

PROTOCOL: Patient Experience Data in Non-Interventional Studies Supporting EMA Marketing Authorisation Applications between 2018 and 2023

Draft Protocol – Version 5.1

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1. Background

Patient Experience Data (PED) can inform medicines' development, marketing authorisation evaluation and post-authorisation monitoring, conveying the experience and preferences of patients (1,2). The patient perspective can complement traditional endpoints, such as objective clinical outcomes and laboratory parameters, which may not always fully capture the impact of a treatment on the patient's life. Thus, stakeholders are broadening their interest in better understanding the patient perspective and include it in medicines decision-making (3,4).

While experience has accumulated over the years with the inclusion of PED - especially patient-reported outcomes (PROs) - in interventional studies submitted for regulatory purposes (5,6), less is known about the use of different types of PED in non-interventional studies (NIS). In particular, there is limited understanding of how PROs collected in NIS, patient preference studies (PPS), and data derived from patient engagement (PE) activities are incorporated into regulatory submissions, and which factors may influence their consideration during regulatory assessment.

2. Objectives

- Primary objective

The primary objective of this study is to characterise the use of PED in non-interventional NIS submitted to support regulatory decision-making within initial marketing authorisation applications (MAAs) and extensions of indication (Eols) incorporating real-world data (RWD) and assessed by the European Medicines Agency (EMA) between 2018 and 2023. This includes describing the regulatory lifecycle stage (pre- or post-authorisation), study design, objectives, data sources, and the types of PED collected, as well as the instruments and methodologies used.

- Secondary objectives

The secondary objectives of this study are:

1. To identify and describe PE activities reported within regulatory submissions, including the approaches used, their stated objectives, and their role in regulatory assessment.

2. To examine assessors' comments related to the inclusion of PED in NIS, with a focus on challenges highlighted during regulatory evaluation.

3. Methods

3.1. Definitions

According to the EMA Reflection Paper on Patient Experience Data, PED are defined as “*data collected through a variety of methodologies, including patient engagement activities, that directly reflect the experience of a patient or carer without input and/or interpretation by a healthcare professional, other third party or (AI-based) device*”. Additionally, “*patient experience can include, but is not limited to, aspects such as health status, symptoms, disease course, treatment preferences, quality of life and impact of healthcare*” (7).

According to the PED definition and considering the study's objectives, PED will include Patient-Reported Outcomes (PROs) included in NIS, Non-Interventional Patient Preference Studies (PPS) and data considered from Patient Engagement (PE) activities, defined as follows (7):

- “*PROs refer to a health/treatment outcome reported directly by the patient without the interpretation of a clinician or another person.*”
- “*PPS refer to how desirable or acceptable is to patients a given alternative or choice among all the outcomes of a given medicine.*”
- “*PE refers to all activities involving interaction with patients to gather their experience on disease, preferences, outcomes and treatments.*”

3.2. Sample – Eligibility criteria

Applications for initial MAAs and EoIs incorporating RWD submitted to the European Medicines Agency (EMA) between 2018 and 2023 and finalised (i.e. authorised, refused, withdrawn, or surrendered) will be eligible for inclusion. Submissions incorporating RWD were selected as the starting sample given their higher likelihood of including NIS, in line with previous regulatory analyses conducted at the EMA by Flynn et al. (8) and ongoing institutional work updating these analyses. This approach will allow the present study to build on and leverage existing EMA experience to systematically identify procedures relevant for the assessment of PED in NIS. Generic medicines, biosimilars, informed consent applications, and well-established use applications (Annex I of Directive 2001/83/EC) will be excluded (9).

3.3. Data collection

3.3.1. Administrative information extraction

MAAs, EoIs and the respective administrative information will be extracted from product Information and Application Tracking System (SIAMED). Additional administrative information,

such as paediatric use, ATMP status and PRIME status, will be collected from other EMA databases. Where such information is unavailable through internal sources, it will be complemented using publicly available information from the EMA website for the relevant medicinal product.

3.3.2. Data sources

Regulatory documents associated with the included MAAs and EoIs will be reviewed to identify NIS with PED, as well as PE activities. The primary data sources will include non-public EMA regulatory documents accessed under regulatory authorisation, namely Committee for Medicinal Products for Human Use (CHMP) Assessment Reports, Risk Management Plans (RMPs), and, where applicable, protocols and assessment reports of post-authorisation studies, including those assessed by the CHMP and/or the Pharmacovigilance Risk Assessment Committee (PRAC).

3.3.3. Identifying PED use

The presence of PED will be identified through a structured keyword search strategy applied to the regulatory assessment documents screened. Keywords will be selected based on published literature and prior regulatory research (Table 1) (6,10). A binary categorical variable (“yes”/“no”) will be recorded to indicate whether relevant keyword hits corresponding to PED were identified.

Table 1 – Keywords to be used for identifying Patient Experience Data.

