IMI2 821520 - ConcePTION

ConcePTION

WP6 – Cross-stakeholder engagement, endorsement and adoption

D6.1 Roadmap of planned project outputs, including qualification advice submissions, mapped to stakeholder needs and planned stakeholder interactions

Lead contributors	The European Institute for Innovation through Health Data dipak.kalra@i-hd.eu Takeda Pharmaceuticals International AG (Zurich) christine.allan@takeda.com
Other contributors	European Forum for Good Clinical Practice The Synergist ASBL Katholieke Universiteit Leuven European Institute for Women's Health Limited The European Medicines Agency Janssen UCB Novartis Eli Lilly Teva

Document History

Version	Date	Description	Authors
V0.1	27 Feb 2020	First draft, consolidating inputs from several contributors	Dipak Kalra
V0.2	27 Feb 2020	Comments	Christine Allan
V0.3	27 Feb 2020	Editorial and layout corrections, for WP review	Dipak Kalra
V0.4	3 Mar 2020	Incorporating feedback from WP6 members	Dipak Kalra
V0.5	17 Mar 2020	Incorporating feedback from MB members	Dipak Kalra
VX.X	dd Mmm YYYY	Final Version	[Name]; [Name]

Abstract

IMI ConcePTION is developing new methods and establishing new pipelines for the generation of evidence on the appropriate (safe and effective) use of medicines in pregnancy and during breast feeding. It is doing this because there are ethical difficulties with generating evidence in the classical and well accepted method: through randomised controlled trials (RCTs). This new evidence is largely being derived from real-world data (e.g. longitudinal observational studies, registries, electronic health records, pharmacovigilance), from animal models and simulations, *in vitro* human and animal cell-based models and by scaling up the availability of breast milk samples through a network of milk bio-banks.

Many different stakeholders need to make critical decisions on the basis of clinical evidence, including regulators who might approve a new medicinal product or a new indication area or target population, healthcare providers who need to make prescribing decisions, pregnant and lactating women and their families who need to know what medicines they can trust and use with confidence. There is a history and tradition amongst the stakeholders of knowing how to appraise and base decisions on RCT evidence. There is far less experience and confidence in how to evaluate real-world evidence, on its own and in combination with RCT evidence, since each form brings different strengths and weaknesses.

This project has placed the engagement of stakeholders as a high priority. This is firstly in order to understand the evidence gaps and decision-making challenges they presently face, and to match those to the kinds of evidence that the project is likely to be able to generate in its five years, and the ground it could lay down for future evidence generation. Secondly, it is important to engage with stakeholders on the kinds of new evidence that are being created in the project, in order to arrive at the best possible consensus on how they should appraise and make use of it for decision-making.

Work package 6 is dedicated specifically to stakeholder engagement, and this report is its first deliverable. It reports on how WP6 has defined guiding principles for stakeholder engagement, to apply to all of our meetings and materials that we circulate. We have established a framework for project-wide engagement with stakeholders, started to chart out the engagement aspirations and needs of each work package, and also helped the consortium to understand the formal channels that can be used with regulators such as the European Medicines Agency (EMA).

Contents

Executive Summary

The overall objective of ConcePTION is to provide improved tools and methods to generate more valuable, reliable (better quality) and timely communication of information to pregnant and breastfeeding women, the general public and Health Care Practitioners (HCPs). It is evident, in order for the project to be successful, we need to understand our stakeholder requirements, their perceptions and provide suitable forums and methodologies to enable all viewpoints to be heard, understood and supported. This project attempts to formulate new approaches to address these issues to generate and disseminate reliable evidence-based information regarding effects of medications used during pregnancy & breastfeeding to women and their healthcare providers. Work Package 6 plays a key role in ensuring that the considerations for stakeholder engagement are captured and supported across all work packages.

ConcePTION aims to bridge major gaps in the field of pregnancy and breastfeeding pharmacovigilance with the ultimate outcome being the formation of an ecosystem that provides a regulatory endorsed framework and approach for the collation, analysis, interpretation and communication of data collected in WP1 (Electronic Health Records), WP2 (exposed pregnancy reports) WP3&4 (animal models and lactation exposures) according to a structured and co-ordinated approach.

To gain support, trust and sustainability of the ConcePTION ecosystem and solutions, WP6 is performing assessments of the information needs and aligns the opinions and judgements of key decision makers and influential stakeholders on their ethical and scientific acceptability and feed this back to all WPs. This includes understanding evidence needs across stakeholders, helping to establish and promote the criteria for robust real-world evidence generation and its appropriate and trusted role in regulatory and healthcare decision making.

This first WP6 deliverable reports on how we have established a framework for project-wide engagement with stakeholders, started to chart out the engagement aspirations and needs of each work package, and also helped the consortium to understand the formal channels that can be used with regulators such as the European Medicines Agency (EMA).

It is important that the process of engaging external stakeholders should be undertaken in a trustworthy way. WP6 has therefore developed a set of engagement guiding principles, after undertaking an extensive review of various principles and good practices produced by other projects and bodies. These guiding principles are presented in Chapter 1 of this deliverable.

Chapter 2 summarises an initial survey that was undertaken by telephone interview with the other work package leaders in the summer of 2019, in order to canvass their initial proposals for which stakeholders they felt most likely to wish to engage with, and which forms those engagements might ideally take.

This survey enabled WP6 to develop a formalised process for raising a future potential engagement need or intent with WP6. This process is described in Chapter 3. A documented process was considered necessary in order to allow WP6 to coordinate possible overlapping stakeholder engagement needs arising from different work packages, and to provide expert advice (if needed) on the chosen engagement method and how to optimise it to achieve the desired objectives.

The survey also helped to prioritise the possible engagement methods that might be used, which has informed the development of a toolkit: a collection of guides on how to use each of the engagement methods (e.g. how to run a focus group). This toolkit will be the subject of a later WP6 deliverable.

One of the highest impact outcomes of ConcePTION will be the formal endorsement of new

methodologies to generate or validate evidence by regulators, in particular EMA. EMA has the mechanism of Qualification Advice (QA), as one pathway that could be utilised. Qualification Advice in particular, but also the other channels, can be resource intensive to develop and may require a submission fee. The consortium therefore needs to select wisely the cases for submission that it works up during the project. WP6 has run webinars to help educate the consortium about these EMA channels (with input from our EMA partner), identified future candidate topics that might be considered for one of these channels. It also established a formal process by which a work package can notify WP6 of a candidate methodology or evidence result for EMA submission. This outreach within the consortium and the process of notifying WP6 are described in Chapter 4.

As new evidence findings are generated by the project, and also as evidence needs are highlighted by different stakeholder groups, the project will need to classify these topics. Chapter 5 presents a classification framework for evidence needs and evidence findings.

In year two of the project WP6 anticipates putting the content of these chapters into action, in particular through providing expert advice to other WPs on their stakeholder engagements and beginning to collect candidates for EMA advice. It will also synthesise findings from stakeholder engagements, including surveys, undertaken by other WPs which capture evidence needs and acceptance factors.

1. Guiding principles for stakeholder engagement

A stakeholder is an individual, organisation or initiative that participates in, is involved with, influences the outcomes of, or is influenced by the outcomes of, or implications of, a certain activity. The main stakeholders that ConcePTION will engage with are: mothers and families (directly, via social networks and via representative organisations such as patient organisations), healthcare professionals, legal privacy protection officers, data sources, research scientists in maternal and child health, pharmaceutical companies, regulators, and public health agencies, healthcare payers (public and private funders) and former publicly funded projects.

To make sure that all stakeholders become equally engaged and to create a common understanding of the ethical principles that the Consortium would like to adhere to when engaging with each other internally, and even more so with external stakeholders, it was considered important to create common stakeholder policy for ConcePTION.

