HMA
Heads of Medicines Agencies

EMA
EUROPEAN MEDICINES AGENCY

Joint HMA/EMA multi-stakeholder workshop on Patient Registries

Workshop report

12-13 February 2024

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Executive summary

A two-day hybrid multistakeholder workshop on Patient Registries organised by the Heads of Medicines (HMA) and the European Medicines Agency (EMA) in the context of the HMA/EMA Big Data Steering Group Workplan 2023-2025 took place on 12&13 February 2024 to address the following objectives:

1. Discuss the EMA qualification procedure for patient registries with the aim to clarify the benefits, identify current limitations, and propose measures to optimise the process;
2. Establish the value and enable the use of patient registries for regulatory decision-making by considering contexts of use for which registry data are 'fit for purpose' and examining tools to support data discoverability and assessment.

The event follows on a series of disease-specific patient registries workshops organised by EMA in the frame of the Initiative for Patient Registries launched in 2015.

The meeting was attended by representatives of registry holders, regulatory agencies, industry, patients representatives, healthcare professionals, academia, and health technology assessment bodies (HTA) with experience on the EMA qualification of patient registries, and/or on the use of patient registries for regulatory purposes. All workshop related documents, as well as the recording, can be found here.

In addition to public plenaries, participants took part in breakout sessions to exchange views within smaller groups on various topics, such as i) ways to optimise the qualification of patient registries taking into account known challenges; ii) means to enhance the description of data quality, data discoverability, data interoperability; iii) and how to facilitate the evaluation of the fitness for purpose of a registry (in view of a specific study question and design) to support regulatory decision-making.

All stakeholders showed strong interest and positive engagement in working together to enable the use of patient registries for regulatory purposes. The following key recommendations were identified (and are further elaborated in Tables 2 and 3 of this report) to concretely tackle the challenges highlighted during the two-day open dialogues. As a next step, the European Medicines Regulatory Network (EMRN) will identify the relevant channels to follow-up on the recommendations, and will ensure continuous interactions with stakeholders represented at the workshop.

Workshop Objectives	Recommendations
Discuss the EMA qualification procedure for patient registries	Whilst participants recognised that the process requires a lot of work from both registry holders and EMRN sides, all agreed that qualification is valuable to improve the quality of registries, and to strengthen their use for regulatory purposes, provided the following recommendations are considered: • Clarify the concept of qualification of patient registries (aims, contexts of use, and expectations) to reach common understanding on what "qualification of patient registries" means, what its added values are, what it implies in terms of content (level of details) / format of the information to be submitted and timelines to help applicants anticipate the resources they may require to go through the procedure. • Review and optimise the procedure to ensure it is fit for purpose to evaluate the use of patient registries in specific contexts, ultimately supporting regulatory decision making; and to accommodate the needs of the applicants and regulatory network experts (e.g., establish scoping pre-submission meetings, post-qualification lifecycle management process). • Develop guidance documentation specific to the qualification of patient registries, which will be complementary to the general guidance on Qualification of Novel Methodologies (QoNM), e.g., checklist for briefing book to guide format and content, Questions and Answers document to clarify operational aspects. • Foster communication on qualification of patient registries to increase awareness, to help stakeholders gain a better understanding of the procedure, to promote transparency, knowledge sharing, and to facilitate engagement with qualified registries. • Reflect on possible approaches to measure the long term impact qualification may have on all parties involved, to identify gaps and opportunities for process improvement.

Workshop Objectives	Recommendations
Establish the value and enable the use of patient registries for regulatory decision-making	• Establish continuous interactions between stakeholders to discuss questions related to registries' development and subsequent updates, to understand needs (including on relevant clinical outcomes) by anticipating future uses/potential future research questions based on medicines pipeline, to understand potential challenges when developing study concepts and protocols. • Increase stakeholders' awareness on the existence of patient registries, and facilitate engagement with them for regulatory purposes thanks to the HMA-EMA Catalogues of real-world data sources and studies, and other platforms administered by the European Commission. Establish linkage between these tools to streamline search capability, discoverability, and avoid duplication of data entries across various catalogues. • Increase support to stakeholders in fostering data quality of patient registries, and in assessing their relevance to specific research questions through the promotion of guidance*, and by exploring potential training needs/gaps linked to the use of registries. **Examples: HMA/EMA Data Quality Framework and its draft Chapter on RWD sources once publicly available, Guideline on Registry-based studies, Good Pharmacovigilance Practices Module VIII on post-authorisation safety studies, and Scientific guidance on post-authorisation efficacy studies*

This report summarises the topics and content of the discussions held over the course of the two-day plenary and breakout sessions. The detailed recommendations and suggested actions can be found in Tables 2 and 3.

Introduction

Patient registries, also referred to in this report as "registry/ies", are important for the generation of evidence on the benefits and risks of medicines[1,2]. They are currently defined in the European Union (EU) as "*Organised system that collects uniform data (clinical and other) to identify specified outcomes for a population defined by a particular disease, condition or exposure. The term 'patient' highlights the focus of the registry on health information. It is broadly defined and may include patients with a certain disease, pregnant or lactating women or individuals presenting with another condition such as a birth defect or a molecular or genomic feature"*.

In 2015, the European Medicines Agency (EMA) launched the Initiative for Patient Registries to explore ways to expand the use of patient registries, to promote dialogue between stakeholders, and to provide methodological guidance on the conduct of registry-based studies for regulatory purposes. Several multistakeholder workshops were organised over the years by the EMA cross-committee Task Force on patient registries leading the initiative. These have been instrumental to shaping our current knowledge on the complex ecosystem of existing registries. Our learnings so far have been translated into the Guideline on registry-based studies, a reference for industry, academia/research organisations and the EU regulatory network, for the conduct of studies on medicinal products based on registry data.

The world is digitalising at an unprecedented pace, and we are now starting to witness the progress towards achieving the vision of the HMA/EMA Big Data Steering Group to improve regulatory decision-making by strengthening data collection and analysis. Patient registries have an important role to play here, as they have the capability to collect long term granular data on patients with a particular disease or condition, providing in some situations a unique way to monitor medicines' safety and effectiveness over time.

In order to share knowledge on the use of registries in regulatory contexts, and exchange evolving data needs among stakeholders, a workshop on patient registries was included as part of the HMA/EMA Big Data Steering Group Workplan 2023-2025. In addition, this workshop provided the perfect opportunity to follow-up on the recommendations from the April 2023 EMA multi-stakeholder workshop on qualification of novel methodologies.

The two-day hybrid HMA/EMA workshop on Patient Registries brought together multiple stakeholders to address the following objectives:

1. 12 February afternoon: Discuss the EMA qualification procedure for patient registries with the aim to clarify the benefits, identify current limitations, and propose measures to optimise the process;
2. 13 February all day: Establish the value and enable the use of patient registries for regulatory decision-making by considering contexts of use for which registry data are 'fit for purpose' and examining tools to support data discoverability and assessment.

[1] McGettigan P, Alonso Olmo C, Plueschke K, Castillon M, Nogueras Zondag D, Bahri P, Kurz X, Mol PGM. Patient Registries: An Underused Resource for Medicines Evaluation : Operational proposals for increasing the use of patient registries in regulatory assessments. Drug Saf. 2019 Nov;42(11):1343-1351. doi: 10.1007/s40264-019-00848-9. Erratum in: Drug Saf. 2019 Sep 5;: PMID: 31302896; PMCID: PMC6834729.
[2] Jonker Carla J. , Bakker Elisabeth , Kurz Xavier , Plueschke Kelly. Contribution of patient registries to regulatory decision making on rare diseases medicinal products. Frontiers in Pharmacology 2022. DOI=10.3389/fphar.2022.924648

Objectives, participants, and methods

Objectives

Table 1 – Workshop Objectives

Workshop Objectives	
Day 1 Discuss the EMA qualification procedure for patient registries	• Identify the benefits of registry qualification. • Identify current limitations and gaps, as well as possible measures to optimise the procedure. • Propose a check list to guide the structure and content of qualification applications. • Explore opportunities for strengthened and effective mechanisms to ensure standards of qualified registries are sustained over time.
Day 2 Establish the value and enable the use of patient registries for regulatory decision-making	• Examine contexts of use for which registry data are 'fit for purpose' and demonstrate the value of patient experience data across the spectrum of regulatory use cases. • Share experience on addressing challenges to foster the use of registries for regulatory purposes, through enhanced description of data quality, increased data discoverability, and promotion of data interoperability. • Consider the key elements of a 'feasibility assessment' to evaluate the relevance of a registry in view of a specific study question and design. • Identify areas for collaboration between stakeholders to strengthen the use of registries for regulatory purposes and decision making.

Participants

The workshop was chaired by Peter Arlett (EMA, Head of Data Analytics and Methods Task Force, TDA) and Patricia McGettigan (Queen Mary University Of London, Pharmacovigilance and Risk Assessment Committee (PRAC) Independent Scientific Expert, and Big Data Steering Group (BDSG) member). It was attended by 80 people onsite with experience on the EMA qualification of patient registries, and/or on the use of patient registries for regulatory purposes. These included representatives of registry holders, regulatory agencies, industry, patients, healthcare professionals, academia, and health technology assessment bodies (HTA). The meeting was also followed by 400 online participants.

Methods

Pre-work package

A few weeks before the workshop, EMA sent participants a pre-work package with questions tailored to each type of stakeholders. The aim was to seek their views on various topics, including on the qualification of registries, contexts of use and fitness for purpose of registry data. All responses helped guide the content and facilitate the running of the breakout sessions held over the 2-day workshop. The aggregated feedback can be found as *Supplementary Material* at the end of this report.

Plenary sessions

The agenda, the presentations, and the recording of the workshop can be found on the EMA event page Joint Heads of Medicines Agencies (HMA)/European Medicines Agency (EMA) Multistakeholder workshop on Patient Registries.

Breakout sessions

The 2-day workshop included breakout sessions; whereby onsite participants were divided evenly into several working groups composed of 2 moderators to exchange views on the following topics:

- Workshop Day 1 (3 groups):
    A. Benefits of the qualification of patient registries, limitations, reaching common understanding on stakeholders' expectations, measures to optimise the process.
    B. Draft check list for the qualification application to guide the structure and content of requests, and other means to ease the procedure.
    C. Mechanisms to ensure standards of qualified registries are sustained over time (post-qualification lifecycle management).
- Workshop Day 2 (2 times 2 groups discussing in parallel):
    A. Two groups: Fostering the use of patient registries for regulatory decision-making through enhanced description of data quality, increased data discoverability, and promotion of data interoperability (e.g., HMA/EMA Data quality framework (DQF) for EU medicines regulation and its chapter on Real-World Data (RWD), EMA catalogues).
    B. Two groups: Key elements of a 'feasibility assessment' to evaluate the relevance of a registry in view of a specific study question and design, areas for collaborations to strengthen the use of registries for regulatory purposes and decision-making.

The outcomes of the discussions held within the groups were then reported back to the plenary sessions. They provided content for this final workshop report.

Summary of Day 1 – Plenary session

Objective 1	
Day 1 Discuss the EMA qualification procedure for patient registries	• Identify the benefits of registry qualification. • Identify current limitations and gaps, as well as possible measures to optimise the procedure. • Propose a check list to guide the structure and content of qualification applications. • Explore opportunities for strengthened and effective mechanisms to ensure standards of qualified registries are sustained over time.

