subjective assessments and families being denied access to the necessary care. For example, SMA **Finland (FI)** has reported several cases of challenges to receiving appropriate care due to the complexity and bureaucracy involved in the process.[125]

Further to this, many patient organisations report that patients often have difficulty accessing the necessary care despite measures that have been put in place. For example, in **Spain (ES)**, SMA was classed as a disabling disease, eligible for full disability support, regardless of disease progression in 2011 by the Spanish government in collaboration with the FEDER.[126] However, there are still reports that many patients must fundraise to access the appropriate aids such as home assistance.[127]

In **Russia (RU)**, **Ukraine (UA)** and **Serbia (RS)** social support for patients is reportedly limited, with **many basic provisions not reimbursed or there is a lack of transparency in what is provided by the health service**. For example, devices such as mobility aids are not provided reimbursed in **Serbia (RS)**; and in **Ukraine (UA)**, while some palliative care is reportedly available, the level of reimbursement is not clear (**Figure 12**).

Figure 12: Status map – Selected care provisions



123) Socialstyrelsen (2020). (1) "Society's Support Efforts". (2) "Act (1993: 387) on support and service for certain disabled people". (3) "Social Services Act (2001: 453)". (4)"Health Care Act (2017: 30); (5) "Patient Act (2014: 821)". All available via https://www.riksdagen.se/sv/dokument-lagar/

124) Trygginastofnun (2021). "Örorkulífeyrir (Disability pension)". Available at https://www.tr.is/ororka/ororkulifeyrir

125) KELA (2021). "Sairaanhoitokorvausten taksat (Medical reimbursement tariffs)". Available at https://www.kela.fi/documents/10180/0/Sairaanhoitokorvausten%20taksat%201.1.2021%20%28pdf%29/cfc6dc0c-2161-4aa7-8795-cdb08ce27e33

126) Ministerio de Trabajo e Inmigración (2011). "Real Decreto 1148/2011". Available at https://www.boe.es/buscar/pdf/2011/BOE-A-2011-13119-consolidado.pdf

127) Diario de Huelva (2021). "The Order seeks funds to finance the rehabilitation of Darío, a boy with Muscular Atrophy". Available at https://www.diariodehuelva.es/2021/06/03/familia-busca-fondos-rehabilitacion-dario/

Appendix

Detailed methodology

RESEARCH METHODOLOGY

The development of the policy and access analysis was conducted through secondary desk research. All information included within the analysis is from publicly available information sources and provided in the country-specific material. In total ~120 relevant sources were identified and included in the analysis presented. A comprehensive literature review was conducted between November 2020 and January 2021, with subsequent updates in 08 August, 2021 of two metrics, **(6) efficiency of the diagnostic pathway** and **(10) treatment availability**, due to the rapidly changing landscape across European countries.

Electronic databases (PubMed, Orphanet, EURODIS, EMA), available policy documents and disease-specific websites (TREAT-NMD, EURO-NMD, patient advisory group (PAG) and MoH sites) were searched at the national and European level. A search strategy was used, and keywords included the following: 'Spinal Muscular Atrophy (SMA)', 'rare diseases' or 'orphan diseases', 'orphan drugs', 'orphan medicines', 'access', 'patient advocacy', 'campaign', 'availability', 'accessibility', 'registries', 'centres of excellence', 'pricing', 'market access', 'marketing authorisation', 'regulation', 'policy', 'newborn screening', 'diagnosis', 'social security', 'physiotherapy'. Dates of published literature ranged from 2001 to 2021. The search was primarily conducted in English at the European level, with native language searches conducted for country-level analyses.

Information collected was reviewed and validated by Biogen colleagues and SMA Europe member organisations from each country in scope. Validation of findings was conducted through a written review and feedback or through approximately 10 video conferences with Biogen colleagues or SMA Europe member organisations, with iterative reviews conducted to ensure the information gathered best reflects the national landscapes.

COMPARATIVE ASSESSMENT

For each metric, a three-tiered categorisation was developed after the collection of insights across all 23 countries. The three tiers were developed to allow for a comparative assessment to be made across countries and are broadly based on the following categorisation: **red** (not good enough), **yellow** (room for improvement), **green** (good) (Table 19). The objective of providing a simple three-tiered categorisation is to ensure easy understanding of (a) the status of each metric across the 23 different European countries; and (b) the overall performance of a specific country across all 11 metrics.

