doi.org/10.36721/PJPS.2026.39.11.310.1

Real-world pharmacoclinical implementation of risdiplam under a national SMA protocol: A hospital pharmacy registry-based case series

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Abstract: **Background**: Spinal muscular atrophy (SMA) is a rare neuromuscular disorder treated with disease-modifying therapies such as risdiplam. In Spain, its use is regulated by a national pharmacoclinical protocol that requires structured monitoring. **Objectives**: To evaluate real-world use, protocol adherence and registry completeness of risdiplam in routine clinical practice. **Methods**: A retrospective registry-based case series was conducted including patients with spinal muscular atrophy treated with risdiplam.Variables included age, SMA subtype, SMN2 copy number, diagnostic confirmation, treatment sequence and persistence. Protocol adherence was assessed according to national criteria. **Results**: Ten patients were included in the study. SMA types II and III predominated, with one presymptomatic case. SMN2 copy number ranged from three to four in documented cases. Protocol adherence was confirmed in 70% of patients, while 30% lacked key eligibility variables. No off-protocol prescribing was identified. Treatment persistence was 100% and 60% of patients had previously received nusinersen. **Conclusion**: Risdiplam was used appropriately in accordance with protocol criteria. Registry incompleteness, rather than clinical deviation, was the main limitation and standardized data capture is essential for real-world evaluation.

Keywords: Hospital pharmacy; Pharmacoclinical protocol; Risdiplam; Real-world data; Spinal muscular atrophy

Submitted on 08-04-2026 – Revised on 10-05-2026 – Accepted on 21-05-2026

INTRODUCTION

Spinal muscular atrophy (SMA) is a rare autosomal-recessive neuromuscular disorder characterized by progressive degeneration of anterior horn motor neurons, leading to muscle weakness, functional decline and, in severe cases, early mortality (Mercuri *et al*., 2018). The disease results from mutations or deletions in the *SMN1* gene, which encodes survival motor neuron (SMN) protein, a critical factor for motor neuron viability and neuromuscular junction integrity (Lefebvre *et al*., 1995; Mercuri *et al*., 2018). The clinical severity of SMA is modulated by the number of *SMN2* gene copies, which partially compensate for SMN protein deficiency through alternative splicing mechanisms (Wirth, 2021); SMN2 copy number is considered one of the main prognostic and disease-severity modifiers in SMA and constitutes a key eligibility criterion within the Spanish national pharmacoclinical protocol (Ministerio de Sanidad, 2024). This results in a clinical spectrum ranging from severe infantile-onset disease (type I) to milder later-onset forms (types II–III) and rare adult-onset phenotypes (Wirth, 2021).

The therapeutic landscape of SMA has changed dramatically with the introduction of disease-modifying therapies. Nusinersen, an antisense oligonucleotide administered intrathecally, was the first disease-modifying therapy approved for SMA and acts by promoting inclusion of exon 7 in SMN2 transcripts within the central nervous system (Hagenacker *et al*., 2020). Clinical studies have demonstrated improvements in motor function and survival across several SMA phenotypes, although its administration requires repeated lumbar punctures and hospital-based monitoring (Hagenacker *et al*., 2020). In contrast, risdiplam is an orally administeredsmall-molecule splicing modifier that increases systemic production of functional SMN protein by promoting exon 7 inclusion in *SMN2* transcripts (Mercuri *et al*., 2022; Baranello *et al*., 2021). Clinical trials and real-world studies have demonstrated that risdiplam improves motor outcomes and survival across SMA phenotypes, establishing it as a standard therapeutic option (Mercuri *et al*., 2022; Oskoui *et al*., 2023). Recent systematic reviews and real-world studies have additionally shown that risdiplam is associated with stabilization or improvement of motor and respiratory outcomes in both pediatric and adult SMA populations, particularly when treatment is initiated early (Giess *et al*., 2024; Pascual-Morena *et al*., 2024).

Given the high cost and chronic nature of these therapies, healthcare systems have implemented pharmacoclinical governance frameworks to ensure appropriate use (Facey *et al*., 2020). In Spain, risdiplam is reimbursed under a national pharmacoclinical protocol that defines eligibility criteria based on SMA subtype, *SMN2* copy number and clinical characteristics and mandates structured data collection within registry-based systems (Ministerio de Sanidad, 2024). These protocols are closely linked to national monitoring initiatives, such as VALTERMED,

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which aim to generate real-world evidence and support reimbursement decisions.