Introduction by the Chairs

The first day of the workshop started with a reminder on the EMA Qualification of novel methodologies for medicine development (QoNM), which allows any interested party to voluntarily seek scientific evaluation by the Committee for Medicinal Products for Human Use (CHMP) through its Scientific Advice Working Party (SAWP), on the acceptability and suitability of innovative drug development methods and tools for use in a specific context related to medicines development[3]. The evaluation leads to a qualification opinion or advice. An opinion is based on the assessment of comprehensive data submitted to the Agency and is subject to a public consultation before the final opinion is published. A qualification advice is based on the assessment of the scientific rationale, validation plans/protocols and preliminary data submitted to the Agency and provides recommendations on how to move towards a qualification opinion at a later stage. A letter of support aiming to encourage data-sharing and collaboration may be published at the time of the advice, if the novel methodology under evaluation meets a clear unmet need, and the proposed further evidence generation appears likely to support future qualification. The default outcome of qualification advice is a confidential qualification advice letter. The EMA Regulatory science strategy to 2025 (RSS) has set a goal to develop guidelines and strengthen the current process. A multi-stakeholder workshop on qualification of novel methodologies was held in April 2023 as a first step to review the scientific and operational aspects of the current framework, aimed to best support translation of innovation into patient benefits. One of the sessions focused on the qualification of RWD sources and led to several recommendations, which this patient registry workshop aimed to address. These include the need to better define the (regulatory) contexts of use of such data, to enhance data quality, to strengthen communication between interested parties, and to increase the agility of the process before, during and after initiating a qualification procedure.

Main lessons learnt so far on the qualification of registries

In a second presentation, registry holders provided a summary of the main lessons they have learnt so far on the qualification of registries. Between 2018 and 2023, eight RWD sources, including seven registries sought qualification (see Appendix Table 4), out of which three received a qualification opinion, and 5 received an advice letter, highlighting areas of

[3] E.g. diagnostics and prognostics methods, clinical outcome assessments, clinical endpoints including surrogate, biomarkers, data sources (including registries), modelling & simulation, digital health technology and artificial intelligence/machine learning related methods etc – see Opinions and letters of support on the qualification of novel methodologies for medicine development

improvement before a qualification opinion may be granted. The overview clearly highlighted the reasons for going through the process, the opportunities it brings to registry holders, the challenges encountered, and suggestions for improvement at each stage of the procedure. All these aspects were illustrated by the experience gained by two registry holders, the BigMS Data Network and the European Cystic Fibrosis Society Patient Registry and were later on discussed in more detail during the breakout sessions.

The European Federation of Pharmaceutical Industries and Associations (EFPIA) went on to present the results of a survey conducted across its members to assess industry's experience on using qualified and non-qualified registries, and to identify discussion points that may increase clarity and streamline the qualification process. EFPIA recognised that qualification may ensure a certain level of regulatory acceptability and encourage the use of data by many stakeholders. The members expressed their wishes to explore 1) the value of qualification for different purposes and stakeholders; 2) how it can inform fitness-for-purpose assessments in light of emerging tools such as various data quality frameworks; and 3) moving towards a future state where quality frameworks and maturity models foster a sustainable "quality by design" approach to registries that may help reduce the need for qualification over time. Finally, from a procedural perspective, EFPIA highlighted the value of guidance documents for future applicants, as well as having channels for multi-stakeholder dialogues (e.g., between regulators, registry holders, and industry).

Finally, a regulatory perspective on the qualification of registries was conferred by the PRAC Chair, who outlined the data needed for PRAC assessment on medicines. These include e.g., data on drug utilisation patterns (including off label use, discontinuation, switching and dosing), patient experience, background incidence of adverse events, disease epidemiology/natural history, and post marketing safety information. The strengths and usefulness of registries in the post-authorisation setting were highlighted, with an important nuance that to provide useful evidence for regulatory decision-making, registry data have to be accurate (precise and reliable), adequate (e.g., in terms of range of characteristics of the population covered, duration of follow-up), consistent (across countries / data sources), timely (lag time for data availability) and valid (internal and external validity). For regulators, data quality is more important than quantity. Some registries used in post-authorisation safety studies (PASS) assessed by the PRAC have been considered fit-for-purpose, even though they have not been qualified. Due to yet limited experience, uncertainties remain as to whether the qualification is currently shaped in an optimal way to ensure data sources will meet post-authorisation requirements.

Questions and answers

The plenary was followed by a questions and answers session with the in-person and online audience:

- These included e.g., what could the PRAC bring-in as part of the qualification process. It was felt that currently, SAWP is well equipped to assess data quality aspects, but that the involvement of PRAC is still important to ensure the committee's awareness on the registries of interest. PRAC could bring other expertise based on its data needs, e.g., on the relevance of long-term follow-up data, as well as data in pregnancy.
- Another question related to the possibility for national disease specific registries to join the Data Analysis and Real World Interrogation Network (DARWIN EU®), so their data become available to EMA and its scientific committees/working parties to conduct studies in support for their evaluation of medicines. The EMA clarified that in order to be part of DARWIN EU, registries should be converted into the Observational Medical Outcomes Partnership (OMOP)

common data model. The current strategy is to onboard data partners with a wide range of data across different disease areas, which might not be the case at the moment for (rare) disease specific registries. However, registries covering an umbrella of diseases (e.g., cancer) may consider applying in the future, as it was done by the Netherlands Cancer Registry (NCR) which is today an official DARWIN EU® data partner. Moving forward, it might be interesting to explore if and how the lessons learnt from the DARWIN EU® data partners onboarding process can help inform the review of the qualification process.

- Finally, the participants reflected on the existence of multiple registries for the same disease. Whilst these may be complementary, especially in case of a rare disease, efforts should be made to raise awareness amongst registry holders on the availability of other registries, on their similarities and differences.

Summary of Day 1 – Breakout sessions

Session A: Benefits of the qualification of patient registries, limitations, expectations, and measures to optimise the process

Discussion

Potential benefits: The session started with a discussion on the potential benefits of the qualification of patient registries.

Stakeholders have different expectations from the procedure:

- Registry holders clearly outlined that qualification can help them 1) improve the quality of their data, 2) increase trust in their data, and therefore increase their use in the frame of medicines regulation, 3) establish a dialogue with regulators to learn about the regulatory system/requirements, 4) reach public recognition of the registry's professionalism, which may facilitate interactions and access negotiations with future users of their data (e.g., industry, research organisations, regulators), ultimately leading to financial support for continuous improvement and sustainability.
- For regulators, qualification provides the opportunity to assess if a registry is fit to generate valid evidence for decision making in a specific context of use. The experience gained so far with the use of qualified registries for regulatory purposes is however still limited, and there are currently no measures in place to assess the long-term impact of qualification on the use of registry data. It was noted that registries can still be used for regulatory purposes, even if they have not (yet) been qualified, as long as the data are considered relevant for the specific research questions of interest. Indeed, patient registries are already being used extensively as data sources for PASS studies requested by the PRAC. This being said, regulators recognised that the qualification process is an important step to increase awareness about the data collected by a registry and its level of data quality. Ideally, this should lead to a proactive better understanding of the relevance of a registry for a specific context of use, ultimately facilitating the assessment of subsequent study protocols/results using the registry's data, and expediting the evaluation of medicines, reimbursement and access to patients.
- Industry representatives emphasised the unique role of the qualification procedure in obtaining regulator input on a novel method unrelated with a specific drug development program. They highlighted that despite the number of qualified registries being relatively limited, the advice received during qualification is considered helpful to clarify for all stakeholders the level of data quality considered acceptable by regulators to answer specific questions. They noted that qualification fosters dialogue across all interested parties in the context of a regulatory procedure.

Scope: Participants from regulatory agencies importantly reminded the audience that qualification is not granted on the registry infrastructure, but instead on (a) specific context(s) of use, which the applicants should clearly outline in their requests. Examples of contexts mostly supported by the participants were the use of the registry data for post-authorisation studies, in studies on the disease epidemiology/natural history, or on drug utilisation patterns, and the use of registry data as clinical trial control arm. The use of registry data in the context of paediatric drug development was also underlined and should clearly be described when applicable as part of the context of use for which qualification is sought.

It was highlighted that prior to seeking an opinion, it may be wiser for applicants to first seek qualification advice on a specific context of use in order to clarify and receive some orientation from regulators on which data are required to be submitted for opinion assessment.

Limitations: Registry holders expressed their difficulties in navigating through the current process due to the (sometimes) limited knowledge on the many regulatory requirements, the time-consuming administrative steps to submit/update information through the online system, and the short timelines which do not always allow multinational (network of) registries to go back to all their partners for internal discussions and consultations. Clarification on regulatory expectations towards registry holders in terms of the information to be submitted for qualification opinion on one side, and qualification advice on the other side, would be helpful to understand upfront resources needed to go through this voluntary substantial exercise.

As the assessment of qualification applications also requires substantial amount of resources from the European Medicines Regulatory Network (EMRN), a review of the process will be beneficial to ensure it is fit-for-purpose for the evaluation of patient registries in a specific context of use. Subsequent communications on the procedure should be adapted to reflect the scenarios for which qualification is recognised as most valuable to support medicines' development and monitoring, and which benefits it may bring to the patient registries (patient-led and clinician-led) seeking qualification.

There are currently no measures in place for post-qualification lifecycle management. The need to ensure that the quality standards agreed during the qualification are maintained over time was therefore strongly emphasized.

Main take aways

Whilst participants recognised that the process requires a lot of work from both registry holders and EMRN' sides, all agreed that qualification is valuable to improve the quality of registries, and to strengthen their use for regulatory purposes provided the aspects highlighted below are considered.

The interesting discussions highlighted the following suggestions for improvement of the qualification of patient registries going forward:

- Clarify the aims, the scope (applications should be based on (a) specific context(s) of use), and stakeholders' needs and expectations. There is a strong wish to reach common understanding on what "qualification of patient registries" means, what its added values are, what it implies in terms of content (level of details)/format of the information to be submitted, and of resources required to manage the procedure. The advantages and benefits of qualification should more evidently be outlined.
- Review the procedural steps and timelines to optimise the qualification of patient registries, by increasing its flexibility to accommodate the needs of the applicants and regulatory network experts. This should include the possibility to hold informal dialogues before the submission, as well as the establishment of a post-qualification lifecycle to periodically review the standards agreed in the context of the qualification.
- The involvement of experts during the qualification assessment beyond the members of the SAWP, PDCO, CHMP and PRAC should also be considered (e.g., patient representatives to ensure the collection of patient-relevant data).

- Increase the support to registry holders and regulatory network experts through:

✓ Guidance on the format and content of qualification applications focusing on patient registries, e.g., checklist/template for briefing book, a Questions and Answers (Q&A) document;

✓ Guidance on the procedural steps including e.g., simple and easy flowcharts, Q&A;

✓ Continuous interactions with EMA/regulators throughout the qualification process (e.g., scoping pre-submission meetings to clarify regulatory requirements related to qualification, format/content on the applications, and procedure steps) but also after the procedure.

