MethodsX 16 (2026) 103771

Contents lists available at ScienceDirect

MethodsX

journal homepage: www.elsevier.com/locate/methodsx

Knowledge, support, and networking for Phelan-McDermid syndrome: a study protocol

Luca Colnaghi [a,b], Giulia Villa [c], Ilaria Marcomini [c,*], Andrea Poliani [c], Maya Fedeli [d], Claudio Losi [e], Debora Rosa [c], Duilio Fiorenzo Manara [c]

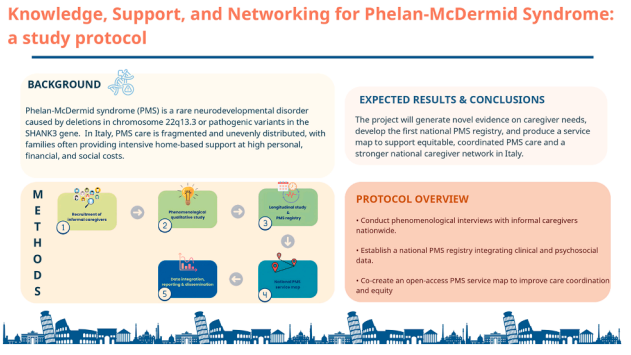
[a] Division of Neuroscience, IRCCS San Raffaele Scientific Institute, Milan, Italy
[b] School of Medicine, Vita-Salute San Raffaele University, Milan, Italy
[c] Center for Nursing Research and Innovation, Faculty of Medicine and Surgery, Vita-Salute San Raffaele University, Milan, Italy
[d] Research Policy Office, Research Development Area, Vita-Salute San Raffaele University, Milan, Italy
[e] Associazione Italiana per la Sindrome di Phelan-McDermid, Piazza Achille Leoni 5 - Rovereto (TN) 38068 Italy

PROTOCOL OVERVIEW

- Conduct phenomenological interviews with informal caregivers nationwide.
- Establish a national PMS registry integrating clinical and psychosocial data.
- Co-create an open-access PMS service map to improve care coordination and equity

GRAPHICAL ABSTRACT

Graphical abstract.



ARTICLE INFO

Keywords:
Phelan-McDermid syndrome
Rare diseases
Informal caregivers
Participatory research
National disease registry

ABSTRACT

Background: Phelan-McDermid syndrome (PMS) is a rare neurodevelopmental disorder caused by deletions in chromosome 22q13.3 or pathogenic variants in the SHANK3 gene. Individuals present with intellectual disability, autism-spectrum traits, seizures, gastrointestinal and motor issues, and sleep disturbances, requiring lifelong multidisciplinary care. In Italy, PMS care is

Related research article: None

* Corresponding author:.
E-mail address: marcomini.ilaria@unisr.it (I. Marcomini).

https://doi.org/10.1016/j.mex.2025.103771
Received 30 October 2025; Accepted 15 December 2025
Available online 16 December 2025

fragmented and unevenly distributed, with families often providing intensive home-based support at high personal, financial, and social costs.
Methods: This national participatory Citizen-Science study, conducted with the Italian Phelan-McDermid Syndrome Association (AISPHEM), will engage informal caregivers of individuals with genetically confirmed PMS across Italy. A qualitative phase using semi-structured online interviews will explore caregiving experiences, unmet needs, barriers to care, coping strategies, and social isolation. Insights will guide the creation of the first Italian PMS registry, capturing longitudinal clinical, socio-demographic, and caregiver-related data.
Expected Results & Conclusions: The project will generate novel evidence on caregiver needs, develop the first national PMS registry, and produce a service map to support equitable, coordinated PMS care and a stronger national caregiver network in Italy.

Specifications table

This table provides general information on your protocol.

Subject area	Medicine and Dentistry
More specific subject area	Rare diseases; neurodevelopmental disorders; caregiver research; participatory citizen science
Name of your protocol	Knowledge, Support, and Networking for Phelan-McDermid Syndrome: a study protocol
Experimental design	The study is designed as a mixed-methods, multi-phase participatory research project adopting a Citizen Science approach in collaboration with the Italian Phelan-McDermid Syndrome Association (AISPHEM). It combines semi-structured qualitative interviews with informal caregivers, the development of a national Phelan-McDermid Syndrome (PMS) registry to collect longitudinal clinical, socio-demographic, and caregiver-related data, and the co-creation of an open-access PMS service map integrating healthcare, educational, and social resources.
Trial registration	Not applicable
Ethics	This study was reviewed and approved by the Territorial Ethics Committee CET1 Lombardia (Approval No [234/2025], dated [09/07/2025]). All procedures comply with the Declaration of Helsinki, the ICH-GCP guidelines, and applicable Italian and European regulations. Informed consent will be obtained electronically from all participants before enrolment
Value of the Protocol	1-Establishes the first national registry for Phelan-McDermid syndrome in Italy, integrating clinical and caregiver data. 2-Generates evidence on the lived experience, needs, and psychosocial burden of informal caregivers. 3-Co-produces a national PMS service map to improve care coordination, accessibility, and equity across regions.

Background

Phelan-McDermid syndrome (PMS) is a rare neurodevelopmental disorder primarily caused by terminal deletions in the 22q13.3 chromosomal region or by pathogenic variants in the SHANK3 gene [1]. The SHANK3 protein is crucial for synaptic organization and neuronal signaling, and its disruption is considered the leading cause of the cognitive, behavioral, and motor abnormalities observed in affected individuals [2–4]. The estimated prevalence of PMS is about 1 in 20,000 live births. However, this number is likely an underestimate due to significant phenotypic variability, incomplete penetrance of some SHANK3 variants, and historically limited access to advanced genetic testing [5].