The core of this policy consists of a one-page document (Section 1) that summarizes the 10 key principles that were determined most critical for the type of stakeholder engagements that the Consortium wishes to undertake over the course of the project. This one pager will be published on the ConcePTION website and it is also intended as a stand-alone, high-level document to be distributed to stakeholders ahead of each meeting.

The 10 stakeholder engagement principles for ConcePTION are based on 2 sources. The first source was a comprehensive internet research that looked for existing “guidelines”/”policies” for “patient” or “public” or “stakeholder engagement”/”interaction”, in the context of medicines development or health research. The search primarily focused on EU-wide guidelines but exceptionally also local guidance documents were considered as well, provided they were available in English. These search findings are given in Appendix 1. The search was complemented by internal knowledge, as many members of the Consortium have already been part of other multi-stakeholder initiatives or partnerships.

When analysing the results of our research, it soon became apparent that the principles of good stakeholder engagement generally centre around several different aspects ranging from good communication principles, elements of transparency, inclusivity, neutrality and objectivity, a sense of purpose, and elements of sustainability. The principles identified in the web-based research, and also those proposed by Consortium members, were therefore selected and grouped according to these criteria. Once a first set of principles had been defined, it was shared with WP 6.3 for consultation and then further refined in two consecutive consultation rounds, with input from the entire WP6 and the Management Board.

The final stakeholder engagement principles for ConcePTION are shown in Figure 1. They are applicable to all stakeholders – private and public stakeholders-- still recognizing the fact that pregnant women and their families deserve particular attention and protection.

In addition to the 10 guiding principles, the stakeholder policy also includes an overview of the most important EU regulations defined by law when interacting with stakeholders or exchanging personal data. This overview is included in Appendix 2. It was compiled with the help of internal legal experts, and it also includes some of the regulations (soft law) that the pharmaceutical industry adheres when interacting with health care professionals or patients (see Section 3). The policy should be considered a living document, which will be refined with increasing stakeholder exposure, and on an as-needed basis (e.g. should the legal environment change, etc). How adherence to this policy will be ensured and whether there is a need for it to be monitored still needs to be defined. The establishment of a simple governance structure that provides a place and process to report concerns or declare a potential conflict of interest is currently under consideration.

The ten guiding principles

One of the key objectives of ConcePTION is to engage with pregnant women and their families, all stakeholders, including healthcare professionals/providers (HCPs), regulators and the public to enquire about their information needs, potential ethical issues and to co-create solutions together. To do this in an ethical and sustainable way, the Consortium has devised guiding principles that will be adopted during these stakeholder interactions (Figure 1).

1. **Responsive and reciprocal:** a two-way process to appreciate the benefits of mutual learning.
2. **Inclusive:** facilitate the involvement of those potentially interested or affected, including those that are harder to reach (e.g. minority or lower health literacy groups) or those who may not be as vocal as other stakeholders.
3. **Conscious of the need for clear communication, used with discretion**: adapt your communication style to the target audience and tailor the information accordingly to ensure all stakeholders will understand and be able to provide input.
4. **Neutral, objective and free of conflict of interest:** Ensure information is accessible, balanced and objective and facilitates engagement with all interested stakeholders
5. **Open, transparent, accountable and trustworthy:** provide information so stakeholders can participate in a meaningful way and thereby foster a culture of sharing ideas. Embrace and react to conflicting stakeholder interests/opinions and see how they can be addressed and balanced. Constructive and factual criticism is encouraged.
6. **Respectful:** value stakeholders' views and use their input to improve policy and outcomes, actively listen to and understand stakeholder needs, seeking to understand how they want to be engaged, based on their particular circumstances. Value stakeholders' rights and respect their privacy, by guaranteeing the protection of the confidentiality of their contribution.
7. **Purposeful and well-prepared:** Stakeholders should be clear about the purpose of the engagement and desired outcomes. The shared purpose of ConcePTION overall or of a specific activity should be validated with all partners around the table before, during and after the outreach. Stakeholder interactions should be well-prepared and co-ordinated with other partners and work packages so there is a centralised introduction and entry point wherever possible, to avoid stakeholders being contacted by different ConcePTION partners simultaneously for different requests. Logistic, financial and administrative aspects related to the stakeholder engagement should be addressed in good time.
8. **Proportional:** the total number and hours of interaction with stakeholders and the possible benefits and burdens from interaction should be considered carefully and communicated in advance, whenever possible.
9. **Non-interfering:** interactions between members of the Consortium and pregnant/ breastfeeding women should not interfere with the critically important doctor-patient or healthcare professional-patient relationship.
10. **Impactful and sustainable:** Stakeholder interactions should aim at making an impact for the activity, for stakeholders themselves and for the benefit of society in general. They should pave the way for future interactions, building capacity for patients, Healthcare Professionals/providers, researchers and regulatory authorities to continuously work together. All stakeholders involved should be satisfied with the outcome.

Figure 1 – Principles for stakeholder interactions in ConcePTION

The next steps are to actively promote these principles, for example on our project web site, so that all site visitors are aware of these (ethical) principles that will govern all of our interactions. They will be shown in a slide early on within meetings we hold, and possibly as a printed flyer tabled at workshops. We will also monitor each WP engagement with external stakeholders, by requesting each engagement organiser to indicate in advance how they will comply with these principles and afterwards to verify that compliance.

2. Mapping stakeholder engagement needs

The objective of this task was to map work package (WP) plans for stakeholder engagement, in order to avoid duplication, to understand potential areas of overlap, and to build synergies and opportunities for collaboration between WPs.

After having defined a template to capture the information needs on stakeholder engagement across WPs (Who? Why? How? By when?), between July 1 and August 31, 2019 we carried out telephone interviews with all WP leaders. Additional contact points within WPs contributed to completing the information gathered during these conversations.

The interviews covered two main areas: which categories of stakeholder were a priority to engage with, initially within the first two years of the project, and secondly what methodologies of engagement were most likely to prove appropriate to elicit the desired inputs. Table 1 below shows the indicative framework that was used to drive these WP discussions.

Type of SE involvement	Definition Aim	SE Methodologies/SE Tools
Learn	Gain information/feedback from stakeholders Aim: to confirm/expand on initial internal findings	Interviews; focus group; surveys
Monitor	Keep continuous record of stakeholders' views Aim: to keep abreast of stakeholder's views; to react if needed	Media and internet tracking. Second-hand reports from other stakeholders possibly via targeted interviews.
Inform	Provide balanced, accurate and consistent information to stakeholders Aim: to be transparent; keep stakeholders up-to-date	Information Tools (Brochures, reports, websites. Speeches, conference, public presentations. Press releases, press conferences, media advertising); Open houses, scientific cafés
Educate	Advance the knowledge of stakeholders Aim: to achieve a measurable impact on status quo	Educational Tools (Online learning, etc)
Consult	Gather feed-back e.g. on analysis, alternatives, or outcomes Aim: to inform decisions made internally	Surveys. Non-guided F2F meetings (advisory fora; expert meetings)
Involve	Work directly with stakeholders throughout process Aim: to ensure concerns/needs are consistently understood and considered in decision making	Workshops; Co-creation methods; Multi-stakeholder forums; Focus groups
Collaborate	Partner on equal footing with other stakeholders involved Aim: to develop mutually agreed solutions and joint plan of action	Participatory decision-making tools; joint/experimental projects
Empower	Integrate stakeholders in governance structure Aim: to delegate decision making on a particular issue to stakeholders	Steering committees
Consensus	Seek and obtain agreement within a group/various groups of stakeholders Aim: adoption by larger group	Consensus building processes (e.g. Delphi method; expert panels)
Prioritize	Select stakeholders/topics with the highest relevance Aim(s): achieve focus; target communication to most important stakeholders; act upon most burning issues	Prioritization tools; preference eliciation tools

Table 1: Framework for stakeholder engagement

Table 1 shows the types (purposes) of stakeholder involvement that WPs might consider and, for each, which methodologies might be most relevant to consider using. This was shared in advance with the leaders of each WP as a prompt, before conducting the telephone interview.