- Explore ways to measure the impact qualification may have on all parties involved (including, but not limited to registries, regulators, and industry) to understand the value of this comprehensive review process in the long term, to identify gaps and opportunities for process improvement.

Session B: Qualification procedure checklist

Discussion

Prior to the workshop, EMA developed and circulated a draft checklist to guide the structure and content of qualification applications on patient registries. The main objective of this session was to discuss and collect feedback on the document aimed to complement the new qualification briefing book currently under development.

Participants expressed the need to better define in a guidance the outputs of the assessment, i.e., the qualification advice with its advice letter, and the qualification opinion. There should be clear instructions on the steps to undertake prior to the submission, during and after the evaluation. The group agreed that a scoping meeting (in advance of the submission) to guide on the administrative steps and on regulatory needs would be very useful. The involvement of HTA was suggested to identify at an early stage the effectiveness and patient data to be collected.

Questions were raised on who can request qualification, e.g., a consortium, or a university part of a consortium. EMA clarified that only a legal entity can seek qualification. Unlike a university, a consortium is not a legal entity. It was also underlined that the qualification procedure is a scientific advice procedure, meaning that scientific advice fees apply, as well as fee incentives for applicants with small and medium enterprise status or for methods solely used in the context of paediatric development.

Participants also discussed if the methodology for data collection alone would be sufficient for qualification. The group agreed that thresholds to characterise robustness of data were highly recommended. It was noted that registry holders should focus their qualification opinion requests for the context(s) of use for which they can best demonstrate the relevance of the data. For other less established uses, holders may request qualification advice to receive guidance on what is required to reach an opinion. Participants enquired if a qualification opinion and a qualification advice could both be sought within a unique procedure on various contexts of use depending on their maturity. This would need to be considered carefully in light of potential logistical challenges. Qualification for additional context(s) of use could of course be sought at a later stage whenever registry holders are considered ready to apply.

Comments on the checklist, including suggestions for improvement, were made:

- The document should be a supportive document, not all items are mandatory.
- In its current form, the document appears more like a briefing document template than a checklist, tick-boxes list could be added where relevant.
- Concrete examples of data needed to be provided for each context of use could be added as they would increase understanding of the regulatory requirements.
- A glossary of terms would be helpful to ensure all stakeholders talk the same language, e.g., on what is meant by long-term follow-up, or on medication switch.
- Clear documentation of the informed consent process is key, in particular for the re-use of data within Europe, as different processes may apply across countries.
- Differentiation between data elements considered “need-to-have” versus “nice-to-have” should be made.
- Demonstration that the data elements collected can be adapted over time as clinical practices evolve would be useful (e.g., pregnancy outcomes). One missed opportunity mentioned was that a proactive, horizon scanning discussion on upcoming products could be used as a trigger to understand what issues need data collection within registries.
- Opportunities for linkage to other data sources and description of the linkage process should be described.
- Registry population: the representativeness of the registry patient cohort should be estimated to prevent bias (e.g., representativeness may be limited if the registry only collects data on newly diagnosed patients, or only in reference centres); paediatric registries should have the possibility to continue data collection in adults.
- The time to collect, curate and make the data available should be defined.
- Examples of characteristics and metrics required to demonstrate and enhance data quality, such as clear description of roles (e.g., of a data manager), data monitoring, the use of coding systems, like SNOMED and MedDRA would be useful.
- Participants enquired about expectations for data verification and validation, and about the value of a “CE mark” for the software used by the registry.

Main take aways

- The checklist is recognised as a good start to guide the structure and content of applications and should be amended taking into account the comments received.
- Guidance is needed on the steps to be followed and data to be submitted depending on the context(s) of use (including on level of data quality) when seeking either qualification advice, or opinion or both.
- Scoping meetings with registry holders would help clarify stakeholders’ expectations, and regulatory requirements.
- Data collection should be a dynamic process, with changes in the data elements to be collected over time in order to adapt to evolving clinical practices.

Session C: Mechanisms to ensure standards of qualified registries are sustained over time

Discussion

The group agreed that, despite no existing legal basis, a post-qualification lifecycle management process should be established in order to maintain a continuous dialogue between registry holders, regulators and other interested parties such as industry, and to ensure the data remains relevant over time for the context(s) of use qualified. These interactions should take place at regular time points, with a frequency and scope to be agreed as part of the qualification outcome, together with an outline of what information will need to be reviewed and any actions needed to sustain the qualification status.

Scope: The participants stressed that this post-qualification lifecycle management process should be reasonably balanced between the aspects of the registries to be checked in line with the context(s) of use qualified, and the potential burden these regular reviews may place on registry holders and the EMRN. Elements identified during the discussions as being important to reassess include e.g., any changes in data extensiveness, reliability and coherence, external factors impacting the registries' data quality management mechanisms, patients' relevant data, follow-up data, registries coverage, and accrual rates. The review should also cover any other elements evaluated as part of the original qualification, and which have not changed, to determine continuous relevance.

Frequency of review: It should be adjusted depending on the requirements for each context of use. Time points for checks should be set during the qualification process in order to make regulatory expectations clear to registries, with the added caveat that they should proactively contact EMA if any unexpected changes occur, which may lead to major impact on the use of the data for regulatory purposes. A minimum annual touch point for all registries was suggested. However, this will need to be agreed on a case-by-case basis.

Post-qualification collaboration: The parties to be involved in the review should be defined during the qualification process to ensure consistency across qualified registries. Careful considerations should be made on a case-by-case basis to perform the review in an optimised way.

Communication: The participants highlighted that qualification outcomes (related to specific context(s) or use) should be precisely communicated to increase awareness of all stakeholders as a reward for going through this extensive and thorough review process, e.g., through an EMA webpage dedicated to the qualification of data source. Tailored information should also be distributed through targeted communication channels (to be explored). Suggestions were made that for patients, the patient information leaflet could contain information to guide them towards the registries considered relevant to the product they are using; and that one specific group which should be made more aware of the qualification of registries is the one of medical practitioners.

To improve communication and engagement with registries, a general contact point specified on the EMA website for the qualification-related questions would be welcomed.

Some participants suggested examples of incentives for qualified registries, such as being prioritised in specific searches related to registries through the HMA-EMA Catalogues of real-world data sources and studies, or having an explicit mention encouraging the use of those registries in the context(s) they have been qualified for in the qualification letter of support / opinion as applicable. This would in turn potentially emphasise the engagement of the registries

to do all they can to sustain their qualification status. It is important to note that these examples correspond only to ideas raised during the breakout sessions, and therefore do not constitute formal workshop recommendations. The future review of the qualification of patient registries referred to in the above section *Day 1 - Session A* will ensure the assessment of applications, and subsequent communication of the outcomes are conducted in a fair, impartial and transparent way.

Main take aways

- Consider ways to establish post-qualification lifecycle management process to maintain regular interactions between all relevant parties and to ensure agreed characteristics of registries for the qualified context(s) of use are sustained over time. This should take into account the elements to be reviewed, the frequency, the parties to be involved.
- Foster communication on qualification outcomes, and explore possible mechanisms to increase awareness about, and engagement with qualified registries.

Summary of Day 2 – Plenary session

Objective 2	
Day 2 Establish the value and enable the use of patient registries for regulatory decision-making	• Examine contexts of use for which registry data are 'fit for purpose' and demonstrate the value of patient experience data across the spectrum of regulatory use cases. • Share experience on addressing challenges to foster the use of registries for regulatory purposes, through enhanced description of data quality, increased data discoverability, and promotion of data interoperability. • Consider the key elements of a 'feasibility assessment' to evaluate the relevance of a registry in view of a specific study question and design. • Identify areas for collaboration between stakeholders to strengthen the use of registries for regulatory purposes and decision making.

The plenary sessions can be viewed through the video recording published on the event webpage.

The second day started with opening remarks from the EMA executive director, a representative of a National Competent Authority and the European Commission (LINK1, LINK2), to set the scene on the crucial role of the EMA Patient Registry Initiative, and opportunities for synergies on multinational registries through EU research & innovation programmes.

What are the regulatory needs in terms of registry data?

The first session focused on the regulatory needs in terms of registry data. These were outlined by the CHMP Vice-Chair. Whilst randomised controlled trials remain the gold standard for providing information regarding drug efficacy and safety, the value of RWD is increasingly acknowledged beyond the traditional use for long-term safety evaluation of medicines. Regulators cannot afford not to use registry data as their value is being established across all phases of drug development. In the pre-authorisation phase, registries can help better understand diseases characteristics, natural course, and standards of care; they can also support the planning and validity of clinical studies through identification of biomarkers, relevant endpoints, or confirmation of their representativeness. In the post-marketing phase, such data can provide insight into medicines' utilisation patterns, on effects associations (short and long terms), and on the impact of regulatory actions. Challenges however remain, as shown by the preliminary results of a web-based survey conducted within the More-EUROPA project in a regulators' cohort. Data quality, access and lack of knowledge on the data sources are seen as potential weaknesses of using data from existing patient registries for regulatory decision-making and should therefore be the main focus areas of improvement to complement data generated by clinical trials.

Use case highlighting opportunities and challenges of registries for regulatory decision-making

The second topic of discussion focused on the lessons learnt from the EMA-funded registry-based study on spinal muscular atrophy disease (SMA), which objectives were to describe SMA patients' characteristics at baseline and throughout the course of disease, as well as clinical

management and its evolution over time across the multiple disease phenotypes and genotypes in at least 5 European countries. A secondary objective was to learn about how regulators can work with registries to improve evidence generation on medicines. The study was conducted by Aetion in collaboration with TREAT-NMD. Following a thorough feasibility assessment, 6 registries within the TREAT-NMD network covering 9 European countries were selected, compiling data from 2188 patients treated or never treated. TREAT-NMD indicated that the results and study report were shared with the participating registries, which can in turn share them with the patients enrolled.

The learnings from the study have been numerous:

- The use of multiple registries in rare disease provided complementary information and increased sample size.
- The feasibility assessment phase is key to identify the most relevant registries. The EMA guideline on registry-based studies and the SPIFD framework helped in guiding and structuring the review of registries' suitability to answer the study questions. However, further quantitative counting (e.g., to determine extent of missing data) and higher granularity in defining the required data should be considered in future projects.
- Early and continued dialogue with registries beyond a specific study should be promoted to convey the value these data can contribute to regulatory research, so registries are willing and prepared to take part in a regulatory-type of project, in terms e.g., of data elements and systematic data quality assurance processes required for a study. A comment was made on whether the reasons for registries not to participate in such project should be made transparent, to better understand the underlying issues which may prevent further engagement.
- Understanding the extent of missing data is important and can to some extent be addressed through linkage of SMA registries with other data sources available at a country level (e.g., electronic health records, claims, pharmacovigilance reporting tools, death registries etc.). One particular challenge highlighted by registries was about the lack of capture and reporting of adverse events of special interest (AESIs). This may be explained by the fact that SMA registries have not been originally developed for routine data collection of such elements, and consequently, for monitoring of safety of medicines. Collection of safety data in registries may be a gap where practical regulatory guidance may be needed.
- Logistical challenges with accessing registries and providing statistical analyses (e.g., due to ethical approval and contracting challenges) can be addressed through early engagement with registries.
    - Some participants suggested that a standardised informed consent template to be implemented across registries could help speed up approval process. In any case, the importance of having patient representation in the registry governance would facilitate patient engagement in sharing their data. European Reference Networks (ERN) have implemented a standardised consent template for data collection in registries that is freely available on the European Joint Programme for Rare Diseases EJP RD website).

