folia medica

Folia Medica 68(5)
DOI: 10.3897/folmed.68.e194832

Research Article

A decade of implementing rare disease policy: insights from a national framework

Rumen S. Stefanov[1,2], Georgi S. Stefanov[2,3], Elena N. Mitova[2], Georgi G. Iskrov[1,2]

1 *Department of Social Medicine and Public Health, Faculty of Public Health, Medical University of Plovdiv, Bulgaria*

2 *Institute for Rare Diseases, Plovdiv, Bulgaria*

3 *Department of Social Medicine and Health Management, Faculty of Public Health, Medical University of Pleven, Bulgaria*

Corresponding author: Georgi Iskrov, Department of Social Medicine and Public Health, Faculty of Public Health, Medical University of Plovdiv, Bulgaria; Email: georgi.iskrov@mu-plovdiv.bg

Received: 8 April 2026 ♦ **Accepted:** 21 July 2026 ♦ **Published:** 29 October 2026

Citation: Stefanov RS, Stefanov GS, Mitova EN, Iskrov GG. A decade of implementing rare disease policy: insights from a national framework. Folia Med (Plovdiv) 2026;68(5):e194832. doi: 10.3897/folmed.68.e194832.

Abstract

Introduction: Bulgaria stands out in Eastern Europe for its early and structured engagement in rare disease policymaking through the National Program for Rare Diseases (2009–2013) and Ordinance No. 16/2014, which established the legal framework for rare disease registration and management.

Aim: To present a retrospective policy implementation analysis of Bulgaria's rare disease framework, examining how the provisions introduced by Ordinance No. 16/2014 have been translated into measurable institutional outputs between July 2014 and March 2025.

Materials and methods: A retrospective policy implementation analysis was conducted using aggregated administrative and regulatory data derived from publicly accessible sources, official documents, and materials obtained through formal requests under the Bulgarian Law on Access to Public Information.

Results: The national List of Rare Diseases, adopted in 2015, initially included 116 conditions. Between 2015 and 2025, 149 additional conditions were added following expert review. Median processing times were 112 days from initial review to Commission recommendation and 126 days from recommendation to ministerial approval. During the same period, 34 expert centers were designated, with a median of 139 days from submission to certification. By March 2025, the National Registry contained data on 1685 patients across 76 rare diseases; however, reporting remained incomplete, with only 35.3% of expert centers contributing data.

Conclusions: The Bulgarian model demonstrates that a permanent regulatory framework can improve coordination, visibility, and standardization of rare disease care. Nevertheless, incomplete registry reporting, uneven stakeholder participation, and limited integration within European Reference Networks remain important challenges.

Keywords

epidemiological registry, European reference networks, health policy, healthcare organization

Introduction

Rare diseases, although individually infrequent, collectively are a significant public health concern in the European Union (EU), affecting an estimated 29 million people and encompassing between 5000 and 8000 clinical entities.[1] The majority are of genetic origin, frequently manifested in early childhood, and are associated with diagnostic delays, limited therapeutic options, and substantial challenges in long-term management. These characteristics have prompted the EU to promote targeted policy instruments for rare diseases, encouraging Member States to develop

Copyright by authors. This is an open access article distributed under the terms of the Creative Commons Attribution License (CC-BY 4.0), which permits unrestricted use, distribution, and reproduction in any medium, provided the original author and source are credited.

PENSOFT.

dedicated national plans and to participate in European Reference Networks (ERNs) as a means of pooling scarce expertise and improving equity of access to highly specialized care.[1,2]

Within the Eastern European context, Bulgaria is notable for its early and structured engagement with rare disease policy. The adoption of the National Program for Rare Diseases (2009–2013) preceded the 2009 EU Council Recommendation, providing a platform for initial stakeholder coordination and policy formulation. Subsequently, Ordinance No. 16/2014 established a binding legal and institutional framework for the identification, registration, and management of rare diseases.[3-6] Central to this regulatory structure is the Commission on Rare Diseases, acting in an advisory capacity to the Ministry of Health. Its functions cover the evaluation of proposals for the inclusion of conditions in the national List of Rare Diseases, recommendations for the designation of expert centers, oversight of the National Registry of Rare Disease Patients, and provision of policy guidance on prevention, diagnosis, treatment, and rehabilitation.[6]

Over the past decade, the Commission's scope of activity has expanded beyond its initial remit. In addition to regularly updating the List of Rare Diseases, it has established structured mechanisms for stakeholder engagement, enabling the participation of healthcare professionals, researchers, patient organizations, and policymakers in decision-making processes. It has also promoted greater alignment with EU standards and fostered collaborative links with international partners.[5-7] These developments have contributed to a more transparent and participatory model of governance in the field of rare diseases, although with persistent challenges in implementation efficiency and stakeholder commitment. Despite this progress, the actual impact of Ordinance No. 16/2014 and the broader activities of the Commission have not been systematically assessed.

Aim

In this context, the aim of this study is to present a retrospective policy implementation analysis of Bulgaria's rare disease framework, examining how the provisions introduced by Ordinance No. 16/2014 have been translated into measurable institutional outputs over the period July 2014–March 2025. Drawing on publicly accessible datasets and official documentation, the analysis evaluates the extent to which the legislative framework and institutional processes have been translated into measurable outputs, identifies key achievements and persistent challenges, and explores opportunities to strengthen the sustainability and effectiveness of rare disease policy in Bulgaria.

Materials and methods

Analytical framework

This study was designed as a retrospective policy implementation analysis using routinely available administrative and regulatory data. The evaluation focused on the implementation of the regulatory framework established by Ordinance No. 16/2014 and assessed its operational outputs through predefined domains, including the development of the national List of Rare Diseases, designation of expert centers, and establishment of the National Registry of Rare Disease Patients. These implementation areas provide the analytical framework for the present study.