Specifically, detailed criteria for the red, yellow and green categories of each metric have been developed in an iterative process in collaboration with Biogen and SMA Europe to ensure sufficient differentiation between the varied landscapes observed. These criteria ensure that the variation across countries is characterised appropriately. The categorisation selected reflects the evidence collected by CRA, in addition to the interpretation of Biogen and SMA Europe of that evidence to best represent 'high', 'moderate' and 'low' performing countries for each metric in the current environment.

The three-tiered categorisation has been applied in a consistent manner across all countries, based on the validated information collected by CRA to provide an objective comparative assessment. The categorisation was reviewed independently by Biogen and SMA Europe to ensure accuracy and objectivity.

DRAFTING PROCESS

After the information was collected and the policy landscape analysed across all the countries in scope, the metric ratings of each country were compiled and **assessed for key trends, successes and challenges in a comparative assessment** across each metric. CRA, in collaboration with Biogen and SMA Europe, used this comparative assessment to develop policy recommendations calling for changes across each policy area identified, and to identify key stakeholders for engagement.

Table 19: Metric status criteria

(1) National strategies for rare / genetic disorders	Currently valid national rare disease strategy Expired/outdated national rare disease strategy No national rare disease strategy
(2) Patient organisations and advocacy	Dedicated patient group supporting SMA patients which both directly supports and politically advocates for patients Dedicated patient group supporting SMA patients with mandate focusing on patient support rather than political advocacy No dedicated patient group supporting SMA patients
(3) Epidemiology estimate	Country-specific epidemiology data from registry or literature with patient characteristics (e.g. type, age) Incomplete country-specific data of limited reliability / granularity (e.g. only total population number is available, old data) No reliable data on the country's SMA population; estimated population is based on global/EU prevalence
(4) National SMA patient registry	Consolidated national patient registry that captures both epidemiological and clinical history data Consolidated national patient registry that captures only epidemiological data and no report of clinical history No consolidated national patient registry (no registry or only fragmented local/product-specific registries)
(5) Infrastructure	Easy access to designated CoEs for the treatment of SMA (defined by ≥0.80 CoEs per million population) Limited access to designated CoEs for the treatment of SMA (defined by 0.21–0.79 CoEs per million population) Very limited access to designated CoEs for the treatment of SMA (defined by 0.00–0.2 CoEs per million population)
(6) Efficiency of diagnostic pathway	Inclusion of / commitment to include SMA in national newborn screening programme with follow up and provision of genetic counselling; and there is reimbursed and efficient access to genetic diagnostic resources No commitment to include SMA in national newborn screening, but there are ongoing/planned pilots; and there is reimbursed and efficient access to genetic diagnostic resources No permanent or pilot inclusion of SMA in newborn screening programmes; and there is reimbursed access to diagnostic resources, but there have been reported diagnostic barriers such as delays in diagnosis
(7) Post-MA early access pathways	Well-established reimbursed early access programme available on a cohort and named-patient basis after MA Early access programme with partial reimbursement; only available for individual applicants after MA No reimbursed early access programme available after MA; only MNF-funded programmes are available
(8) Specialised HTA / reimbursement pathways	Specialised reimbursement/HTA pathway tailored to orphan products for fair and efficient access to treatment Standard reimbursement/HTA pathway with the possibility of accelerated access to orphan products No specialised reimbursement/HTA pathway tailored for orphan products or orphan products are required to overcome additional hurdles to gain access
(9) Treatment and care guideline recommendations	The country has adopted guidelines that provide treatment and care recommendations that reflect the most recent clinical consensus and evidence The country has adopted guidelines that provide recommendations on care that reflect the most recent clinical consensus and evidence, but no recommendations on treatment The country has not adopted any guidelines and do not provide any treatment or care recommendations
(10) Treatment availability	Treatment is reimbursed and there are no access restrictions to the relevant regulatory label Treatment is reimbursed but there are access restrictions applied to the relevant regulatory label A negative reimbursement decision has been made resulting in no access for indicated patients Treatment is reimbursed through a formally agreed early access program Product does not yet have marketing authorisation; or reimbursement decision not yet finalised
(11) Selected care provisions	Selected care provisions analysed are reimbursed for SMA patients and caregivers without major issues experienced in gaining access to these services Selected care provisions analysed are reimbursed for SMA patients or caregivers, but there are issues for patients in accessing the necessary care Selected care provisions analysed are not reimbursed or are limited for SMA patients or caregivers