D6.05 'Qualification of Novel Methodologies' Stakeholders guide

116026 – HARMONY

Healthcare Alliance for Resourceful Medicines Offensive against Neoplasms in Hematology

WP6 PAYER/PROVIDER, HTA, EMA
alignment and optimization

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List of Acronyms

Acronym	Description
AEMPS	Agencia Española de Medicamentos y Productos Sanitarios
CAR-T	Chimeric antigen receptor-T
CHMP	Committee for Medicinal Products for Human Use
COPD	Chronic Obstructive Pulmonary Disease
DoA	Description of Action
EDWP	Early Dialogue Working Party
EMA	European Medicines Agency
EUnetHTA	European Network for Health Technology Assessment
F2F	Face-to-Face
FDA	Food and Drug Administration
GBA	Gemeinsamer Bundesausschuss
HAS	French National Authority for Health (Haute Autorité de Santé)
HTA	Health Technology Assessment
IMI	Innovative Medicines Initiative
IMI EU-AIMS	European Autism Interventions - a multicentre Study for Developing New Medications
IMI MACUSTAR	Intermediate age-related macular degeneration (AMD): development of novel clinical endpoints for clinical trials in patients with a regulatory and patient access intention
IMI PROactive	Physical Activity as a Crucial Patient Reported Outcome in COPD
IMI-EPAD	European Prevention of Alzheimer's Dementia
NICE	National Institute for Health and Care Excellence
NOMA	Norwegian Medicines Agency
QoNM	Qualification of Novel Methodology
R&D	Research and Development
SAWP	Scientific Advice Working Party
SME	Small-to-Medium enterprise
TC	Teleconference
TLV	Swedish Dental and Pharmaceutical Benefits Agency
ZIN	Dutch National Health Care Institute

Qualification of Novel Methodologies stakeholder guide

1. PUBLISHABLE SUMMARY:

The European Medicines Agency's (EMA) Qualification of Novel Methodologies (QoNM) is a voluntary scientific pathway launched in 2009 to establish the regulatory acceptability of a specific use of a methodology for the development of medicinal products. The qualification process addresses innovative methods developed by consortia, networks, public/private partnerships, or pharmaceutical industry with the stipulation that the ultimate use of the novel methodology should be in a pharmaceuticals research and development context. Recent adaptions to the qualification process allow for the inclusion of Health Technology Assessment (HTA) bodies and non-EU regulatory bodies for providing the QoNM.

The process can result in either an opinion, qualification advice or letter of support from a selected Committee for Medicinal Products for Human Use (CHMP). Inclusion of HTA organisations within the QoNM allows for additional and wider advice on the acceptability of an approach or methodology with potentially minimal extra requirements regarding resources (dependent on which organisations are selected). A positive opinion allows adoption of the relevant methodology by CHMP prior to their use in submission documents to regulatory or HTA bodies. For HARMONY the QoNM process could provide a mechanism to ascertain the suitability of a number of potential aspects that the various work packages are developing including biomarkers, clinical outcomes, statistical approaches, and innovative trial methodologies including database constructs and quality. The selection of suitable candidates for a pilot joint qualification procedure will need to be agreed and further defined by the consortium. There are resource implications regarding fees from the EMA and other agencies if selected for a parallel process and capacity with regard to assembling a technical dossier for submission that are not detailed specifically within Description of Action (DoA) for other work packages.

2. SCOPE:

The scope of this report is limited to the Description of Action (DoA) to develop an explanatory document that "ascertains the feasibility and mechanisms for joint parallel Regulatory-HTA/Payer Qualification of Novel Methodologies", and to consider whether this approach is viable in the future with consideration to resource and costs of participation. The document highlights the processes and steps towards submission into the Qualification of Novel Methodologies and represents the initial report which will be updated and revised to include learnings from the process in M60 (December 2021).

3. PURPOSE AND OBJECTIVES:

This report aims to detail the process and ascertain the feasibility of undertaking a joint parallel HTA/EMA Qualification of Novel methodologies (QoNM) procedure for an innovative and appropriate output of the HARMONY IMI project.

Objectives:

- To ascertain and gather information on the process and mechanism for joint parallel Regulatory HTA QoNM;
- Provide detail on examples of completed QoNM relevant to HARMONY;
- Determine the potential value the QoNM approach holds for HARMONY;
- Consider how to identify methods and topics from HARMONY that are suitable for QoNM;
- To consider whether this approach is viable for HARMONY in the future with consideration to resource and costs of participation.

4. Background

4.1. Qualification of Novel Methodologies overview

The European Medicines Agency (EMA) Qualification of Novel Methodologies is a voluntary scientific pathway launched in 2009 to establish the regulatory acceptability of a specific use of a methodology for the development of medicinal products. The process was established as a response to the drug development bottlenecks and inefficiencies, but also to the availability of new methodologies, not yet integrated in the drug development and clinical management paradigm. The qualification process addresses innovative methods developed by consortia, networks, public/private partnerships, learned societies or pharmaceutical industry with the stipulation that the ultimate use of the novel methodology should be in a pharmaceutical research and development context. Methodologies do not need to be product related and can include biomarkers, clinical outcome assessments, imaging methods, new animal models, statistical methods, innovative trial methodologies and big data approaches (EMA website).

4.1.1. Qualification Procedure

The process can take between 160-250 days to complete (depending on whether advice or opinion is provided). The timeline for Qualification Opinion is as follows:

- Day -60:
  - A letter of intent (standardised form) is submitted to the EMA specifying the intended use of the approach in the drug development context and its scientific rationale.
  - A complete draft dossier should be submitted.
  - Reports of initial informal discussion at EMA or international level can be submitted as supportive appendices.
  - An initial validation step will be performed by the EMA. There is potential to have an informal teleconference/face-to-face meeting with the EMA scientific officer and relevant experts. The applicant may be asked to provide additional information/data after this interaction.
- Day -30: A qualification team reflecting the expertise needed will be appointed.
- Day -15: Preparatory meeting between the applicant and the EMA scientific advice office. The preparatory meeting may provide preliminary feedback on whether the data set submitted is likely to be sufficient for a qualification opinion or for CHMP qualification advice.
- Day 0: Start of the procedure.
- Day 15-30: The data will be primarily assessed by the qualification team experts and a list of questions developed through discussions will be sent to the applicant after the Scientific Advice Working Party (SAWP) meeting at Day 30.