The findings from these interviews are summarised below. It should be noted that these WP intentions were correct as of summer 2019 and will inevitably evolve. WP6 therefore intends to review and update this picture periodically throughout the project.

Findings

The stakeholder prioritisation by work package is shown in Table 2.

Identification of ConcePTION's Stakeholders									
		Work packages							
		WP1	WP2	WP3	WP4	WP5	WP6	WP7	WP8
Stake-holders	Mothers, women of childbearing age and wider society					1		1	1*
	Patient organisations and women's groups	1	1			2		3	
	Health professionals	1	1	1		1			1*
	Professional societies	1	1			2			
	Healthcare payers; actors of policy and funding decisions		1						1
	Regulators	1	1	1		3	1	2	1
	HTA		1	1					
	Public Health institutions including WHO Europe	1	1						
	Pharma industry, EFPIA	1	1				1		1
	Clinical research institutions	1	1				2		
	Data access providers	1	1	1			2	1	1
	Ethical, Legal, Societal and Implication experts		1	1				2	
	Other:		1			1			

Table2: Prioritization of Stakeholders for each WP (1 to 3 - High to Low relevance)
(1 = funders, 1* = data providers)

The actual WP engagement plans are summarised below, as of summer 2019.

1. WP 1 will collect information from patients ‘and providers ‘organizations, in order to get their views on the quality of evidence and relevance of information, by M10 – 18 and by M54. Alignment with WP 2 and WP 5 planned activities described below is recommended.
2. WP 2 is planning to run 5 virtual workshops for healthcare professionals and patient organizations. There is potential overlap with the survey planned by WP5
3. WP 3 is planning F2F meetings (advisory forums, expert meetings) with regulators and should talk with WP 6 and WP 4 about coordinating outreach to these contacts
4. WP 4 plan to work on a human milk samples whereas WP 3 will work on in-vitro studies and a PBPK modelling. There is a potential need to align with WP6 on QA.
5. WP 5 focus: to better understand information needs of patients and healthcare professionals, develop a detailed survey to be preceded by a pre-survey, both addressed to these stakeholder (SH) groups as well as plans to run focus groups. WP 5 should align with WP 1 and 7 on regulations; with WP6 on QA; with WP 2 on obtaining information from women and health care providers since target audiences are similar at the category level, if not at the individual level
6. WP1 and WP 7 are both working on regulation and qualification (as is WP 6 on QA); included as a deliverable for WP 7 is a fit-for-purpose ConcePTION infrastructure for regulatory decision making, by M60, so there is ample time for discussion and coordination
7. By M18, WP 7 will have completed interviews and focus groups with patients of participating hospitals to understand the ethical hurdles in generating information about the safety of medicines in pregnancy – there is a potential risk of targeting the same stakeholders as WP 2 and WP 5, albeit with different questions. However, depending on how surveys are organized, they might not reach out to the same populations of pregnant women. WP 7’ s plan includes building a bridge between preclinical and clinical studies on reprotoxicity.
8. WP 8’s final deliverable is an information system/set of tools that can be trusted, used, funded and sustainable, providing value for money. WP8 will coordinate with all other WPs over the whole course of the initiative.

The use of the following engagement methodologies was explored with each of the WPs:

- In depth interviews
- Semi-structured interviews
- Structured interviews
- Didactic interviews
- non-guided F2F interactions (advisory for a/expert meetings)
- Focus group discussions
- Public meetings/Citizens Jury
- Workshop
- Surveys
- Open houses/scientific cafes
- Media/Internet tracking
- Participatory decision-making processes
- Joint (experimental) projects
- Integration in governance structure

- Information tools
- Educational tools
- Preference elicitation tools
- Prioritisation techniques
- Consensus building tools

An indication of the highest priority methodologies was fed into Task 6.3 of this work package, which is developing a portfolio of methodology guides as a toolkit to support parts with their engagements. Toolkit development is ongoing and will be published in WP6 deliverable D6.3 at Month 24.

This interview exercise helped unlock areas of potential overlap in terms of stakeholder typology, timing and content of the interactions and opportunities for synergistic approaches to stakeholder engagement were highlighted. It should be noted that these WP intentions were correct as of summer 2019 and will inevitably evolve. It was suggested to map the Consortium's internal competencies, skills, connections and contacts, as well as to repeat these calls with all WPs regularly over the course of the initiative.

More recent WP engagement interactions

WP6 representatives are engaging with WP1 and WP2 on a proposed joint workshop to be held in the spring or early summer of 2020. The objectives of this workshop will be to clarify the elements of evidence that regulatory decision makers need, for example when determining what to approve on a product label, and secondly to learn from women and healthcare professionals about the types of information that they most need for prescribing decision making, with a focus on safety. WP6 is helping to facilitate the cross-stakeholder value from this workshop and will provide neutral moderation of some of the sessions.

The recently established Communications Task Force has reached out to all of the work packages to clarify the topics on which they foresee communicating in the coming months, to which stakeholders and with what messages and intended impacts. Some of these are channels for one-way communications (dissemination), but others are also forms of two-way engagement. The interviews that were undertaken to understand the stakeholder engagement needs of the different Work Packages, to enable better collaboration between the Work Packages, and avoid potential duplication of effort. One example is with the Task 5.1.3 survey to understand the user needs and preferences of women and healthcare professionals.

The interviews indicated that several Work Packages (WP1, WP2, WP7, WP8, besides WP6) were interested in gathering the input from these stakeholder groups, and that therefore there was a risk that the same groups might be contacted at the same time. During the creation of the preliminary survey for 5.1.3 in M5-6, further inquiries determined that WP2 was planning their own survey and engagement workshops to understand stakeholder preferences in submitting data on medicine use in pregnancy and breastfeeding. WP2 and WP5 had several calls to exchange needs and ideas. As WP2 had decided not to include women in their survey, WP2 provided a list of questions that could be integrated into the WP5.1.3 survey. In turn, the WP2 survey was shared with WP5 partners including the 5.2 Knowledge Bank team who provided feedback. WP2 and WP6 were also consulted in the development of the main 5.1.3 survey besides the WP5 and WP8 partners.

Additionally, the interviews revealed that it could be beneficial to map the Consortium's internal competencies, skills, connections and contacts. When the 5.1.3 preliminary survey was launched in M7 it was decided that this would be a good opportunity to initiate this mapping. An email was sent

to the Consortium inviting partners to share their connections, so that these connections could be used in cascading the survey to reach as many women as possible. Another need that was identified was to find a way to keep track of new stakeholder connections as they are made by partners in different Work Packages, to avoid the same stakeholders being contacted simultaneously by different partners. This issue was discussed during the Management Board in M9, and using the opportunity of the outreach effort for the main Task 5.1.3 survey, a simple tracking tool using Excel will be piloted starting in M12.