Clinical presentation of PMS is notably broad and often changes over the lifespan. In infancy, common signs include neonatal hypotonia, feeding difficulties, and global developmental delay [6]. As children grow, many develop intellectual disabilities, autism-spectrum behaviors, language impairments, motor and gastrointestinal issues, seizures, and sleep disturbances [7]. Most children with PMS are non-verbal or have extremely limited speech, which profoundly affects communication, social interaction, and daily functioning. In adulthood, intellectual disability usually persists, while behavioral and psychiatric challenges, chronic medical complications, and the loss of pediatric specialist follow-up create additional complexities [2,8,9]. This evolving clinical profile demands ongoing, flexible, multidisciplinary care for families, caregivers, and healthcare systems.

Despite these needs, PMS care remains fragmented. In Italy, as in many countries, diagnostic and treatment pathways differ markedly between regions, with rural and southern areas often experiencing reduced access to genetic testing, specialised rehabilitation, domiciliary assistance, and coordinated transitional care [10]. Families may have to travel long distances or forgo recommended interventions because of logistical and financial barriers [11]. Equally under-recognised is the experience of informal caregivers (typically parents or close relatives) who provide intensive, long-term home-based support. Many of these caregivers reduce or abandon employment to care for their family member, resulting in consequent financial strain, heightened stress, and social isolation [12]. These caregivers frequently report a lack of respite services, difficulties navigating fragmented healthcare structures and limited guidance on daily symptom management [9,13]. Although their well-being is crucial to the quality of patient care, research addressing their needs remains scarce.

Furthermore, the lack of a centralized, standardized registry for PMS cases worsens the problem: without systematic data collection, it is difficult to describe the natural progression of the syndrome, analyse comorbidity patterns over time, or allocate resources effectively [14].

Improving PMS management, therefore, requires a multi-pronged strategy. Strengthening links with specialised centres,

simplifying pathways to multidisciplinary expertise and building clear referral networks are essential to enhance outcomes [11].

In light of these challenges, the current protocol outlines a family-centred, participatory research project to address the most pressing gaps in PMS care in Italy. The study combines several approaches: a qualitative exploration of caregivers' experiences and longitudinal data collection within a national registry, capturing both the personal and clinical dimensions of PMS care. The study primarily focuses on informal caregivers because the majority of individuals with PMS have severe intellectual disability and limited or absent verbal communication, which substantially restricts their ability to participate in qualitative research and self-report outcomes directly. Caregivers, therefore, represent the most reliable and ethically appropriate source of information on daily functioning, care needs, service utilization, and quality-of-life impacts for people living with PMS. It also includes co-creating a service map to help families and professionals navigate the often fragmented network of available resources. Together, these components aim to generate actionable evidence for clinicians, empower families as active partners in research and advocacy, and lay the groundwork for more integrated and equitable care pathways for individuals living with PMS.

Description of protocol

Aims

The study will aim to improve PMS management across Italy by involving families in a participatory research process that will actively engage them in shaping care pathways and research priorities. Specifically, the primary outcome of the study will be the feasibility of the Italian PMS registry, assessed through enrollment rates, geographic representativeness, and completeness of pre-defined core variables. Secondary outcomes will include the longitudinal clinical and functional characterization of individuals with PMS, the description of diagnostic and care pathways over time, caregiver-reported burden, and unmet needs. In addition, a qualitative component will explore in depth the lived experiences, perceptions, and daily challenges of informal caregivers of people living with PMS, providing a comprehensive understanding of caregiving trajectories and contextual factors that may not be captured through quantitative measures alone.

Study design

The project will adhere to the principles of Citizen Science methodology [15]. This approach actively involves non-professional participants (in this case, caregivers and families of individuals with PMS) throughout all stages of the research. Caregivers will not be viewed solely as study subjects but as co-creators of knowledge, sharing their lived experiences and insights to ensure that the research questions, outcomes, and tools address real-world priorities and challenges [16]. The central partner in this process will be the Italian Association for Phelan-McDermid Syndrome (AISPHEM), which will facilitate recruitment, support communication with families, and collaborate in the co-design and dissemination of study materials. The active involvement of AISPHEM is expected to strengthen trust between researchers and participants, improve accessibility for geographically dispersed families, and enhance the relevance and impact of the project's outputs. By integrating caregivers' perspectives and AISPHEM's organisational expertise, this participatory approach seeks to bridge the gap between scientific evidence and the everyday needs of affected families, fostering inclusivity, transparency, and shared ownership of the results. Ultimately, this collaboration aims to generate findings that are not only scientifically robust but also directly applicable to improving clinical care, service delivery, and policy decision-making for individuals living with PMS.

This study will be developed in five sequential yet interrelated phases. The first phase will focus on the nationwide recruitment of informal caregivers of individuals with a confirmed diagnosis of PMS.The second phase will consist of a phenomenological qualitative study, inviting informal caregivers to participate in individual semi-structured interviews. The third phase will involve a descriptive longitudinal study, including the establishment of a condition-specific PMS registry based on baseline data. Data will be collected directly from caregivers and will include clinical information on individuals with PMS, as well as socioeconomic factors, caregiver burden, burnout, and other caregiving characteristics, with follow-up assessments conducted for research purposes.In the fourth phase, families, caregivers, and healthcare professionals will co-design a dedicated PMS service map, informed by findings from the qualitative and longitudinal components. This interactive tool will support families and providers in navigating the often fragmented healthcare and social service landscape and will aim to improve access, coordination, and equity of care.The fifth and final phase will focus on data integration, interpretation, and dissemination, ensuring that study findings are shared with families, clinicians, policymakers, and the scientific community, and translated into practical recommendations to improve PMS management and caregiver support. The overall duration of the study will be 24 months

Eligibility criteria

The project has a national scope and will involve collecting data from informal caregivers of individuals with PMS across Italy. The actual geographic coverage of the study will depend on the distribution of enrolled participants, who will be identified through the networks of the AISPHEM and through snowball sampling.

