An Effective Methodological Framework for Executing Multinational, Patient-Centred Cross-Sectional Surveys in Rare Diseases

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Operationalising Cross-Country Patient Insight Generation Through Centralised Infrastructure, Local Adaptation, and Advocacy-Led Recruitment

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BACKGROUND

The Evidence-Generation Challenge

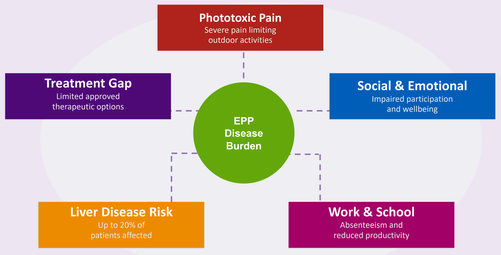
Generating robust patient insights in rare diseases is challenging due to small and geographically dispersed populations,[1] inconsistent local research requirements,[2] limited patient-identification pathways, and the high cost of running separate country-level studies. Clinical trials focus on safety and efficacy endpoints and the patient's perception of living with rare disease is often overlooked.

Acute Need for Cross-Country Evidence

These challenges are particularly acute when sponsors need cross-country evidence to support health technology assessment, reimbursement, market access, patient engagement, and commercial planning.[3] Traditional approaches often treat each country as a separate research workstream, requiring duplicated protocols, regulatory reviews, vendors, databases, translations, and recruitment pathways.[4]

Study: EPP

EPP/XLP (erythropoietic protoporphyria/X-linked protoporphyria), rare genetic diseases of the heme synthesis pathway, (prevalence 1:57,000–1:200,000)[5,6] exemplify typical rare disease burden.



Project Aim: A Centralised Methodological Framework

This project set out to develop and test a centralised methodological framework for conducting multinational, patient-centred, cross-sectional surveys in rare diseases.

The framework was designed to enable simultaneous or near-simultaneous data collection across European markets while allowing appropriate country-specific adaptation combining centralised infrastructure with local adaptation to overcome the limitations of traditional, siloed, multinational rare disease research.

Central to the framework is the patient perspective — questionnaire content, recruitment, and participation experience are shaped to minimise burden, respect participants' time, and capture the lived realities that drive health-related quality of life (HRQoL), treatment preference, and unmet need.

The EU EPP LIGHT (Life Impact and Genetic Health Trajectory) Study, a survey describing the burden of EPP and XLP from the European patient perspective, demonstrated that the operational framework can deliver high-quality patient insights efficiently across five European markets (UK, France, Germany, Italy, and Spain).

OBJECTIVE

To develop and validate a methodological framework for multinational, patient-centred, cross-sectional surveys in rare diseases, marked by severe symptoms, impaired HRQoL, and unmet therapeutic needs, prioritising:

- Generalisability to diverse rare conditions where lack of evidence and understanding of local markets impede reimbursement and commercial viability
- Scalability through adaptable, cross-disciplinary methods drawn from epidemiology, statistics, and regulatory science
- Inclusive, advocacy-driven patient recruitment to fill data gaps that traditional siloed approaches leave unaddressed

METHODS

Framework overview

The framework combines centralised infrastructure with country-specific local adaptation, enabling a single sponsor–partner team to deliver multinational rare disease research through one harmonised process rather than five parallel studies.

Developed in collaboration between a US biopharmaceutical sponsor (Disc) and Sciensus, a life sciences organisation specialising in patient access, engagement, and insight solutions, the framework was applied to the EU EPP LIGHT Study conducted simultaneously across five European countries: UK, France, Germany, Italy, and Spain.

1 Protocol Review & Adaptation

Adapted the North American protocol for EU use. Reviewed wording against ethics committee requirements. Revised consent forms. Incorporated patient and public involvement in study design. Produced master protocol for country-specific derivation.

2 Regulatory Mapping

Mapped ethical/regulatory requirements per country: full ethics (Italy, Spain), proportionate review (UK), alternative pathways (France, Germany). Mapped consenting requirements including parental consent for adolescents (≥12 years).

3 Country-Specific Protocols

Generated national protocol versions from master. Adapted screening (nurse-led vs patient organisation in France due to General Data Protection Regulation (GDPR) requirements) and compensation (prohibited in Italy).

4 Patient Identification

Recruited via study adverts disseminated by in-country patient advocacy organisations through digital channels. Emphasised diversity: age, sex, education, geography, diagnosis duration.

5 Screening & Eligibility

Clinical study nurse verified eligibility: age ≥12 years, confirmed EPP/XLP diagnosis, target country residency. In France, patient organisation acted as screener. Quality control checks addressed false registrations.

6 Survey Administration

Unique link sent post-screening via email. Used Climedo's electronic data capture (EDC) system with multilingual support (six languages). Adaptive logic: country, age (adult/adolescent), incentive eligibility. Embedded data validation rules.

7 Data Quality & Translation

Missing data review: contact if more than three unanswered. Cross-validation rules (e.g., age vs symptom duration). Free text translated by external provider. All extracted data standardised in English.

8 Analysis & Dissemination

Descriptive analyses were conducted overall and by age group. Subgroup analysis explored differences by demographics, disease characteristics, treatment satisfaction, and quality of life. Results were published onto the French Health Data Hub and ISRCTN registry. Summary in layman's terms were shared with participating patient advocacy groups.