Post meeting note regarding ongoing work at international level on the incorporation of patient's perspective to improve the quality, relevance, safety and efficiency of drug development and inform regulatory decision making (see ICH Reflection Paper on Patient-Focused Drug Development (PFDD))

    - Common dictionary and data model can also facilitate and expedite analyses (e.g., analytics and statistical library).

- Registries need more support in terms of funding and resources to adapt to regulatory needs.

The topic of SMA continued with the presentation of an initiative launched in 2017 by the marketing authorisation holder of one of the three disease modifying therapies for SMA to support a global, collaborative network of SMA registries. The aim is to enable the collection of high-quality RWD to meet the key needs of the SMA community, healthcare providers, researchers, regulators, payers, and industry. This is being done by establishing collaborations with multiple SMA registries to improve the capacity and capability of registries to collect reliable patient-level data, to standardize data across clinician-entered registries with an international aligned core data set (TREAT-NMD), and to implement data collection and ensure sustainability through financial support. As the availability and quality of registry data are crucial to their utility, any steps to enhance these aspects are welcome, such as the HMA/EMA Data Quality Framework, feasibility assessments, checklists, as well as inventory of all (qualified) registries.

Fit for purpose and Data Quality Framework

These latter tools were discussed in more details during the second session, starting with the HMA/EMA Data Quality Framework (LINK), which describes data quality determinants, dimensions and metrics that should be used to characterise a data source.

Data discoverability: EMA catalogues on RWD sources and studies

This topic was followed by a presentation on the HMA-EMA Catalogues of real-world data sources and studies (LINK) planned to be launched by EMA in February 2024 to replace the former European Network of Centres for Pharmacoepidemiology and Pharmacovigilance (ENCePP) Resources Database, and the EU PAS Register. They aim to define RWD data sources and studies through a set of collected metadata to increase discoverability, and to help researchers identify relevant resources when investigating the use, safety, and effectiveness of medicines. The platform hosting the catalogues contributes to the transparency of observational research, as it promotes good practices aligning with 'FAIR' data principles for Findable, Accessible, Interoperable, and Reusable data. In the coming years, the platform will integrate with other catalogues, the European Health Data Space (EHDS) and similar initiatives, but also with EMA website content (e.g., EPARs, product information, qualification opinions, PRAC decisions). Before the launch of the catalogues, various stakeholders took part in a pilot, whereby data holders needed to complete the list of metadata for their data source before these were transferred into the platform. A pilot participant outlined the steps of the process, and highlighted that it had been a straightforward and positive experience. Besides the HMA/EMA catalogues, other tools exist, such as the European Rare Disease Registry Infrastructure ERDRI, which facilitates the search and discoverability of data in rare disease registries, as well as the Virtual Platform of the European Joint Programme for Rare Diseases (EJP RD), including catalogues of resources, registries, biobanks, knowledge bases and tools compliant with agreed standards. A future opportunity could be to link all these tools together in view to reduce duplication of entries and streamline findability.

Interoperability between registries and other data sources: HARMONY Big Data Platform

Interoperability between real-world data sources in the field of haematological malignancies was promoted through a presentation on the HARMONY big data platform, developed via an European public-private collaboration, and collecting data from 34 countries. The system uses the OMOP common data model for data standardisation and interoperability across the different sources, including registries. It includes data visualisation tools, as well as dashboards to support data analyses. One aim is for example to create a more accurate risk prediction on the likelihood of relapse in patients with acute myeloid leukaemia and help determine in which patients allogeneic hematopoietic stem cell transplantation should be performed. Despite clear added value for many stakeholders, some challenges remain to be fully addressed, including e.g., data heterogeneity, data quality, lack of funding and data protection requirements.

Summary of Day 2 – Breakout sessions

Session A: Fostering the use of patient registries for regulatory decision-making

Discussion

Data quality framework: The first objective of this session was to raise awareness on and to discuss the HMA/EMA Data Quality Framework (DQF) for EU medicines regulation and its draft Chapter on Real-World Data (RWD), which were provided to the participants prior to the workshop. Two parallel groups were asked to provide feedback on the content of the documents, and to consider the applicability of the principles outlined by registries holders on their registry data.

Participants agreed that the Chapter helps better grasp the concepts outlined in its parent document, and how these may apply to RWD sources. It is therefore recognised as an important tool to facilitate the use of patient registries for regulatory purposes. However, holding discussions about data quality of RWD sources outside a specific research question was considered difficult. The groups indicated that the Chapter on RWD would indeed benefit from some concrete examples based on context of use of registry data, e.g., to study natural history of diseases, drug utilisation, or long-term efficacy and safety of medicines.

Registry holders will need time to gain experience on the concepts of the DQF and its Chapter on RWD sources before these can be fully implemented within registries. More fundamental issues were raised that may need to be addressed as a first step, such as the lack of funding, as well as extensive change management and engagement campaigns to ensure broad awareness and integration into registries processes for sustained accurate data collection.

The importance of involving HTA at an early stage of registries development was raised in order to identify their data needs and level of quality required for medicines reimbursement purposes.

Several participants emphasised the value of clarity around informed consent related to the use of personal data. If patients and healthcare professionals understand what, how, and for which purposes their information are used (e.g., through regular feedback), this should ultimately have a positive impact on data quality.

HMA/EMA catalogues on data sources and non-interventional studies: The second objective of this session was to raise awareness of and discuss the opportunities and potential challenges of the catalogues launched by EMA in February 2024. The two parallel groups noted the improvements made compared to the former ENCePP Resources Databases and EU PAS Register, and acknowledged the usefulness of the new catalogues to increase discoverability of RWD sources including registries, as well as of the non-interventional studies they are part of. Linkage between studies and data sources' interfaces is of great value. Some additional information would be valuable, such as the date of last update of the registry or study entry, and a link to data dictionaries (i.e. variables names, min-max values, minimum data requirements etc.), which may help develop protocols, and determine the fitness for purpose of a data source in view of a study question.

To promote the registration of metadata related to RWD sources, studies, institutions/networks, and ultimately transform the catalogues into comprehensive easy to use resources, extensive and regular communication campaigns will be needed, including publicly available trainings and training materials.

Participants noted the existence of other catalogues, e.g., the European Platform on Rare Disease Registration (EU RD Platform), or the European Joint Virtual Platform on Rare Diseases administered by the European Commission, and expressed their wish to have these systems interact with each other. Such linkage would reduce the number of data entries and updates across different databases, may facilitate and ultimately increase the engagement in maintaining the information up to date.

Interoperability between registries/data sources: the usefulness of such setting was recognised and several examples were mentioned, such as the Nordic registries or the HARMONY big data platform. The main limitations mentioned for interoperability between infrastructures were the General Data Protection Regulation (GDPR) and national laws, which restrict the possibility to share and transfer health data within and across countries. Federated models could counter these constraints to some extent and could minimise the potential loss of granularity that would result from the use of a common data model (CDM). However, participants indicated that for new registries, guidance on CDM would be useful.

Main take aways

- Explore possibility of linkage between HMA/EMA catalogues and platforms administered by the European Commission.
- Consider all comments received on the DQF, its draft Chapter (once available) and on the HMA/EMA catalogues to continuously improve guidance.
- Ensure continuous promotion of existing tools through adequate communication channels and trainings on the DQF/Chapter, on the HMA/EMA catalogues.

Session B: Key elements of a 'feasibility assessment' to evaluate the relevance of a registry in view of a specific study question and design, areas for collaborations

Discussion

Two parallel groups where tasked to consider several topics, including: 1) the meaning of "fit-for-purpose registry", 2) the data elements required for specific contexts of use, 3) if, and when patient experience data may contribute to regulatory assessment and decision making, and 4) key areas where collaboration between stakeholders should be increased to strengthen the use of registries for regulatory purposes and decision-making.

Fit-for-purpose registry: These terms are understood to relate to a specific research question, and include meeting data quality requirements for this particular question in view of a study design.

Patient registries are developed for (a) particular purpose(s), but follow a learning curve to augment their data in a way which can meet stakeholders' requirements on research questions. The "fitness for purpose" is not strictly fixed in scope and time, and should be seen as a continuum. For a given context of use (e.g., to study drug utilisation patterns), a registry might be considered fit to answer a specific research question (e.g., use of antiepileptics in adults), but not another (e.g., use of antibiotics in children) due to various factors, starting with the data variables collected, which may evolve over time. Participants noted that reference should be made to the DQF for guidance, where the concept is defined.

In addition to assessing the fitness for purpose of registry data, which includes the data quality dimensions presented in the DQF (extensiveness, coherence, reliability, timeliness and relevance), it is also important to clearly understand the data collection, management and accessing/sharing processes in place to conclude on whether a registry is suitable for a study. This can be achieved by performing a thorough feasibility assessment, which should help identify the opportunities, limitations, and gaps of the registry data for a given question and study design. If not, data holders may consider whether the systems can be adapted accordingly.

Data variables relevant for specific contexts of use/study questions: Participants were provided before the workshop with examples of data variables to be collected for different contexts of use. They were asked during the breakout sessions to explore which ones would be key to inform the assessment of the fitness for purpose of the registry data, and to identify any elements which may be missing for such assessment.

A summary of the discussions held by the two parallel groups can be found in the Appendix Table 5. It should not in any way be understood as being an endorsed final overview of variables, but rather as a "working" list which may help stakeholders when assessing the fitness for purpose of the data for a specific research question pertaining to a particular context of use. Appendix Table 5 might be used to inform guidance on fitness for purpose and feasibility assessment.

The attendees agreed on the following general aspects:

- Regulators favour "disease" registries over "product" registries. A registry restricted to one product will limit the contexts of use, as clearly outlines in the Guideline on Registry-based studies.
- Registries cannot collect all key data for all scenarios. Balance between quantity and quality of data captured is key.
- Registries are not the optimal place for a timely reporting of all adverse events. They could however confirm/adjust risk for disease-specific complications or drug-specific adverse events from clinical trials.
- Patient experience and patient relevant data can be very valuable to better understand patients' perspective on the use of a treatment. Efforts should be made to explore how such data could be more systematically collected through registries.
- Linkage between data sources can augment registry data and therefore increase their relevance for a specific context of use/research question for a given study design.
- Timeliness for data sharing and/or data access is particularly crucial to determine fitness for purpose. This makes periodical updates necessary.
- Registries should evolve as standards of care evolve (e.g., collection of new diagnostics methods, new treatments, new outcomes measures including from patients perspective (e.g. patient experience data, patient relevant data).
- The need for new data elements is often emphasised, but registries should also stop collecting elements which are not considered relevant any longer.
- Reasons for loss to follow-up should be documented in the registries (e.g., participation in a clinical trial, patient cured from disease, patient changed centre).

