



EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

15 December 2023
EMA/569008/2023
Scientific Evidence Generation Department

European Medicines Agency multistakeholder workshop on Qualification of Novel Methodologies

Summary report



Official address Domenico Scarlattilaan 6 • 1083 HS Amsterdam • The Netherlands

Address for visits and deliveries Refer to www.ema.europa.eu/how-to-find-us

Send us a question Go to www.ema.europa.eu/contact **Telephone** +31 (0)88 781 6000

An agency of the European Union



© European Medicines Agency, 2023. Reproduction is authorised provided the source is acknowledged.

European Medicines Agency multistakeholder workshop on Qualification of Novel Methodologies

Ensuring innovative methods for use in the development of medicines are valid, accessible to developers and help create patient benefit

Executive summary

On 17 and 18 April 2023, the European Medicines Agency organised a virtual multi-stakeholder workshop on the 'Qualification of Novel Methodologies' (QoNM) framework, a voluntary, scientific pathway allowing developers of innovative drug development methods or tools to request from European medicines regulators the qualification of these instruments.

During the workshop, participants from patient organisations, learned societies, academia, registry holders, HTA bodies, industry (pharmaceutical and medical devices), Notified Bodies, Public-Private-Partnerships, the European Commission and medicine regulators exchanged experiences, views and ideas on how to further strengthen and futureproof the QoNM platform.

In the journey from innovation and discovery to qualified tools, QoNM is key to enabling application of innovative methods for evidence generation to support benefit/risk assessment of medicines and to ensure that scientific progress translates into patient benefit. However, evidence requirements to support successful qualification are often underestimated during development/evidence generation and only realised during regulatory assessment, thus creating delays towards the ultimate qualification. The dialogue with regulators should start early and continue in an iterative way through to an ultimate Qualification Opinion. Revised guidance should clarify the scope of QoNM including its limits and what falls outside such scope. It should also stress the importance of Context of Use and how its evolution links to corresponding evidentiary requirements. Engagement of patient organisations, learned societies, academia and small companies with QoNM should be facilitated, e.g., by early interactions ahead of formal qualification requests and/or introduction of early scoping meetings. Broad support was expressed for publication of currently not-published high-level information from Qualification Advice (QA) requests to facilitate collaboration and avoid duplication of efforts. Pre-competitive collaboration could be promoted by regulatory direction towards areas of unmet methodology needs, while monitoring and reporting on the uptake and impact of qualified methods in regulatory decision making can inform whether such needs are being met.

Patient-reported outcome measures (PRO(M)s) (as well as observer-reported outcome measures (ObsRO(M)s) and other Clinical Outcome Assessment (COA) measures) are key elements of patient-centred medicines development. In clinical trials supporting drug development, COAs can provide reliable information on the treatment benefit on individual and population level depending on the clinical context and objectives of the trial. These factors and the stringency of the COA validation determine the context of use and potentially the positioning of the COA in the order of endpoints for a given study. It is important to find ways to convey the value of qualification to PRO(M) developers, in particular to patient organisations and professional/learned societies who are little familiar and inexperienced with regulatory qualification. Involvement of patients on the side of the PRO developer from inception of a project as well as on the side of regulators throughout QoNM interactions is pivotal. Parallel qualification interactions with HTA bodies would also be valuable given the importance of patient experience data for comparative value assessments. Finally, public repositories of available

measures, including those which have been accepted for regulatory decision making, could help avoid duplicative efforts, improve access and increase visibility of acceptable PRO/ObsRO measures.

Methods based on modelling and simulation, digital health technologies and artificial intelligence/machine learning will play a pivotal role in the future development and regulation of medicines. Reliable, robust and efficient Qualification of methods based on these technologies is expected to have a high impact with a view to improving treatment options for patients. Qualification is highly recommended for Modelling and Simulation (M&S) methods including iterative interactions and submission of code and raw data. There is interest in more objective and patient-relevant measures of treatment benefit conferred by digital health technologies (DHTs) whilst respecting privacy, equity and reliability. DHT-based measures and endpoints sit at the intersection of different regulatory frameworks (medicinal products, medical devices, in-vitro diagnostics) involving different regulatory bodies. This introduces complexities which should be reflected and managed in an optimised, possibly multi-decision-maker QoNM platform involving novel, relevant expertise. Considering the rapid development of underlying technologies, lifecycle management becomes a very important consideration in order to allow efficient extensions of context of use statements of qualified methods. Especially for artificial intelligence/machine learning-based methods, lifecycle management should establish definitions of relevant change of methodology requiring re-assessment vs. management as part of a quality management system.

