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Questions and answers: Qualification of digital technology-based methodologies to support approval of medicinal products

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1. What is the purpose of this document?

This document highlights some of the key points to consider for the successful qualification of digital technology-based methodologies intended to support approval of medicinal products.

The principal focus of the document is to support Qualification of methodologies based on digital technologies in the context of medicinal product development. It may also be of assistance to applicants in the preparation for other types of EMA procedures and interactions, such as Innovation Task Force (ITF) meetings, scientific advice briefing books drafting, and preparation of Marketing Authorisation Applications (MAAs).

This Q&A document is not intended to provide comprehensive guidance; instead, it reflects EMA's current experience at the time of publication. As this is an area of rapid evolution, further considerations may be added as EMA's experience increases.

Due consideration should be given to general guidance documents on Qualification available on the EMA website¹, which is supplemented by this Q&A document focusing on aspects specific to digital technologies.

2. Why a Q&A on digital technologies?

Increasingly, digital technologies are becoming part of the conduct of clinical trials for medicinal products. Examples include continuous patient monitoring for clinically relevant parameters, electronic data capture of laboratory values, digital/remote monitoring of drug intake, electronic signatures on consent forms, and direct data entry by clinicians into case record forms.

When it comes to using data captured in this way, particularly for the purpose of benefit-risk evaluation of medicines, questions often arise regarding the extent to which these technologies can be considered to be in line with, better, or less reliable than the more established means of data capture as foreseen by GCP. Additionally, given the characteristically rapid evolution of such technologies, the validity of the data collected in support of the benefit-risk balance of a medicine must be ensured throughout development. The qualification assessment needs to consider a detailed and robust methodology, while capturing it in a sufficiently flexible way for it to remain valid after, for example, relatively minor software or device updates.

3. What is meant by digital technologies, and which ones fall under EMA remit?

The scope of this document is to offer the broadest support to applicants when using methodologies based on digital technologies in the development of medicinal products, therefore a precise definition would not be warranted, as it may result in the exclusion of innovative approaches that cannot be foreseen at time of writing.

While digital technologies can cover a broad range of applications, EMA's remit is limited to the specific use of a methodology in the development, use or monitoring of medicinal products pre- or post-authorisation, taking into account the expected role of such technologies in the development, evaluation and ultimately use of medicines. Examples may include sensors (e.g. ingestibles, implantables), mobile health (mHealth) tools (e.g. wearable device carried by patients to measure certain health related parameters, remote patient monitoring), tele-healthcare in clinical trials (e.g.

¹ <https://www.ema.europa.eu/en/human-regulatory/research-development/scientific-advice-protocol-assistance/qualification-novel-methodologies-medicine-development>

video consultations), health data analytics (e.g. data processing systems that support bioinformatics modelling) and digital record systems (e.g. digital applications, also referred to as “apps”, that function as patient diaries).

In summary, if a digital technology is used in the context of medicinal product development, evaluation or monitoring, and is expected to impact, even potentially, on the benefit-risk assessment of a Marketing Authorisation Application (MAA), then relevant aspects of the technology will be discussed at the time of MAA evaluation. A qualification, or another form of regulatory input such as scientific advice, should be considered by the applicant during the product development, and this Q&A document may provide useful considerations for the preparation of the submission documents to EMA.

The following examples of digital health technologies are considered within the scope of the digital methodologies qualification programme:

Digital endpoint: A Digital Endpoint (a precisely defined variable intended to reflect an outcome of interest that is statistically analysed to address a particular research question) is derived from or includes a digital measurement. Digital endpoints can be clinical outcome assessments (clinical relevance established *De Novo*) or biomarkers (reliable relationship with existing clinical outcome can be established).

Digital Biomarker (BM): A digital biomarker is an objective, quantifiable measure of physiology and/or behaviour used as an indicator of biological, pathological process or response to an exposure or an intervention that is derived from a digital measure. The clinical meaning is established by a reliable relationship to an existing, validated endpoint.

Electronic Clinical Outcome Assessment (eCOA): An eCOA is a quantifiable measure used as a measure of how patients feel, function or survive that is derived from a digital measure. The clinical meaning is established *de novo*. Clinical outcomes can be assessed through a report by a clinician, a patient, a non-clinician observer or through an active performance-based assessment or passive monitoring of patient behaviour or performance.

Digital measures: Objective, quantifiable measure of physiology and/or behaviour collected and measured through digital tools.