- Day 60: Discussion between the applicant and qualification team in the framework of the SAWP meeting. Additional interactions can be organised via teleconferencing to discuss additional data submission or further analyses of data to be provided in preparation of the discussion meeting.
- Day 70-90: The draft report (prepared in consultation with the qualification team members and enriched by the face-to-face interactions with the applicant) will be reviewed by the SAWP. The SAWP will recommend whether the procedure will be eligible for a qualification opinion or a qualification advice.
- Day 100: CHMP adoption of qualification advice and discussion of qualification opinion.
- Day 130-190: Public consultation (for qualification opinion only). Following discussion and adoption at the plenary CHMP, the draft qualification opinion will be forwarded to the applicant prior to publication on the website of the EMA. Depending on the outcome of the public consultation, a workshop may be organised subsequently with the qualification team and the applicant prior to finalisation of the CHMP qualification opinion.
- Day 190: Adoption of the final CHMP qualification opinion.

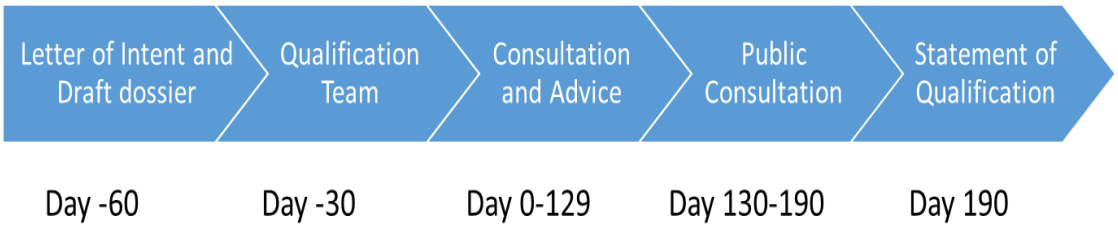


Figure 1. Simplified processes diagram (expanded flow chart available in appendix)

4.1.2. Stakeholder input into the Qualification process

The qualification team and team experts include a range of stakeholders (and maybe multi-disciplinary) with the exact composition being dependent on the methodology under assessment. It is not uncommon for the team to include Regulators, Payers, Patients and Notified Bodies. Public workshops may also be held that can include HTA bodies as in the recent QoNM for Cellular therapy module of the European Society for Blood & Marrow Transplantation Registry in haematological malignancies (https://www.ema.europa.eu/documents/regulatory-procedural-guideline/draft-qualification-opinion-cellular-therapy-module-european-society-blood-marrow-transplantation_en.pdf).

4.2. Outputs from the Qualification of Novel Methodologies

4.2.1. EMA outcome

The EMA qualification process, on the basis of recommendations by the Scientific Advice Working Party (SAWP), leads to either a CHMP opinion or qualification advice on innovative methods or drug development tool. It is not mandatory at the time of the start of the procedure to decide on the procedural route to be followed:

- CHMP Qualification Opinion on the acceptability of a specific use of the proposed method in a research and development (R&D) context (non-clinical or clinical studies) is based on the assessment of submitted data. The CHMP evaluation is open to public consultation for scientific scrutiny and discussion prior to final adoption of qualification advice. If the methodology is not accepted for qualification the procedure will turn into a "qualification advice on future protocols and methods for further method development towards qualification" which will not be made public.
- CHMP Qualification Advice on future protocols and methods for further method development towards qualification is based on the evaluation of the scientific rationale and on preliminary data submitted. The qualification advice can result in a Letter of support if proposed by EMA, when the novel methodology under evaluation cannot yet be qualified but is shown to be promising based on preliminary data. Letters of support aim to encourage data-sharing and to facilitate studies aimed at eventual qualification for the novel methodology under evaluation. These letters include a high-level summary of the novel methodology, context of use, available data, and on-going and future investigations. The Agency publishes letters of support on this page, if the sponsors agree.

European Medicines' Regulators take the CHMP Scientific Advice/Opinion provided into consideration during the Marketing Authorisation Application. It should be noted that the applicant for future market authorisation needs to justify fully any deviations from the advice given.

4.2.2. HTA outcome

A number of HTA bodies where contacted to ascertain their position with regard to the QoNM- including GBA, TLV, NoMA, ZIN, NICE, EUnetHTA, HAS and AEMPS. The majority of bodies responded and indicated that they had not had themselves undertaken a QoNM procedure, but all indicated a willingness in principle to participate in one in the future. All respondents indicated that this would be seen as an extension of their Scientific Advice mechanisms and processes. This means that the advice given within this procedure by each stakeholder would not be legally binding and would reflect state of the art of medical science and national requirements at the time of advice. Likewise, without consent the HTA bodies cannot identify and publish material in relation to QoNM and EUnetHTA and parallel consultation.

4.3. Status and outcomes of the Qualification process

There are 19 Qualification Opinions (including drafts) currently available on the EMA website (October 2018) and an EMA review indicated that 76 Qualification Advices had been finalised up to December 2016. A trend of increasing numbers of qualification requests to CHMP was noted, indicative of the pace that targeted drug development and personalized medicine is gaining and the need to bring the new tools from research to drug development and clinical use.