Patient experience for regulatory assessment and decision making: Patient experience data (PED) have been defined as "*data collected via a variety of patient engagement activities and methodologies to collect patients' experience of their health status, symptoms, disease course, treatment preferences, quality of life and impact of health care"*[4]. These may include patient reported outcomes (PRO), questionnaires on patient preference (PP), quality of life (QoL) data, health-related quality of life (HRQoL) data, patient satisfaction, psychosocial data, or observer outcomes. They cannot be considered standalone but need to be contextualised within medicines regulatory applications. Specific EU guidelines on the collection, incorporation within medicines' dossiers and use of such data for benefit-risk assessment are necessary to translate regulatory expectations. The EMA Regulatory Science to 2025 and the HMA-EMA joint Big Data Steering Group Workplan 2023-2025 aim to reinforce patient relevance in evidence generation, and a Reflection Paper is currently under development to address this matter.

Key areas for collaboration between stakeholders: The planning for the development of a patient registry should ideally include all relevant stakeholders. Beyond registry holders and funders, future users like clinicians, patients, industry, regulators, HTA and academia should be consulted at an early stage. This should help understand data needs, align expectations on data access/sharing, reduce duplication of efforts, and ultimately foster the use of the registry for regulatory purposes and decision-making.

Registry holders present at the meeting expressed their strong need for an easy way to reach out to regulators at any time, including outside a regulatory procedure, to discuss questions they have on their registries. The creation of an informal group to facilitate such interactions was proposed. It should be composed of EMA as well as relevant multi-stakeholders as appropriate depending on the registry and topics of interest.

Main take aways

- Explore training needs/gaps linked to the use of registries (e.g., training for registries on regulatory requirements, regulatory needs, DQF, training for all stakeholders on the use of Patient Experience Data, on feasibility assessment).
- Explore the possibility to establish a channel for informal dialogues with EMA/regulators and other relevant stakeholders as appropriate to discuss questions related to registries.
- Anticipate future uses by exploring possible research questions based on data needs.
- Consider ways to promote tripartite active dialogues (industry, registries, regulators) on study concepts and protocols to better understand challenges ahead. HTA and patients could also be involved in these discussions as appropriate.

[4] European Medicines Agency (EMA). Patient experience data in EU medicines development and regulatory decision-making: Outcome of the workshop on 21st September 2022. (2022). https://www.ema.europa.eu/en/documents/other/executive-summary-patient-experience-data-eu-medicines-development-and-regulatory-decision-making-workshop_en.pdf

Key recommendations and suggested actions

The following tables aim to translate the main take aways of the two-day plenary and breakout sessions into recommendations and suggested actions moving forward.

As a next step, the EMRN will explore any existing channels/initiatives which could be leveraged to address the recommendations. Close interactions will be maintained with all stakeholders to ensure appropriate experts' involvement and consultation on the suggested actions.

Table 2 – Recommendations and suggested actions for Objective 1

Objective 1: Discuss the EMA qualification procedure for patient registries with the aim to clarify the benefits, identify current limitations, and propose measures to optimise the process.

As an outcome of the April 2023 multi-stakeholder workshop on qualification of novel methodologies, the guidance to applicants on Qualification of novel methodologies for drug development is being revised, creating the perfect opportunity to address the below recommendations related to the qualification of patient registries.

Recommendations	
Clarify the concept of qualification of patient registries (aims, scope i.e. contexts of use, values and expectations of stakeholders on the qualification of patient registries)	To identify common grounds, reach common understanding on what "qualification of patient registries" means, what its added values are, what it implies in terms of content (level of details)/format of the information to be submitted and timelines, to help applicants anticipate the resources they may require to go through the procedure. *Suggested action* As a starting point for follow-up discussions, consolidate the input received from stakeholders in the margin of the workshop (i.e. through the prep-work, during plenary and breakout session).
Review and optimise the process	To ensure it is fit for purpose to evaluate the use of patient registries in specific contexts in view to support regulatory decision making, and to accommodate the needs of the applicants and regulatory network experts. *Suggested actions* • Establish scoping meetings: To provide the opportunity for informal discussions with regulators before the submission of an application (e.g., to clarify regulatory requirements, expectations, operational aspects). • Consider ways to confirm the standards of qualified registries are maintained over time (post-qualification lifecycle management process): Regular interactions between all relevant parties to ensure agreed characteristics of registries for the qualified context(s) of use are sustained over time (e.g., variables, data quality metrics etc). This may also take into account new data variables added after qualification, and how these may impact on data quality.

Recommendations	
Develop guidance documentation (complementary to the general guidance on QoNM, and specific to the qualification of patient registries)	To support registry holders by increasing clarity on aims/scope, values, expectations, submission requirements and operational aspects. *Suggested action* Develop documentation focusing on patient registries based on the two above recommendations, which will complement the general guidance on QoNM, e.g.,: • Questions and Answers (Q&A) document; • Checklist for briefing book on format and content.
Foster communication on qualification of patient registries	To help stakeholders gain a better understanding of the procedure, to promote transparency and increase knowledge sharing. *Suggested action* Explore possible mechanisms to increase awareness about, and facilitate engagement with qualified registries. E.g., include a field to show the qualification status of registries in the HMA/EMA catalogues, including links to the qualification opinion.
Understand the added value of qualification of patient registries in the long term	To identify potential gaps and opportunities for process improvement. *Suggested action* Reflect on possible approaches to measure the impact of qualification for various stakeholders.

EMA = European Medicines Agency; HMA = Heads of Medicines Agencies; QoNM: Qualification of Novel Methodologies

Table 3 – Recommendations, actions, actors and timelines for implementation - Objective 2

Objective 2: Establish the value and enable the use of patient registries for regulatory decision-making by considering contexts of use for which registry data are 'fit for purpose' and examining tools to support data discoverability and assessment.

Recommendations	
Establish continuous interactions between stakeholders, starting at an early stage of registries' development	To discuss questions related to registries' development and subsequent updates, to understand needs (including on relevant clinical outcomes), to anticipate future uses/potential future research questions taking into account medicines pipeline, to improve the data quality for regulatory purposes, to understand potential challenges when developing study concepts and protocols. *Suggested actions* • Explore the possibility to establish a channel for informal dialogues with EMA / regulators and other relevant stakeholders as appropriate (experts forum). Involve more systematically industry, patients, HTA in registry-related discussions. • Explore ways to promote tripartite active dialogues (industry, registries, regulators) when developing study concepts and protocols to better understand challenges ahead.
Increase stakeholders' awareness and engagement on the use of patient registries for regulatory purposes	To strengthen the use of registries for regulatory decision-making, by improving registries' data quality, and discoverability, and by supporting the assessment of the relevance of registries in view of specific research questions. *Suggested actions* • Ensure continuous promotion of existing tools through adequate communication channels. E.g., HMA/EMA Data Quality Framework and its draft Chapter on RWD sources once publicly available, the HMA-EMA Catalogues of real-world data sources and studies, the Guideline on Registry-based studies, the Good Pharmacovigilance Practice Module VIII on post-authorisation safety studies, and the Scientific guidance on post-authorisation efficacy studies. • Explore potential training gaps linked to the use of registries. E.g., training for registries on regulatory requirements/needs (linked to and beyond the QoNM as per Table 2), training for all stakeholders on Patient Experience Data etc. • Explore possibility of linkage between HMA/EMA catalogues and platforms administered by the European Commission (e.g., EU RD platform and EJP RD Virtual Platform) to increase search capability, and avoid duplication of data entries across various catalogues.

EMA = European Medicines Agency; EJP RD virtual platform = European Joint Programme on Rare Diseases virtual platform; EU RD platform = EU Rare Disease Platform; GVP = Good Pharmacovigilance Practices; HMA = Heads of Medicines Agencies; HTA = health technology assessment; RWD = Real-World Data

Conclusion

The 2-day workshop showed the strong interest and positive engagement of all stakeholders in enabling the use of patient registries for regulatory purposes. Through open and honest dialogues, participants acknowledged the opportunities, but also the challenges of registry data in various contexts of use.

The qualification of patient registries was recognised as a valuable process to reinforce the use of these data sources to support regulatory assessments. The meeting was an eye-opener on the differences in stakeholders' understanding and expectations related to the qualification of patient registries. Clear recommendations and suggested actions were identified to address these differences, to improve the procedure and the support provided to the different parties involved.

Awareness was raised on important tools to increase data quality, discoverability, to improve assessment of fitness for purpose, and access to relevant data to support regulatory assessment. These include the HMA/EMA Data Quality Framework, the HMA/EMA Catalogues of RWD sources and non-interventional studies, other Catalogues for rare diseases, feasibility assessment, common data models and interoperability between data sources. Simplified communication channels will help fill the current gaps between registry holders and regulators to hold informal dialogues on the use of registry data.

By working together on the implementation of the suggested actions outlined in this report, regulators, registry holders, industry, patients, healthcare professionals, academia, and HTA will contribute to a better integration of registry data in regulatory assessment and decision-making, for safe and effective medicines for patients.

Glossary

AESI	Adverse Events of Special Interest
CDM	Common Data Model
CHMP	Committee for Medicinal Products for Human Use
DARWIN EU®	Data Analysis and Real World Interrogation Network
DQF	Data Quality Framework
EC	European Commission
EBMT	European Society for Blood and Marrow Transplant Society
ECA	External Control Arm
EFPIA	European Federation of Pharmaceutical Industries and Associations
EHDS	European Health Data Space
EJP RD	European Joint Programme for Rare Diseases
EMA	European Medicines Agency
EMRN	European Medicines Regulatory Network
ENCePP	European Network of Centres for Pharmacoepidemiology and Pharmacovigilance
Enroll-HD	Enroll-Huntington's disease
EPAR	European Public Assessment Report
ERN	European Reference Networks
EUnetHTA	European Network for Health Technology Assessment
EU RD platform	European Union Rare Disease platform
GDPR	Generalised Data Protection Regulation
GVP	Good Pharmacovigilance Practices
HARMONY big data platform	
HMA	Heads of Medicines Agencies
HRQoL	Health-Related Quality of Life
HTA	Health Technology Assessment body
MedDRA	Medical Dictionary for Regulatory Activities
NH	Natural History
OMOP CDM	Observational Medical Outcomes Partnership Common Data Model
PAES	Post Authorisation Efficacy Study
PAS	Post Authorisation Study

PASS	Post Authorisation Safety Study
PED	Patient Experience Data
PP	Patient Preference
PRAC	Pharmacovigilance Risk Assessment Committee
PRO	Patient Reported Outcome
PROM	Patient Reported Outcome Measures
PREM	Patient-Reported Experience Measures
QoL	Quality of Life
Q&A	Questions and Answers
RSS	Regulatory Science Strategy
RWD	Real-World Data
RWE	Real-World Evidence
SAWP	Scientific Advice Working Party
SMA	Spinal Muscular Atrophy
SNOMED	Systematized Nomenclature of Medicine
SPIFD framework	Structured Process to Identify Fit-For-Purpose Data
TREAT-NMD	Treat NeuroMuscular Disease