It is important to try and identify early the components of the digital technology that could fall within EMA’s remit and those that are not, so that relevant assistance can be received during development, if desired.

As an example, if an applicant is interested in qualifying the use of clinical variables captured by using a wearable device to collect data from clinical studies, which are expected to be evaluated as part of an MAA, aspects on how such data support the benefit-risk assessment (e.g. endpoint outcomes, reliability, accuracy, sensitivity to change, clinical and technical validity aspects, compliance, clinical relevance of data collected, data reflected in the product information) may fall within EMA’s remit. However, aspects related to the technical design and in-use safety and performance of the wearable, which are not expected to impact benefit-risk assessment of medicinal product, would generally not be considered by EMA: the Agency strongly encourages developers to consult with the relevant decision makers holding the legal mandate to review these specific issues.

As a further example, the qualification of digital biomarkers or electronic COA for use in a clinical trial to support the development of a medicinal product in a given therapeutic area would be within the scope of the EMA qualification procedure; this would not include requirements on how to meet the conformity assessment of a medical device software or for medical devices used to administer medicinal products, if applicable. However, to ensure that the EMA assessment is in the correct

context, it is recommended to provide high level information on the technology in the background to the request.

4. What is the applicable legal framework?

The development plan should conform to the general standards, guidelines and legal framework set for medicines development.

Consideration should also be given to meeting the requirements of any additional current legal and regulatory frameworks that may apply beyond the medicinal product regulatory framework, depending on the digital technology. These may, for example, include:

- Medical Devices legislation;
- ICH E6 (R2) (GCP) and other applicable ICH guidance requirements need also to be respected and specifically those on validation of electronic systems and audit trail. The sponsor remains ultimately responsible for ensuring that the conduct of the clinical studies and the final data generated by those studies comply with the regulatory requirements. This applies in particular to the safety of the subjects and the integrity, reliability and robustness of the data generated in the clinical study;
- Ethical aspects;
- ISO;
- Data protection. EMA would like to draw the developers' and applicants' attention to the utmost importance of ensuring compliance with all applicable EU data protection requirements, in light of the sensitive health data processed by the device to be used in combination with the proposed medicinal product. The assessment of such compliance falls outside of the scope of EMA remit. Developers and applicants are reminded that the monitoring and enforcement of data protection compliance in this regard is within the remit of the national data protection authorities of Member States.

The principal mode of action will determine the applicable regulatory framework, and how (and if) the product will be reflected in the medicine's accompanying product information (PI). For those technologies that are likely to have an impact on the safe and effective use of the product, and are to be reflected in the PI, it is important that the submitted Qualification briefing document clearly explains how they are going to be used, and the potential impact that they may have on the use of the medicinal product and the clinical outcomes.

5. Is it possible to consult EMA in advance of a planned submission?

EMA encourages early contacts to assist prospective applicants in identifying the best regulatory interaction route, and to advise on the content of submissions.

EMA assistance can be sought in several forms for example in the form of Scientific Advice pre-submission, ITF pre-discussion, regulatory-only questions.

The EMA Small and Medium Enterprise SME office also offers specific support to these categories of companies.

6. What should be the content of a request for qualification advice/opinion?

To achieve a timely and successful submission, while limiting requests for additional information, it is important that the documentation provided is relevant, comprehensive and focused.

A qualification submission should provide insight into the reliability, accuracy, precision, clinical validity, generalisability and clinical applicability of the methodology to be qualified, at a level of detail that is sufficient for assessment, yet not so detailed as to invalidate the qualification when, for example, minor software updates are implemented.

Given the speed of evolution of technologies versus the duration and lifespan of a qualification process, the qualification will focus on how the technology will provide clinically meaningful data and not on requirements how to meet technical specifications.

The focus of the EMA qualification process will be to assess whether the clinical measure taken with the technology is fit for the intended use in regulatory decision making during drug development, whether a clinically meaningful interpretation of the concept of interest is possible, and whether or not the underlying method used is reliable and robust. In the case of digital health technology tools, evidence to support the adequacy and transparency of performance characteristics will need to be part of the qualification briefing book, but this should not include an assessment of the adequacy of the technical performance of the device. If available, relevant certificates for devices used in the studies should be appended to the documentation submitted to EMA.