4.3.1. Published Qualification opinions

Qualification opinions already exist on the suitability of:

- Registries:
  - Patient registry for Cystic fibrosis, European Society for Blood & Marrow Transplantation Registry for CAR-T therapy in haematological malignancies (draft)
- Biomarkers/surrogate endpoints:
  - Parkinson's disease, COPD, paediatric ulcerative colitis, patient adherence, polycystic kidney disease, renal disease, Alzheimer's disease, mobile applications
- Statistical analytical methods:
  - Dose finding studies
- Disease progression models:
  - Alzheimer's disease

4.3.2. Topics of relevance to HARMONY-RWE/Big data

In addition to the topics outlined in 4.3.1, the following topics of relevance to HARMONY have been published:

4.3.2.1. Big Data approaches

eSource Direct Data Capture (DDC) qualification opinion- eSource direct data capture refers to an electronic application and/or device that allows direct entry of source data, and to directly identify some of these data as Case Report Form data, for clinical trial purposes at the point of care by investigator site staff, for example via an electronic tablet. It is not intended to identify or support a specific, proprietary system, but to discuss some of the characteristics a system for direct data entry should present. It should also be noted that guidance on Electronic Systems is currently under development at EMA, and once into force it would constitute the definitive guidance.

Draft qualification opinion on stride velocity 95th centile as a secondary endpoint in Duchenne Muscular Dystrophy measured by a valid and suitable wearable device- endpoints generated from wearable devices.

4.3.2.2. RWE

European Society for Blood & Marrow Transplantation Registry for CAR-T therapy in haematological malignancies (draft)

Qualification Opinion on The European Cystic Fibrosis Society Patient Registry (ECFSPR) and CF Pharmaco-epidemiology Studies adopted methodology- the report provided the context of use describing where ECFSPR is deemed by CHMP as an appropriate data source for post-authorisation studies to support regulatory decision making on medicines for the treatment of cystic fibrosis, together with CHMP's response to the questions posed by the Consortium.

Letter of support for Patient Data Platform for capturing patient-reported outcome measures for Dravet syndrome. Requested an opinion and received a letter of support for Patient Data Platform as an

electronic tool for capturing patient reported outcomes in paediatric epilepsies. The idea is that it will support longitudinal tracking of patient symptoms (including PROs) and treatment and therefore be a useful tool for clinical trials in paediatric epilepsy.

4.4. Availability of joint parallel qualifications

Since the drafting of the initial HARMONY DoA, the EMA has established a mechanism for the QoNM for involving additional stakeholders (such as HTAs and non-EU agencies) and encourages this whenever possible. In fact, International regulatory agencies - specifically the Food and Drug Administration (FDA) - have contributed to numerous QoNM. It should be noted that the EMA encourage all applicants to the QoNM process to apply in parallel to the EMA and FDA providing agreement if possible from the EMA and FDA. If this is possible, then both agencies undertake and then communicate their independent assessments and a tripartite meeting is conducted.

Current online instructions (and correspondence with the EMA 19/11/2018) state that the process is voluntary; that it is the responsibility of the applicant requesting a QoNM to contact other agencies (or notify EMA that they are requesting parallel advice) that they wish to include within the procedure; and that all arrangements and agreements are required to be in place prior to the start of the procedure. In this regard, the EMA has developed processes for sharing confidential information across different organisations which aligns with that for the Parallel Scientific advice process. It has been noted that factors such as procedural flow between agencies is important and challenging, and that preparatory interactions with all agencies should start early when an applicant is considering this approach. All agencies will attend the SAWP meeting at day 60 and each agency will issue separate responses to the applicant's questions in line with their usual procedures for Scientific Advice.

A review of documents publicly available on the EMA website has identified only one publicly available parallel EMA-HTA advice procedure and no parallel opinions have been produced. The advice procedure resulted in a letter of support and included EMA, FDA and HTA (NICE) advice on the qualification of a novel biomarkers and development of novel clinical endpoints within age related macular degeneration and was completed in February 2018. It is noted within the letter of support that the applicant (an IMI consortium) intends to apply for follow-up and repeated interactions using the biomarker qualification advice procedure, indicating that they have found this process useful.

When including EUnetHTA in a joint QoNM, the process followed is similar to the process for Parallel consultation advice which also aligns to the parallel scientific advice since early 2018. Since this change, no joint parallel HTA-EMA QoNM have been published and the details of how the process of incorporating EUnetHTA into QoNM is unclear. This new platform comprises enhanced collaboration for Parallel regulatory HTA Scientific Advice/Early Dialogues (hereafter referred to as Parallel Consultation) between EMA and EUnetHTA. For all submitted requests, the EUnetHTA Early Dialogue (ED) Secretariat facilitates centralised HTA recruitment. The EUnetHTA HTA Early Dialogue Working Party (EDWP) applies selection criteria order to decide which pathway the ED will follow for Parallel Consultation. There are two different pathways that a Parallel Consultation can take: Consolidated and Individual. The primary difference between the two is the mode of participation of HTA bodies. Consolidated Parallel Consultation includes the full participation of the EDWP plus up to 3 additional HTA bodies whereas in

Individual Parallel Consultation, HTA bodies participate based on their own national priorities. In both cases, the process on the HTA body side is overseen by the EUnetHTA ED Secretariat. https://www.eunethta.eu/wp-content/uploads/2018/03/Guidance-on-Parallel-Consultation.pdf provides details.

The EMA also stated that for interactions with HTA bodies they include the following extra contacts:

- pre submission TC (highly recommended) with HTAs and applicants
- a pre F2F TC with HTAs, exchanging of lists of issues,
- F2F meeting with HTAs and Applicant. The F2F might need to be longer than 1.5 hours.

The EMA also noted that they can provide a higher level of flexibility in defining the timelines for QoNM due to additional loops of questions and responses that are often required.

5. Value of QoNM

5.1. IMI projects

It is clear from the uptake and volume of published QoNM that the QoNM mechanism is valued by consortia, networks, public/private partnerships, learned societies, and the pharmaceutical industry. The number of successful and adopted opinions by CHMP indicates that this process is delivering a meaningful outcome for regulators in the adoption of innovative methodology.