Keywords		
checklist	patient(-)reported	satisfaction
diary	preference	scale
discrete choice	qol	score
engage	quality(-)of(-)life	self(-)reported
index	questionnaire	survey
interview		

3.3.4. Extraction of details regarding PED use

For submissions in which PED are identified, individual studies will be further screened to extract detailed information on PED use. Variables to be collected are predefined and described in Table 1 of the Annex, and will include, among others, study setting, objectives, study design, type of PED, and assessors’ appraisals. In addition to predefined categories, free-text fields will allow for the recording of additional observations or contextual information relevant to PED use.

3.4. Data analysis

3.4.1. Descriptive analysis of PED use

Descriptive statistics will be used to summarise the characteristics of PED use across the identified NIS. Quantitative variables will be analysed descriptively, including counts, percentages, means and medians. Statistical analyses will be performed using Excel.

3.4.2. Qualitative analysis of assessors' comments

Assessors' appraisals related to PED inclusion will be extracted from assessment reports and analysed qualitatively to characterise regulatory considerations influencing PED use. Qualitative coding will be applied to organise the data and facilitate the identification of recurrent themes, categories, and relationships related to operational, methodological, and analytical challenges.

3.5. Data quality control (QC)

To ensure the quality and robustness of data extraction and interpretation, the following quality-control measures will be implemented:

- QC1: A random sample comprising 10% of the MAAs and EoIs included in the initial phase will be selected. Keyword searches and data extraction will be independently performed by three researchers: one researcher will extract data for all products, while two additional researchers will each independently extract data for half of the selected sample. Results will be compared, discrepancies discussed, and consensus reached; data extraction will be repeated where necessary. The data extraction table will be piloted using this sample.
- QC2: At the final stage of data collection, extracted data from a random sample corresponding to 20% of all analysed MAAs and EoIs will be independently cross-checked by additional researchers. Any discrepancies will be resolved by consensus and, where required, an additional researcher will be consulted. Data extraction might be repeated.

4. Outputs and dissemination

The results of this study will be disseminated through multiple channels to support regulatory learning, transparency, and scientific exchange. Findings will be presented internally at the European Medicines Agency, including relevant scientific or regulatory fora, as appropriate. In addition, results will be submitted for presentation at external scientific conferences in the form of posters and/or oral communications. Finally, the study findings will be submitted for publication in a peer-reviewed scientific journal.

5. References

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ANNEX

Table 2 – Variables to be extracted.

ADMINISTRATIVE INFORMATION EXTRACTED FOR EACH MAA AND EOI			
Variables	Description	Value	Source
<i>1.1. Administrative information automatically extracted from SIAMED</i>			
Product name	Brand name of the product	<i>Text</i>	SIAMED
International Non-proprietary name	Active substance	<i>Text</i>	
Orphan status (as of XX)	A medicine for the diagnosis, prevention or treatment of a life-threatening or chronically debilitating condition that is rare (affecting not more than five in 10,000 people in the European Union) or where the medicine is unlikely to generate sufficient profit to justify research and development costs (11)	<i>Categorical</i> Yes; No	
ATMP status (as of XX)	Companies can consult the European Medicines Agency (EMA) to determine whether a medicine they are developing is an advanced therapy medicinal product (ATMP). The procedure allows them to receive confirmation that a medicine, which is based on genes, cells or tissues, meets the scientific criteria for defining an ATMP (12)	<i>Categorical</i> Yes; No	
Application number	Application number attributed by the EMA	<i>Text</i>	
Application type	Application type categories according to EMA classification.	<i>Categorical</i> Initial MAA Line extension Type II Workshare	
Marketing authorization legal basis	Legal basis of the marketing authorization application according to Directive 2001/83/EC (13)	<i>Categorical</i>	

		Full or full-mixed application (complete dossier, new active substance) Well established use application (literature only) Fixed dose combination (components already authorised separately) application Hybrid medicinal product application Similar biologic product application	
Marketing authorisation type	Type of marketing authorization that the European Commission has granted based on the CHMP opinion (13,14)	<i>Categorical</i> Standard (full) Conditional Exceptional	
Submission date	Date when EMA received the dossier	<i>Text</i>	
Accelerated assessment	Applications may be eligible for accelerated assessment if the CHMP decides the product is of major interest for public health and therapeutic innovation.	<i>Categorical</i> Yes; No	
CHMP opinion date	Date of the meeting whereby CHMP provided its opinion on the application	<i>Text</i>	
CHMP opinion	Conclusion of the CHMP assessment to authorize or not the application	<i>Categorical</i> Positive; Negative	
EC decision date	Date of the meeting when the EC issued its decision on the application following CHMP opinion	<i>Text</i>	
Application status (as of XX)	Indication on the stage of the evaluation, i.e. if it is finalized (closed/completed) or still ongoing	<i>Categorical</i> Close/completed Withdrawn	