3. Guidelines to WPs for planning stakeholder engagement

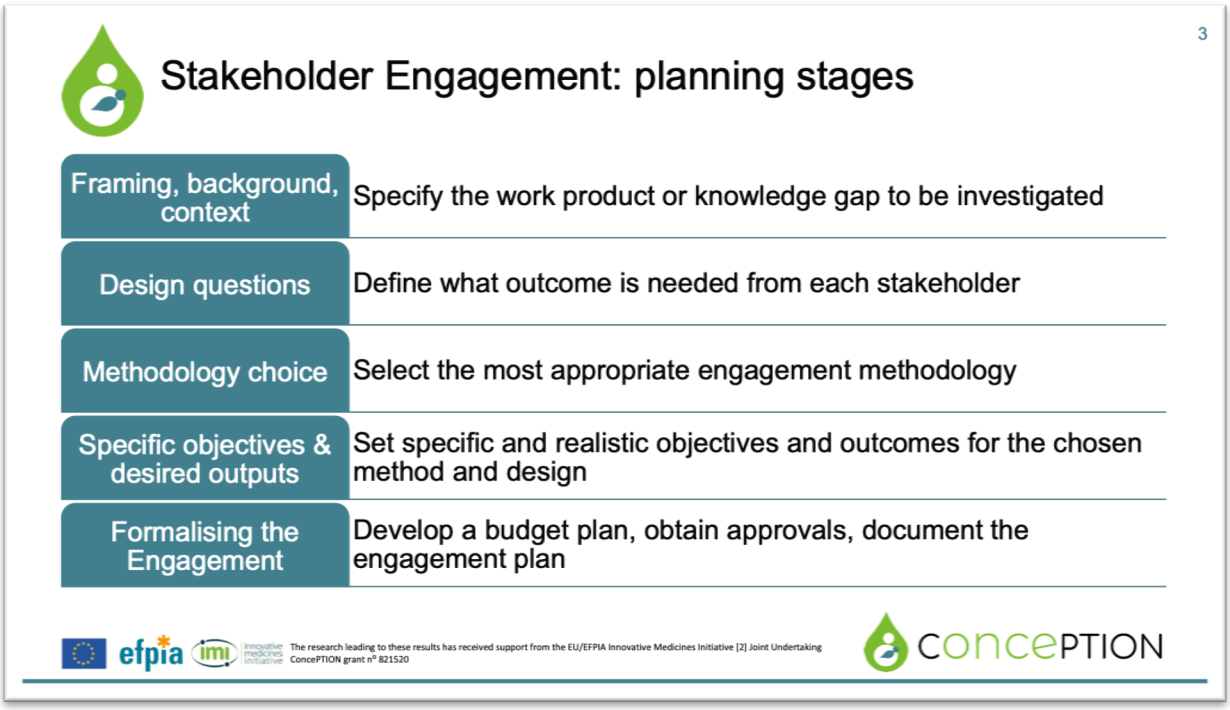
The following guidance and process has been developed by WP6 and disseminated across the consortium. It is also included in the Project Handbook.

Introduction

Teams within individual work packages or across work packages are expected to plan carefully any engagement they may require with internal or external stakeholders, and to consult with work package 6 so that we can provide appropriate support, help ensure the quality and success of the engagement, and avoid potential duplication across work packages.

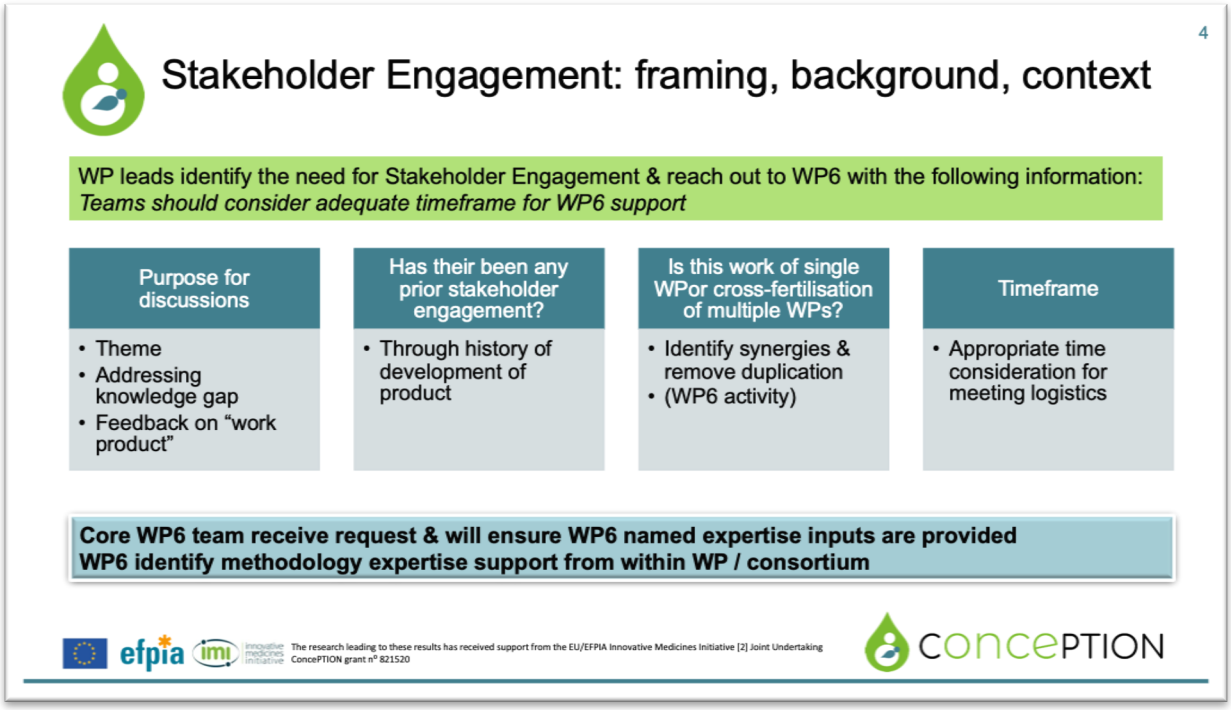
The guidance document outlines the different steps that teams would need to consider as part of their stakeholder engagement activity and, if necessary, getting approval for a stakeholder engagement activity. It is expected that this workflow will always be used, and that a formally documented stakeholder engagement plan is agreed with WP6 and potentially with the Management Board, before being undertaken.

Developing a stakeholder engagement plan goes through the following five stages.



1. Framing, background, context

Specify the work product or knowledge gap to be investigated



The planning of a new stakeholder engagement needs to begin with a clear description of the work product or knowledge gap to be investigated through stakeholders.

It is important to specify if this work product or planned area of work is being scoped completely in one WP or is the result of a cross-WP collaboration. If the latter, then all WPs involved in developing the work product or intending to utilise the new knowledge should be involved in designing or reviewing the planned stakeholder engagement.

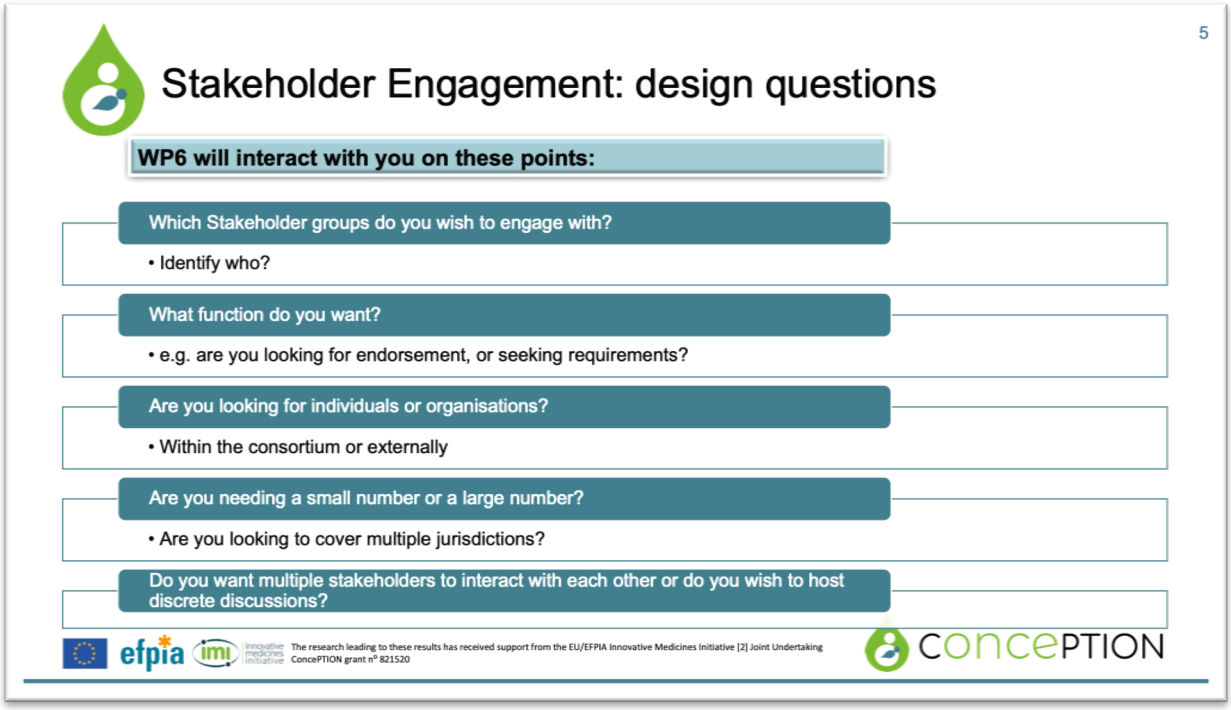
It is also important to make clear in any new engagement proposal if there has been prior related stakeholder engagement e.g. if stakeholders were consulted on requirements and if the same or different stakeholders are now wanted to review or endorse the result. This information will also help WP6 to identify possible alignments or duplications.