Appendix

Table 4 – Overview of RWD sources with EMA qualification advice or opinion

Name	Output	Disease(s)	Launch date	Geographical coverage	Nb of patients	Purpose for qualification
European Cystic Fibrosis Society Patient Registry (ECFSPR)	Opinion (2018)	Cystic fibrosis	2008	Europe	54 043 (2021)	PAES, PASS
EBMT	Opinion (2019)	Blood-related disorders	1974	Worldwide (centres in each continent)	+700 000 (2023)	Drug utilisation, PAES, PASS
International Niemann-Pick Disease Registry	Advice (2021)	Niemann-Pick disease	2013	Europe, North America, South America	500+ (2024)	PAES, PASS, Natural history (NH) data
Big MS Data Network	Advice (2022)	Multiple sclerosis	2014	Europe + Worldwide	+250 000	PASS
Enroll-HD	Opinion (2022)	Huntington's disease	2012	Europe, North America, Australasia, Latin America	21 561 (2024)	PAES, PASS
TREAT-NMD	Advice (2022)	Neuromuscular diseases	2007	Worldwide (centres in each continent)	65 750	PAES, NH data, Clinical trial control arm data, outcome measures validation
World Federation of Haemophilia Gene Therapy Registry	Advice (2023)	Haemophilia	2023	Worldwide	N/A	PAES, PASS
HARMONY BD platform	Advice (2023)	Blood cancers	2017	Worldwide (centres in each continent)	122 450 (2024)	External control arms, PAES, PASS, surrogate endpoints validation, NH data

Table 5 – Examples of data elements to assess the fitness for purpose of registry data*

** This list has not been endorsed by regulatory bodies. It aims to provide some orientation on important data elements to be considered when assessing the relevance of a patient registry for a given context of use. It is not fully comprehensive, but may be used as a basis for future guidance on the topic.*

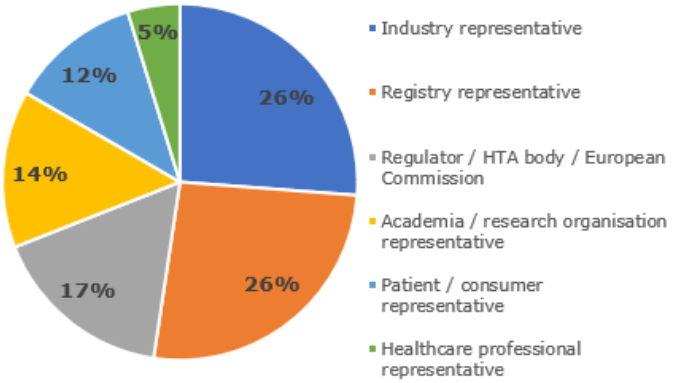
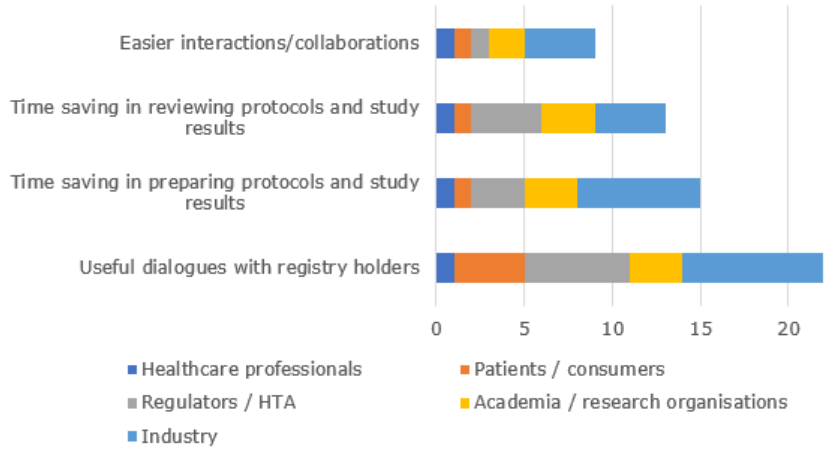
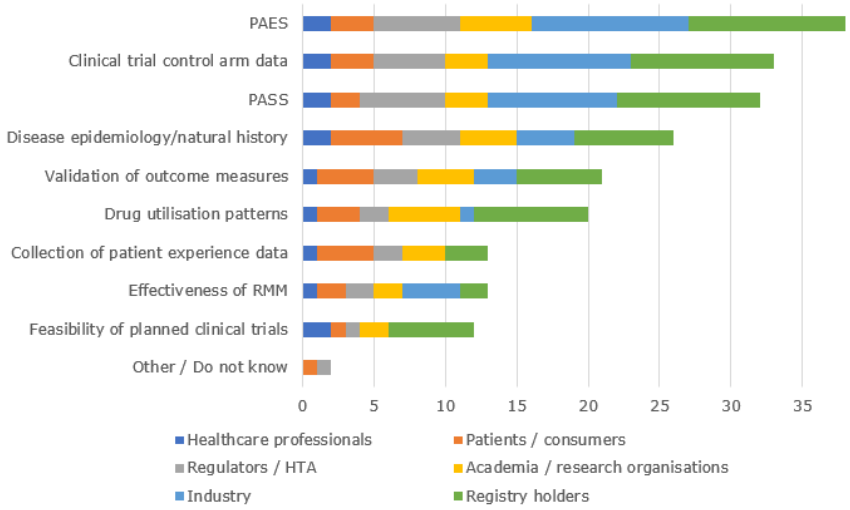
Contexts of use	Examples of data elements to be considered to assess the fitness for purpose of registry data (in no particular order)
General key data (across all use cases)	• Demographics: Age, gender (depending on disease), ethnicity (for trial diversity, genetic and/or phenotype differences) • Risk factors for the diseases, comorbidities • Relevant disease outcome data, endpoints (term from clinical trials) • Symptoms and dates of onset • Diagnostic methods, laboratory measurements • Diagnostic criteria, diagnostic date • Diseases subtypes • Dates of drug dispensation/prescription, information regarding treatments exposure including start/end date, dose, strength, indication (of treatment for the disease of interest and concomitant medicines) • Follow-up duration, loss of follow-up and date • Status of a patient (e.g., ECOG) at diagnosis and during follow-up • Genetic data • Dates of visits • Date of death and cause • Unique identifier to allow for linkage • Availability of data quality measures and indicators on any key variables to support assessment of the extensiveness, coherence, reliability of the data, e.g., for exposure calculation, quality indicators on recording of the treatments of interest, start and end dates will be important. • Pregnancy status as applicable
To study disease epidemiology / natural history	In addition to the general key data above: • Biomarkers (e.g., tumor genetic data), imaging • Information on standards of real-world practice of care and current standard of care (e.g., to assess off-label use) • Disease key progression milestones • Main clinical interventions • Patient self-reported data e.g., PROMs/PREMs • HRQoL (diseases specific + generic scales) • Geographical location (socio-economic data)? • Severity of disease • Environmental context (exposures) • Adverse events observed with standard treatment(s) if available Incidence and prevalence rates *Note: For rare and ultra rare disease registries, the more and broad data elements we can collect the better, to be able to serve different stakeholders*

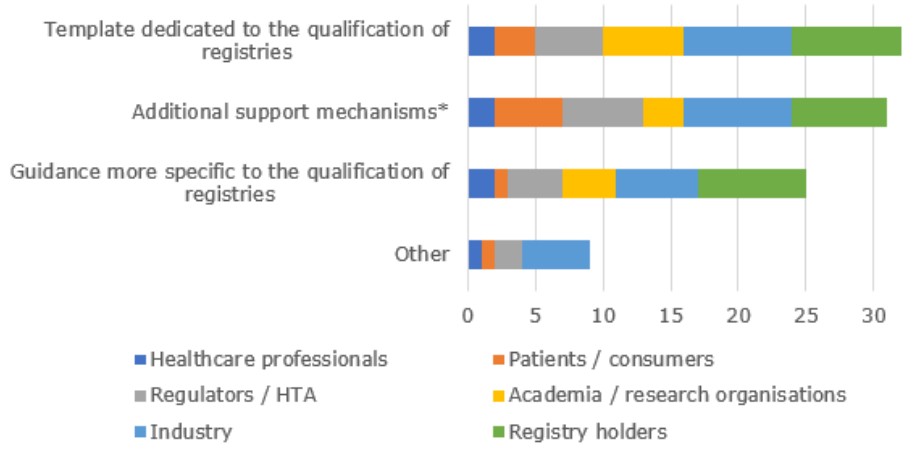
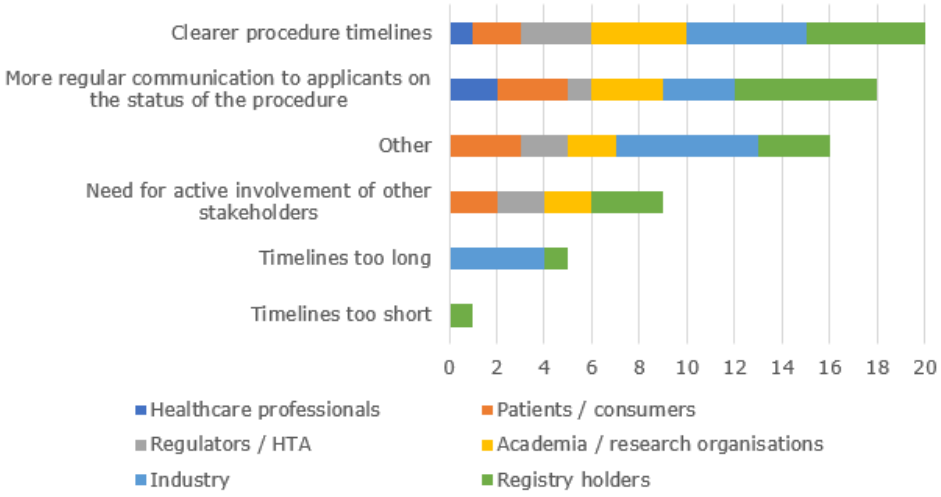
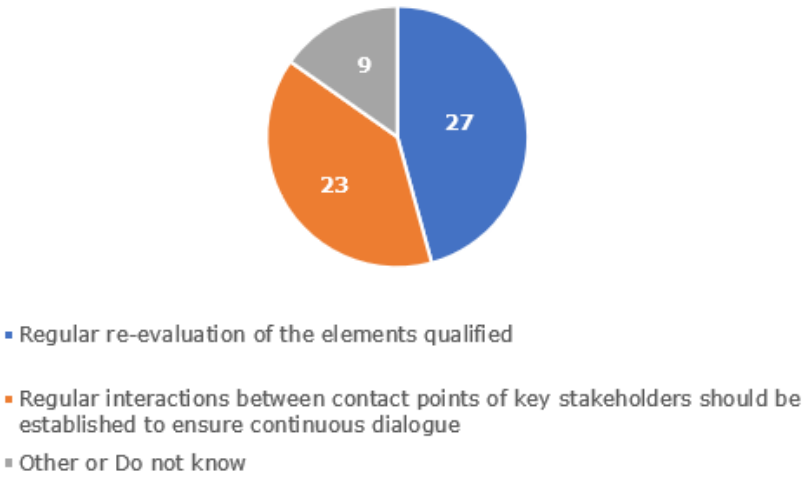
Contexts of use	Examples of data elements to be considered to assess the fitness for purpose of registry data (in no particular order)
To conduct studies on drug utilisation patterns	In addition to the general key data above: • Prescription information on treatment for the disease and co-medications: number of prescriptions, indications (for disease and patient population), route of administration, doses, schedule, duration of use • Information on standards of real-world practice of care and current standard of care (e.g., to assess off-label use) • Diagnostic and staging information as related to drug prescribing at patient level, sequence of drugs used at patient level and likelihood of progressing to next / other drug, discontinuation of drug use and reason, line of therapy information/regimen • Any defined adherence measures if available *Note: Off-label use and switching patterns can be inferred from data on drug usage. These data may inform drug repurposing.*
To assess the feasibility of planned clinical trials	Not discussed during the breakout session
To provide clinical trial control arm (e.g., external control arm ECA)	In addition to the general key data above: • Same elements as for studies on disease epidemiology/natural history above • Availability of same elements collected in the clinical trial • Adverse events observed with standard treatment(s) if available • Elements related to inclusion/exclusion criteria of the clinical trial • Timing of constructing the control arm (ideally contemporary with the trial) • Biomarkers, progression and outcome markers, surrogate endpoints • Patient-reported outcomes measures • Clinical outcomes measures, exposure to standard of care intended as comparator (as applicable) and timelines similar to clinical trial, rates of progression in range with clinical trial • Geographical locations similar to clinical trial • Duration of follow-up similar to clinical trial • Patient experience data *Note: Consultation with regulators (e.g., through Scientific Advice) should be sought before development of the ECA*
To conduct post marketing efficacy / effectiveness studies short and long term	Not discussed during the breakout session