Participants will be enrolled if they are: (a) adults aged 18 or older, (b) providing ongoing, unpaid care at home to a family member or another individual with a confirmed PMS diagnosis, and (c) able to demonstrate sufficient proficiency in Italian to understand the study materials and give informed consent fully. More than one informal caregiver from the same family may participate in the study, provided that each meets the inclusion criteria and gives individual informed consent. This approach acknowledges the shared, often

distributed nature of caregiving within families and enables the capture of complementary perspectives on caregiving roles and burden. Caregivers will be excluded if they are (a) professional or paid caregivers, (b) provide only occasional or non-continuous care, or (c) are unable to provide informed consent due to insufficient language proficiency or cognitive impairment.

Sample size determination

In the qualitative component, the sample size cannot be precisely predetermined because it is guided by the principle of data saturation, which is reached when additional interviews no longer provide new relevant insights [17]. Based on the research team's experience and aligned with the recommendations of Sandelowski [18], approximately 20 interviews are expected to be sufficient to achieve theoretical saturation. Participants will be selected using purposive sampling to capture a wide range of caregiving experiences. This approach will ensure representation of different caregiving roles, including parents and other informal family caregivers such as siblings or grandparents; different life stages of individuals with PMS, with particular attention to the transition from pediatric to adult care; and diverse geographic and service contexts across Northern, Central, and Southern Italy. Together, these criteria will allow for a rich and nuanced understanding of caregivers' experiences across settings and stages of care. To provide an a priori estimate of the minimum sample size for the main quantitative objective, we conducted a power analysis in G*Power for a linear multiple regression model with caregiver burden as the dependent variable (F test: linear multiple regression, fixed model, R^2 deviation from zero). Assuming a medium effect size (Cohen's $f^2 = 0.15$), $\alpha = 0.05$, and $1–\beta = 0.80$, a minimum sample size of approximately 92 participants is required for a model including five predictors. Models including a larger number of predictors would require proportionally larger samples. Given the rarity of PMS, model complexity will therefore be adapted to the achieved sample size, prioritising parsimonious models and estimation with confidence intervals. Although the study aims to include all eligible caregivers who consent to participate, heterogeneity will be actively monitored throughout recruitment. Recruitment will be supported by AISPHEM and conducted across different Italian regions, care settings, and family contexts. If early enrolment shows over-representation of specific subgroups (e.g., families from a single geographic area or caregiving role), targeted recruitment strategies will be implemented to encourage participation from under-represented groups, thereby enhancing diversity in caregiving experiences and contexts. The recruitment strategy will therefore focus not only on maximizing enrolment within the recruitment period but also on ensuring a heterogeneous sample that reflects the variability of the PMS caregiving population.

Study variables

The project will collect a comprehensive set of variables across its qualitative, longitudinal, and service-mapping components to capture the multidimensional impact of PMS on caregivers.

For the qualitative phase, variables are exploratory and include daily caregiving challenges, unmet needs, perceived barriers to accessing services, coping strategies, and the emotional and social consequences of long-term caregiving.

The longitudinal component is guided by the Stress-Process Model of Caregiving developed by Pearlin et al. [19], which conceptualises caregiving as a dynamic process in which the caregiver's well-being is shaped over time by the interplay between stressors and protective factors. According to this model, primary stressors arise directly from the health condition of the care recipient. Secondary stressors capture the broader repercussions of caregiving on other areas of life, including social isolation, financial strain due to out-of-pocket expenses, and conflicts between caregiving responsibilities and family or occupational roles. These stressors influence the caregiver's physical and psychological health and quality of life, while mediating factors such as perceived social support, coping strategies and access to services can buffer or exacerbate their impact.

Guided by this framework, the PMS registry will capture an integrated range of variables:

- Patient-level clinical variables (e.g., age, gender, year of diagnosis, intellectual disability, motor/gastrointestinal disorders, autism-spectrum features, epilepsy, sleep disturbances, hospital admissions, and use of medical devices with related logistical and financial barriers).
- Contextual and socio-demographic variables (educational attainment, household economic conditions, living environment, activation of home-care services, hours spent bedridden).

Table 1
Variables.

Domain	Variables Collected
Caregiver experiences	Daily caregiving challenges, unmet needs, perceived barriers, coping strategies, emotional and social impact
Patient socio-demographics	Age, phenotyping of the disease, sex, year of PMS diagnosis, educational history, living environment
Patient clinical profile	Intellectual disability, motor & gastrointestinal disorders, autism-spectrum features, epilepsy, sleep disturbances, comorbidities, hospital admissions (reason, number, length), hours spent bedridden, use of medical devices and related costs/barriers
Caregiver socio-demographics	Age, sex, employment status, caregiving workload (weekly hours, types of support), household income/economic conditions
Caregiver well-being	Perceived social isolation, psychological impact of caregiving, overall quality of life
Service availability	Clinical centres, educational/rehabilitation/psychological services, community networks, patient associations, accessibility and referral pathways

- Caregiver-level variables, including socio-demographics (age, gender, employment status), workload (weekly hours of direct care, types of support provided), pre-existing psychological or medical conditions, perceived social isolation, quality of life, and psychological well-being.

For the service-mapping phase, variables will include the geographic distribution and type of available clinical, rehabilitative, educational, psychological, and community-based services, as well as their accessibility and referral pathways. The variables to be collected in the study are summarised in Table 1.

Procedures

The project will be conducted in five sequential yet interdependent phases, each designed to address a specific aspect of PMS Syndrome care while collectively capturing its multidimensional impact on affected families.

Phase 1: Recruitment of Informal Caregivers. The first phase will focus on recruiting informal caregivers of individuals with a confirmed PMS diagnosis. The AISPHEM Association will support this recruitment by disseminating study invitations through its website and communication channels to reach families providing continuous home-based care.