Qualification is valuable in providing registries with recognition and visibility translating into improved utilisation and resources needed to ensure continuous and reliable collection of high-quality data. When preparing QoNM for registries and data sources, a clear definition of the intended Context of Use, defined in this context as the type of regulatory questions that may be answered with the data contained in the specific registry, as well as consideration of data quality frameworks are important reference points, and the publication of the EMA data quality framework, possibly aided by regulatory checklists, will facilitate QoNM preparations. As registries evolve over time, qualification opinion is not the end and there is a need for lifecycle management of qualified registries; periodic post-qualification dialogues between the registry holder, medicine developers performing studies based on registry data and regulators would help lifecycle management, including considerations of a need to reconfirm validity.

For the future, key aspects in the evolution of the QoNM framework include optimising procedural support and regulatory guidance, ensuring involvement of all necessary expertise to advise on and assess methods based on highly innovative technologies, defining useful procedural flexibility, standardising and optimising output formats, improving communication of successful qualifications in order to facilitate their implementation, uptake and impact and introducing effective but proportionate ways of lifecycle management of Qualification Opinions. Fostering pre-competitive collaboration for the development of novel methodologies, increasing awareness and transparency amongst developers of novel methodologies and exploring options for multistakeholder interactions (e.g., with HTA bodies) should also be considered.

Background and objectives

The qualification of novel methodologies process (QoNM) is a voluntary, scientific pathway allowing developers of innovative drug development methods to request from European medicines regulators the qualification of these instruments within a pre-defined Context of Use. Since its introduction in 2008 it has provided a platform for iterative prospective discussion and agreement of evidence generation plans for future qualification (Qualification Advice), as well as for publication of CHMP Qualification Opinions once a novel methodology has been demonstrated to be valid for evidence generation to inform benefit/risk decision making. It has also offered publication of 'Letters of Support' aiming at fostering further development when a novel methodology cannot yet be qualified but is showing promise based on preliminary data.

The European Medicines Agency (EMA) Regulatory Science Strategy (RSS) to 2025 has put forward a clear vision: *'To underpin its mission of protecting human health, EMA must catalyse and enable regulatory science and innovation to be translated into patient access to medicines in evolving healthcare systems'*, and has laid out strategic goals and core recommendations many of which are facilitated by the qualification of novel methodologies platform, e.g.:

- Enhance early engagement with novel biomarker developers to facilitate regulatory qualification: Critically review the EMA's biomarker validation process, including duration and opportunities to discuss validation strategies in advance, to encourage greater uptake and use.
- Support the development of robust digital endpoints through qualification, scientific advice and the establishment of a multi-stakeholder platform to obtain feedback on their utilisation.
- Establish an EU framework for data quality and representativeness. Develop guidelines, a strengthened process for data qualification through Scientific Advice, and promote across Member States the uptake of electronic health records, registries, genomics data, and secure data availability.

In 2022, a focus group of industry representatives and EMA has identified methodologies which will need qualification in the future and explored ways to futureproof the process. Discussions on how to foster development of robust novel methodologies and optimise regulatory qualification support have also been ongoing in other fora, e.g., the EFPIA Multistakeholder Workshop 'Enhancing patient-centric outcome measures and clinical trials with Digital Health Technologies' in December 2022, or in the context of the [EMA Multistakeholder workshop on 'Patient Experience data in medicines development'](#) in September 2022.

On 17 and 18 April 2023, the EMA organised a virtual multi-stakeholder [workshop on the 'Qualification of Novel Methodologies' \(QoNM\) framework](#). The workshop brought together patients, academia, learned societies, public-private-partnerships, consortia, HTA bodies, Notified Bodies, regulators and industry to explore the scope, process and outcomes of the qualification of novel methodologies platform, to share and discuss focus group learnings and to identify ways to optimise the process to further support the integration of science and technology in medicines' development while ensuring efficient and robust qualification of methodologies.