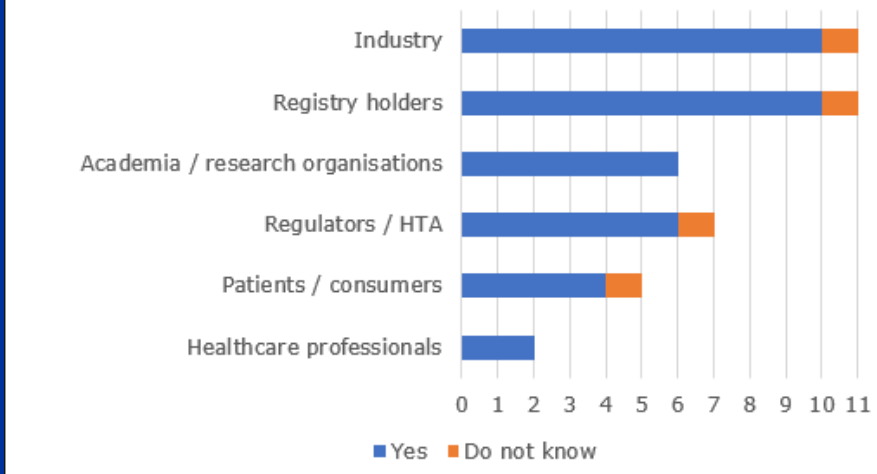
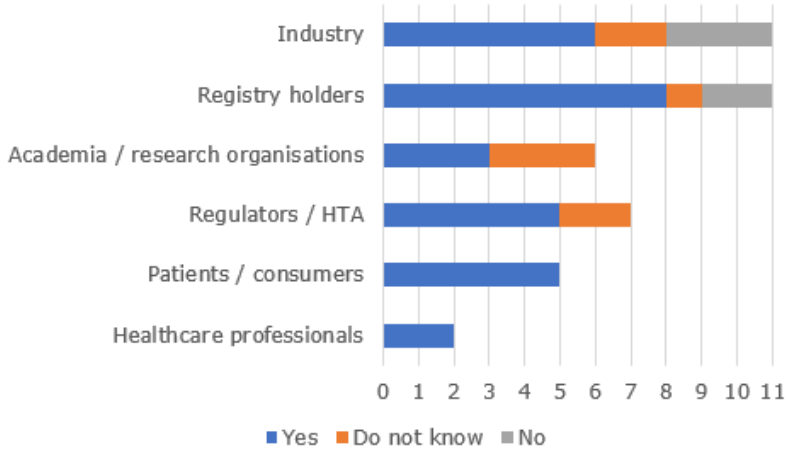
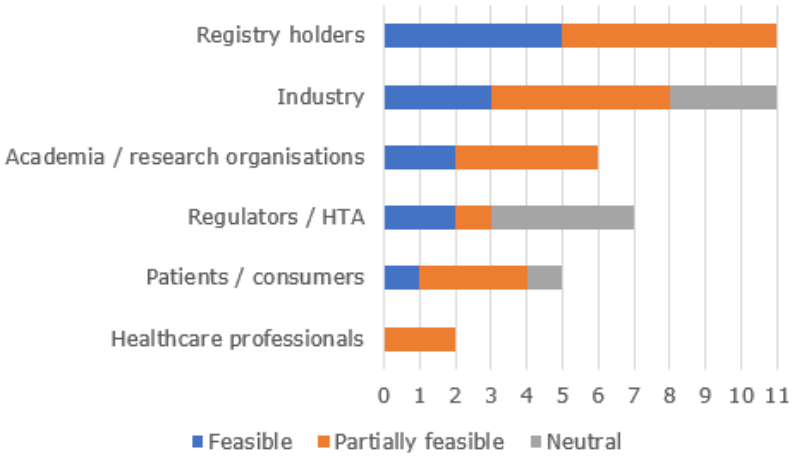
Contexts of use	Examples of data elements to be considered to assess the fitness for purpose of registry data (in no particular order)
To conduct post marketing safety studies (PASS) short and/or long term	In addition to the general key data above: • Adverse events observed with standard treatment(s) if available • Adverse drug reactions if available • Patient experience data
To support validation of outcome measures	In addition to the general key data above: • Same elements as for studies on disease epidemiology/natural history • Same elements as for PASS above if available • Proxy outcome measure as needed • Patient experience data
To assess the effectiveness of risk minimisation measures	In addition to the general key data above: • Same elements as for studies on disease epidemiology/natural history above • Same elements as for PASS above if available • Same elements as studies on drug utilisation patterns
To collect data on patient experience	• Patient reported outcomes • Questionnaires on patient preference • QoL data, HRQoL • Patient satisfaction • Observer outcomes (e.g., caregivers)

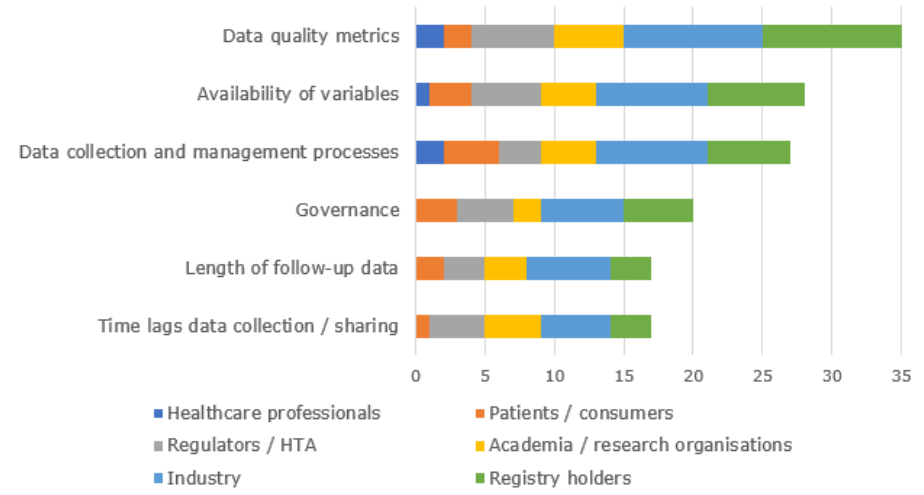
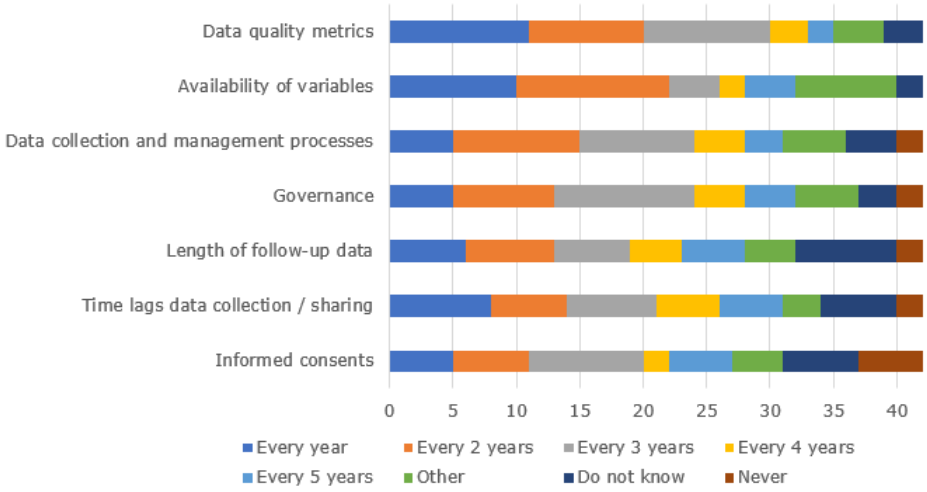
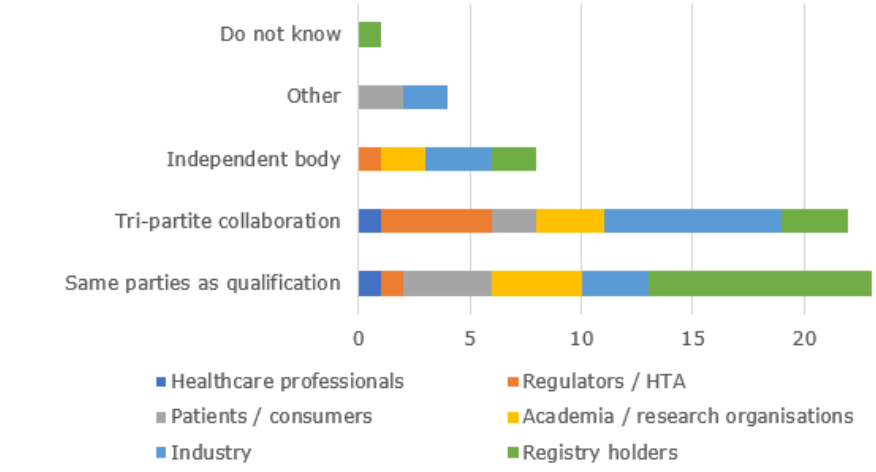
Supplementary Material