Phase 2: Phenomenological Qualitative Study. In the second phase, we will explore in depth the lived experiences of informal caregivers. The interview guide (Supplementary Material) is designed to capture the dyadic nature of caregiving, examining the reciprocal influence between the caregiver's experience and the patient's well-being and clinical stability. Furthermore, the interviews explicitly investigate the families' trajectory through the diagnostic journey and the subsequent care pathway, identifying the challenges, support needs, and turning points encountered from the onset of symptoms to long-term management. Semi-structured interviews will be conducted online to maximize accessibility for participants across Italy. The interviews will be conducted by experts in qualitative methodology (MNS or PhD) and will be audio-video recorded, with the participants' consent.

Phase 3: Descriptive longitudinal study and development of a PMS registry. The third phase of the project will involve establishing a national PMS registry aimed at capturing both clinical and contextual information on individuals living with PMS in Italy. The registry will be constituted using the baseline (T0) data collected within the longitudinal observational study and will represent a standardized snapshot of individuals with PMS at the time of enrolment.The longitudinal follow-up assessments (T1, T2) are not intended to populate the registry, but are included exclusively for research purposes, to describe temporal patterns in caregiver-reported outcomes. In parallel, the protocol includes a descriptive longitudinal observational study conducted on a defined cohort of caregiver–patient dyads, with data collected at baseline (T0) and at two follow-up time points at six-month intervals (T1, T2). For this study, data will include immutable baseline characteristics of individuals with PMS, such as age, gender, year of diagnosis, and comorbidities, as well as repeated assessments over time. Six-month follow-up intervals were selected to explore whether caregiver-reported burden varies over time in relation to the duration and cumulative demands of caregiving, rather than to assess acute clinical changes or intervention effects. At each assessment,caregivers will report new comorbidities, major PMS-related health problems (including intellectual disability, motor and gastrointestinal disorders, autism-spectrum features, epilepsy, and sleep disturbances), the use of medical devices (e.g., percutaneous endoscopic gastrostomy, ventilators, urinary catheters, tracheostomy), difficulties obtaining device supplies and associated out-of-pocket costs, hours spent bedridden during the day, activation of home-care services, and details of hospital admissions in the preceding six months including the reason for admission, number of stays, and length of stays. We will also record contextual variables to characterize the living environment, including educational history, household economic conditions, and caregiver workload expressed in weekly hours of direct care and types of support provided. Additionally, we will collect parallel data on the caregivers themselves, including age, gender, employment status, pre-existing emotional or psychological conditions, the psychological impact of caregiving, perceived social isolation, and overall quality of life. Perceived social isolation is included due to its recognised role as a key determinant of caregiver burden and a risk factor for adverse mental and physical health outcomes. To assess caregivers' quality of life, psychological well-being, burden, and social connectedness, validated instruments will be used. Overall quality of life will be assessed using the World Health Organization Quality of Life – BREF (WHOQOL-BREF) [20], a widely used questionnaire that evaluates physical health, psychological well-being, social relationships, and environmental domains. Caregiver burden will be measured using the Zarit Burden Interview (ZBI) [21], a validated instrument specifically designed to capture the perceived impact of caregiving on emotional, physical, social, and financial domains.Perceived loneliness will be assessed using the De Jong Gierveld Loneliness Scale (DJG-LS) [22], which measures emotional and social loneliness, while perceived social isolation and social network size will be evaluated using the Lubben Social Network Scale (LSNS-6) [23], a brief and validated tool assessing the strength and frequency of social ties with family and friends. Together, these instruments will provide a comprehensive assessment of caregivers' well-being, burden, and social resources. Before full implementation, a pilot test will be conducted with a small group of informal caregivers (a maximum of four), in collaboration with AISPHEM, to assess the clarity, relevance, and feasibility of the questionnaires and study procedures. Pilot participants will be asked to complete the baseline survey and provide structured feedback on item comprehensibility and relevance to their caregiving experience. Pilot data will not be included in the final analyses.For the longitudinal component, participants will be assigned a unique study identifier at baseline, allowing responses to be linked across time points while preserving anonymity. Follow-up surveys at T1 and T2 will be distributed through automated email invitations generated by the study platform, each containing a personalised survey link. Automated reminder emails will be sent at predefined intervals to participants who have not completed follow-up assessments. Where appropriate and with participants' consent, AISPHEM will support engagement by disseminating general reminders through its communication channels, without access to individual-level data.All data will be collected via Microsoft Forms and stored on secure Microsoft servers compliant with the General Data Protection Regulation (GDPR). Access to raw data will be restricted to authorised members of the research team through role-based permissions and

password-protected accounts. Data will be exported to encrypted institutional storage systems for analysis, with regular backups performed. All analytical datasets will be fully anonymised, and personal identifiers will be stored separately in accordance with institutional and regulatory requirements.Clinical and contextual information on individuals with PMS will be collected exclusively through caregiver report; verification against medical records is not planned due to ethical, logistical, and regulatory constraints. To enhance data quality, the study will employ standardised questionnaires, predefined response formats, clear instructions, and internal consistency checks during data cleaning and analysis.

Phase 4: Findings from both the qualitative and longitudinal components will inform the creation of a dedicated, interactive PMS service map. Data for the map will be gathered through multiple complementary channels: insights provided directly by caregivers during interviews and surveys, information shared by AISPHEM, and direct outreach to specialised reference centres and community-based facilities to verify and update service details.

The resulting map will catalogue specialised clinical centres, as well as educational, rehabilitative, psychological support services, and community-based networks and patient associations operating across Italy. Services will be included in the map if they meet predefined criteria, including: (i) formal recognition within the public or accredited private healthcare, educational, or social care system; (ii) documented experience or declared expertise in supporting individuals with PMS or comparable rare neurodevelopmental conditions; and/or (iii) regular accessibility to families (e.g., availability of outpatient, community-based, or remote services). Both national and regional services will be included, provided that their scope, referral requirements, and geographic coverage can be clearly specified. Given the study's focus on caregiver well-being, the map will also include general mental health and psychosocial support services accessible to caregivers, even when not PMS-specific, where these are identified as relevant within caregiver-reported care trajectories. Integrated into the AISPHEM website, this open-access resource will enable families and healthcare professionals to navigate available services and facilitate timely referrals more easily.