A further consideration in proposing an engagement design will be the time frame within which the insights will be needed, as some forms of engagement need a long preparation time or execution time.

WP6 will require enough time and notice to provide support to planned engagements, for example, to review and test draft versions of an online survey or to contribute to the design and moderation of a focus group.

2. Engagement design questions

Define what outcome is needed from each stakeholder



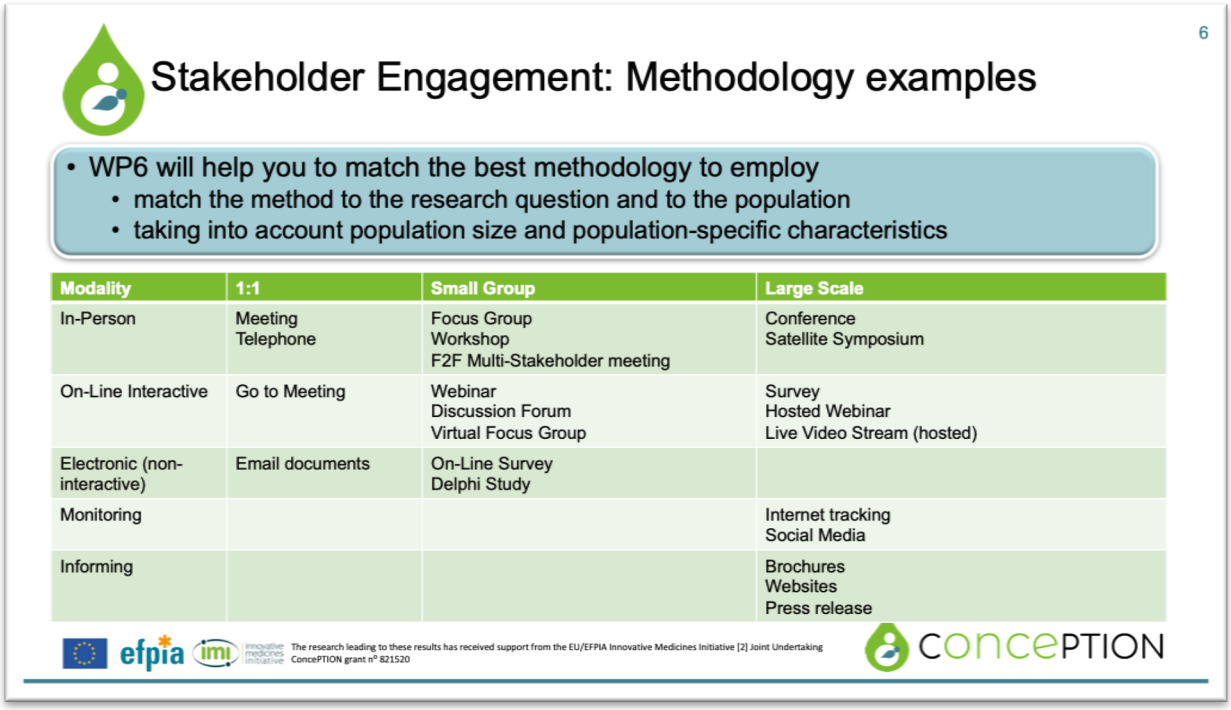
The engagement plan needs to be clear about what kind of outcome are needed from engaging with each proposed stakeholder group, and whether that outcome needs to be representative, reflective of a wide range of views, or authoritative.

Apart from determining which kinds of stakeholders are needed to provide input, the engagement plan needs to be clear about why that engagement is needed (i.e. what outcome is needed: for example, to provide requirements, to provide feedback on a candidate proposition or prototype, to comment on results, to provide endorsement of a result or to advise on how to promote a result). This will help to determine if it is better to target stakeholder organisations or networks of individuals, how many and if cross-European coverage is important.

The plan should also be clear at the outset if a multi-stakeholder environment is preferable, so that they can interact, or if separate engagements will serve the purpose better.

3. Engagement Methodology

Select the most appropriate engagement methodology



The choice of engagement method will depend on the purpose of the engagement and the above design answers, Including the scale and the time frame.

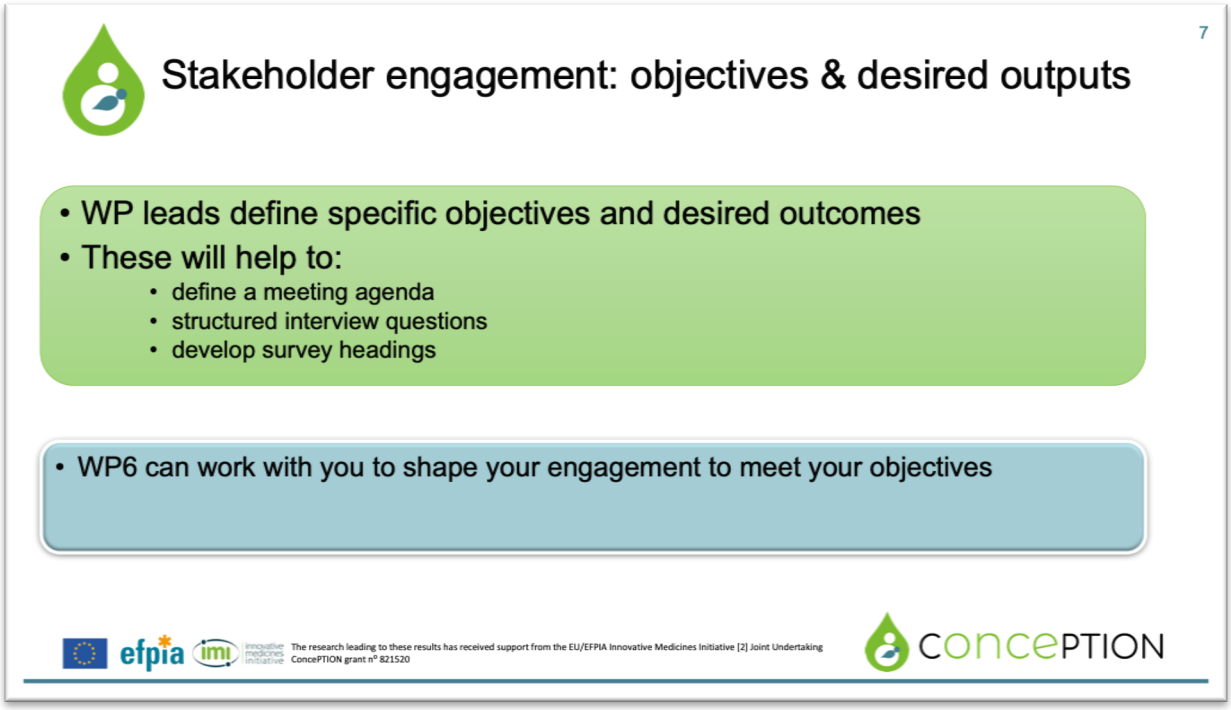
Some methods can be designed and delivered more rapidly. Some can be deployed online at a low cost, others are more labour intensive or incur physical meeting costs.