The objectives of the workshop were to:

- Explore the scope of qualification of novel methodologies in the light of ever accelerating development of science and technologies to best help translate innovation into patient benefit.
- Look at use case examples of different groups of methodologies, share procedural experiences and solicit input from stakeholders to identify recommendations to future proof the qualification of novel methodologies process and its outcomes.

Opening Session: Welcome and setting the scene

Since inception of the QoNM framework in 2008, 208 QoNM procedures have been completed, including 27 published Qualification Opinions and 39 Letters of Support. In a procedure duration analysis including 66 Qualification Advice and 6 Qualification Opinion procedures requested between 2019 and 2022, the average procedure duration was 170 days (minimum: 100 days) and 196 days (minimum: 130 days) for Qualification Advice and Qualification Opinion, respectively. The analysis suggests that there are mainly 2 time limiting procedural steps: a) many Applicants require more than one SAWP meeting cycle to address issues raised for the discussion meeting (up to 48%), and b) EMA requires more time to agree and publish draft Qualification Opinions (up to 84%).

Furthermore, learnings were presented from a survey sent to 28 Qualification Opinion and 39 Letter of Support holders, of whom 12 responded. Respondents represented all applicant groups for QoNM (public-private partnerships, academia, pharmaceutical industry, non-profit organisations, one startup and SMEs). Points raised by the majority of respondents included that timelines for final qualification opinion (QO) drafting and publication are not sufficiently transparent and/or not well communicated, that there should be a mandatory publication of high-level qualification advice information and that Letters of Support facilitate further evidence generation towards qualification opinion. For further details, please refer to the presentation on [QoNM current process and experiences](#).

Session 1: From innovation to qualified tools – the scope of qualification of novel methodologies

The session focused on ways to enable and foster seamless transition from early research into qualified opinions, to promote increased uptake of the QoNM procedure and to increase the impact of qualification opinions.

Qualification is not an easy undertaking: a recent analysis found that 70% of biomarker-related Innovation Task Force meetings between 2008 and 2020 did not result in a subsequent regulatory qualification or scientific advice interaction (please refer to [The journey of innovation](#) and references therein). Evidence generation to support regulatory qualification is a challenging exercise and the effort required to pursue and achieve qualification is often underestimated, so that for large public-private consortia it is very challenging to succeed within the funding horizon of 5-6 years ([EU public-private funded project landscape – how to enable a more seamless transition into Qualifications](#)). Evidence requirements supporting a Qualification Opinion should be clarified in future guidance allowing developers to have a better understanding on whether their data may meet the evidentiary expectations of regulators to qualify tools.

On the other hand, clear and concise Context of Use (CoU) definitions are paramount for successful regulatory qualification. Beyond initial qualification, evidence used previously to support a qualification opinion could be re-used to support evolving CoUs or technological changes in the context of life-cycle management of qualification opinions ([The Scope of Qualification of Novel Methodologies: Pharma perspective](#)). Early and iterative interaction with regulators is key: if regulatory qualification is the objective of consortia, suitable regulatory and evidence generation strategies with definition of regulatory milestones need to be in place from the start of a project. Especially for EU-funded research projects (e.g., IHI), awareness of the need for regulatory qualification is critical and regulatory interactions should be planned from the start of projects. In some cases, it is even advised that regulators should become members of the consortium (e.g., projects related to the European Health Data Space (EHDS)). Academics are encouraged to contact the regulators (EMA) to help them identify the best interaction pathway. In this context, the [STARS project](#), a Horizon 2020-funded Coordination and Support Action (CSA) on Strengthening Training of Academia in Regulatory Science aimed to reach

out to medicine innovators in academia, bridge the regulatory knowledge gap and enhance dialogue between academia and regulatory authorities.

As QoNM procedures require significant resources, projects to be considered for regulatory qualification could be selected based on their expected impact. Suggestions included an early meeting (e.g., [ITF](#) or other early scoping meeting format to be developed) on the basis of regulatory stewardship/single point of contact as an option for exchange between developers and regulators, where suitability/relevance of a project to pursue qualification could be discussed and clarified. Moreover, given the increasing complexity of novel methodologies to support medicines development, multi-stakeholder involvement (e.g., medicine and medical device regulators, HTA bodies, patient representatives) is key to enhance the quality of assessment and utility of qualified methodologies.