Under Ordinance No. 16/2014, the Commission on Rare Diseases has a central role in shaping and overseeing rare disease policy and practice at the national level. Its statutory functions encompass the evaluation and issuing of formal opinions on proposals for adding new conditions to the national List of Rare Diseases, recommendations for the designation of expert centers and reference networks, and the assessment of the performance of both the National Registry of Rare Disease Patients and the designated expert centers.[5-7]

The List of Rare Diseases serves as the official national catalogue, publicly accessible and maintained in the Bulgarian language with the expert evaluation of the Commission. Applications for inclusion are most often submitted by medical specialists, reflecting the central role of clinical expertise in identifying conditions that warrant national recognition. It includes only conditions meeting the EU rarity criteria, based on dossiers reviewed and endorsed by the Commission. Updates are enacted through a formal order by the Minister of Health, in full compliance with the procedural and legal provisions of Ordinance No. 16/2014. The List constitutes the primary reference tool for structuring diagnostic, therapeutic, and specialist medical services for individuals with rare diseases across Bulgaria. Its regular revision, guided by emerging medical evidence and consistent selection criteria, is essential to preserving its practical value for healthcare providers and policymakers.[5-7]

Expert centers for rare diseases function as specialized units within existing healthcare institutions, holding official designation from the National Center of Public Health and Analysis (NCPHA), after assessment and recommendations from the Commission. These centers are not independent legal entities but rather specialized departments formally recognized for their capacity to manage conditions included in the national List. Eligibility criteria include evident clinical expertise, adequate infrastructure, and the ability to deliver comprehensive care in line with national and EU standards. Their responsibility extends beyond direct patient care, covering also registry maintenance, professional training, and contribution to the continuous development of rare disease services. Designation is subject to periodic review by the Commission to ensure sustained quality and policy compliance.[5,6]

The National Registry of Rare Disease Patients, also established under Ordinance No. 16/2014 and administered by the NCPHA, is a centralized electronic platform for the systematic collection, storage, and analysis of data on patients diagnosed with conditions listed in the official national List. The registry provides epidemiological surveillance, supports strategic planning and service evaluation, and facilitates monitoring of disease incidence, outcomes, and resource distribution.[6,7] Although the Registry's day-to-day management is outside the direct operational scope of the Commission, its structure and function are linked with the List and expert centers, making it a necessary component of this assessment.

Data sources

Data for this analysis were obtained from publicly accessible resources hosted on the NCPHA website. All web-based resources were accessed and retrieved between 10 February and 10 March 2025.

Sources were systematically identified to ensure comprehensive coverage of the Commission's main activities between July 2014 and March 2025 **(Table 1)**. Where additional details were required, they were acquired through formal requests in accordance with the Bulgarian Law on Access to Public Information. All materials analyzed were either in the public domain or officially provided under the applicable legal framework.

Data analysis

The analysis followed a policy implementation framework that combined descriptive assessment with evaluation of implementation outputs (regulatory decisions, institutional capacity, and registry development) rather than clinical or health outcome indicators. Descriptive statistical methods were applied to characterize the evolution of the principal policy outputs. The quantitative dataset encompassed the following: (i) the total number of conditions included in the national List of Rare Diseases; (ii) the number of officially designated expert centers; (iii) the cumulative number of patients registered in the National Registry; and (iv) temporal patterns in the Commission's formal recommendations and associated decisions. To ensure transparency and data reliability, data extraction and verification were conducted independently by authors who are not members of the Commission.

For the purpose of assessing time trends related to the inclusion of new conditions in the List or to the designation of expert centers, three chronological milestones were recorded for each case: (i) the date of the Commission's initial review; (ii) the date of its final recommendation; and (iii) the date of the Ministerial order, formalizing the update to the List or, in the case of expert centers, the date of official certification by the NCPHA. Where applicable, intermediate requests for supplementary documentation or clarifications were also noted.

Given the considerable variation in the time intervals between the Commission's recommendations and the subsequent ministerial or NCPHA approvals, results are expressed as median values. The distribution of these intervals was positively skewed, rendering mean values less representative for this dataset and justifying the use of medians as a more robust measure of central tendency. All statistical analyses were conducted using Microsoft Excel (Microsoft 365 Office Version 2512 Build 16.0.19530.20184).

Results

Development and evolution of the List of Rare Diseases

Immediately after its establishment, the Commission on Rare Diseases did an administrative review of rare condi-

Table 1. Data sources used for analysis of the Commission's deliverables

Activity/Task	Data/Deliverables	Main variables extracted	Source
Commission on Rare Diseases	Official protocols of Commission's meetings and recommendations	Date of Commission initial review; Date of Commission recommendation	https://ncpha.government.bg/index/130-protokoli-ot-zasedania-na-komisiata.html[8]
List of Rare Diseases	Ministerial orders approving and updating the list for Bulgaria	Date of Ministerial order	https://ncpha.government.bg/index/115-komisii.html[9]
Expert Centers for Rare Diseases	Registry of designated expert centers in Bulgaria	Date of NCPHA certification	https://ncpha.government.bg/index/131-registur-na-ekspertnite-centrove-po-redki-zabolliavania.html[10]
Bulgarian National Registry of Rare Disease Patients	Aggregated epidemiological data	Total number of registered patients; Distribution of patients by main characteristics	Obtained through a formal public information request to NCPHA[11]

tions already recognized in Bulgaria as having established diagnostic and/or therapeutic pathways. The review served as the foundation for the national List of Rare Diseases. It included 116 conditions and was officially endorsed through a Ministerial order on 27 November 2015. This initial version ("Initial List") represented 43.8% of the total entries registered by March 2025 **(Table 2)**.