Product status	Indication on the state of the product, i.e. whether it is authorized, refused, or whether its MAA is withdrawn	<i>Categorical</i> Pending Refused Surrendered (i.e. withdrawn after authorisation) Valid (authorised) Withdrawn	
ATC code	ATC code attributed by WHO	<i>Text</i>	
Full therapeutic indication	Information related to the indication(s) of the product	<i>Text</i>	
1.2. Administrative information extracted manually			
PRIME designation	PRIME is a scheme launched by the EMA to enhance support for the development of medicines that target an unmet medical need. This voluntary scheme is based on enhanced interaction and early dialogue with developers of promising medicines, to optimize development plans and speed up evaluation so these medicines can reach patients earlier (15)	<i>Categorical</i> Yes; No	EMA website
Paediatric indication	Product intended for use in the pediatric population (16)	<i>Categorical</i> Yes; No	EPAR
Compassionate use	If Member States have authorized the use of the medicine in special care setting before an MA is granted	<i>Categorical</i> Yes; No	CHMP AR: EMA DREAM
CHMP AR DREAM link	Link of the CHMP AR in DREAM	Link	CHMP AR: EMA DREAM
1.3. PED inclusion information extracted manually through keyword search			
PED inclusion	Indication on whether the applicant has submitted PED within the application or proposes to collect PED post-A according to the keyword search performed	<i>Categorical</i> Yes; No	CHMP AR: EMA DREAM Post-authorisation studies protocols/reports: Common repository

OVERALL PED INCLUSION IN MAAs AND EOIs (<i>per study</i>)			
Variables	Description	Value	Source
Study ID	Study ID referred in the CHMP AR/RMP	<i>Text</i>	CHMP AR RMP: EMA Common repository Study protocols submitted by the Applicant: EMA common repository Assessment reports of post-authorisation studies: EMA DREAM
Setting	Whether the PED was provided pre-authorisation, or is proposed to be used post-authorisation, or both.	<i>Categorical</i> Pre-A Post-A Both NA	
Pre-authorisation: Study nature	As described in the CHMP AR, usually in section 2.5 Clinical efficacy	<i>Categorical</i> Main Supportive Both NA	
Post-authorisation: RMP category	Categorisation of the post-marketing study as decided by the CHMP: EU RMP category 1 (imposed as condition of marketing authorisation), EU RMP category 2 (specific obligation of marketing authorisation), EU RMP category 3 (required) If not indicated in the CHMP AR, this information can be found in the latest RMP stored in the common repository .	<i>Categorical</i> Category 1 Category 2 Category 3 NA	
Objective(s)	As described in the CHMP AR or in the study protocol	<i>Categorical</i> Efficacy/effectiveness Safety Disease epidemiology Drug utilisation Benefit-risk trade-off	

		Overall patient experience Mix (respect above order)	
Study design	As described in the CHMP AR or in the study protocol	<i>Categorical</i> Interventional Cohort Interventional Case-control Interventional Nested case-control Interventional Cross-sectional Interventional Ecological Interventional Case-only design Non-Interventional Cohort Non-Interventional Case-control Non-Interventional Nested case-control Non-Interventional Cross-sectional Non-Interventional Ecological Non-Interventional Case-only design Survey of patients Other Mix	
PED ID	Name of the PED/instrument used.	<i>Text</i>	
PED type	Categories of PED	<i>Categorical</i> PRO PPS PE activities Other	

PROM/PP Method	If PRO/PP is indicated, detail which is the PROM or PP methodology accordingly	<i>Categorical</i> Unspecified PROM Generic PROM Disease-specific PROM Hybrid PROM Unspecified PP Explored PP Elicited PP Hybrid PP	
PED endpoint category	Endpoint category in which PED, especially PROs, is included for the study	<i>Categorical</i> Primary endpoint Secondary endpoint Exploratory endpoint Baseline characteristics Other NA	
PED purpose	Information that PED brings to the study (17–21).	<i>Categorical</i> Quality of life Signs/Symptoms Functional status Events Health behaviour Patient satisfaction Benefit-risk trade-off Mix Other NA	

Frequency of PED collection	Frequency of PED collection during the study duration, in months	<i>Categorical</i> Annually Every 6 months Monthly Once (baseline) Other	
PED collection	Primary or secondary PED collection	<i>Categorical</i> Primary Secondary Both NA	
PED source(s)	Secondary data sources where PED was extracted from.	<i>Categorical</i> Electronic health records Claims database Registry Compassionate use programme Other Mix N/A	
PED provenance	Region represented in the study	<i>Categorical</i> EU US Other regions Mix Unknown	
Population	Target population of the study	<i>Text</i>	
Sample size	Sample size of the study	<i>Number</i>	

General assessors' appraisal on PED	CHMP/PRAC views on the added value or limitations of PED	<i>Text</i>	
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