Within this framework, hospital pharmacists play a central role in validating eligibility criteria, ensuring appropriate prescribing and maintaining the integrity of pharmacoclinical registries. However, the effectiveness of such governance models depends not only on clinical adherence but also on the completeness and quality of recorded data.

Despite increasing use of risdiplam in routine clinical practice, evidence on its implementation within protocol-based healthcare systems remains limited. In particular, there is a lack of data on pharmacoclinical adherence and registry completeness in real-world hospital settings. Recent multicenter real-world cohorts have highlighted the growing importance of long-term registry-based evaluation of risdiplam effectiveness and tolerability in adult SMA patients (Parmova *et al*., 2026; Jaworek *et al*., 2025).

Therefore, the present study aimed to evaluate real-world use of risdiplam, assess adherence to the Spanish national pharmacoclinical protocol and analyze registry completeness in a hospital pharmacy setting.

MATERIALS AND METHODS

Study design and setting

This retrospective observational case series was conducted in a tertiary care hospital within the Spanish National Health System. The study was designed as a pharmacoclinical audit using data from institutional registries linked to national monitoring systems.

Study duration

The study included patients treated with risdiplam between January 2022 and December 2025.

Study population

All patients with a confirmed diagnosis of SMA who were receiving risdiplam and were recorded in institutional pharmacoclinical registries were included. A flow diagram summarizing patient identification, eligibility assessment and final inclusion is provided in figure 1.

Data collection

Data were extracted from structured pharmacoclinical registries and included:

- Demographic variables (age, sex).
- Age at treatment initiation.
- SMA clinical subtype.
- SMN2 copy number.
- Confirmation of clinical and genetic diagnosis.
- Treatment initiation and continuation status.
- Therapy sequence (first-line or switch from nusinersen).

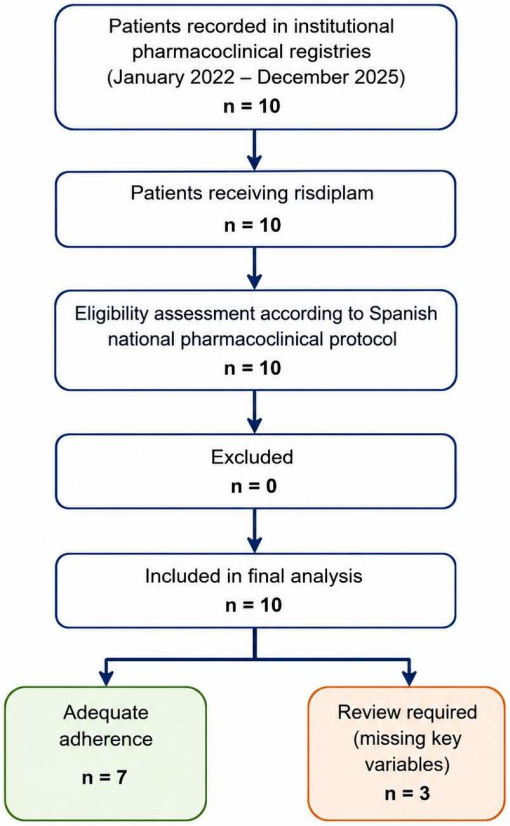

Fig. 1: Flowchart of patient selection and analysis. All patients recorded in the institutional pharmacoclinical registries who received risdiplam during the study period (January 2022–December 2025) were included in the analysis. No patients were excluded. Seven patients fulfilled all protocol eligibility criteria and documentation requirements, whereas three required review because of missing key registry variables.

Patients were categorized as pediatric (≤15 years) or adult (>15 years), consistent with national protocol definitions.

Assessment of protocol adherence

Adherence classification was defined operationally based on compliance with the Spanish national pharmacoclinical protocol criteria (Ministerio de Sanidad, 2024). Patients with complete fulfillment and documentation of all eligibility criteria were categorized as "adequate adherence", whereas patients with missing key variables were categorized as "review required".