Subsequent additions were carried out through an application-driven process, whereby any stakeholder (most commonly a medical specialist) could formally request the inclusion of a new rare disease. Each submission underwent expert evaluation by the Commission, which then issued a recommendation to the Ministry of Health. Conditions added via this route are referred to here as "Subsequent Additions." Between December 2015 and March 2025, 149 new entries were included in the List through this process.

Median processing times for inclusion are summarized in **Table 2**. The median interval between the initial Commission review and recommendation was 112 calendar days. From recommendation to Ministerial approval, the median duration was 126 days, while the total median time from first review to official inclusion was 165 days.

The evolution of the List showed clear periods of administrative delay **(Fig. 1)**. Between 2016 and 2022, recommendations from the Commission were not systematically followed by timely Ministerial orders, resulting in the largest single update occurring on 4 November 2022, when 107 conditions were added at once. Since early 2023, approvals have been issued on a regular basis, with the List updated promptly after a positive opinion by the Commission.

During the entire period, only one application received a negative recommendation. Submissions returned for additional information (*n*=17/149, 11.4%) were associated with significantly longer timelines than straightforward cases.

Designation and activity of expert centers for rare diseases

From 2016 to 2025, 34 expert centers were formally designated in Bulgaria, following certification by the NCPHA upon recommendation from the Commission **(Fig. 2)**. The first implementation wave in 2016 (coinciding with the launch of the ERNs at the European level) included 16 designations, representing 47.1% of all centers. After a period of low interest, five new centers were designated in 2023 and seven more in 2024. Two applications were declined, and three remain under review.

Table 2. Processing time intervals for inclusion of conditions in the Bulgarian List of Rare Diseases

Time interval (in calendar days)	Initial List (*n*=116) Median	Subsequent Additions (*n*=149) Median (Q_1 – Q_3)	Overall (*n*=265) Median (Q_1 – Q_3)
From initial review to Commission recommendation	112	91 (91 – 127)	112 (91 – 112)
From Commission recommendation to Ministerial approval	53	395 (332 – 1983)	126 (53 – 871)
Total (review to inclusion)	165	486 (486 – 2110)	165 (165 – 1129)

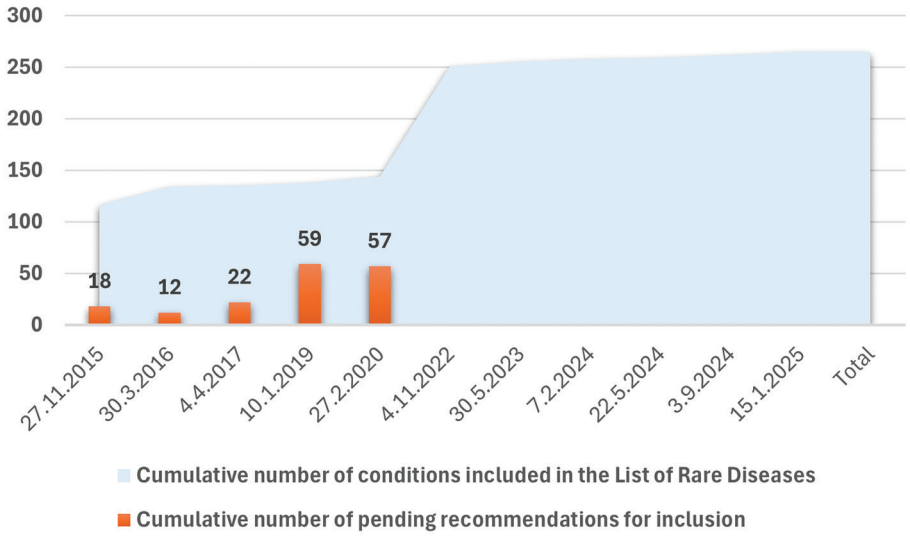

Figure 1. Evolution of the Bulgarian List of Rare Diseases (2015–2025).

The median interval from submission to a Commission recommendation was 74.5 days, while the overall median time from submission to official certification reached 139 days **(Table 3)**. Cases in which additional documentation was requested (17 of the 34 designated expert centers; 50.0%) required substantially longer processing, with a median of 175 days compared to 77 days for cases approved without further requirements. The most protracted delay (2341 days) occurred in a situation where legal provisions required the rare condition to be added to the national List before a designation for the expert center could be granted.

Geographically, designations were highly concentrated in Sofia (28 centers), followed by Varna (3), Pleven (2), and Plovdiv (1). Fifteen centers underwent redesignation following the expiration of their initial five-year term. As of March 2025, five centers were full ERN members, and one held associated membership status.

National Registry of Rare Disease Patients

As of 1 March 2025, the National Registry of Rare Disease Patients in Bulgaria contained records for 1685 individuals **(Fig. 3)**. Of these, 907 (53.8%) were male and 778 (46.2%) female. The largest proportion were children and adolescents aged 0–17 years (*n*=532, 31.6%), followed by those aged 18–29 (*n*=271), 30–39 (*n*=167), and 40–49 (*n*=202). Patients were registered across all administrative regions, with the highest counts reported in Sofia (380 cases), Varna (162), Burgas (132), and Plovdiv (129).

Despite the Registry's potential as a comprehensive epidemiological resource, reporting remains incomplete. Only 12 (35.3%) of the 34 designated expert centers had submitted data during the observation period. The largest contributions came from the Expert Center for Congenital Heart Malformations at the National Cardiology Hospital (322 cases) and the Expert Center for Rare Endocrine Diseases at the University Hospital for Endocrinology "Acad. Ivan Penchev" (278 cases), both based in Sofia **(Table 4)**.

By the reference date, the Registry held epidemiological data for 76 distinct rare diseases. This corresponds to 28.7% of the 265 conditions included in the national List of Rare Diseases. The five most frequently recorded were panhypopituitarism (ORPHA code 90695; 213 patients), acromegaly (ORPHA code 963; 144), beta-thalassemia major (ORPHA code 231214; 136), hemophilia A (ORPHA code 98878; 119), and Laubry–Pezzi syndrome (ORPHA code 99094; 105). Fourteen conditions were represented by a single registered case.