The device used with a medicine, unless integral, will not normally be specified (i.e. named) in the PI and European Public Assessment Report (EPAR), however its characteristics will be described. Should a named technology be specified in the PI, lifecycle regulatory maintenance implications, depending on the nature and impact of the change, will need to be considered.

Aspects beyond the medicines' legal and regulatory framework, such as those mentioned under Q4, are not normally expected to be discussed in a qualification procedure, as the technology will be expected to fulfil the existing and applicable legal (including national) and regulatory requirements.

In planning their submission, Applicants should reflect on how they will meet these requirements. It is recommended to explain the chosen approach in the briefing book introduction, as this provides a background to the scientific assessment. As some of these aspects might raise questions about an impact on the reliability of clinical data collection or on the benefit-risk of the medicinal product, providing this background information avoids unnecessary questions during assessment, thus speeding the qualification process. Information on how the essential principles of the Medical Device Regulation are met (or planned to be met) strengthens the overall picture on the reliability of the proposed tool, and is likely to contribute expedition assessment.

In most cases, for digital tools that are considered medical devices and for in vitro diagnostics, a CE mark would not normally be required at development/advice stage. Applicants are, however, reminded that it is their responsibility to meet the applicable legal and regulatory requirements prior to submitting or granting of a MAA.

In general, the following aspects should be considered when preparing an application:

For a **clinical outcome assessment (COA)**:

1. Content validity
 - a. Context of use definition

- b. Variable selection to evidence that the instrument measures the concept of interest. Derive variable selection from qualitative work to select the variable of interest and select digital features based on the sensitivity to the concept of interest.
- c. Patient understanding and patient burden

2. Construct validity

Demonstrate that the filtered, transformed, or otherwise processed raw sensor data are accurately measuring the concept of interest that is intended to be directly measured, often done by:

- a. Correlation/concordance with other related measures (cross-sectional) or other means if there are no measures to correlate against.
- b. Discrimination of known groups (healthy volunteers/ patients, different phenotypes)
- c. Specificity in discriminating potential confounding factors.

3. Reliability

- a. Test-retest reliability (variability of successive measurements of the same test carried out under the same conditions)
- b. Biological/physiological and environmental variation (physiological variability of test without measurement error and under stable disease conditions; e.g.: data collection environment, duration of data collection period, days of the week for monitoring). Elements of data analysis: data file preparation and transfer, missing data rules,
- c. Total variation (total variability of repeated measurements under stable disease conditions)

4. Sensitivity to change

- a. Mean-to-SD ratio of decline (longitudinal change of score over time period during which disease is expected to progress relative to population variability)
- b. Longitudinal correlation with clinical assessment
- c. Longitudinal change predictive value (could be applicable depending on COU)

For a **digital biomarker**, the following aspects should be considered in the evaluation for qualification:

1. Context of use and proposed biomarker category.
2. Rationale to support the added benefit as compared to traditional methods:
 - a. Biological/physiological rationale compared to the proposed context of use.
 - b. Potential added value to drug development (e.g.: improved clinical trial efficiency, improved subject safety)
 - c. Anticipated consequences if the biomarker is unsuitable for its intended use (e.g.: underpowered trial, missing data handling, inappropriate approval decision)
3. Reliability
 - a. Test-retest reliability (variability of successive measurements of the same test carried out under the same conditions)
 - b. Biological/physiological and environmental variation (physiological variability of test without measurement error and under stable disease conditions; e.g.data collection

environment, duration of data collection period, days of the week for monitoring).
Elements of data analysis: data file preparation and transfer, missing data rules,

- c. Total variation (total variability of repeated measurements under stable disease conditions)
4. Sensitivity to Change and Treatment:
 - a. Correlation of longitudinal change in biomarker domain score with respective change in clinical assessments of interest during the same time period
 - b. Correlation of longitudinal change in biomarker with a disease modifying intervention
5. Data supporting relationship between the biomarker and clinical outcome of interest.
6. Evolution of the device throughout the validation program; what changes were made to the system, when, and their potential impact.

The points above detail the general qualification principles for digital COAs and biomarkers. The applicability of individual points will be dependent on the context of use.

7. What are the considerations regarding Context(s) of Use (CoU) of a digital technology?

The Context of Use is the critical reference point for the regulatory assessment of any qualification application. One aim of the qualification procedure is to obtain clear insight into the robustness of the method across the settings in which it is to be used, and to scientifically justify the selection of a specific technology for a specific study or given purpose. Therefore, a full, clear detailed description of the way the digital methodology is to be used, and the medicine development related purpose of the use needs to be provided (phase of development, nature of endpoint (primary, secondary, exploratory), which parameter, which devices components).