Country-Specific Adaptations

Aspect	UK	France	Germany	Italy	Spain
Ethics	Proportionate review	CNIL (Commission Nationale de l'Informatique et des Libertés) declaration	Standard GDPR and consent regulations	Full ethics	Full ethics
Screening	Clinical nurse	Patient org	Clinical nurse	Clinical nurse	Clinical nurse
Compensation	Voucher	Voucher	Voucher	Not permitted	Voucher
Go-Live	Aug 2025	Aug 2025	Aug 2025	Sep 2025	Sep 2025

RESULTS

Summary

The methodology applied allowed for the study to be successfully delivered in under eight months. The team leveraged positive relationships with patient advocacy groups, which allowed for 101 participants (90 adults, 11 adolescents) to be recruited, meeting the sample size goal. Some participants had to be removed from the project as they were found to be fraudulent and were only seeking the compensation that was offered (e.g., could not answer appropriate questions to validate diagnosis and treatment). This meant an additional eligibility check was implemented. The study outcomes were successfully achieved and patient insights were captured across multiple domains. 100% of patients successfully completed the study. The study was also delivered to an agreed budget, supporting the sponsor in their fiscal management.

EU EPP LIGHT Study Population

N=101 (90 adults, 11 adolescents)
Mean age: 43.0 years (SD 16.6; range 12–87)
Female: 67.3% | Male: 30.7%
Mean age at diagnosis: 17.4 years (SD 15.4)

Study Timeline & Key Metrics

5 European Countries | **100%** Completion | **101** Participants | **<8** Months Total

Patient Insights Captured

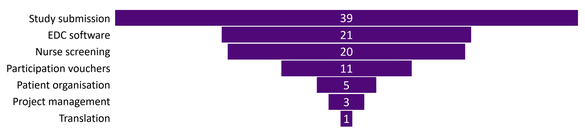
Measures were successfully collected across multiple domains, including demonstrating patients' ability to carry out activities, identify lost time from work, capture patient-reported outcome measures via a validated instrument, and patients' disease-related concerns and impact (in this case, sun exposure and pain from direct sun exposure).
For example, the following study results were achieved:

- 41% impacted in ability to do things
- Employed Europeans missed 2.4 hours of work/month
- PROMIS SRA*: 45.4 vs 50 general population norm
- 78% USUALLY/ALWAYS worried about sun exposure symptoms
- 69% experienced pain within 30 minutes of direct sun; reactions took a mean of 5 days to resolve

*PROMIS=Patient-Reported Outcomes Measurement Information System SRA=Satisfaction with Social Roles and Activities

Project Cost Distribution (% by Broad Category)

Details of costs of study resource items are presented below to illustrate key drivers of costs in view of planning for future studies.



Patient Perspective
Patients valued compensation, found questions relevant, and expressed pride in contributing to a pan-European initiative. Most completed questionnaires same-day. 100% completion rate achieved.

BENEFITS

- Launched in five European countries using a single centralised database
- Highly cost-effective: one infrastructure vs five independent studies, critical for rare diseases with small populations
- Empowering for patients and advocacy organisations: pan-European initiative fostered pride and engagement
- Patient compensation supported 100% completion rate
- Complete study cycle in under eight months

LESSONS LEARNED

- Limitation of the approach: Because EPP diagnosis was via self-report, not independently confirmed by a physician, a mechanism was applied to identify and remove fraudulent responders due to the compensation provided
- Effective communication with in-country regulatory specialists is essential to align expectations early (scope, language needs, reviewers), reducing review cycles
- Insufficient early distinction between master documents, national English versions, and translated versions caused duplicated effort
- Ethics submissions timed during July–August holiday periods in Italy and Spain caused delays and reduced recruitment windows
- Staggered go-live dates (UK/FR/DE in August; IT/ES in September) required adaptive management of recruitment timelines

RECOMMENDATIONS

- Establish clear document hierarchy early: master protocol vs national versions vs translated documents to prevent rework
- Screen country-specific regulatory timelines and institutional holiday periods before committing to milestones
- Appoint a dedicated coordination lead for managing in-country specialist communication across all markets
- Build contingency for staggered go-live dates while maintaining unified data collection periods
- Allow additional buffer time for ethics submissions in countries where summer closures are routine

CONCLUSIONS

This project demonstrated that patient viewpoint can successfully be captured via a centralised, locally adaptable framework. It can support efficient multinational patient-centred survey research in rare diseases. Across five European countries, the model enabled:

- Patient-centred outcome data across multiple domains
- Strong patient advocacy group collaboration to drive advocacy-led recruitment and 100% participant survey completion
- Harmonised survey deployment across five European countries
- Multilingual data collection (six languages)
- Country-specific regulatory and operational adaptation
- An accelerated timeline with study delivery in under eight months

The framework offers a transferable approach for generating patient insights in rare diseases where small populations, fragmented evidence, and country-specific research requirements often limit traditional study models.

Future applications should prioritise early regulatory mapping, clear document governance, flexible recruitment pathways, and country-specific planning for country-specific activation timelines.

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Disclosures

AQ Amaefule and C Norregaard are employed by Disc Medicine and shareholders. M Loiseau, N Gregory, K Duncalf, and W Hart are employed by or have been contracted by Sciensus Pharma Services Limited and have prepared this information on behalf of Sciensus International B.V. This study was funded by Disc Medicine.

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