Numerous IMI projects (with some submitting numerous procedures) (IMI-EPAD, IMI MACUSTAR, IMI PROactive, IMI EU-AIMS) have recently submitted to this process as seen in the published opinions or letters of support. Within these documents the projects received advice on their approach, design, and developmental strategy. Likewise, the use of the QoNM approach has been used to aid other international consortium such as Safer and Faster Evidence-based Translation Consortium and Critical Path Institute's Predictive Safety Testing Consortium and TARGID consortium, and foundations such as the Dravet Syndrome Foundation to gain a valuable insight into the acceptability from regulators on their strategy and advice on adaptations and changes that may be required.

This fits with the aims of the QoNM procedure which aims to provide early and preferably iterative involvement to support the design and development of strategy during the project at key milestones, with commitment to evaluate data from agreed studies and to provide opinion (EMA Qualification of Novel Methodologies – Streamline DDT development for regulatory Qualification Presented by Thorsten Vetter on 25 September 2015 'Science Advice Office EMA).

5.2. HARMONY

The QoNM holds many potential benefits for HARMONY. Firstly, gaining either advice or opinion from the regulatory perspective gives credence to innovative methodologies and their applicability and the potential for these to be adopted within CHMP guidance. QoNM enables engagement at an early stage with the EMA/HTA bodies ensuring that they are forewarned about new methodologies and potential processes/analytics which may be included as part of the evidence base in subsequent submissions. As

part of the QoNM procedure HARMONY will be provided with opinions and advice on the current acceptability of topics which may be selected for this process. Utilisation of this early stage advice will enable HARMONY to address any highlighted concerns and adapt outputs which could ultimately result in positive recommendations from regulatory/HTA agencies. This will hopefully lead to earlier patient access to innovative technologies.

Using the parallel approach, and ideally including multiple HTA bodies, HARMONY will benefit from a broader spectrum of opinions that will be brought together in joint meetings. This advice has the potential to align stakeholders and their expectations in the joint face-to-face meetings. This approach mitigates the risk of gaining a narrow viewpoint if only individual agencies were utilised and potential provides advice which may not be applicable across all EU jurisdictions.

6. Identifying topics for HARMONY

Deliverables from WP2 (outcome definitions and coordination of proof of principle HM studies), WP3/4 (Quality checking of dataset, harmonization of them and linkage of database), WP5 (identify specific biomarkers, which better define outcome parameters), WP6 (tools to quantify the added value of new technologies), and WP8 (double brokerage anonymization procedure to allow further processing of previously collected data in HARMONY) were indicated within the DoA as potential suitable candidates for a pilot joint qualification procedure, but the final selection of a deliverable to undergo this pilot approach will need to be agreed and further defined by the consortium.

6.1. Assessment of readiness

In order to identify candidate topics/methodologies for 'pilot QoNM' within HARMONY and engaging with Consortium and Monitoring progress, NICE has undertaken the following tasks:

- Monitoring the progress of tasks to identify when data /methods will be mature enough within the pilots to participate within a QoNM.
    - Active membership of HARMONY including attendance at a number of F2F sessions and General Assemblies to gauge how the project is progressing.
- Developing in house timelines based on deliverables of DoA for tasks that may be suitable for a QoNM.
- Developing a Checklist for readiness to start initial preparation for a QoNM procedure.
- Regularly checking the community platform to check for progress reports.
- Liaising with WP leads around task.
    - Update at monthly WP meets on HARMONY progress.
- Undertaking correspondence (TCs emails and email correspondence).

Initial suggestions and discussions with consortium lead at the kick-off meeting in Salamanca highlighted that a QoNM focused on either biomarker or surrogate endpoint validation would be a good option for HARMONY. Hence, NICE have been monitoring the progression of tasks lead by WP2 and the progress of WP3-5 to generate methods and data to align to this proposal.

It was apparent from presentations and progress reports delivered at the first General Assembly in Berlin and conversations with members of the Steering Committee that the first year of HARMONY had proved challenging in regard to addressing ethical and legal issues involved in the sharing of data for establishing the database as ascertained by presentations and progress reports delivered at the first General Assembly in Berlin.

NICE have attended 3 face-to-face meetings within the HARMONY consortium that include WP2/6 following on from the first General Assembly. At each meeting, we endeavoured to engage and assess how HARMONY is progressing to ascertain if any methods or outputs are at a stage to include within a QoNM.

At the General Assembly 2018 in Valencia, data was still to be uploaded into the database for the first pilot in AML, and agreements where still discussed around obtaining data for other HMs. This would suggest that as of October 2018, HARMONY was not ready to draft a submission dossier for a QoNM on biomarker or surrogate endpoints. However, since then progress had been made in relation to the pipeline for data, and therefore this is currently under investigation as a possible option for QoNM.

Currently the WP6 lead is having initial discussions with EMA about the possibilities for HARMONY to put forward a QoNM proposal relating to establishment and quality of the novel HARMONY database, specifically around the de-identification and pseudo-anonymization, legal and ethical methods, and solutions and quality checks of the data. This could be a case study of how this has been carried out in for the AML data, which has been the first data to enter the platform. The work carried out by work packages 3, 4 and 8 so far on this is at a stage where reports and methodology can be drafted as judged by personal correspondence and a preliminary TC and the use of 'Checklist for readiness to start initial preparation for a QoNM procedure' to be approaching the stage with the use of the AML data as a case study as an option for QoNM. If this proves to be of interest, we will then actively pursue whether a joint parallel process will be a viable option.