Qualification opinions are publicly available reference points indicating to all developers the acceptability of an innovative method in the qualified context of use, while scientific advice provides confidential feedback solely related to the development of a specific medicinal product. In the [Regulatory Science Research Needs](#), the EMA has identified several gaps which ideally should be addressed to improve regulatory considerations and actions. Monitoring and reporting on the uptake and impact of qualified methods in regulatory decision making can inform whether such needs are being met. The challenge is that all stakeholders need to work more systematically towards such improved methods being widely used in all areas of medicines research, i.e., development, evaluation and use. In this respect, potential proprietary technology constraints could prevent wider application of qualified tools ([The Scope of Qualification of Novel Methodologies: Pharma perspective](#)).

Session 2: PRO, ObsRO, ClinRO – key elements of patient centred medicines development

Patient reported outcomes (PROs), Observer reported outcomes (ObsROs) and Clinician reported outcomes (ClinROs) together with Performance outcomes (PerfOs) collectively comprise Clinical Outcome Assessment (COA) measures. In the medicines regulatory context ([Regulatory perspective on the qualification of PROs, ObsROs and ClinROs](#)), COAs are meant to provide reliable information on the change of the condition(s) of patients by a pharmacological treatment in the context of a clinical trial and hence on the treatment benefit on individual and population level. The relevance and importance of COAs for evaluation of treatment benefit is dependent on the underlying disease and the objectives of a clinical trial (functional diseases vs. life-threatening diseases; disease modification vs. symptomatic treatment). This relationship as well as the stringency of the COA validation relevantly determine the 'positioning' of the COA, i.e., as primary, secondary, or exploratory endpoint. COA validation is necessary for its use for regulatory purposes and it is usually divided into at least two important steps: Content validation, which includes concept elicitation (evaluation of literature, input from experts, patient centred interviews) and cognitive debriefing (patient understanding, refinement, correction, 'early psychometrics'); and Psycho-/clinimetric validation, which involves use in observational and randomised treatment trials and evaluation of consistency, test-re-test validity, construct validity, discriminant validity, responsiveness and determination of the minimal clinically important difference (MCID).

In a recent analysis of the regulatory output (Advice Letters or Opinions) of EMA qualification procedures finalised between January 2013 and December 2018 ([Silva-M et al., 2023](#)), qualification procedures were generally considered more appropriate to obtain detailed feedback on PROs/ObsROs and PerfOs than including questions on such tools into product-centred scientific advice. The frequency of general questions/statements suggested a need for discussion and guidance on principles of development of COA tools despite relevant literature and guidance being available.

Patients and healthcare professionals should be in the lead of COA development and appropriate patient input during method development and the regulatory qualification of COAs is paramount and must be ensured. Many academic/learned societies and patient organisations have little familiarity with the QoNM process, they perceive it as long and burdensome and they would like to see an abbreviated process, tailored to the needs of specific methodologies/stakeholders. Regulatory qualification of COAs is important for their uptake by clinical trial sponsors in late stages of clinical development and improved communication between learned societies, medicinal product developers and regulators is critical. Engagement of regulators in learned society meetings could help to inform on available regulatory interactions and how already developed measures could be qualified ([development of a PRO for upper limb function in Duchenne Muscular Dystrophy \(DMD\)](#), [PROMS for studies in rheumatology - ASAS health index as an example](#)).

Repositories of available COA measures could help avoid duplicative efforts and facilitate access. The need for new tools should be carefully assessed and such tools should preferably be developed by consortia to avoid parallel development. Introducing early interactions between the various stakeholders involved in COA development when preparing regulatory qualification could help on many levels, not least for prioritising instruments which address high unmet measurement needs.

Session 3: Methods based on Modelling and Simulation, Digital Health Technologies and AI/ML

The session discussed modelling and simulation-based methods, digital health technologies-based endpoints and outcomes and artificial intelligence/machine learning-based methods.

Qualification is highly recommended for Modelling and Simulation (M&S) methods, particularly if the method is intended for high impact regulatory decision making, if platforms are to be used in many development programmes and for complex models built on retrospective data. Factors which have historically supported successful qualification opinion requests were prior qualification advice (QA) and submission of raw data and code allowing the Qualification Team to perform analyses. Published Qualification Opinions (e.g. [Islet Autoantibodies as enrichment biomarker for Type 1 Diabetes prevention clinical trials](#)) provide valuable insights to developers regarding the evidentiary expectations for Qualification ([Regulatory perspective on qualification of Modelling and Simulation based methods](#)).