Protocol adherence was evaluated according to Spanish national pharmacoclinical criteria (Ministerio de Sanidad, 2024), including:

- Exclusion of SMA types 0 and IV.
- Eligibility of presymptomatic patients with 1–3 SMN2 copies.
- Eligibility of SMA types II–III with ≤4 SMN2 copies.
- Mandatory confirmation of genetic diagnosis.

Table 1: Individual patient-level pharmacoclinical dataset.

	Age group	SMA subtype	SMN2 copies	Genetic confirmation	Treatment line	Protocol adherence	MA	Persistence
1	Pediatric	Type II	3	Yes	Switch	Adequate	No	Yes
2	Pediatric	Type II	4	Yes	Switch	Adequate	No	Yes
3	Pediatric	Type II	3	Yes	First-line	Adequate	No	Yes
4	Pediatric	Type III	4	Yes	First-line	Adequate	No	Yes
5	Pediatric	Presymptomatic	3	Yes	First-line	Adequate	No	Yes
6	Pediatric	Not recorded	NA	No	Switch	Review required	Yes	Yes
7	Adult	Type II	4	Yes	Switch	Adequate	No	Yes
8	Adult	Type III	4	Yes	Switch	Adequate	No	Yes
9	Adult	Not recorded	NA	No	Switch	Review required	Yes	Yes
10	Adult	Not recorded	NA	No	First-line	Review required	Yes	Yes

Footnote: MA: Missing Data. Data are presented at the individual patient level. Age group was categorized according to national protocol criteria (≤15 years pediatric; >15 years adult). Protocol adherence was defined according to Spanish pharmacoclinical criteria. "Review required" indicates missing key eligibility variables (SMA subtype, SMN2 copy number, or diagnostic confirmation). Persistence was defined as ongoing treatment at last follow-up.

Patients were classified into:

- Adequate adherence: complete documentation and fulfillment of criterio.
- Review required: incomplete key variables.

Analysis

No statistical software was required because only descriptive analysis was performed. Descriptive analysis was performed. Given the small sample size, no inferential statistical analysis was conducted. Results are presented as counts and proportions.

RESULTS

Ten patients treated with risdiplam were identified in the pharmacoclinical registries. The study flow is presented in figure 1. All patients identified in the institutional pharmacoclinical registry met the inclusion criteria and were included in the final analysis.The cohort included both pediatric and adult patients, reflecting the heterogeneous population typically observed in real-world SMA management. Age at treatment initiation showed substantial variability, indicating that risdiplam is used across different stages of disease progression (Table 1).

SMA phenotype distribution showed predominance of type II patients, followed by type III and one presymptomatic patient. In three cases (30%), SMA subtype was not recorded in the registry, representing a relevant documentation gap.

SMN2 copy number was documented in seven patients and ranged from three to four copies. All recorded values were consistent with national protocol eligibility criteria. In three patients, SMN2 copy number was not documented. All patients with complete data fulfilled protocol eligibility criteria. No cases of treatment outside protocol-defined indications were identified. However, three patients (30%) were classified as requiring review due to missing key variables, including SMA subtype, SMN2 copy number or diagnostic confirmation.

Treatment patterns reflected real-world clinical practice. Sixty percent of patients had previously received nusinersen, indicating frequent switching from intrathecal to oral therapy (Hagenacker *et al*., 2020). Risdiplam was used in both pediatric and adult patients, suggesting broad implementation across different age groups.

Treatment persistence was high, with no discontinuations recorded during follow-up. The observed 100% treatment persistence may reflect favorable treatment acceptability, reduced administration burden associated with oral therapy and the absence of repeated intrathecal procedures required for nusinersen administration. All patients remained on therapy at last evaluation, suggesting sustained clinical acceptance and tolerability.

DISCUSSION

This study provides real-world evidence on the pharmacoclinical implementation of risdiplam within a national protocol framework from a hospital pharmacy perspective. The results demonstrate high adherence to protocol criteria among evaluable patients, supporting appropriate clinical use in routine practice.

A key finding was incomplete registry documentation in 30% of patients. Importantly, these gaps were not associated with inappropriate treatment selection but rather with limitations in data recording. This distinction is critical, as registry completeness directly affects the ability to evaluate pharmacoclinical adherence and real-world effectiveness. Incomplete registry documentation may additionally compromise pharmacoeconomic analyses, long-term reimbursement monitoring, regulatory

evaluations and comparative effectiveness research in rare diseases, where registry-based evidence frequently supports healthcare decision-making (Facey *et al*., 2020).