If different digital technologies can be utilised (e.g. “bring your own” (BYO) device trials) within the same trial, the impact on the quality of data collected, and on how this may bias population selection in actual use should be discussed, since this is expected to have a potential impact on benefit-risk assessment. For example, this approach allows subjects to use a technology they are familiar with and minimises the burden to carry additional devices. This is also the case if several devices or a device system are used concomitantly (e.g. mobile app accompanied by actimeter or ingestible sensor). While there is little experience of BYO trials at present to comment on with any certainty, it is expected that data will need to be available in the dossier to demonstrate that the technology has been verified, validated, and a control system, including specifications, is in place to ensure its functionality also in accordance with the applicable European Union data protection legislation (see section 4 in this regard). This includes demonstrating consistency across mobile devices in measuring and collecting the data; technical specifications (e.g. operating system, storage capacity, sensors); performance specifications (e.g. accuracy and precision); and operational considerations, including, for example, security of data processing, provision of technical assistance to patients and study sites, availability of sponsor-issued devices if the patient does not possess a suitable one, consent of data subjects, confidentiality and data ownership. A risk management plan should include, for example, interference with other applications on the device, data security breaches, effect of upgrades, etc.

It is advised to have automated and centralised data monitoring, to detect potential calibration errors.

When used for regulatory submission purposes, the mobile technology should have gone through a process of Computer System Validation (CSV) according to the relevant standards. This CSV needs to be documented.

It is considered essential that the applicant and the regulators have the possibility to access the CSV documentation in order to ensure data integrity, reliability and robustness². (See also section 4)

Equally, if the study site selection or the general applicability of a digital technology (if intended for patient care or monitoring) might be impacted by the device/technology choice, a discussion on the implications for extrapolating to different contexts of use is warranted.

8. How should clinical usefulness and expected use be discussed?

Clinical utility is defined by whether a product improves health outcomes, diagnosis or treatment. The clinical usefulness (usability of the technology plus its utility³) should be discussed in terms of the benefits and drawbacks of the use of digital technology. Examples of benefits may include shorter assessment time at sites compared to non-digital assessments, the possibility to include rare-disease patients from remote locations, or the ability to execute study designs that reduce the number of patients or have shorter duration because of denser data and more sensitive measurement. Examples of drawbacks may include the requirement that patients have to be trained, and sites need to oversee compliance with assessment schedules. A comparison with standard of care methods should also be considered.

The impact on diagnostic thinking, patient management and clinical outcome must be specified and justified. Adding to the CoU described above, applicants are encouraged to clearly map out the expected pathway of use of the device/technology and whether its implementation, either at development stage or market use, presents a burden for the healthcare professional (HCP), the patient, or has an impact on patient care.

9. What is a best practice guide, and why is it important?

Ensuring the correct use of the technology is critical, and a best practice guide explaining the following aspects should be included. Even at an early development stage, an attempt at discussing foreseen patient/HCP education on the use of the tool is recommended, in order to avoid discussions later in development that might compromise adherence to the tool and data quality as part of the MAA. Aspects to be considered are whether the measures should be taken for certain periods of time, whether in all environments e.g. at school, at home, outdoor or indoor, clinics, during weekdays and weekend, what kind of training or support is needed, whether feedback or monitoring will be used. A description of how compliance will be assessed is also desirable.

10. How should a digital endpoint be selected?

Conceptually, the selection process of a clinically relevant endpoint is not different for methodologies based on digital technologies as compared to traditional approaches: the choice of a digital method of

² Notice to sponsors on validation and qualification of computerised systems used in clinical trials, EMA/INS/GCP/467532/2019, 7 April 2020. <https://www.ema.europa.eu/en/human-regulatory/research-development/compliance/good-clinical-practice/ga-good-clinical-practice-gcp>

³ Coravos, A., Doerr, M., Goldsack, J. *et al.* Modernizing and designing evaluation frameworks for connected sensor technologies in medicine. *npj Digit. Med.* **3**, 37 (2020). <https://doi.org/10.1038/s41746-020-0237-3>

data collection should be grounded in identifying and measuring concepts that are relevant and clinically meaningful to the target population, or correlated with a clinically relevant outcome.