Phase 5: Data Integration, Reporting, and Dissemination. The final phase involves integrating and analyzing data from all earlier phases. The results will be interpreted collaboratively by the research team, AISPHEM representatives, and other stakeholders. The study's findings will be shared with families, clinicians, policymakers, and the wider scientific community through detailed reports, scientific presentations, and publicly accessible materials. The aim of this phase is to turn evidence into practical recommendations that support more coordinated, equitable, and evidence-based care for individuals with PMS and their caregivers nationwide.

The study's phases are described in Fig. 1.

Data analysis

For the analysis of interview transcripts, we will use Sundler's reflective thematic analysis method [23], which highlights an open, interpretive approach to participants' lived experiences. Researchers will act as attentive and thoughtful observers, staying aware of how experiences are expressed and maintaining a reflective attitude to boost self-awareness and reduce interpretive bias. The method emphasizes repeated interaction with the data to find meaning units and emerging themes. Data analysis will follow the three phases of reflective thematic analysis as described by Sundler et al. [17]. In the first phase (Preparation), researchers will immerse themselves in the empirical material to understand its content, tone, and context, laying the foundation for subsequent coding and interpretation. During this phase, the recorded material will be transcribed verbatim, and the data will be organized to ensure anonymity. Researchers will then engage in thorough reading and re-reading to familiarize themselves with the content and grasp the overall sense of the data. Finally, they will record initial reflections and impressions, identifying and reflecting on their own biases, expectations, and positions regarding the phenomenon to maintain a rigorous and transparent approach, preventing personal interpretations from distorting the meaning of the collected data.In the second phase (Thematic Organization), researchers will organize the material to identify, group, and define core themes. This involves initial coding, where the text is analyzed line-by-line, assigning labels and codes that represent concepts, emotions, behaviors, and experiences relevant to the research question. Subsequently, the emerging codes will be grouped and compared to ensure internal consistency, followed by theme development to further synthesize and identify central themes. Throughout this phase, researchers will continue to reflect critically on their interpretive role, ensuring that themes remain firmly grounded in the data rather than derived from preconceptions.The third phase (Interpretive Reflection and Reporting) is dedicated to the interpretive synthesis and presentation of findings. Researchers will critically analyze the themes identified in the previous phase, exploring underlying meanings and the connections between different themes and subthemes. A consistency and validity check will then be performed through a systematic review of the internal coherence of each theme and external differentiation to ensure that

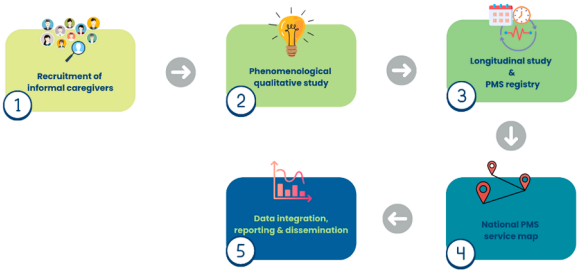


Fig. 1. Phases of the study.

themes are clearly distinct; themes may be renamed during this process. Finally, the results will be presented in a narrative form, supported by exemplary quotes that give voice to the participants and illustrate the meaning of the themes. In this final stage, researchers will reflect on their role in the analytical process to ensure they do not unduly influence the interpretation of the results. To increase rigor, transparency, and analytic efficiency, qualitative data will be managed and analyzed using NVivo software (version 14) immediately after transcription. The analysis will be conducted by at least two researchers who will perform the coding process independently. To ensure consistency and resolve any discrepancies, regular consensus meetings will be held throughout the analytical phase. In accordance with Sundler's reflective thematic analysis [17], inter-coder rigor and reliability will not be quantified through statistical agreement measures; instead, they will be guaranteed through continuous reflective dialogue, peer debriefing, and the maintenance of a transparent audit trail of all analytical decisions. Achieving data saturation will be decided in a collegial meeting of the research group. During the results processing phase, a member checking phase is planned with the interview participants. Consistent with the participatory approach of the study, representatives of AISPHEM will be involved at a later stage of the analytic process through consultative feedback sessions, in which preliminary themes and interpretations will be discussed to enhance relevance, contextual validity, and interpretative resonance, without influencing the initial coding or analytic independence of the research team. Regarding the longitudinal study, descriptive statistics will be used to summarise the socio-demographic, contextual, and clinical characteristics of individuals with PMS and their informal caregivers at baseline and across follow-up assessments. Caregiver burden will be treated as the primary outcome variable in multivariable analyses. Multivariable regression models will be used to explore associations between these predictors and caregiver burden. Given the repeated-measures design, the longitudinal dataset will also enable advanced modelling techniques, including mediation and moderation analyses. Planned mediation analyses will examine whether perceived social support and psychological well-being mediate the relationship between caregiving demands (e.g., hours of care, patient clinical complexity) and caregiver burden. Moderation analyses will explore whether socio-demographic factors (e.g., employment status, household economic conditions) and access to services modify these associations over time. These models will be specified a priori and conducted only if the sample size and data structure allow for stable estimation.All statistical tests will be conducted using a two-sided alpha level of 0.05. Given the exploratory nature of the study and the limited sample size typical of rare disease research, formal adjustments for multiple comparisons will not be systematically applied; however, effect sizes and confidence intervals will be reported to support cautious interpretation of findings.To address missing data, multiple imputation will be used under the assumption of missing at random, complemented by sensitivity analyses, including complete-case analyses and comparisons between participants with complete versus incomplete follow-up data, to assess the robustness of results to different missing data assumptions.

All statistical analyses will be conducted using SPSS (version 26) for descriptive and preliminary inferential tests and Mplus (version 7) for advanced longitudinal modelling, including structural equation models to assess indirect and interaction effects.

Source of bias

Several potential sources of bias have been identified and addressed to ensure the validity and reliability of the study findings.