7. Resource Input

7.1. Capacity

7.1.1. Applicant input

The QoNM is a very thorough process and requires applicants to submit a scientific rationale - including current limitations in methodology or clinical area - and need for novel methodology with reference justifications. Each applicant for an opinion will be required to provide data (case studies-detailed protocols and reports), a systematic review of the area/methodological approach, statistical analysis plan validation, validated outcomes if applicable, proposals for how the methodology can be integrated into current regulatory methodological plans and its impact, current methods within EMA guidance, and method limitations (examples of summary information and EMA opinion responses can be seen on the EMA website).

Applicant input:

Qualification opinion: protocols, study reports and supportive data to establish the use of a defined novel methodology for a specific purpose in drug development.

Qualification advice: draft protocols and development plans for future studies to establish the use of a defined novel methodology for a specific purpose and any data available so far to support these plans.

There is a published guidance for applicants (Qualification of novel methodologies for drug development: guidance to applicants) and in December 2017, the EMA also published a guide that details common major challenges and limitations which compromise successful qualification of innovative methods 'Essential considerations for successful qualification of novel methodologies'. Dates for scheduled meetings of 2019 SAWP meetings and submission deadlines can be seen in the appendix 2.

In addition to the activity detailed above there will be several face-to-face meetings throughout the procedure with the qualification team and team experts (minimum 4) and teleconferences to clarify points and information and feedback via consultation processes.

7.1.2. Task 6.4. Deliverable 6.05 roles

Whilst NICE staff on HARMONY can act as a coordinator for the QoNM for HARMONY, the process will clearly require a significant input from other HARMONY consortium members and work packages. This will require a collaborative approach with cross working across work packages to strict timelines once the process has commenced. It is envisaged that the consortium members who have undertaken the pilot methodology will provide and draft the dossier information, clarify and provide information as requested by the SAWP.

Which consortium members involved and inputting within the QoNM will be dependent on the methodology selected to take forward into the trial.

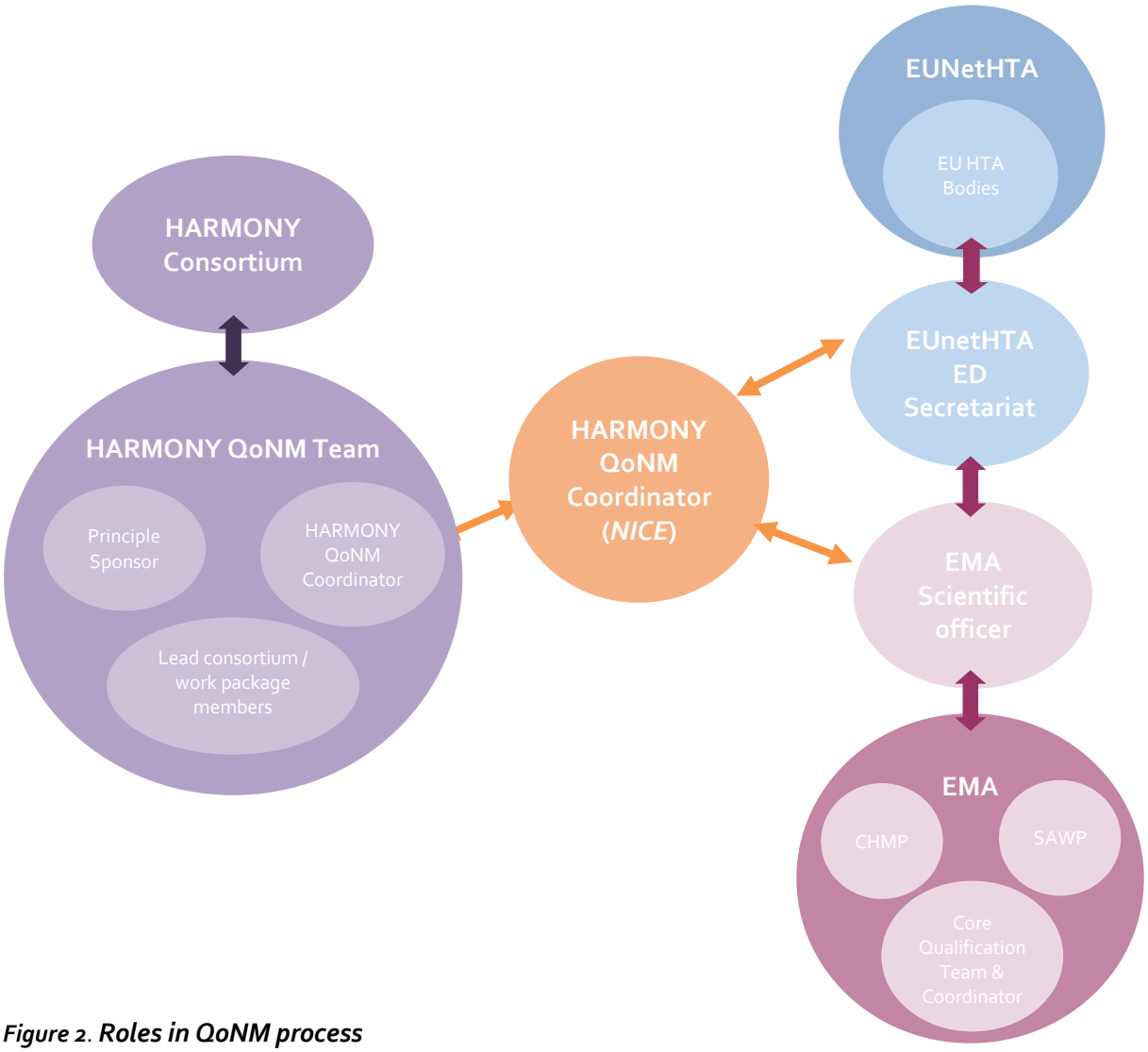


Figure 2. Roles in QoNM process

7.1.3. Task 6.4 Deliverable 6.05 process and checklists

In order to aid and facilitate the process of development of a submission for QoNM, NICE have investigated the process and its requirements and prepared a number of checklists and a process flow chart to assist in delivery and project management of a QoNM for the proof of principle deliverable 6.05 (figure 3).