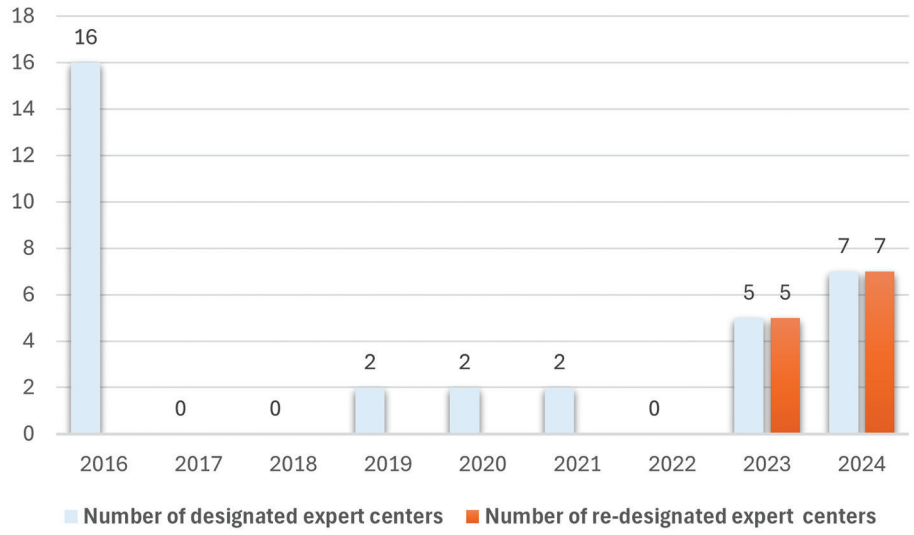

Figure 2. Evolution of designated expert centers for rare diseases in Bulgaria (2016–2025).

Table 3. Processing time intervals for designation of expert centers for rare diseases in Bulgaria

Time interval (in calendar days)	First wave (*n*=16) Median (Q_1 – Q_3)	Recent applicants (*n*=18) Median (Q_1 – Q_3)	Overall (*n*=34) Median (Q_1 – Q_3)
From initial review to Commission recommendation	77 (43.75 – 114)	70 (56 – 139)	74.5 (49.5 – 114)
From Commission recommendation to NCPHA certification	41.5 (35.25 – 42.75)	52.5 (25 – 92.5)	42 (27.25 – 65)
Total (initial review to certification)	120.5 (87.75 – 156.5)	140.5 (79.5 – 194.75)	139 (79.5 – 185)

Folia Medica

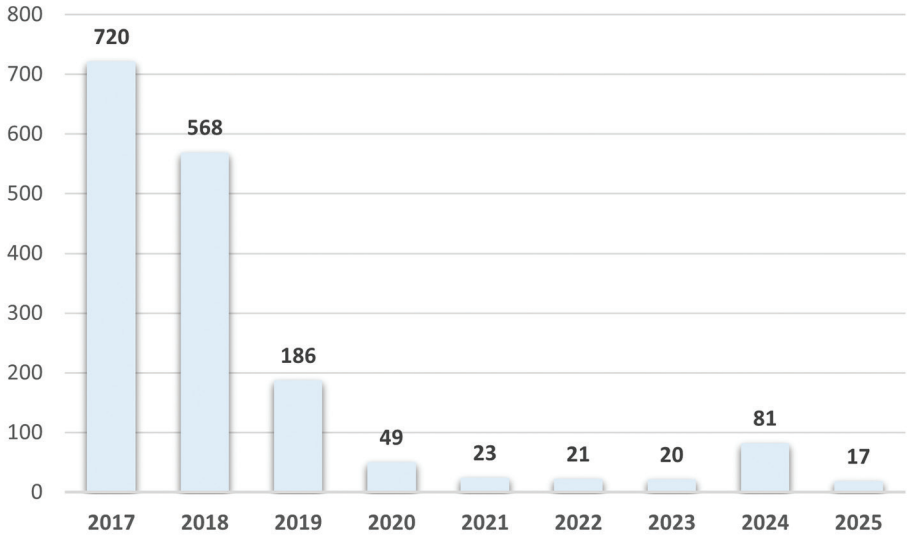

Figure 3. Annual number of newly registered patients in the Bulgarian National Registry of Rare Disease Patients.

Table 4. Number of patients registered in the Bulgarian National Registry of Rare Disease Patients by reporting expert center (as of 1 March 2025)

Reporting expert center for rare diseases	Number of registered patients
Expert Center for Congenital Heart Malformations, National Cardiology Hospital, Sofia	322
Expert Center for Rare Endocrine Diseases, University Hospital for Endocrinology "Acad. Ivan Penchev"", Sofia	278
Expert Center for Primary Immunodeficiencies, University Hospital "Alexandrovska", Sofia	239
Expert Center for Rare Endocrine Diseases, University Hospital "St. Marina", Varna	227
Expert Center for Coagulopathies and Congenital Anemias, Specialized Hospital for Hematology, Sofia	155
Expert Center for Porphyria, University Hospital "St. Ivan Rilski", Sofia	154
Expert Center for Coagulopathies and Rare Anemias, University Hospital "St. Marina", Varna	145
Expert Center for Hereditary Metabolic Liver Diseases, University Hospital "St. Ivan Rilski", Sofia	57
Expert Center for Dystonia, University Hospital of Neurology and Psychiatry "St. Naum", Sofia	39
Expert Center for Pulmonary Arterial Hypertension, National Cardiology Hospital, Sofia	30
Expert Center for Fabry Disease, University Hospital "Alexandrovska", Sofia	21
Expert Center for Huntington's Chorea, University Hospital of Neurology and Psychiatry "St. Naum", Sofia	18

Taken together, the demographic distributions and disease statistics should be interpreted strictly as outputs of the Registry dataset, which currently has incomplete national coverage and is likely affected by reporting bias.