Given the rarity of PMS and the voluntary nature of participation, there is a risk that caregivers who enroll in the study may differ from those who do not, for example, in terms of motivation, digital literacy, or access to support services. Recruitment in collaboration with AISPHEM, while essential for reaching a geographically dispersed population affected by a rare condition, may result in an over-representation of families already connected to patient advocacy networks, more engaged, and better informed. This may lead to the under-representation of caregivers with fewer resources, limited access to digital tools, or those not affiliated with AISPHEM. To mitigate this risk, recruitment will be conducted nationwide using both association-based and open-access strategies. In addition to dissemination through AISPHEM channels (website, newsletters, webinars), the study will be publicly advertised through open online calls, social media posts, and direct contact with clinical reference centres and healthcare professionals involved in PMS diagnosis and care, to reach families who are not members of patient associations. These complementary approaches are intended to broaden participation and improve the representativeness of caregivers from diverse geographic, socio-economic, and service-access contexts.

A substantial portion of the clinical and contextual data will be self-reported by caregivers, which may introduce recall errors or subjective reporting. To minimise this risk, the study will use validated instruments, standardised electronic forms with predefined fields, and clear instructions for data entry. Formal checks for completeness, accuracy, and internal consistency will be conducted on all questionnaires and interviews, supported by SPSS and NVivo to improve data quality and traceability.

Given the longitudinal design of the registry, loss to follow-up and incomplete responses are anticipated and could introduce bias if participants who discontinue differ systematically from those who remain. Mitigation strategies will include automated reminders, user-friendly online questionnaires, ongoing engagement through AISPHEM, and the application of statistical techniques such as sensitivity analyses and, where appropriate, multiple imputation to address missing data.

To ensure coherence with study objectives and timely identification of critical issues, a structured monitoring system has been established. A shared project timeline (chronogram) will guide all activities, supported by monthly internal reports that summarise progress and propose adjustments. These reports will be discussed during regular meetings between the research team and AISPHEM representatives, strengthening collaboration and maintaining oversight of the scientific, ethical, and operational aspects of the study.

Ethical aspects

This clinical study was reviewed and approved by the Territorial Ethics Committee CET1 Lombardia (Approval No [234/2025], dated [09/07/2025]) prior to initiation. The approval covered the full study protocol, the informed consent documents, and all

associated study materials, in compliance with Italian national regulations and European guidelines.

All procedures will be conducted in accordance with the principles outlined in the Declaration of Helsinki of the 18th World Medical Assembly [24], the ICH Guidelines for Good Clinical Practice [25], and all applicable international and national laws and regulations.

In line with citizen science principles, anonymized interview transcripts will be shared where ethically and legally appropriate. Data will be carefully de-identified to minimize re-identification risks, particularly within rare disease communities. Participants will be informed during consent and may opt in or out of data sharing. Transcripts will be made available as supplementary material or through controlled-access repositories, with access conditions defined collaboratively with citizen and patient representatives.

The investigators will ensure strict adherence to the approved protocol, accurate data recording, and the availability of qualified staff and adequate facilities for the proper and safe conduct of the study. Any deviation undertaken to mitigate an immediate hazard to participants will be documented, justified, and promptly reported to the Ethics Committee, together with any proposed amendments.

Dissemination

The findings of this research will be disseminated to the public and all relevant stakeholders through presentations at national and international conferences, congresses, and symposiums, as well as through publication in peer-reviewed scientific journals. In addition, the research team will prepare a comprehensive final report, which will be presented to families affiliated with the AISPHEM Association to ensure that the results are accessible to those most directly affected by the study. Feedback on the report will be collected and integrated in the final version of the report, in line with the co-creative approach that characterizes the whole project.

All manuscripts, abstracts, and communications arising from the study will require prior approval by the research group. Data included in scientific publications or presented at congresses, conferences, or seminars will be released only after rigorous statistical analysis and will be presented solely in aggregated and anonymised form, in full compliance with privacy and data-protection regulations.

Protocol validation

This project is expected to deliver both new knowledge and practical tools to enhance the quality of care for individuals with PMS and their families. By systematically collecting data on caregivers' needs and lived experiences, it will capture the daily challenges, unmet requirements, and barriers to accessing services, enabling a comprehensive mapping of difficulties reported by all participating caregivers. These insights will provide a robust evidence base for guiding service provision and informing policy decisions.

A key outcome will be the establishment of the first national PMS registry, designed to collect clinical, socio-demographic, and caregiving data on individuals with PMS and their families. This registry will be instrumental in characterising the epidemiology, comorbidity profiles, and care needs of this population and will serve as a resource to guide the development of targeted interventions that promote social inclusion, caregiver support, and equitable healthcare planning.

Additionally, the project will deliver a service map that integrates healthcare, educational, and social resources to enhance the navigation of available services. The map aims to enhance accessibility, coordination, and informed decision-making for families and professionals.

In line with citizen science principles of openness, reuse, and community empowerment, the project will document and share its technical architecture, governance model, consent processes, and engagement tools, enabling other patient communities and organizations to adapt the registry with minimal technical effort. Wherever possible, open standards and interoperable components will be adopted to support reuse across rare disease contexts. In this way, the project aims to function not only as a condition-specific registry, but also as a scalable citizen-science model for strengthening the rare disease ecosystem in Italy.

A central goal of the project is to strengthen connections among families, facilitating the development of a national caregiver network. This network will enable families to share experiences, exchange practical advice, and collectively voice their needs, fostering peer support and advocacy for better services and policies. Through the integration of qualitative insights, longitudinal registry data, and co-designed tools the project aims to deliver a comprehensive, evidence-based picture of the PMS care landscape in Italy. This integrated approach is expected to generate actionable recommendations to enhance equity, accessibility, and care coordination, while also promoting community empowerment and social connectedness among families affected by PMS nationwide.