The observed differences in documentation may be explained by the route of administration. Nusinersen requires hospital-based intrathecal administration and multidisciplinary follow-up, which promotes structured data capture. In contrast, risdiplam is administered orally in outpatient settings, potentially reducing the intensity of registry documentation. Similar patterns have been reported in rare-disease registries, where differences in care pathways influence data completeness (Facey *et al*., 2020). Within the Spanish National Health System, structured pharmacoclinical governance mechanisms, including multidisciplinary evaluation, mandatory institutional validation procedures and registry-linked reimbursement monitoring, likely contribute to the absence of off-protocol prescribing observed in this cohort.

Treatment persistence was uniformly high, with no discontinuations observed. Although functional outcomes were not available, treatment persistence is widely accepted as an indirect indicator of effectiveness and tolerability in chronic diseases (Schneeweiss, 2019). The absence of discontinuities suggests sustained perceived benefit. Recent observational studies have similarly reported high treatment satisfaction, stabilization of motor function and favorable tolerability profiles with risdiplam in adult SMA populations (Bjelica *et al*., 2024; Keritam *et al*., 2025). Compared with nusinersen, risdiplam may provide additional practical advantages, including outpatient oral administration, avoidance of repeated lumbar punctures and potentially improved convenience for both pediatric and adult patients. These characteristics may contribute to high treatment persistence and patient acceptability in routine clinical practice.

Switching from nusinersen to risdiplam was frequent, reflecting evolving treatment strategies. This likely reflects differences in administration burden rather than efficacy, as described in previous real-world studies (Hagenacker *et al*., 2020). The convenience of oral administration has consistently emerged as a major determinant of patient preference and treatment continuation in recent real-world studies comparing risdiplam with intrathecal therapies (Jaworek *et al*., 2025; Cesarone *et al*., 2026).

From a hospital pharmacy perspective, these findings highlight the importance of structured pharmacoclinical monitoring systems. Registry completeness is essential for evaluating treatment effectiveness, supporting reimbursement decisions and ensuring appropriate use of high-cost therapies.

The study has several limitations inherent to retrospective registry-based case series design. The sample size was small and derived from a single center. Functional outcome measures were unavailable, limiting a direct assessment of effectiveness. Registry incompleteness also reduced evaluability in some cases. Future multicenter studies with standardized functional outcome measures and harmonized registry collection may help overcome these limitations and improve comparative real-world evaluation of SMA therapies.

CONCLUSION

Risdiplam was implemented in routine clinical practice in accordance with the Spanish national pharmacoclinical protocol in all evaluable patients. The main limitation identified was incomplete registry documentation rather than inappropriate prescribing. These findings highlight the importance of standardized pharmacoclinical registries and reinforce the role of hospital pharmacists in ensuring appropriate implementation and monitoring of high-cost therapies in spinal muscular atrophy.

Overall, risdiplam was used in accordance with national pharmacoclinical criteria in all evaluable patients in this real-world hospital cohort. The main limitation identified was incomplete registry documentation rather than inappropriate clinical use.

These findings highlight the importance of standardized pharmacoclinical data capture and reinforce the role of hospital pharmacy in ensuring appropriate implementation of rare-disease therapies.

Acknowledgments
The authors acknowledge the use of an artificial intelligence-based language tool (ChatGPT, OpenAI) for minor language editing and to improve linguistic clarity. No AI tool was used for data analysis, interpretation, or scientific decision-making. All authors are fully responsible for the content of the manuscript.

Authors' contributions
RL: Conceptualization, study design, data análisis and manuscript drafting; CB: Data collection, review and editing. All authors approved the final manuscript.

Funding
There was no funding.

Data availability statement
The datasets generated during the current study are available from the corresponding author on reasonable request.

Ethical Statement
This retrospective observational study used fully anonymized data routinely collected during clinical practice. According to the applicable institutional and

national regulations, formal Ethics Committee approval was not required for this type of study. Therefore, no ethics committee approval or exemption was requested. This study was performed in adherence with the RECORD guidelines. See supplementary file for the RECORD checklist.

Conflict of interest

The authors declare no conflict of interest.

Supplementary data

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