Discussion

This study provides one of the first operational policy implementation analyses examining how a national rare disease regulatory framework has translated into measurable institutional outputs and identifying the principal facilitators and bottlenecks of implementation over a ten-year period. Comparable evaluations of national rare disease policy implementation remain scarce, limiting opportunities for international benchmarking. This underscores the originality of the present study and its potential value as a reference point for future research examining similar policy mechanisms in other countries.

Advancing process efficiency and standardization

The present 10-year review indicates measurable advances in both the operational efficiency and the institutional consolidation of Bulgaria's rare disease policy framework. The regular annual updates to the national List of Rare Diseases, together with the faster pace of expert center

designations observed since 2022, point to a transition toward a more stable, organized, and transparent governance model. A noteworthy development within this process is the routine publication of a comprehensive disease profile for each newly listed condition on the NCPHA website.[12] This ensures that healthcare professionals nationwide have access to authoritative, regularly up-to-date information in the Bulgarian language, which in turn facilitates the standardization of diagnostic criteria and the harmonization of clinical management guidelines.

Over time, the List has extended its role beyond a purely legal register and has become a practical decision-support instrument, mapping the continuum of care from initial diagnosis to long-term follow-up. This function is particularly important for ultra-rare conditions, where national expertise is limited and much of the specialized knowledge remains concentrated within a few international centers.[13,14] In this respect, the List serves not only as a regulatory mechanism but also as a tool for incorporating global expertise into national healthcare practice.[7]

Nevertheless, the findings also highlight some procedural constraints. A particularly persistent bottleneck is the extended timeframe for Ministerial approval of proposed additions to the List – a prerequisite for both the official recognition of new rare diseases and the initiation of expert center designation procedures. Similar delays have been reported in other EU Member States and are frequently linked to multi-tiered administrative processes and extensive documentary requirements.[15,16] Setting explicit deadlines within the regulatory framework, removing unnecessary procedural stages, and ensuring stronger coordination between institutions could markedly shorten approval times, which in turn would enable faster access to specialized healthcare services.

Bulgaria's engagement in European Reference Networks

ERNs, established under Directive 2011/24/EU, are a cornerstone of the EU's strategy for enhancing cross-border collaboration, consolidating expertise, and ensuring equitable access to highly specialized care for patients with rare diseases.[17] Active involvement in ERNs offers a range of benefits, from improved diagnostic accuracy and participation in multi-center research initiatives to the adoption of better standards of care across Member States.[18]

Despite these advantages, Bulgaria's current level of ERN participation remains modest compared with that of many other EU countries. The absence of new calls for ERN membership since 2019 has compounded this disparity, with a particularly pronounced impact on expert centers in Eastern Europe, where opportunities for integration into these networks have been fewer.[19] This structural limitation not only restricts access to collective expertise but also slows the diffusion of innovative diagnostic and therapeutic approaches into the national healthcare system.

To mitigate these constraints, the ERN Board of Member States has recommended embedding ERN participation criteria into national accreditation and designation procedures for expert centers.[20] In the Bulgarian context, such alignment is anticipated by Ordinance №16/2014, which already incorporates EU requirements into the eligibility framework for expert center designation. Further strengthening this link would facilitate the harmonization of clinical care pathways, reinforcement of clinical networking, and improvement of the referral systems, enabling more frequent use of cross-border virtual consultations. For Bulgaria, such an approach could accelerate the adoption of best practices and advanced knowledge, directly benefiting patients through earlier and more accurate diagnoses and more timely access to specialist interventions.[21] To stimulate existing national expert centers to seek ERN membership, targeted administrative and financial support from the state would be essential, helping them to meet procedural requirements, sustain participation, and maximize the benefits of network integration. Strengthening ERN engagement should therefore be regarded both as a policy priority and as a practical means of closing existing gaps between national and European rare disease care capacities.[22-24]

Scope and limitations of the National Registry

National rare disease registries are a critical component of health system capacity, serving multiple roles – from epidemiological surveillance and healthcare resource allocation to monitoring the impact of policy interventions.[25-27] The Bulgarian National Registry of Rare Disease Patients was conceived as a centralized platform to consolidate epidemiological data and inform evidence-based decision-making. In practice, however, its current scope and data completeness remain limited. Only a small proportion of designated expert centers submit data on a regular basis, leading to considerable underreporting and fragmented disease surveillance. This gap not only constrains accurate prevalence estimation but also reduces the registry's utility for service planning and evaluation.[25,28-29]

International experience provides compelling examples of how registry performance can be strengthened. Success often rests on a combination of legal mandates for reporting, integration with national electronic health record systems, provision of structured feedback to reporting institutions, and, in some cases, incentives for ensuring data completeness and quality.[25,27-29] Involving patient organizations in governance has also been shown to enhance both completeness and relevance, as it aligns registry content with the real-world needs of those directly affected.[30]

Across Europe, there is growing emphasis on bringing national registries in line with the FAIR principles, which require health data to be findable, accessible, interoperable, and reusable. These standards form the basis of EU-level initiatives such as DARWIN EU and the European Health Data Space.[31] For Bulgaria, adopting a FAIR-compli-

ant framework would call for more intensive cooperation among clinicians, specialists in data standardization, and health IT professionals. While the essential challenges of rare disease registries (small and geographically dispersed patient populations and disease heterogeneity) cannot be fully eliminated, adopting these principles and embedding stronger institutional support could substantially improve coverage, reliability, and ultimately the policy value of the National Registry.[32]

Policy integration of rare cancers

The management of rare cancers continues to present a complex policy challenge, particularly regarding whether they should be incorporated into broader rare disease strategies or addressed through already existing dedicated oncology frameworks.[33,34] In Bulgaria rare cancers are primarily managed within standard oncology pathways, and their formal inclusion in the national List of Rare Diseases has been deferred, awaiting a clearer strategic consensus.