Limitations

Several limitations should be acknowledged when interpreting the findings of this study.Concerning the qualitative component, the voluntary nature of participation may lead to the over-representation of caregivers who are more motivated, engaged, or willing to share their experiences. Although purposive sampling will be used to ensure heterogeneity of perspectives, the findings may not fully capture the experiences of caregivers who are less connected to support networks or less inclined to participate in interviews. For the longitudinal and registry component, the rarity of PMS inherently constrains the achievable sample size. Although efforts will be made to enroll as many caregivers as possible nationwide, the overall number of participants is expected to remain limited. This may restrict the generalisability of the results and reduce the statistical power of some subgroup and multivariable analyses. In individuals with Phelan–McDermid syndrome, severe language impairment or absence of verbal communication is a core clinical feature. Consequently, self-report of health status and symptoms is not feasible, and caregiver proxy reporting represents the standard and necessary approach for data collection in this study. Caregivers are therefore asked to report on the individual's health conditions based on their

continuous, first-hand observation of daily functioning, clinical events, and healthcare use. Proxy reporting will focus on observable health indicators and care-related experiences, including comorbidities, seizure activity, sleep and feeding difficulties, functional abilities, behavioral manifestations, and interactions with health services. Structured guidance and standardized instruments will be provided to support consistency and accuracy of reporting. While proxy-reported data may entail inherent limitations, it constitutes the most appropriate and ethically sound method for capturing health-related information in this population, and will be reported and interpreted transparently within this context. Missing data represent a further anticipated challenge in the longitudinal component. Given the demands placed on caregivers and the extended follow-up period, incomplete responses and participant attrition are likely to occur over time. Missing information may affect the completeness of the registry and introduce bias into longitudinal analyses. Strategies to address this limitation will include automated reminders for follow-up data entry, user-friendly online questionnaires, and statistical approaches such as sensitivity analyses and, where appropriate, multiple imputation. Finally, regarding the service-mapping component, the completeness and accuracy of the map will depend on the availability and up-to-date status of information provided by caregivers, associations, and service providers. Despite efforts to verify and regularly update service details, some services may be under-represented or subject to changes over time, which should be considered when interpreting and using the map.

CRediT author statement

Conceptualization, L.C., G.V., D.R., I.M., M.F., C.L.; methodology, L.C., G.V., D.R., I.M.; writing—original draft preparation, I.M.; writing—review and editing, G.V., L.C., D.F.M., D.R., M.F., A.P., C.L.; supervision, D.F.M. All authors have read and agreed to the published version of the manuscript.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Acknowledgments

LC, GV, MF, DR, DFM gratefully acknowledge support from Vita-Salute San Raffaele University. This research received no external funding.

Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.mex.2025.103771.

Data availability

No data was used for the research described in the article.

References

[1] A. Kolevzon, B. Angarita, L. Bush, A.T. Wang, Y. Frank, A. Yang, R. Rapaport, J. Saland, S. Srivastava, C. Farrell, L.J. Edelmann, J.D. Buxbaum, Phelan-McDermid syndrome: a review of the literature and practice parameters for medical assessment and monitoring, J. Neurodev. Disord. 6 (2014) 39, https://doi.org/10.1186/1866-1955-6-39.

[2] O. Bozdagi, T. Sakurai, D. Papapetrou, X. Wang, D.L. Dickstein, N. Takahashi, Y. Kajiwara, M. Yang, A.M. Katz, M.L. Scattoni, M.J. Harris, R. Saxena, J. L. Silverman, J.N. Crawley, Q. Zhou, P.R. Hof, J.D. Buxbaum, Haploinsufficiency of the autism-associated Shank3 gene leads to deficits in synaptic function, social interaction, and social communication, Mol. Autism 1 (2010) 15, https://doi.org/10.1186/2040-2392-1-15.

[3] A.M. Grabrucker, M.J. Schmeisser, M. Schoen, T.M. Boeckers, Postsynaptic ProSAP/Shank scaffolds in the cross-hair of synaptopathies, Trends Cell Biol 21 (2011) 594–603, https://doi.org/10.1016/j.tcb.2011.07.003.

[4] L. Soorya, A. Kolevzon, J. Zweifach, T. Lim, Y. Dobry, L. Schwartz, Y. Frank, A.T. Wang, G. Cai, E. Parkhomenko, D. Halpern, D. Grodberg, B. Angarita, J. P. Willner, A. Yang, R. Canitano, W. Chaplin, C. Betancur, J.D. Buxbaum, Prospective investigation of autism and genotype-phenotype correlations in 22q13 deletion syndrome and SHANK3 deficiency, Mol. Autism 4 (2013) 18, https://doi.org/10.1186/2040-2392-4-18.

[5] K. Phelan, H.E. McDermid, The 22q13.3 deletion syndrome (Phelan-McDermid Syndrome), Mol. Syndromol. 2 (2011) 186–201, https://doi.org/10.1159/000334260.

[6] K. Phelan, R.C. Rogers, L. Boccuto, in: M.P. Adam, J. Feldman, G.M. Mirzaa, R.A. Pagon, S.E. Wallace, A. Amemiya (Eds.), Phelan-McDermid Syndrome-SHANK3 Related, University of Washington, Seattle, Seattle (WA), 1993. GeneReviews®, http://www.ncbi.nlm.nih.gov/books/NBK1198/ (accessed October 3, 2025).

[7] Y. Frank, The neurological manifestations of Phelan-McDermid syndrome, Pediatr. Neurol. 122 (2021) 59–64, https://doi.org/10.1016/j.pediatrneurol.2021.06.002.

[8] S. De Rubeis, P.M. Siper, A. Durkin, J. Weissman, F. Muratet, D. Halpern, M.D.P. Trelles, Y. Frank, R. Lozano, A.T. Wang, J.L. Holder, C. Betancur, J.D. Buxbaum, A. Kolevzon, Delineation of the genetic and clinical spectrum of Phelan-McDermid syndrome caused by SHANK3 point mutations, Mol. Autism 9 (2018) 31, https://doi.org/10.1186/s13229-018-0205-9.