Some methods will enable stakeholder interaction, others will solicit only individual responses.

WP6 can provide methodology expertise and guidance tools to help the relevant WP to make the best fit methodology and design choice.

4. Specific objectives and desired outputs

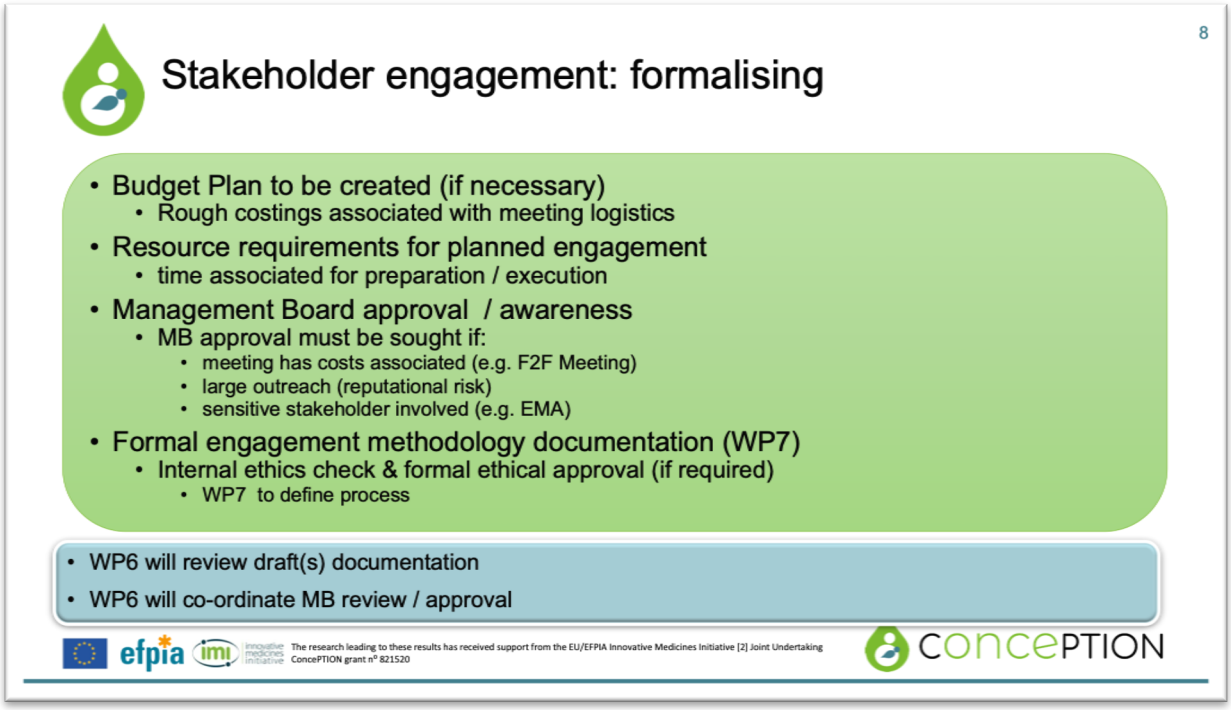
Set specific and realistic objectives and outcomes for the chosen method and design



Although a high-level set of objectives may have triggered the stakeholder engagement, once the design is clear some more specific and realistic objectives need to be set. These specific objectives, and the outputs that the chosen methodology could achieve, will be used to structure the actual engagement. This could, for example, be through the headings used to organise a survey, the questions to put to a focus group, the organisation of the slides of a webinar and the discussion after it. WP6 could interact with you on these.

5. Formalise the engagement plan

Develop a budget plan, obtain approvals, document the engagement plan



Formally cost the planning, execution and analysis phases of the engagement, considering costs to be incurred by the partners in the WP and any requests for central financial support. Also formalise the in kind support you would like (or have already received) from WP6 and other WPs.

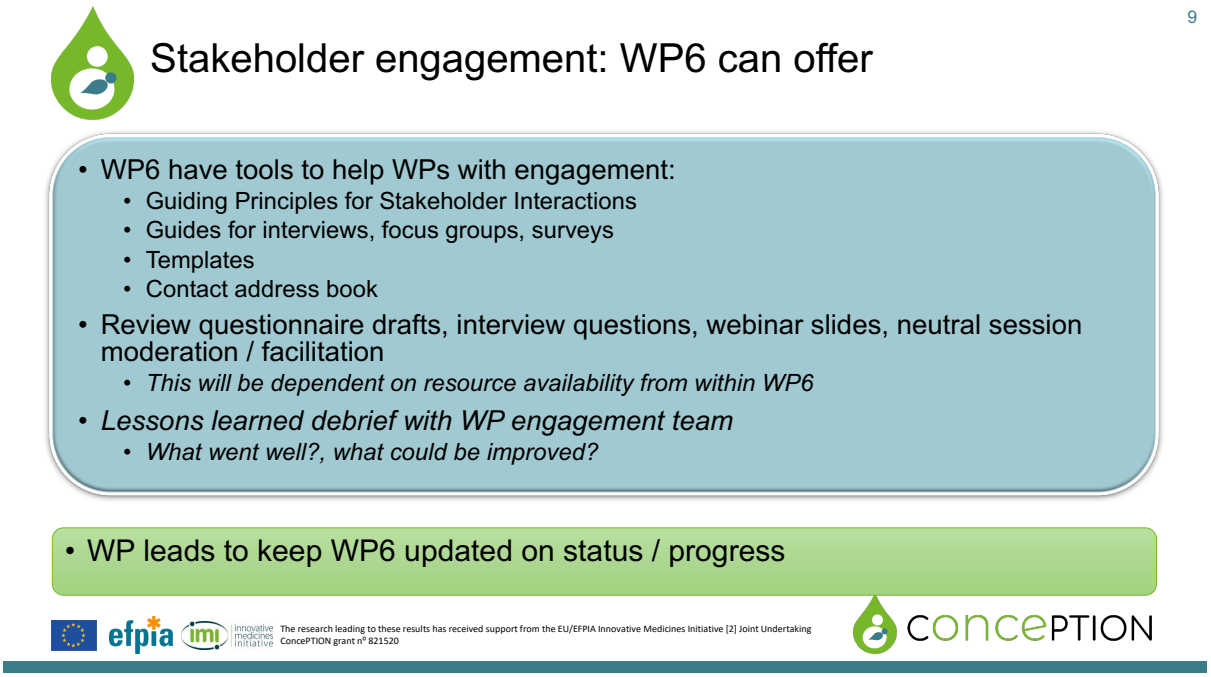
Seek Management Board approval for any request for central funds and for the effort inputs needed from other WPs.

Also request the go-ahead from the MB if this is a large-scale engagement or involves sensitive stakeholders such as regulators.

Ethics approval will be needed, initially internal but potentially from an external ethics committee if needed. WP7 can advise on this.

WP6 will review drafts of the engagement plan (if resources permit) and will co-ordinate the approvals of the MB.

6. How WP6 can support other WPs with stakeholder engagement



WP6 are developing various resources (tools) to help WPs with engagement planning and conduct. This includes a contact list of network leaders who may be willing to cascade your survey or invitation letters to their network. WP6 is developing guides and templates on the commonly used engagement methods.

It will be for each WP to design its own actual instruments, such as a questionnaire, interview structure or webinar slides. Each WP will have the domain expertise to drive that development process. WP6 may be able to review drafts and provide general methodology feedback, to help meet the objectives.

WP6 will want to follow up the outcome of the engagement activity, to gather some basic information about what took place and what was achieved. We will actively seek feedback about our support to the activity leads and which resources were used, if they were helpful or could be improved. We will therefore arrange a debrief with them after your engagement activity.