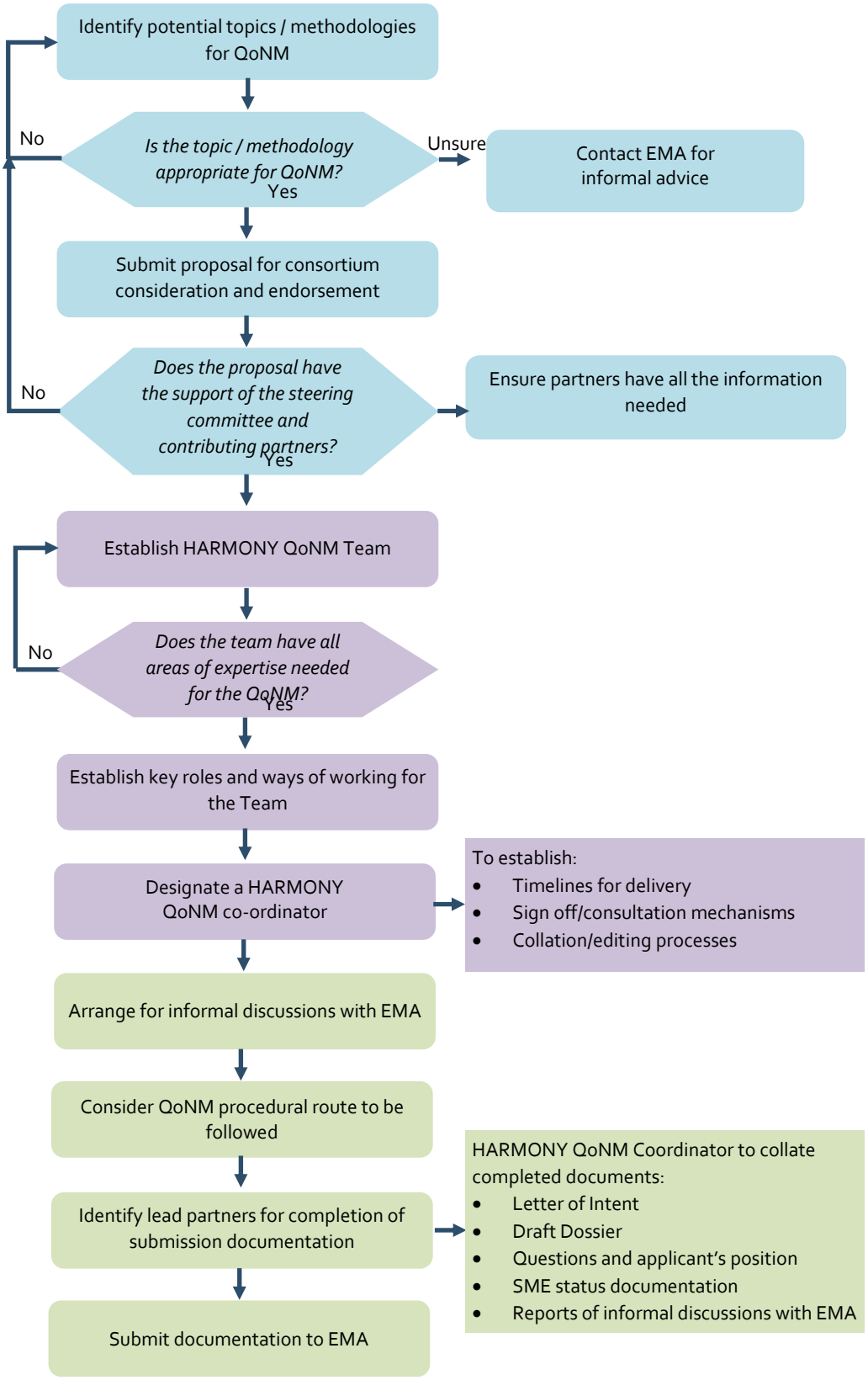


Figure 3. Process flow chart

Yes

7.1.3.1. Checklists

7.1.3.1.1. Checklist for readiness to start initial preparation for a QoNM procedure

The Readiness Checklists are lists of expectations for consortium partners that are preparing or considering submitting to the EMA for a Qualification of Novel Methodologies (QoNM) or a joint parallel QoNM. The Checklists itemise various capacities, documents, and activities that should be considered and completed as far as possible before a letter of intent is submitted to the EMA. The Checklists assist the primary sponsor of the QoNM, other consortium members and project management in recording actions and ensuring that steps have been undertaken to prepare for QoNM submission. The Checklists do not assist the sponsors to develop documentation or ascertain if it meets the requirements set out within the EMA's guidance for applicants.

		Complete
Initial Preparation Checklist	Determines eligibility and support for seeking QoNM	☐
Infrastructure Checklist	Determines if the sponsors of the QoNM have capacity and processes established that are essential for being prepared for undertaking a QoNM procedure.	☐
Submission Dossier Checklist	Determines inputs, processes and consultation of dossier elements are in place at the time of submission.	☐

Table 1. Overview of checklist

These checklists can be used to document progress made in preparing to participate in a QoNM procedure:

- In completing the checklists for the first time, review each task and indicate the initial status.
- In subsequent reviews, the "X" mark for the task may move into other columns until the task is complete or established. The date of completion may be entered in the last column.
- These readiness checklists are for internal use within HARMONY only. The completed checklists are not to be submitted to EMA/HTA.