Digital Health Technologies (DHTs) present unique challenges as they fall at the interface of different regulations (pharmaceutical, medical device, in vitro diagnostic) and require involvement of different regulatory bodies. Clear regulatory pathways and increased efficiency through the set-up of coordinated multistakeholder advice is considered essential by relevant developers. Regulatory guidance could provide more details on patient acceptance/usage and device clinical utility; on lifecycle management of qualified measures for extensions of the context of use so as to ensure continued validity (Quality management system); and on the requirements for device analytical and clinical validation (e.g., need for interventional studies, [Case study on the development and QoNM interaction of digital measures of nocturnal scratch in Atopic Dermatitis](#)). From the regulators' perspective, the relevance of the Context of Use of DHT-based methods for drug development is critical to ensure that the methodology to be qualified falls within the scope of the QoNM. Given the different legal frameworks and regulators (medicinal product, medical device) involved, technical and clinical validation should be separate. Clinical performance evaluation is central to method qualification, and it should be related to the (specific) Context of Use and application. Ideally, the method to be qualified should be device-agnostic and minimum requirements for technical performance of devices used in the application of the method should be defined and published ([Regulatory perspective on qualification of methodologies based on DHTs and AI/ML](#)). On the other hand, Notified Bodies cannot be involved in consultancy or advice activities for MDs/IVDs they are expected to assess for conformity assessment;

however, other options for engagement with regulators may be explored ([Notified Body \(NB\) perspective – opportunity to collaborate with medicine regulators for Qualification of Novel Methodologies?](#)).

For artificial intelligence (AI)/machine learning (ML)-based methods, the biggest challenge is evolution of the AI/ML model over time and determining what changes can be controlled via a quality management system and which ones may require re-qualification ([AI-based pathology](#)). Regulatory standards should avoid suffocating this dynamic and quickly evolving field due to over-regulation. Robustness in AI/ML model development may make the model stable over time and reduce the need for constant changes or allow these to be managed via a quality management system. Interpretability and explainability are paramount for regulatory acceptability. As with DHT-based methods, technical and clinical aspects need to be separated for meaningful advice. Use of public model repositories and federated methods could allow moving into a future of open-source models used by multiple companies, thus creating standards of quality ([Regulatory perspective on qualification of methodologies based on DHTs and AI/ML](#)).

Session 4: RWE – Qualification of data sources

EU regulators have progressed to enable the use and establish the value of Real-World Evidence (RWE) in regulatory decision making for years. A [Guideline on registry-based studies](#) was published in 2021 and some disease registries have received either Qualification Opinions or Letters of Support. Workshops have been held both on patient registries in general ([Patient Registries Workshop Report 28/10/2016](#)), [Multistakeholder workshop on Patient Registries 12-13/02/2024](#)) and on disease-specific registries. Important considerations regarding the qualification of registries include the extent of data elements to be collected and data quality issues. Co-medication and medicine safety data have often been missing in registry qualifications to date which have primarily intended to support the conduct of post-authorisation safety studies and issues of feasibility and data missingness have been highlighted in early proof-of-concept studies ([Regulatory perspective on the Qualification of data sources](#)). Registries utilised as data sources for DARWIN EU do not undergo a formal qualification process, but DARWIN follows [Kahn's data quality framework](#) implemented with thousands of checks via code on the data sources (internal consistency, validity, timeliness etc.). This quality assessment is part of the onboarding process of a data source. The EMA is also building an overarching [data quality framework](#).

Registry qualification is not a one-off process, it requires life-cycle management, and potentially there is need for confirmation over time. Registry holders perceived the procedural timelines as short towards addressing the questions raised and highlighted the need for continued regular triangular exchange between registry holder, EMA and MAHs who use qualified registries as data source; currently, post authorisation study discussions are usually limited to MAH and EMA. Such post-qualification exchange will allow for transparency on impact and uptake of the qualified registry and will help to monitor the need for eventual re-qualification of the registry for lifecycle management ([The European Cystic Fibrosis Society Patient Registry Qualification opinion experience](#), [The Treat-NMD Qualification of Novel Methodologies experience](#)). Checklists may be offered to applicants preparing qualification requests applying data quality frameworks, focusing on minimum requirements and metrics for data quality.