Evaluating reliability, convergent validity and ability to detect change are also important psychometric properties to establish.

Where relevant, diagnostic and prognostic performance (sensitivity and specificity) as well as sensitivity to change in clinical status should be demonstrated. Predictive values for medicine response and likelihood ratio (LR) are to be provided, and levels of positive or negative predictive value are to be characterised.

The collection of a potentially very large dataset via frequent or continuous data capture based on digital methods to support endpoint qualification needs careful consideration and discriminating analysis of the results.

A discussion on estimands may be needed⁴, considering that these tools potentially allow the investigation of completely new estimands. On the one hand, intercurrent events related to the use of digital endpoints such as misuse of the digital endpoint need to be identified upfront to the extent possible. A plan to handle intercurrent events and missing data should be documented. Given the lack of knowledge and the speed of evolution in new technologies, frequent or continuous monitoring might be necessary to collect this information, as compared to occasional scheduled monitoring. On the other hand, digital tools might enable new ways of collecting data on intercurrent events and reasons for missingness and this should in turn be considered to strengthen the robustness of the statistical analysis and interpretation of results.

There is increased use of digital technologies such as “apps” to input and collect patient and HCP data that was previously recorded in paper and other physical supports. This includes, for example, apps that function as patient diaries or collection of certain patient-reported outcomes (PROs) or apps that allow recording of prescriber-reported data. In principle, these digital solutions represent an important support to healthcare but its relevance for qualification by the EMA is expected to be limited, essentially because the aspects that impact benefit-risk in these cases are not expected to be linked to the technology used, but to the evidence collected in itself (that could in other ways be collected by physical support). Interest on the use of the qualification procedure would focus on the use of technology without which evidence collected would not have the same clinical depth and value for a benefit-risk assessment (e.g. a tool for constant, 24h collection of patient data instead of punctual data collection only at HCP appointments).

11. What is the best time during development to submit a qualification request?

Applicants can choose to request qualification advice at any time during the development of the technology: as for all areas in rapid evolution, the importance of early dialogue is emphasized. The EMA offers several informal initial contact avenues to assist applicants in identifying the most suitable regulatory route (e.g. Scientific Advice, ITF).

In the case of digital technologies, an iterative qualification process is a possible and often desirable option for applicants, to allow a flexible interpretation of the findings and refinement of the validation plans as knowledge progresses.

⁴ https://www.ema.europa.eu/en/documents/scientific-guideline/ich-e9-r1-addendum-estimands-sensitivity-analysis-clinical-trials-guideline-statistical-principles_en.pdf

Data from an initial exploratory trial are generally considered as supportive to an MAA. It is acknowledged that initial versions of the digital technology used for early stage data collection may be different from the final digital technology presented at the qualification opinion stage.

The exploratory use of digital technologies in early trials (e.g. proof of concept, before pivotal development) does not require the qualification of a technology: the need arises once the technology is used to support or collect the main body of data that will be considered pivotal to the assessment of the benefit-risk balance of a new medicine. Therefore, applicants are encouraged to perform early testing in exploratory studies that will be supportive to an MAA, since such evidence will be fundamental to start a qualification procedure. Ideally, the pivotal studies should be conducted with a technology as near as possible to the one likely to be commercialised. If this is not the case, an in-depth assessment of the impact of any changes will be expected.

An iterative qualification process means that an exploratory, proof of concept test may be the subject of an initial qualification, to be followed by a more extensive validation to allow, eventually, use of the technology to support the pivotal data in an MAA. This bridging approach, similar in principle to the approach taken for bridging data for manufacturing changes, allows for a comprehensive assessment of the methodology at a given point in time and for a specific context of use, which could be consolidated in successive qualification steps at key milestones, following a plan pre-discussed with the Agency.

Exploratory studies are also an opportunity to gain insights on the development of a robust technology management plan, assess the suitability/usability for a variety of users, to monitor the occurrence of unanticipated consequences (including audit trails), and ensure familiarity with the nature of the data outputs and the correct analytical approach.

12. What if my development/specifications change? Is a follow-up possible?

The stepwise approach discussed above may also support a risk-based change management plan⁵. The Applicant will need to assess the impact of the change and demonstrate equivalence between technologies in order not to affect the validity of the data.