Task	Action points	Yes/No
Is the methodology applicable to the QoNM? (https://www.ema.europa.eu/en/human-regulatory/research-development/scientific-advice-protocol-assistance/qualification-novel-methodologies-medicine-development) *If the exact nature of the methodology is not within those detailed on the EMA website then the principle sponsor may need to contact the EMA for informal advice.*	*A brief scope and rationale should be drafted to aid wider and further discussions by the principle sponsor[1]. This may need to be adapted as the process progresses.*	
Does the Work Package lead/s from the principle sponsor support the proposal?	*Ensure that work package lead/s are familiar with the process and requirements to facilitate making this decision.*	
Are other consortium members and any other WPs who will be participating or from whom input will be required supportive of the proposal?	*Ensure that contributing partners are familiar with the process and requirements to facilitate making this decision*	
Check if the proposal should be considered by the Steering Committee lead first?	*WP lead of primary sponsor to put the proposal to the Steering Committee*	
Does the Steering Committee support the WP lead and primary applicant seeking to undertake a QoNM?	*Ensure that the Steering Committee is familiar with the process and requirements to facilitate making this decision.*	
Has the Steering Committee considered the costs and implications of applying for this particular QoNM?		
All items in this Initial Preparation Checklist of readiness should be answered "yes" before the moving forward to the next stage.		

Figure 4. INITIAL PREPARATION CHECKLIST - Consortium consideration and endorsement

[1] *Principle sponsor will be the consortium partner who is the primary contact point regarding technical input*

Please note this checklist is not in sequential order

Task	To consider	Responsible Staff	Not Yet	Under way	Yes	Date Determined to be in Place
HARMONY QoNM Team						
Establish a HARMONY QoNM Team for proposal	*Each member will be leading on aspects required and representing those contributing to that aspect. Members will need to have capacity to attend TC and F2F meets in the QoNM*					
Establish and document any specific responsibilities or roles for the HARMONY QoNM Team						
Establish requirements for the collaborative working relationship/structure for the QoNM	*Individual partner's preferences and requirements and frequency of interaction*					
Designate a primary contact person for the EMA						
What is the source of costs and has an applicant organisation[2] been assigned?						
Designate a **QoNM co-ordinator** (organisation) to	*Does the QoNM Coordinator have strong organisational*					

[2] *Applicant organisation i.e. organisation who will submit to EMA – consideration should be given to an SME as discounts in fees are available*

provide process and project management support	*and project management skills and capacity and understand the QoNM process? Do they have resource and capacity for this role?*					
Designate a lead from each expected contributor partner organisation to the QoNM	*The lead needs to have authority to make assignments and set deadlines*					
Ensure that the HARMONY QoNM team have data collection, management, analysis and dossier drafting capacity	*All aspects of the dossier need to be considered and expertise identified*					
QoNM Co-ordinator						
Establish agreed timelines to keep **HARMONY QoNM Team** informed of progress	*Flexibility where available and clearly state when not flexible. Factor in sign-off and consultation across the team*					
Establish sign-off and consultation mechanisms across project team; ensure documents are tracked and dated						
Define a collation and editing process						
It is recommended that all items in this checklist should be in place as soon as feasibly possible once a decision has been made to undertake a QoNM. Please note that the items listed in this checklist are key processes but that this is an exhaustive list for the preparation for a QoNM. Teams that are considering undertaking a QoNM need to develop their own unique work plan to ensure that they are ready to start preparing a full dossier for submission to QoNM.						

Figure 5. INFRASTRUCTURE CHECKLIST

Subsections may be required if aspects span across different partners/WP

Task	Further details	Responsible staff for delivery	Responsible staff for QA	Staff involved in delivery	Tasks agreed	Timeline agreed	Deadline to be in place	Complete
Where required, make arrangements for initial informal discussion at EMA or international level								
Letter of Intent for request of QoNM	Complete the Letter of Intent using the template provided on the EMA website: https://www.ema.europa.eu/en/human-regulatory/research-development/scientific-advice-protocol-assistance/qualification-novel-methodologies-medicine-development							
Draft Dossier for QoNM request	To include the following sections (see below for further details): 1. Executive summary 2. Statement of need and impact of proposed preclinical novel methodology(ies) 3. Methodology 4. Results 5. Description of gaps 6. Evidence from Published literature 7. Conclusions							
Collation and filling in proforma for Draft Dossier								

Questions and applicant's position	To be done by QoNM team							
Identification of relevant guidelines (other than CHMP)								
SME status documentation	At the time of submission, provide the fee waiver confirmation document from the EMA SME office							
Reports of initial informal discussion at EMA or international level	Drafting of reports will need to submitted alongside dossier							
Draft Dossier								
1. Executive summary	To contain the following: • The need and impact of proposed preclinical novel methodology(ies); • Characteristics of the proposed novel methodology(ies); • Sources of data and major findings; Remaining gaps and a brief overview of how these will be addressed (if applicable); • Conclusion							
2. Statement of need and impact of proposed preclinical novel	*General introduction* to the novel methodology and may address the intended application of the novel methodology(ies). This							

	methodology(ies)	section should describe the context in which the QoNM is pursued, included intended use, disease areas, currently available tools, scientific rationale and a summary of the technical aspects.						
3.	Methodology	Detailed overview and critical analysis/interpretation of the novel methodology(ies) development programme • Experimental approach: design of the studies, selection of the animal models, definition of the reference standards and positive and negative controls. • Describe the analytical/technological platform(s) used for novel methodology(ies) quantification. More information should be made available in the appendices. • Statistical plan for analytical/technological assay validation and biological qualification.						
4.	Results	Detailed overview including items such as: • Brief summary of design and results of individual studies (in tabular						

	and/or synopsis format). • Analytical/technological assay validation [i.e. repeatability, intermediate precision, reproducibility. • Biological qualification: descriptive statistics or/and ROC curves or/and any other statistical methodology towards qualification.							
5. Description of gaps	Describe remaining gaps and how these will be addressed. Include detailed protocol(s) of planned studies in the appendices							
6. Evidence from Published literature	A systematic review is recommended following a prior protocol for search and analysis.							
7. Conclusions	Summarise the key findings from all evidence sources and how they fulfil the objectives of the novel methodology qualification request.							