From the patient perspective, optimal re-use of patient registry data is important; interoperability of data sources is key and dynamic informed consent could help overcome data re-use concerns in the future. New technologies like large language models (LLMs) may in the future allow reliance on unstructured data and facilitate patient contribution. Finally, patient relevant data should be defined in close collaboration with patients during method development and regulatory qualification review.

Session 5: QoNM procedure going forward – ways to optimise

The final 'working' session of the workshop aimed at collecting ideas and recommendations from workshop participants on how to optimise the Qualification of Novel Methodologies platform.

Discussions were organised around six topics as follows:

a) Future scope and expertise needs

EMA qualification is no substitute for medical device (MD) or in-vitro diagnostic (IVD) conformity assessment and qualifications can and should be device-agnostic. There is however a need to agree on performance levels required to qualify e.g., endpoints or COAs using specific tools as device agnostic.

Moreover, qualified methodologies are meant for common use in medicinal product development; therefore, qualification opinions need to include enough detail to allow independent replication and use of the qualified methodology. Intellectual property (IP) is no barrier to qualification and vice versa. Broad adoption of e.g., qualified endpoints can simplify clinical trials, accelerate drug development and provide innovative treatments to patients faster.

b) Regulatory guidance and development support

There is a need for enhanced support for micro, small and medium-sized enterprises (SMEs) and non-commercial applicants (patient organisations, academics, healthcare professionals, hospitals). There are already support mechanisms available (SME office, Patients and Consumers Working Party (PCWP), Healthcare Professionals Working Party (HCPWP), academics support) but these need to be advertised more and perhaps complemented with early support mechanisms specific to QoNM.

General guidance on the definition of specific contexts of use and the evidentiary requirements to support such context of use statements are paramount. There may already be a lot of regulatory guidance available, albeit scattered and not easily accessible, so structuring and improving accessibility of existing guidance may be an important step. Regulatory guidance may not be too normative (e.g. in terms of setting success criteria) and should clarify that a clear definition of the targeted context of use is critical from the planning stage of a qualification exercise to consider the types of experimental designs and the robustness of data needed, but also when progressing to critically reflect whether the evidence generated can support the targeted context of use ('recursive loop'). Moreover, workshops can help progress thinking and deeper understanding in emerging or complex technologies.

c) Procedural timelines and flexibility

The EMA qualification procedure has been criticised as being too long (refer to session 2) or too short (refer to session 4). The process itself is relatively simple and, despite a priori defined milestones, flexibility is applied throughout the process to accommodate both applicant and assessor needs. However, while procedural flexibility is important, many qualification projects are led by public-private partnerships (PPPs) with limited funding horizons, so predictability is equally important. Similarly, clearly defined milestones are helpful for inexperienced applicants.

'Staggered' submissions like a rolling review of incoming data could allow to scrutinise whether the accruing evidence is still in line with the targeted CoU. Such staggered submissions could also avoid exposing reviewers to overly complex dossiers at the end of a qualification exercise. This is already an option through multiple qualification advice requests before a final qualification opinion is issued.

Early regulatory engagement is advisable, and EMA offers enhanced support to less experienced applicants informally and as part of ITF briefing or QoNM pre-submission meetings. ITF briefing meetings have by nature a focus on innovative proposals generally at the stage of early development and draw on the same pool of network experts as the actual qualification process. The pragmatic use of ITF and formal qualification interactions allows responding flexibly to the needs of specific projects

and applicants. Future procedural guidance for Qualifications should better clarify the interplay between early ITF interaction and later qualification. Moreover, there is a need for enhanced support, e.g., in the form of early scoping meetings, for qualification developments falling outside the scope of ITF.

d) Patient involvement in the QoNM procedure

There is a need for training of patient representatives to prepare them for the process and the complex questions of the qualification procedure. Both patient organisations and the EMA could utilise and enhance existing training options. Regulatorily experienced patient representatives could also act as mentors. Moreover, patient contribution could be made transparent in published qualification opinions and more patient input could be solicited during the QO public consultation procedure. Also, there should be reflection on how outcomes from qualification procedures can be better communicated so they become accessible and interesting to all stakeholders, not least to patient organisations.

e) Qualification outcome format and communication

Both the briefing document and the format of the qualification opinion require standardisation. A future common format of qualification opinions should be centred around the Context of Use and explain what (evidentiary) considerations led to the CoU and its restrictions. A structured common format of outcome documents can facilitate retrieval, analysis and sharing of regulatory information on qualified methods. This would facilitate implementation in drug development by any interested parties and could also facilitate monitoring of the uptake of qualified methodologies in regulatory decision making, clinical trials or other studies available in the public domain.