The Applicant will be expected to provide in the MAA a risk assessment of the impact on the validity of the supporting clinical data of any changes introduced to the final digital technology element during development. The same approach as described in ICH Q8, 9, and 10 should be used when performing the risk assessment: with respect to the impact of changes and software updates, these should be viewed under a risk-based approach, conceptually similar to the one taken for manufacturing changes. Impact on the essential performance characteristics, data capture and processing capability, changes in manufacturer, the context of use, and the pivotal or supportive nature of the data are all important in evaluating the degree of risk posed by a given change. Information on the data management, performance management and evaluation protocols and update procedures may be required.

13. What is the best way to present my questions to EMA?

The development of digital technologies in the context of medicines' development, may include a degree of overlap between the remits of authorities responsible for different parts of the assessment (e.g. medicinal product vs medical device). From the experience so far, when submitting to EMA it is useful to frame the questions and supportive documentation in the context of medicinal product

⁵ <https://www.fda.gov/media/122535/download>.

development and subsequent benefit-risk evaluation, as this increases the likelihood of the question being accepted and of the response being relevant.

It is important that the different remits are respected, but additional supportive or clarifying information on the technology may facilitate the benefit-risk assessment and expedite it by reducing questions posed during the assessment.

For example, questions on an endpoint should be tailored, when submitted to EMA, towards the clinical relevance for a medicinal product, whereas, when addressed to a notified body, they are likely to be geared towards the technical considerations to capture those aspects with precision and accuracy, while the main interest of other stakeholders (HTA, physicians, patients) might again focus on other aspects of the technology.

The different perspectives may need to be put together for an exhaustive answer, but this approach increases the likelihood of providing a complete picture to satisfactorily address the research questions prior to an MAA submission.

The EMA actively encourages and supports advice being sought by collaborative groups such as consortia and industry trade associations, as data from different sources can be considered in a confidential space to progress an application.

14. Any additional points to note regarding digital data collection systems/ data handling?

At present, there is no experience at EMA of trials exclusively conducted either remotely or with digital tools. This situation is rapidly evolving.

Some of the visits (including most often enrolment and consent visits) and, generally, the pivotal evidence, are still conducted within traditional well-established paradigms. The use of digital technologies to supplement these in-clinic visits could support progressive increase of knowledge and trust in digital technologies, if transparency and a strong dialogue and collaboration between scientists, developers of technology, companies and the regulatory network is maintained.

At the time of writing, a draft guideline on electronic systems and electronic data in clinical trials is under development by the GCP Inspectors Working Group. It has a focus on digital data entry and will consider, among others, definitions of source data, audit trails, system validations, electronic informed consent, database decommissioning, etc. It will constitute definitive guidance on these matters once adopted.

The statistical analyses should be pre-planned according to the applicable regulatory framework (refer to ICH E9): a post-hoc data analysis is generally not considered appropriate to support validation of a methodology.

At present, studies using high-quality real-world data (such as those provided by internationally recognised disease registries) would be considered another potential means to achieve validation of endpoints, if such real-world evidence is of acceptable quality, robust enough, and ideally *a priori* agreed upon with the regulators.

Digital tools currently in use for patient management, or to collect data in clinical trials, could be envisaged to be repurposed also to collect real world data (e.g. different digital-web-based platforms such as those for MS, diabetes, etc) for initial or post authorisation data collection. The repurposing of these tools needs careful consideration of how the requirements of the pharmaceutical legislation and of other legal frameworks (e.g. including personal data protection) are to be met.

15. Which experts will be involved in the assessment?

While most of the expertise is available within the regulatory network, it is likely in some cases that external experts (through the EMA expert database) or bodies that have the responsibility for specific aspects (e.g. medical device authorities) might need to be involved. Early interaction with national Innovation Offices is also encouraged.

Therefore, it is essential that proposals, before submission, are pre-discussed with EMA. This allows the timely identification of an appropriate expert group (the "Qualification Team") for the assessment.

The remit for assessment of different aspects is envisaged as follows.

A. Aspects for which EMA expertise is available or consultation of external stakeholders is well established:

- Medicine/outcome measure development: EMA.
- GCP/inspectability/compliance of data: EMA, GCP IWG.
- QoL/ADL aspects, value, impact at point of care: HTA bodies.
- Patient and HCP input (usability, impact..).
- Use of real-world data/Healthcare data/advanced analytics.