At the European level, two complementary yet distinct policy tracks have emerged. The first, Europe's Beating Cancer Plan, prioritizes prevention, early detection, and equitable access to innovative therapies for rare cancers. However, its operational guidance on clinical standards and healthcare infrastructure remains limited. The second approach situates rare cancers within the broader rare disease policy context, applying instruments such as the Orphan Drug Regulation and utilizing the ERNs' expertise, particularly EURACAN.[35-37]

Some Member States have fully integrated rare cancers into their national rare disease plans. This alignment facilitates coordinated care pathways, standardized data collection and systematic access to ERN-based expertise, thereby enhancing both clinical management and research potential.[22,23,34] For Bulgaria, the adoption of a patient-centered hybrid model may be a pragmatic way forward: ensuring that rare cancer patients benefit simultaneously from the advances in oncology and the specialized resources, networks, and policy mechanisms developed for rare diseases. Such integration would require deliberate alignment of oncology and rare disease policies, clear governance structures, and sustained intersectoral collaboration.[36,38,39]

Bulgaria's experience: from national plans to regulatory integration of rare diseases

Bulgaria was among the earliest European countries to implement a dedicated National Program for Rare Diseases (2009–2013)[3,4], which served as a catalyst for mobilizing stakeholders and initiating coordinated policy action.[40] Although the program generated the political momentum needed to put rare diseases on the national agenda, it was the adoption of Ordinance No. 16/2014 that marked the real transition from strategic intention to an operational, legally binding framework. Through this act, the procedures for identification, registration, diagnosis, treatment, and long-term follow-up of patients with rare diseases were formally institutionalized, ensuring their inclusion within the national healthcare system.

The Bulgarian case illustrates that national plans are highly effective in the early stages, particularly for awareness-raising and building consensus among stakeholders.[26,41] Yet, lasting progress in access, quality, and continuity of care requires that rare disease management be embedded within permanent legislative and regulatory structures. In practical terms, future policy work should focus on enforceable provisions. These may take the form of ordinances or amendments to core health legislation that clearly define how such services are to be funded, managed, and assessed at the national level.

Incorporating the List of Rare Diseases into a wider number of health regulations and linking it to the National Health Information System provides a coherent architecture for faster diagnosis, standardizing clinical pathways and follow-up. This approach moves rare disease care beyond short-term or project-based interventions, securing its place as a stable, predictable, and integral component of the health system.[42]

Ultimately, Bulgaria's trajectory underscores that lasting progress in rare disease governance is driven less by the periodic renewal of national programs and more by the consolidation of stable institutional mechanisms, systematic regulatory alignment, and the operational embedding of rare disease policy into the national health governance architecture.

Limitations

This study relied exclusively on aggregated data obtained from publicly accessible databases and official records. Although these sources offer a solid foundation for outlining policy changes and institutional actions, the scope of analysis remains confined to aspects that are systematically recorded or officially made public. As a result, important dimensions of rare disease care, such as the quality and timeliness of clinical services, patient-reported experiences and outcomes, uptake of novel diagnostic and therapeutic approaches, and broader health system performance, may not be adequately captured.

The relatively low level of reporting by designated expert centers to the National Registry of Rare Disease Patients limits the completeness and representativeness of the available epidemiological data. This underreporting could lead to an underestimation of both the true burden and the complexity of rare diseases in Bulgaria, particularly for conditions managed outside the most active reporting centers.

Furthermore, the aggregated data used in this study do not allow assessment of whether reporting expert centers submitted data for all eligible patients or only for a subset of them, despite the regulatory requirement for comprehen-

sive reporting under Ordinance No. 16/2014. Likewise, the reasons why a substantial proportion of designated expert centers did not contribute data to the Registry cannot be determined from the available sources and warrant dedicated investigation involving the participating institutions.

Another limitation relates to the lack of comparable studies examining the operational role of national rare disease catalogues. This restricts the possibility for direct international benchmarking and comparative evaluation. In this context, the findings presented here may serve as a useful reference for future comparative studies examining similar policy instruments in other healthcare systems.

These constraints highlight the need for future research based on prospective data collection and active engagement with all relevant stakeholders, including clinicians, patient organizations, and policymakers. Such an approach would enable a more comprehensive assessment of rare disease management, care quality, and patient outcomes at the national level.

Conclusions

Over the past decade, Bulgaria has made substantial progress in establishing a coherent framework for rare disease policy and care. The adoption of Ordinance No. 16/2014, together with the development of a national List of Rare Diseases, designated expert centers, and a National Registry, has improved the visibility, coordination, and standardization of services.

However, important challenges remain. Registry coverage is still limited due to incomplete reporting, and Bulgaria's participation in the ERNs remains below its potential. Addressing these gaps will require sustained engagement of all stakeholders, including clinicians, researchers, patient organizations, and policymakers.

Further progress depends on strengthening regulatory and digital infrastructure, expanding stakeholder participation, and enhancing integration into European and international networks. From a policy implementation perspective, the Bulgarian experience demonstrates the value of transitioning from time-limited programs to stable, legally grounded frameworks for rare disease care.

Acknowledgements

The authors have no support to report.