Better communication of qualification outcomes would publicly identify areas in which qualification exercises are ongoing, increase transparency to avoid duplication of efforts and foster pre-competitive collaboration. Both regulatory guidance and presentation of Qualification Opinions and Letters of Support on the EMA website need to be improved. The currently chronological presentation of QOs and LoS on the EMA website, could be replaced by e.g., presentation per type of method or disease area. With a view to lifecycle management, information presentation could be dynamic to enable appropriate reflection of how tools evolve.

Workshops and Q&A documents could facilitate understanding of qualification opinions by stakeholders and build trust. Closer involvement of learned societies and healthcare professionals could increase their awareness of qualified tools and ultimately lead to their inclusion in e.g., clinical guidelines as appropriate. Close collaboration with public-private-partnerships is important and scientific publications on Qualifications help to inform the wider scientific community.

Monitoring, documenting and reporting of use of qualified tools in regulatory decision making would be impactful and help other developers of novel methodologies. If qualified methods have been used to generate evidence to support of benefit/risk assessment for a medicinal product, this should be mentioned in the publicly available documentation (European Public Assessment Report, EPAR).

f) Impact, uptake and lifecycle management of qualification opinions

Comparative quantified reporting of impact and uptake of qualified methods may not be possible given highly heterogenous development targets. Ultimately, monitoring of impact may not be about numerical uptake, but whether the originally targeted unmet measurement need has been addressed and changed the respective study design paradigm.

There is a clear need for lifecycle management of qualified registries involving regular communication between registry QO holder and EMA. Continued feedback on data quality is critical: while the addition of new patients to a registry introduces change over time, performance and validity of other methods should remain more stable with implications for lifecycle management. Monitoring of registry use in

post authorisation efficacy/safety studies (PAES/PASS) is important. It could be considered to update published information on qualified registries with information on studies which have been successfully performed and reviewed by the CHMP. This may however raise the question how to handle qualified registries who have not supported generation of data submitted to regulators over time.

Extensions of the context of use, e.g., between related conditions can already be considered at the time of initial Qualification Opinion including an exploration of the evidence required to broaden the CoU. Structuring and supporting extensions to the CoU is important, including potentially shorter timelines vs. initial qualification. Considering creative and dynamic ways to foster extensions of existing qualifications will be important when futureproofing the process.

Post-workshop survey

A post-workshop survey was conducted to collect additional feedback from workshop participants who may not have had a chance to voice their views during the workshop. 19 responses were received (Primary affiliations of respondents: 14x Pharma/MedTech Industry, 3x Academia, 1x Notified Body, 1x Patient & Consumer Organisation). In terms of additional types of methodologies which could benefit from regulatory qualification, participants indicated synthetic data, pharmacovigilance, non-clinical/3Rs, statistical methods, biomarkers, paediatric models, evidence tools for use specifically with medical devices, data collection platforms, nanotechnologies, 3-D printing and advanced manufacturing techniques. Most respondents supported to keep Qualification Opinions device/software agnostic. The published Qualification Opinion should provide sufficient information on required performance characteristics of device/software to enable bridging exercises when developers utilise different devices/software. Intellectual property may need to be considered on a case-by-case basis. There was near full support by respondents for mandatory publication of high-level information from Qualification Advice to facilitate collaboration and avoid duplication of efforts; few respondents reminded that such information needs to be tailored not to disclose critical proprietary information. Concerning expertise needs, digital health technologies, AI/ML, nanotechnology, gene therapy, and medical device development were mentioned. Other stakeholders considered important for collaboration were HTA bodies, Notified Bodies, professional societies/healthcare professionals and academic experts. Involvement of patients/representatives should be ensured. Most respondents indicated the need for a well-structured overarching general qualification guidance update which highlights key components in the Qualification process: principle of early and iterative interaction from ITF to QO, clear description of procedure flow, definition of the context of use as reference point for the generation of supportive evidence, terminology, evidence generation steps, organising of the data and supportive templates for key procedural documents. While some respondents would appreciate technology specific guidance, most acknowledged that such information may be shared in a more dynamic way by publishing Q&A documents which may be updated more frequently. Early engagement, options for preparatory scoping meetings, streamlined EMA contact points as well as continuous horizon scanning in collaboration with developers/stakeholders to allow for forward looking expertise building were also mentioned.