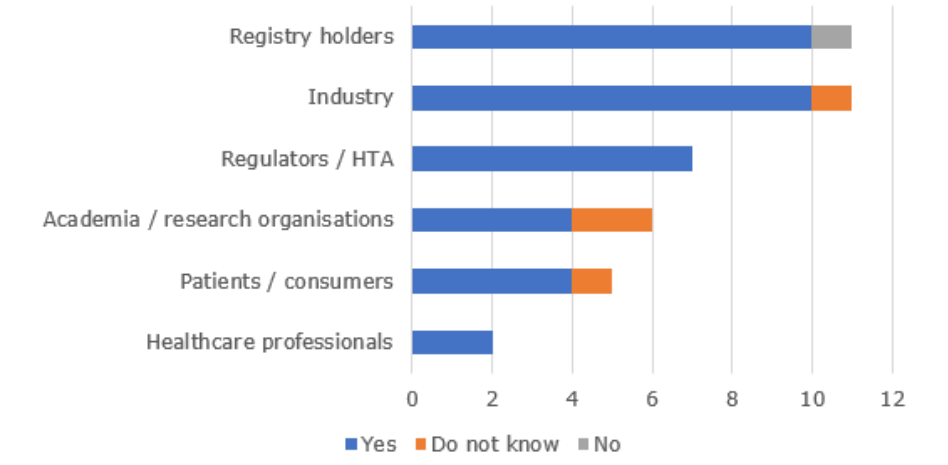
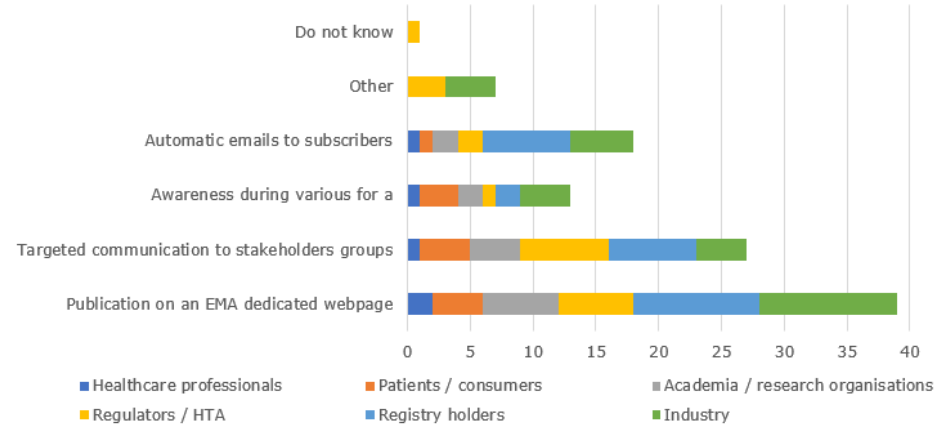
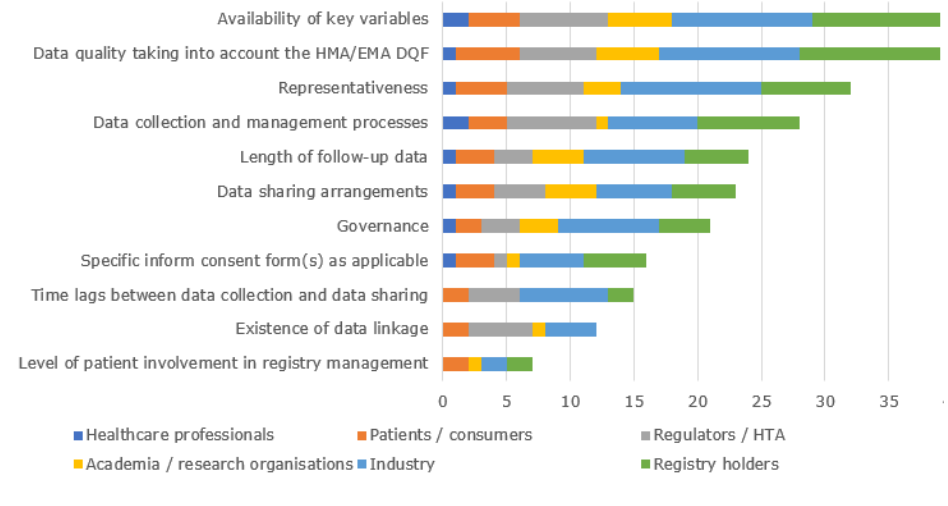
The following charts provide a summary of the aggregated responses to the preparatory questions sent by EMA to the workshop participants before the event. They were used as a basis for the discussion held during the breakout sessions.

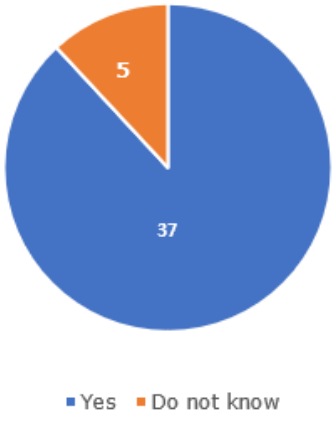
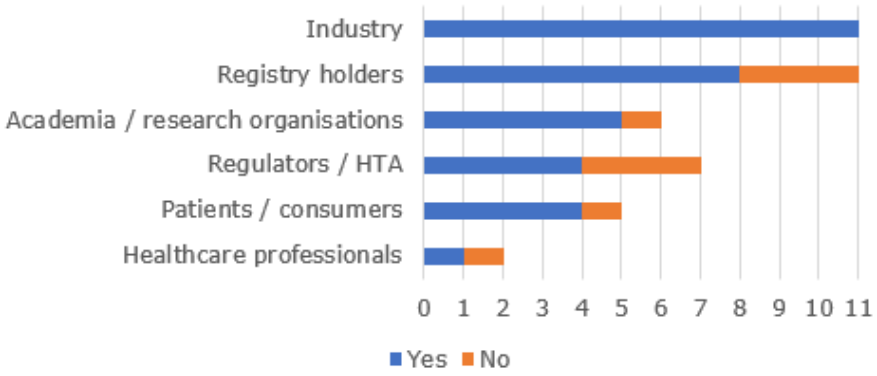
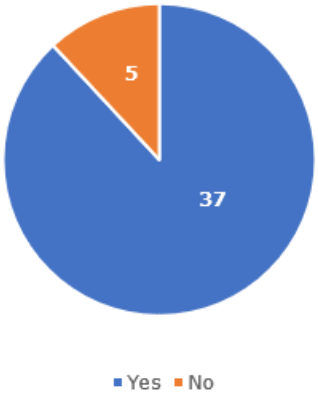
Topics	Aggregated responses
Overview of the respondents (43)	
What may the qualification bring to stakeholders / benefits?	
For which contexts of use of registry data do you think qualification is most relevant to seek?	

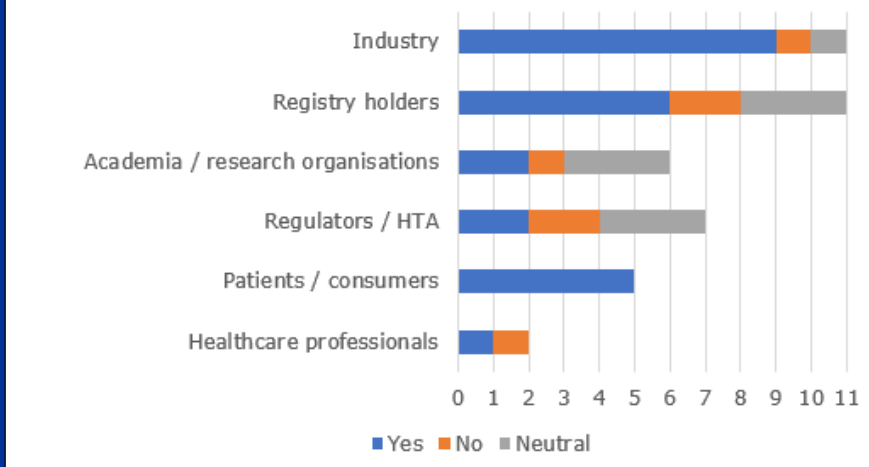
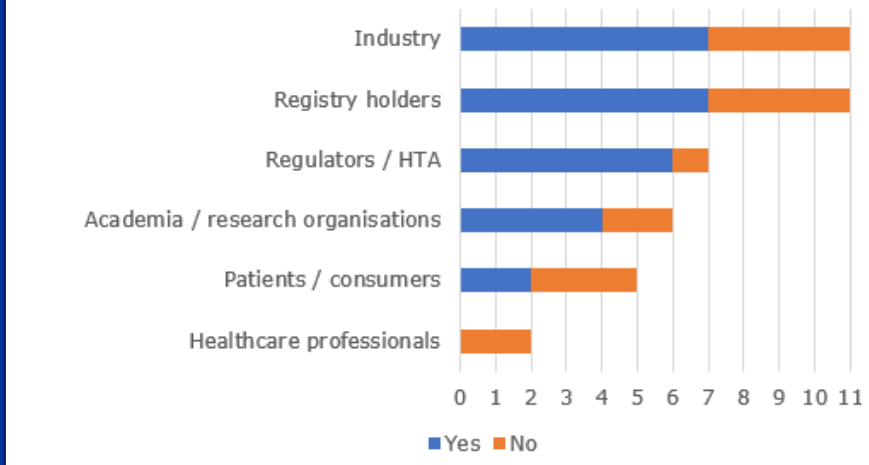
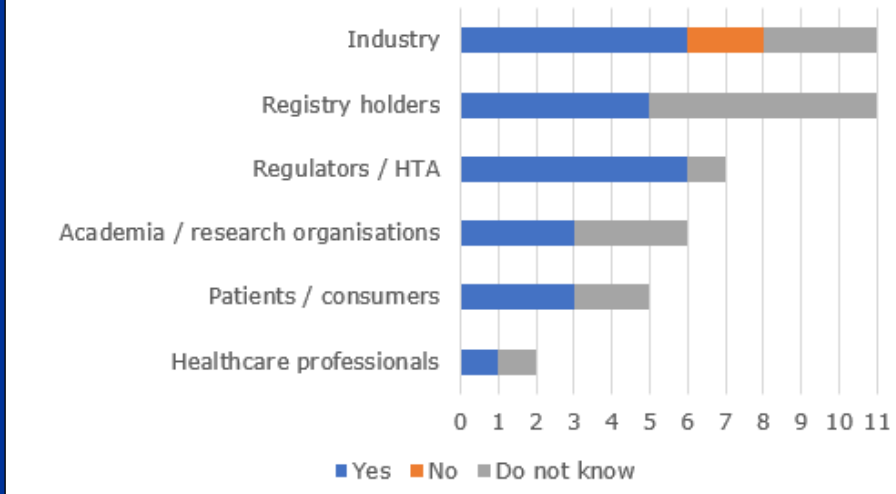
Suggestions for improvements? Pre-qualification application	
Suggestions for improvements? During qualification	
Suggestions for improvements? Post-qualification	

Do you think the Draft Qualification Check list is useful?	
Is the Draft Qualification Check list clear enough?	
How feasible might it be to provide all the information suggested in the draft check list?	

What do you think may be the most important elements to review following qualification of a registry?	
According to which frequency should the following elements be reviewed post-qualification?	
Who should be involved in post-qualification collaborations?	

Interest in receiving information about the qualification outcomes and regular reviews on registries	
Ideas for improvement of communication on qualification outcomes to promote transparency and increase knowledge	
What are the main key elements you would consider to assess the suitability (relevance) of a registry to address a research question?	

Do you think patient experience data can contribute to regulatory assessment and decision making, and when?	
Have you ever heard about the *HMA/EMA Data Quality Framework*?	
Do you think the *Draft DQF for EU medicines regulation - application to Real-World Data chapter* is useful?	

Is the document clear enough?	
Have you ever heard about the HMA/EMA catalogues of data sources and studies?	
Do you think the catalogues can be useful and can support your activities?	

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Joint Heads of Medicines Agencies (HMA)/European Medicines Agency (EMA)
Multistakeholder workshop on Patient Registries
EMA/283985/2024