References

1. Council of the European Union. Council recommendation of 8 June 2009 on an action in the field of rare diseases (2009/C 151/02). Off J Eur Union 2009;151:7–10. Available from: https://eur-lex.europa.eu/legal-content/EN/TXT/?uri=celex:32009H0703(02) (Accessed on 28 January 2026).
2. European Parliament and Council. Directive 2011/24/EU of 9 March 2011 on the application of patients' rights in cross-border healthcare. Off J Eur Union 2011;88:45–65. Available from: https://eur-lex.europa.eu/legal-content/EN/TXT/?uri=CELEX:32011L0024 (Accessed on 28 January 2026).
3. Ministry of Health (Bulgaria). [National program for rare diseases (genetic, congenital malformations and non-hereditary diseases) 2009–2013]. Available from: https://www.mh.government.bg/upload/3424/programa-redki-bolesti-2009-2013.pdf (Accessed on 28 January 2026). (Bulgarian).
4. Pejcic AV, Iskrov G, Raycheva R, et al. Transposition and implementation of EU rare disease policy in Eastern Europe. Expert Rev Pharmacoecon Outcomes Res 2017;17(6):557–66.
5. Hristova E, Raycheva R, Iskrov G, et al. List of rare diseases in Bulgaria. Rare Dis Orphan Drugs 2016;3(3):39–44.
6. Ministry of Health (Bulgaria). [Ordinance No. 16 of 30 July 2014 on the terms and conditions for registration of rare diseases and for expert centers and reference networks for rare diseases]. State Gazette 2014;67. Amended in State Gazette 2019;25. Available from: https://lex.bg/laws/ldoc/2136291444 (Accessed on 28 January 2026). (Bulgarian).
7. Stefanov R, Iskrov G, Stefanov G, et al. [The role of the list of rare diseases established in the Republic of Bulgaria to improve diagnostics and access to treatment]. Redki bolesti i lekarstva siratsi 2025;16(2):19–23. (Bulgarian).
8. National Center for Public Health and Analyses (Bulgaria). Official protocols of Commission on Rare Diseases meetings and recommendations. Available from: https://ncpha.government.bg/index/130-protokoli-ot-zasedania-na-komisiata.html (Accessed on 28 January 2026).
9. National Center for Public Health and Analyses (Bulgaria). Ministerial orders approving and updating the list of rare diseases in Bulgaria. Available from: https://ncpha.government.bg/index/115-komisii.html (Accessed on 28 January 2026).
10. National Center for Public Health and Analyses (Bulgaria). Registry of designated expert centers for rare diseases in Bulgaria. Available from: https://ncpha.government.bg/index/131-registur-na-ekspertnite-centrove-po-redki-zaboliavania.html (Accessed on 28 January 2026)
11. National Center for Public Health and Analyses (Bulgaria). Decision No. 1306/24.03.2025 based on official request No. 1134/10.03.2025 for access to public information.
12. National Center for Public Health and Analyses (Bulgaria). Profiles of conditions included in the list of rare diseases. Available from: https://ncpha.government.bg/index/132-dosieta-na-zaboliavania-vkliucheni-v-spisuka-na-redkite-zaboliavania.html (Accessed on 28 January 2026).
13. Crooke ST. Meeting the needs of patients with ultrarare diseases. Trends Mol Med 2022;28(2):87–96.
14. Willmen T, Willmen L, Pankow A, et al. Rare diseases: why is a rapid referral to an expert center so important? BMC Health Serv Res 2023;23(1):904.
15. Benito-Lozano J, López-Villalba B, Arias-Merino G, et al. Diagnostic delay in rare diseases: data from the Spanish rare diseases patient registry. Orphanet J Rare Dis 2022;17(1):418.
16. Briscoe S, Martin Pintado C, Sutcliffe K, et al. Evidence of inequities experienced by the rare disease community with respect to receipt of a diagnosis and access to services: a scoping review of UK and international evidence. Orphanet J Rare Dis 2025;20(1):303.