B. Aspects that will require development of further expertise or input from other relevant stakeholders, such as medical device authorities or Notified Bodies (either separately or in a parallel consultation with EMA):

- Technical characteristics, specificity, sensitivity, reliability of the technology.

If earlier contacts have taken place with medical device authorities or notified bodies, this information should be shared with EMA to provide a clear background to the assessors and to assist in establishing a communication link.

The ambition is to create multi-expertise teams as more experience in the area is gathered.

As for all qualification procedures, it is also possible for applicants to request the participation of non-EU agencies to the qualification process. A confidentiality agreement between the FDA/PMDA and the EMA allows for a qualification procedure to take place in parallel with more than one agency. If the applicant intends to pursue its request with more than one agency this should be requested and agreed before the start of the procedure by all stakeholders involved. If parallel procedures take place, the agencies will communicate their independent assessments and a tripartite meeting will be planned. This will maximise the chance of reaching scientific consensus. Involvement of a non-EU agency is possible also as observer, and in this case comments, if any, will be provided orally.

16. What are the possible output documents for a qualification?

In line with the encouraged stepwise approach, when considering the applicant's request, the Scientific Advice Working Party (SAWP) will recommend whether the procedure is eligible for a qualification opinion or a qualification advice:

- **Qualification advice for future studies:** The report from the qualification team may recommend adopting a qualification advice on future studies to be performed in order to generate the data required to support the proposed context of use of the method in drug development. This outcome is envisaged

for those cases where sponsors wish to start to explore a potential new development method (e.g. a candidate novel methodology) and require support from the CHMP or when the data submitted for the qualification are still preliminary and not sufficiently supportive of a qualification opinion. In this case, as the novel methodology under evaluation cannot yet be fully qualified but is shown to be promising based on preliminary data, a **letter of support** may be proposed by EMA as an option. This letter, based on the initial qualification advice, includes a high-level summary of the novel methodology, context of use, available data and on-going/future investigations. Letters of support will be made publicly available on the EMA website subject to sponsor's agreement. The objective of the letter of support is to encourage the efforts for data sharing and facilitate studies towards qualification for the novel methodology under evaluation and has been used by developers to discuss with third parties the value of their technology under development.

• **Qualification opinion for public consultation.** When sufficient data is generated, the applicant may request a qualification opinion. In this case, the report of the qualification team may recommend the adoption of a qualification opinion on the acceptability of the innovative method concerned for a specific intended use. Prior to adoption of the qualification, a **public consultation** is conducted, to ensure the broadest possible input on the technology to be qualified, with proactive consultation of relevant learned societies in order to ensure that the views of the wider scientific community are reflected in the final qualification opinion. In the context of the qualification, a workshop may occasionally be organised in order to further enrich stakeholder input before finalisation of the opinion.

17. What are the main take-home messages from this Q&A?

Following the experience garnered so far in the assessment of digital technologies at EMA, the following overarching guiding principles should be kept in mind when preparing a package for submission:

- 1) *Start interacting early:* This permits identification of relevant experts to be involved and is likely to result in shorter review times by allowing the opportunity for EMA to provide input on the content, timing and format of the request.
- 2) *Identify a clear research question:* The concept of interest, a detailed context of use, and identification of a clinically meaningful change should form the backbone of the thinking process behind a qualification submission. The stakeholders relevant for the different aspects should be identified. The benefit of using digital measures over existing methods should be explained. It should be clarified whether the measure is an alternate to an existing method or intended to measure something intrinsically different.
- 3) *Be focused and specific:* Vague or open questions are likely to receive general answers. This document gives suggestions about the approach to presenting the information in a systematic manner. The studies conducted and data arising from the studies to support the validation should be presented in a clear way. Protocols for the studies should be annexed.
- 4) *Frame the questions in a manner relevant to the stakeholders:* It is recognised that a degree of overlap exists between different remits, and different perspectives may need to be put together for a complete answer. Wording a question from the perspective and remit of a given decision-maker increases the likelihood of the question being accepted, appropriately addressed, and the assessment being relevant.
- 5) *Provide a draft best practice:* Provide a guidance for implementation in clinical trials for optimum use, or, if not yet developed, explain the key points of the methodology that will be used to develop. State whether the measures should be taken for certain periods of time, whether in all environments

e.g. at school, at home, outdoor or indoor, clinics, during weekdays and weekend, what kind of training or support is needed, whether feedback or monitoring will be used. Describe how will compliance be assessed.