[9] L. Gizzo, G. Bliss, C. Palaty, A. Kolevzon, Caregiver perspectives on patient-focused drug development for Phelan-McDermid syndrome, Orphanet. J. Rare Dis. 19 (2024) 134, https://doi.org/10.1186/s13023-024-03141-w.

[10] S. Briscoe, C.M. Pintado, K. Sutcliffe, G.J. Melendez-Torres, R. Garside, H.M. Lawal, N. Orr, L. Shaw, J.T. Coon, 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. 20 (2025) 303, https://doi.org/10.1186/s13023-025-03818-w.
[11] S. Srivastava, M. Sahin, J.D. Buxbaum, E. Berry-Kravis, L.V. Soorya, A. Thurm, J.A. Bernstein, A. Asante-Otoo, W.E. Bennett, C. Betancur, T.H. Brickhouse, M. R. Passos Bueno, M. Chopra, C.K. Christensen, J.L. Cully, K. Dies, K. Friedman, B. Gummere, J.L. Holder, A. Jimenez-Gomez, C.A. Kerins, O. Khan, T. Kohlenberg, R.V. Lacro, L.A. Levy, T. Levy, D. Linnehan, E. Loth, B. Moshiree, A. Neumeyer, S.M. Paul, K. Phelan, A. Persico, R. Rapaport, C. Rogers, J. Saland, S. Sethuram, J. Shapiro, P.I. Tarr, K.M. White, J. Wickstrom, K.M. Williams, D. Winrow, B. Wishart, A. Kolevzon, Updated consensus guidelines on the management of Phelan-McDermid syndrome, Am. J. Med. Genet. A. 191 (2023) 2015–2044, https://doi.org/10.1002/ajmg.a.63312.
[12] P. Cardinali, L. Migliorini, N. Rania, The caregiving experiences of fathers and mothers of children with rare diseases in Italy: challenges and social support perceptions, Front. Psychol. 10 (2019) 1780, https://doi.org/10.3389/fpsyg.2019.01780.
[13] C. Bolbocean, F.N. Andújar, M. McCormack, B. Suter, J.L. Holder, Health-related quality of life in pediatric patients with syndromic autism and their caregivers, J. Autism Dev. Disord. 52 (2022) 1334–1345, https://doi.org/10.1007/s10803-021-05030-8.
[14] L. Asta, A. Ricciardello, F. Cucinotta, L. Turriziani, M. Boncoddo, F. Bellomo, J. Angelini, M. Gnazzo, G. Scandolo, G. Pisanò, F. Pelagatti, F. Chehbani, M. Camia, A.M. Persico, Clinical, developmental and serotonemia phenotyping of a sample of 70 Italian patients with Phelan-McDermid syndrome, J. Neurodev. Disord. 16 (2024) 57, https://doi.org/10.1186/s11689-024-09572-7.
[15] M. Haklay, A. Motion, B. Balázs, B. Kieslinger, B.Greshake Tzovaras, C. Nold, D. Dörler, D. Fraisl, D. Riemenschneider, F. Heigl, F. Brounéus, G. Hager, K. Heuer, K. Wagenknecht, K. Vohland, L. Shanley, L. Deveaux, L. Ceccaroni, M. Weißpflug, M. Gold, M. Mazzonetto, M. Mačiulienė, S. Woods, S. Luna, S. Hecker, T. Schaefer, T. Woods, U. Wehn, ECSA's characteristics of citizen science, (2020). https://doi.org/10.5281/ZENODO.3758668.
[16] G. Villa, D. Rosa, I. Marcomini, A. Poliani, P.R. Spena, R. Buccione, D.F. Manara, M. Fedeli, Community-driven research: exploring the potential of citizen science in nursing, Int. J. Nurs. Stud. 169 (2025) 105125, https://doi.org/10.1016/j.ijnurstu.2025.105125.
[17] A.J. Sundler, E. Lindberg, C. Nilsson, L. Palmér, Qualitative thematic analysis based on descriptive phenomenology, Nurs, Open 6 (2019) 733–739, https://doi.org/10.1002/nop2.275.
[18] M. Sandelowski, Sample size in qualitative research, Res. Nurs. Health 18 (1995) 179–183, https://doi.org/10.1002/nur.4770180211.
[19] L.I. Pearlin, J.T. Mullan, S.J. Semple, M.M. Skaff, Caregiving and the Stress Process: An Overview of Concepts and Their Measures, The Gerontologist 30 (1990) 583–594, https://doi.org/10.1093/geront/30.5.583.
[20] WHOQOL-BREF| The World Health Organization, (n.d.). https://www.who.int/tools/whoqol/whoqol-bref (accessed December 17, 2025).
[21] R. Chattat, V. Cortesi, F. Izzicupo, M.L. Del Re, C. Sgarbi, A. Fabbo, E. Bergonzini, The Italian version of the Zarit Burden Interview: a validation study, Int. Psychogeriatr. 23 (2011) 797–805, https://doi.org/10.1017/S1041610210002218.
[22] J. De Jong Gierveld, T. Van Tilburg, The De Jong Gierveld short scales for emotional and social loneliness: tested on data from 7 countries in the UN generations and gender surveys, Eur. J. Ageing 7 (2010) 121–130, https://doi.org/10.1007/s10433-010-0144-6.
[23] J. Gray, J. Kim, J.R. Ciesla, P. Yao, Rasch Analysis of the Lubben Social Network Scale–6 (LSNS-6), J. Appl. Gerontol. 35 (5) (2014) 508–528, https://doi.org/10.1177/0733464814560468.
[24] WMA - The world medical association-declaration of Helsinki, (n.d.). https://www.wma.net/what-we-do/medical-ethics/declaration-of-helsinki/(accessed October 3, 2025).
[25] ICH, E6 Good clinical Practice - Scientific guideline |, European Medicines Agency (EMA), 2002. https://www.ema.europa.eu/en/ich-e6-good-clinical-practice-scientific-guideline (accessed October 3, 2025).