17. Héon-Klin V. European Reference networks for rare diseases: what is the conceptual framework? Orphanet J Rare Dis 2017;12(1):137.
18. European Commission. ERN Continuous Monitoring and Quality Improvement System (ERN CMQIS): ERN Indicators, Version 8.1; November 2023. Available from: https://health.ec.europa.eu/rare-diseases-and-european-reference-networks/european-reference-networks/ern-continuous-monitoring-and-quality-improvement-system_en (Accessed on 28 January 2026).
19. European Commission. European Reference Networks. Available from: https://health.ec.europa.eu/rare-diseases-and-european-reference-networks/european-reference-networks_en#the-24-european-reference-networks (Accessed on 28 January 2026).
20. European Commission. Annex to the Statement of the ERN Board of Member States on Integration of the European Reference Networks to the healthcare systems of Member States; 25 June 2019. Available from: https://health.ec.europa.eu/document/download/8b07d698-e9bc-4266-a3e2-608eb5d5c91e_en?filename=integration_healthcaresystems_annex_en.pdf (Accessed on 28 January 2026).
21. EURORDIS. Recommendations on the Integration of European Reference Networks (ERNs) into National Health Systems; 2018. Available from: https://www.eurordis.org/wp-content/uploads/2018/11/EURORDIS-Recommendations-on-the-Integration-of-European-Reference-Networks-into-National-Health-Systems.pdf (Accessed on 28 January 2026).
22. Graessner H, Storf H, Schaefer F. [Healthcare networks for people with rare diseases: integrating data and expertise]. Bundesgesundheitsblatt Gesundheitsforschung Gesundheitsschutz. 2022;65(11):1164–9. (German).
23. Graessner H, Schäfer F, Scarpa M, et al. [European Reference Networks: Consequences for healthcare in Germany]. Bundesgesundheitsblatt Gesundheitsforschung Gesundheitsschutz. 2017;60(5):537–41. (German).
24. Pieroni F, Marrucci S, Di Pietro L, et al. The Tuscany Regional Network for rare diseases: from European Reference Networks' experience to registry based organization and management model for rare diseases. Orphanet J Rare Dis 2023;18(1):324.
25. Hageman IC, van Rooij IALM, de Blaauw I, et al. A systematic overview of rare disease patient registries: challenges in design, quality management, and maintenance. Orphanet J Rare Dis 2023;18(1):106.
26. Dharssi S, Wong-Rieger D, Harold M, et al. Review of 11 national policies for rare diseases in the context of key patient needs. Orphanet J Rare Dis 2017;12(1):63.
27. Kölker S, Gleich F, Mütze U, et al. Rare Disease Registries Are Key to Evidence-Based Personalized Medicine: Highlighting the European Experience. Front Endocrinol (Lausanne) 2022;13:832063.
28. Ruseckaite R, Caruso M, Mudunna C, et al. Informing a national rare disease registry strategy in Australia: a mixed methods study. BMC Health Serv Res 2023;23(1):1187.
29. Ruseckaite R, Mudunna C, Caruso M, et al. Current state of rare disease registries and databases in Australia: a scoping review. Orphanet J Rare Dis 2023;18(1):216.
30. Klein TL, Bender J, Bolton S, et al. A rare partnership: patient community and industry collaboration to shape the impact of real-world evidence on the rare disease ecosystem. Orphanet J Rare Dis 2024;19(1):262.
31. Schoenmakers DH, van den Berg S, Timmers L, et al. Framework for Multistakeholder Patient Registries in the Field of Rare Diseases: Focus on Neurogenetic Diseases. Neurology 2024;103(6):e209743.
32. Tarride JE, Okoh A, Aryal K, et al. Scoping review of the recommendations and guidance for improving the quality of rare disease registries. Orphanet J Rare Dis 2024;19(1):187.
33. Casali PG, Trama A. Rationale of the rare cancer list: a consensus paper from the Joint Action on Rare Cancers (JARC) of the European Union (EU). ESMO Open 2020;5(2):e000666.
34. Prades J, Trama A, Casali PG, et al. Is rare cancer care organized at national health system level? Multiple case study in six EU countries. Eur J Public Health 2022;32(6):852–7.
35. Berns A, Ringborg U, Celis J, et al. Strategies to reduce the cancer burden and improve access to effective and affordable cancer interventions in Europe. Mol Oncol 2025;19(6):1553–60.
36. Kostadinov K, Iskrov G, Musurlieva N, et al. An evaluation of rare cancer policies in Europe: a survey among healthcare providers. Cancers (Basel) 2025;17(2):164.
37. EURACAN. About EURACAN – Advancing Care for Rare Adult Solid Cancers, 2017. Available from: https://www.euracan.eu/about-us/about-euracan (Accessed on 28 January 2026).
38. Kostadinov K, Popova-Sotirova I, Marinova Y, et al. Availability and access to orphan drugs for rare cancers in Bulgaria: Analysis of delays and public expenditures. Cancers (Basel) 2024;16(8):1489.
39. Van der Graaf WTA, Heiss NS, Hynes CL, et al. Overcoming the barriers to treatment of rare cancer patients in the era of precision oncology: A call to action. Cancer Treat Rev 2025;140:103013.
40. European Parliament. Challenges, opportunities and gaps for action on rare diseases in the European Union: Tackling rare diseases; 2024. Available from: https://www.europarl.europa.eu/RegData/etudes/STUD/2024/754210/IPOL_STU(2024)754210_EN.pdf (Accessed on 28 January 2026)
41. Taruscio D, Vittozzi L, Stefanov R. National plans and strategies on rare diseases in Europe. Adv Exp Med Biol 2010;686:475–91.
42. Angin C, Mazzucato M, Weber S, et al. Coding undiagnosed rare disease patients in health information systems: recommendations from the RD-CODE project. Orphanet J Rare Dis 2024;19(1):28.

Additional information

Ethics approval

Ethical review or prior approval by a Research Ethics Committee was not required for this study, as it relied solely on aggregated, publicly available data and official documentation. No individually identifiable patient records or other forms of sensitive health information were collected, processed, or analyzed at any stage of the study. All data retrieval complied fully with the provisions of the Bulgarian Law on Access to Public Information.

Ethical statement

- This study did not require ethical review or approval because it relied solely on aggregated, publicly available data

and official documentation. No personally identifiable patient information was used. All procedures were carried out in accordance with applicable national laws, including the Bulgarian Law on Access to Public Information.
- The authors declared that no clinical trials were used in the present study.
- The authors declared that no experiments on humans or human tissues were performed for the present study.
- The authors declared that no experiments on animals were performed for the present study.
- The authors declared that no commercially available immortalized human and animal cell lines were used in the present study.

Conflict of interest

Rumen Stefanov served as Chair of the Commission on Rare Diseases from 2015 to 2026. The other authors declare no conflicts of interest.

Artificial Intelligence (AI) use

The authors accept full responsibility for the content of this manuscript. AI-assisted tools (GPT) were used solely for language editing and stylistic improvement. No AI tools were involved in the design, analysis, or interpretation of the study. All authors have reviewed the manuscript following the use of AI-assisted tools and take full responsibility for the resulting content.

Funding

The authors have no funding to report.

Author contributions

RS: conceptualization, methodology, validation, writing–review and editing, and supervision; GS: software, formal analysis, investigation, data curation, writing–original draft, and project administration; EM: software, formal analysis, investigation, data curation, and writing–original draft; GI: methodology, validation, data curation, writing–original draft, and visualization. All authors have read and approved the final manuscript.

Author ORCIDs

Rumen Stefanov https://orcid.org/0000-0003-3587-7278
Georgi Stefanov https://orcid.org/0009-0002-9184-7890
Georgi Iskrov https://orcid.org/0000-0002-0988-0062

Data availability

All primary data used in this study are publicly available and can be accessed through the official website of the National Center for Public Health and Analysis (NCPHA).