The way forward – key recommendations to future-proof the QoNM

- Publish updated general guidance clarifying scope and the role of Context of Use for determination of evidence requirements
- Overarching guidance may be complemented by additional guidance modules for specific method types, using conventional or alternative formats such as Q&As, checklists and/or lessons learned (live) documents

- Update and standardise templates for Briefing Document, Qualification Advice Letter and Qualification Opinion
- Clarify the role of existing regulatory interaction options (e.g., ITF) and introduce qualification-specific early support mechanisms (including scoping meetings)
- Consider involving more external experts within the limits of Conflict-of-Interest considerations (e.g., in cooperation with Working Parties/European Specialised Expert Communities)
- Define needs/criteria for life-cycle management of QO for data sources, registries, DHT, AI/ML related methods, i.e., methods for which conditions and/or technologies change over time or if not used for evidence generation over a period
- Consider a structured approach for extensions of Context of Use of qualified methods
- Improve webpage presentation of procedural guidance, qualification opinions and letters of support to improve visibility, accessibility and uptake; this may include dynamic presentation of qualification opinion information on webpage (e.g., versioning) to reflect how tools evolve transparently and record life cycle management
- Maintain formal assessment process to enable predictability as well as reasonable flexibilities (e.g., clock-stops, additional time for initial assessment or QO prep and publication)
- For registries/data sources, explore post-qualification triangular interactions involving all stakeholders (registry holder, MAH, EMA) as part of life cycle management
- Consider the potential for:
 - Training with public-private partnerships (e.g., IHI, C-Path) for methodology developers as well as for patient representatives (e.g., with EURORDIS patient training/PCWP/PED initiative)
 - Identify specific unmet needs for novel methodologies through Committees or Working Parties by linking to Regulatory Research Science Needs
 - Exploring options for more proactive and transparent involvement of additional decision-makers (e.g., HTA bodies, MD/IVD regulators) and stakeholders (e.g., patient representatives, learned societies, healthcare professionals)
 - Workshops on emerging or complex technologies in the regulatory context (e.g., AI-workshop, RNA workshop, etc.)
 - Mandatory publication of high-level qualification advice elements
 - Workshops and/or Q&As on high-impact Qualification Opinions to facilitate understanding by stakeholders, build trust and clarify the Qualification process
 - Establish active interaction with professional societies developing COAs
 - Scientific publications on specific Qualification Opinions and Advice
 - Monitoring and reporting of evidence from qualified tools considered in regulatory decision making (AI/LLM-based EPAR or scientific literature screening tool, updates from QO holders as part of post-Opinion commitment)
 - Fostering pre-competitive collaboration between industry, academia/learned societies and patient organisations: Support development of IT platforms facilitating collaboration and regulatory interaction; Membership of regulatory experts in public-private partnership scientific advisory groups and in methodology focused working groups of learned societies.

Abbreviations

AI/ML	Artificial intelligence/machine learning
CHMP	Committee for Medicinal Products for Human Use
ClinRO(M)	Clinician Reported Outcome (Measure)
CoU	Context of Use
DHT	Digital Health Technology
EC	European Commission
EMA	European Medicines Agency
EMRN	European Medicines Regulatory Network
FDA	United States Food and Drug Administration
GVP	Good pharmacovigilance practices
IMI/IHI	Innovative Medicines Initiative/Innovative Health Initiative, a joint undertaking between the European Union and the pharmaceutical industry association EFPIA
IP	Intellectual property
ITF	Innovation Task Force
IVD	In-vitro diagnostic
LoS	Letter of Support
LLM	Large language model
MAH	Marketing Authorisation Holder
MD	Medical Device
ObsRO(M)	Observer Reported Outcome (Measure)
PCWP	Patients and Consumer Working Party
PerfO(M)	Performance Outcome (Measure)
PPP	Public Private Partnerships (e.g., IMI/IHI, Critical Path Institute)
PRO(M)	Patient Reported Outcome (Measure)
QA	Qualification advice
QoNM	Qualification of Novel Methodologies
QO	Qualification opinion