Figure 6. SUBMISSION DOCUMENTATION CHECKLIST

7.2. Costs

The QoNM incurs a fee:

EMA Fees

- Basic fee (Level III) for initial requests for scientific advice on qualification advice – 82,400 EURO
- Basic fee (Level II) for follow-up to the initial request on qualification advice – 41,100 EURO
- Reduction for SME (~90%), 'orphan drug status product' and paediatric indications

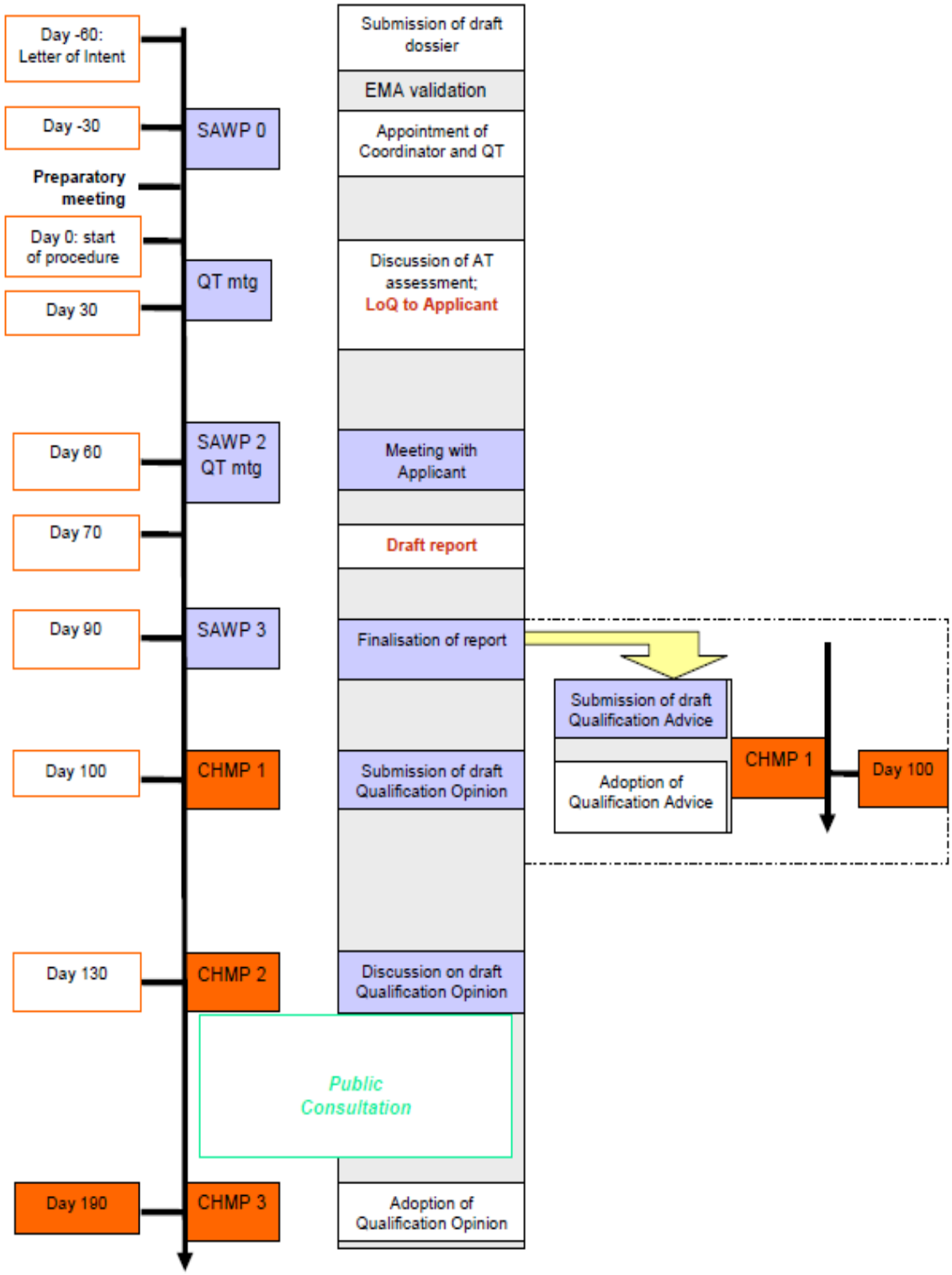
HTA Fees – Costs will vary dependent on which HTAs are engaged

- NICE and G-BA charge as part of Scientific Advice work streams- discounts are available for SMEs
- NICE has contacted a number of HTAs and their fees are normally related to what they charge for scientific advice (Spain/AEMPs, England/NICE, Germany/GBA/IQwIG, Sweden/TLV, Norway NOMA, Netherlands/ZIN)
- Other HTAs charging status is unknown at present including EUnetHTA as they have not responded to email requests.
- Pre-submission discussions with the EMA are free of charge.

List of Tables and Figures

ANNEX 1: Detailed Flow chart of Qualification of novel methodologies process

Taken from EMA website



ANNEX 2: Dates of 2019 SAWP

Scientific advice, protocol assistance, qualification of biomarkers and parallel consultation EMA/EUnetHTA requests. Meeting are all in Amsterdam from March 2019

SAWP Meeting dates 2019	
1st meeting	14 January – 17 January 2019
2nd meeting	11 February – 14 February 2019
3rd meeting	12 March – 15 March 2019*
4th meeting	8 April – 11 April 2019
5th meeting	13 May – 16 May 2019
6th meeting	11 June – 14 June 2019*
7th meeting	8 July – 11 July 2019
8th meeting	2 – 5 September 2019
9th meeting	30 September – 3 October 2019
10th meeting	28 – 31 October 2019
11th meeting	25 – 28 November 2019