Appendix 2 contains the template form to be used by WP leaders to initially communicate to WP6 an intention to engage external stakeholders, to request permission and potentially a budget allocation by the Management Board, notify WP6 of this and optionally to request expertise input.

4. Preparing for interaction with Regulatory Agencies

Currently during the development of new medicines there is limited to no information within the product labels on the safety of medications taken during pregnancy on the pregnancy outcomes at initial launch of a drug. Product labels almost always recommend against breastfeeding as the risks are poorly characterized and there are restrictions to clinical research in pregnant and lactating women. Animal models (mostly rat) are not predictive of humans & human lactation studies are time consuming and costly. Frequently health authorities (HA) request a pregnancy registry at the time of initial approval and data from spontaneous pregnancy reports through pharmacovigilance are not fully utilized, quality and consistency as well as and analysis can be improved.

In order to see tangible benefits within the R&D sector ConcePTION aims to create a paradigm shift in how we generate and disseminate evidence on the effects of medication in pregnancy from existing health data and newly collected data. This will be achieved by generating, cataloguing, linking, collecting and analysing data from pharmacovigilance, pharmacoepidemiology, modelling, and routine healthcare, enabling improved monitoring of pregnant women and their children via a large network.

The project aims to provide validated and regulatory endorsed workflows for fast, optimised evidence generation.

Landscape Analysis Outcomes: supporting ConcePTION Strategy

- HAs to consider alternative approaches to pregnancy registries based on real world evidence
- Unified regulatory framework for collecting case reports of exposures to medicines during pregnancy to improve and quicken the generation and analysis of pregnancy outcomes, both positive and negative
- Animal and in-silico lactation models with higher predictability for humans & improved PKPD model: methodology(ies) presented to Regulatory Bodies for consideration, review and endorsement thus providing more reliable predictions for initial labelling
- Human milk biobank enabling faster and cost-effective analysis of the levels of active substances transferred in breastmilk, thereby avoiding the need for human lactation studies
- Advancing clinical and healthcare practice: Scientifically sound and validated information for implementation into the regulatory guidelines, which will lead to better information for HCPs and patients, and generally improve the health of our next generation. Regulatory bodies will be able to review data generated by individual sponsors that use the same broadly acceptable methodologies, hence making review of the individual product datasets easier. The faster and more efficient way of producing data to assess medication-related adverse pregnancy outcomes will enable regulatory bodies to include enhanced information in the label, providing prescribers and patients with much needed information to guide treatment decisions for the benefit of women and children. Better characterisation and prediction of the transfer of medicines in breast milk will deliver more reliable data to inform the initial label.

Regulatory Intelligence Activities

Work Package 6 acts as the central point for the project to ensure our voice is heard when key regulatory documents that have the potential to impact the scope of ConcePTION are published. Examples of this include:

- EMA joint task force big data summary (March 2019)
- FDA post approval pregnancy safety studies draft guidance (Aug 2019)
- FDA clinical lactation studies draft guidance (Aug 2019)
- Review of Draft GVP Guideline on Pregnant and breastfeeding women (Feb 2020)

These routine intelligence activities allow the consortium to be kept up-to-date with the evolving legislation surrounding topics that have relevance to ConcePTION areas of focus.

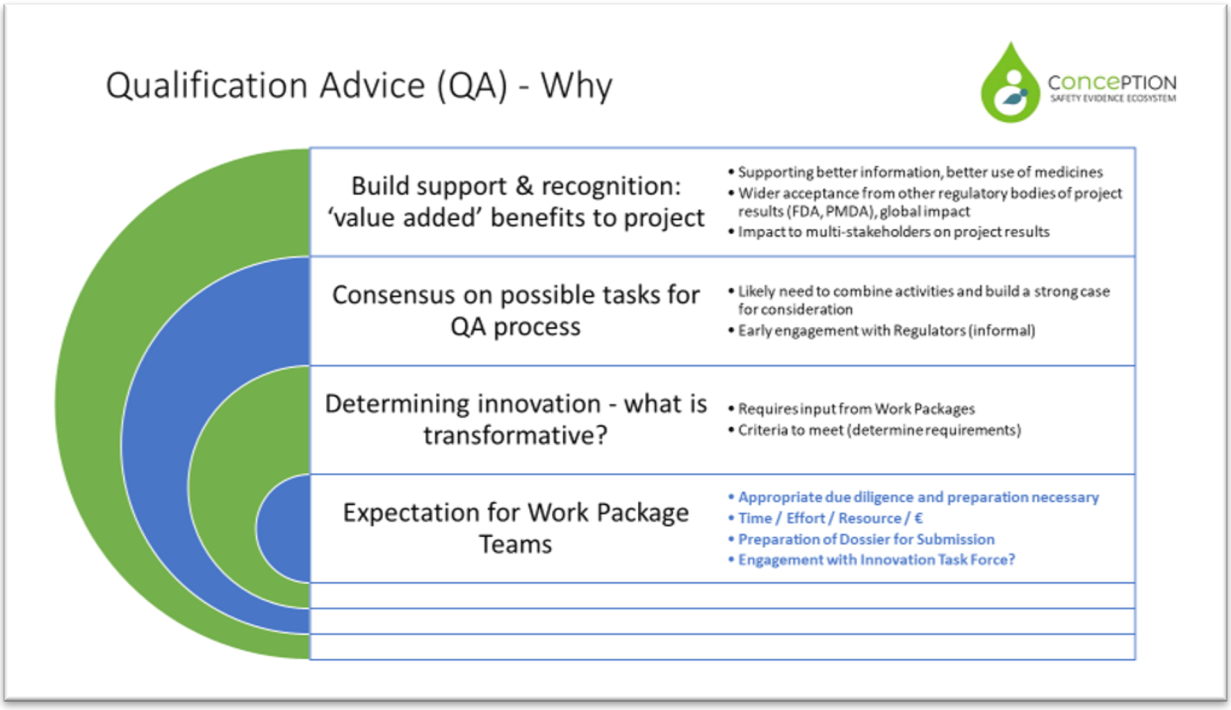
Qualification Advice European Medicines Agency (EMA)

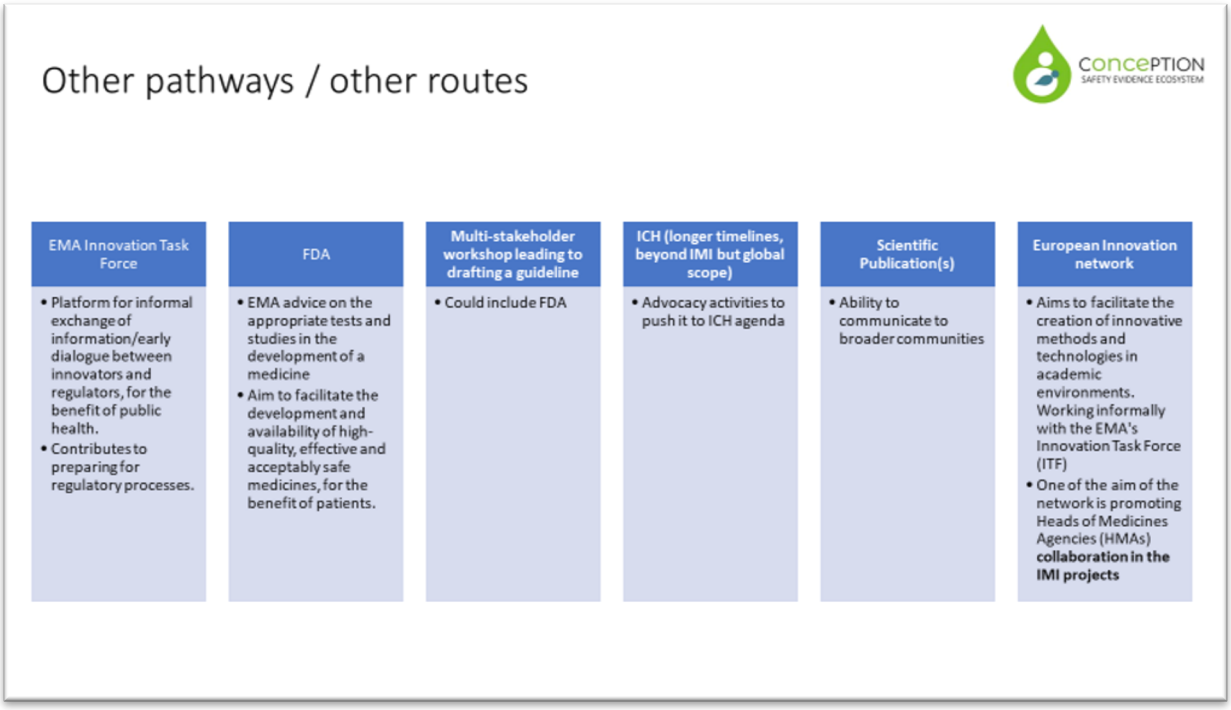
The EMA qualification of novel methodologies is a voluntary scientific pathway to establish the regulatory acceptability of a specific use of a methodology for the development of medicinal products. Outcomes of this pathway are:

- Committee for Medicinal Products for Human Use (CHMP) adoption of qualification advice on future protocols and methods for further method development towards qualification, based on the evaluation of the scientific rationale and on preliminary data submitted.
- CHMP qualification opinion on the acceptability of a specific use of the proposed method (e.g. use of a novel methodology or an imaging method) in a research and development (R&D) context (non-clinical or clinical studies), based on the assessment of submitted data

It is recognised that by utilising Qualification Advice Pathway for certain outcomes from the ConcePTION project we would be able to build support & recognition for these. Having regulatory endorsed methodologies would enable there to be acceptance of the data / evidence generated that could inform information contained within product label and Summaries of Product Characteristics (SmPCs). In addition, having methodologies endorsed by key Regulatory Body such as the EMA may have the potential for wider acceptance from other regulatory bodies of project results (FDA, PMDA), global impact.

To help promote a common understanding of Qualification Advice pathway there have been consortium wide Webinar sessions held (August 2019 & January 2020). All materials shared during these information sharing sessions have been made available to all consortium members and are accessible on the Team SharePoint site and included as embedded PDF files in Appendix 4.





Drug development is a global industry and the project hopes to engage with other regulatory bodies such as the FDA, PMDA throughout the lifetime of the project. The project has had initial engagement with the FDA Task Force on research specific to pregnant women (PRGLAC) and looks forward to continual discussions with them as the project progresses.

Due Diligence within ConcePTION Project: Potential Regulatory Interactions

As a first step in understanding the needs and requirements within ConcePTION for potential areas that could be open to investigate interactions with Regulatory Agencies a core team of SMEs within WP6 reviewed all work package tasks and activities (as outlined within the Description of Action). An overview of the project was developed to help identify and narrow the focus of the team. Through this work the following areas have been identified as having the potential consideration for possible submission to EMA Qualification Advice:

Work Package One

WP1 will test how a variety of existing "population-based data" (registries, healthcare databases, population cohorts) can be employed for evidence generation on medication use, disease impact and medication safety in pregnancy, using well-defined protocol-based studies. A series of protocol-based demonstration projects will test innovations in methods and new data sources and the ability to assess medication use and the impact of selected medications on pregnancy and childhood outcomes.

Work Package Two

WP2 will consider the optimisation of systems for the collection and analysis of pregnancy reports from women and healthcare professionals (i.e. case reports or prospective cohort studies with pregnant women). The aim is to identify and describe data sources with reported pregnancies, and to create a common data model which will serve as the starting point for a standardised method for data analysis of pregnancy reports and novel methods for qualitative and quantitative signal detection.

Work Package Three

WP3 will address the current lack of information regarding transfer of medicines into human breast milk. The main goal will be to develop, characterise, validate and apply a non-clinical testing platform for reliable prediction of drug concentrations in human breast milk along with systemic medication exposure in breastfed infants. This will be done by developing and implementing powerful high-throughput tools for generating quantitative *in vitro* human data. The development of a predictive *in vivo* animal model for lactation and a PBPK model will be used to provide information on the transfer of medications and their metabolites in the milk for inclusion in the initial label

Work Package Four

WP4 will establish the first EU-wide breast milk and blood biobank with accompanying analytical centre able to comply with quality standards capable of measuring medication concentrations in milk and blood/plasma. The purpose is to facilitate high quality research that will accurately characterise medication levels in human breast milk based on donated milk samples from women across Europe.

Work Package Seven

Work package seven facilitates the work for WP1 and 2 by providing support in data and analytics generation readiness and will support the generation of high quality real world evidence on the effects of drugs during pregnancy and lactation.

Decision making for Qualification Advice Candidates within the ConcePTION Consortium

Consideration of QA pathway for ConcePTION
Within the consortium there is clear guidance on seeking endorsement from the Management Board for key decisions and as such, tools to support the work package teams and a decision tree are necessary to ensure rigorous scientific peer review and transparency of decision making is upheld. A template for work package teams has been produced [refer to Appendix 3 Qualification Advice WP Mapping to EMA (Regulatory) Engagement Pathways]. This template has been developed as an internal tool to enable informed discussions between work package members and Management Board.

Each work package has identified experts from WP6 to partner and support them as they consider QA engagement. Work is on-going to provide a RACI (Responsible, Accountable, Consult & Inform) Chart to help teams understand the role each person will play throughout the course of the activity.

Next Steps

- Collating information received from WPs (template population)
- Internal review by WP6
- Virtual Workshops / Face to Face Workshops
- Preliminary Telephone Conference with EMA participation (through consortium)
- Deeper dive on what WPs are looking to gain from this route
- Advice on Pathway (will have input from EMA WP6 colleagues)
- Further work needed (additional evidence: data, stakeholders etc)
- Bring proposal to Management Board for Review & Decision Making

Early discussions with Regulators
ConcePTION will aim to make use of established pathways where informal discussions with Regulatory agencies can take place. For example, the Innovation Task Force (ITF) or Scientific Advice Working Party (SAWP). This platform will allow the project to exchange information and have early dialogue between innovators and regulators. The work carried out by the teams in preparation for ITF / SAWP briefing meetings will contribute to conception preparations for regulatory processes.

Note, it is acknowledged that as a consortium member EMA will participate in early discussions with the different work packages. However, to avoid a conflict of interest EMA ConcePTION members will step away from discussions when a decision to follow the formal route of QA is initiated.
Work related to ConcePTION and the interaction with Regulatory Agencies will be on-going throughout the lifetime of the project. As the different work packages complete their activities, there will be in parallel, appropriate strategic planning put in place to ensure teams are prepared, peer review of scientific methodology and data generated occurs and that the appropriate internal Management board endorsement is given prior to initiation of formal EMA Qualification Advice discussions.

5. Characterising evidence within ConcePTION

Purpose

ConcePTION intends to enlarge the pool of available evidence to support decision making about using medication during pregnancy and lactation, for a range of health purposes. It will also establish a sustainable ecosystem for evidence generation, appraisal, use and dissemination and for safety monitoring, primarily using real world data.

Different WPs and tasks within the project will elicit:

- uncertainties regarding appropriate and safe medication use as perceived by women during pregnancy and lactation and by the health professionals they interact with, perceived by regulators and the pharma industry in terms of what real world evidence they could base decisions on, and perceived by public health agencies for public and patient education;
- new forms of evidence to fill some of these gaps, to the best level of trustworthiness possible from the networks of data available to ConcePTION;
- one knowledge repository (database) that consolidates, groups and publishes the available evidence (existing and new) in ways that support relevant discovery by different stakeholders;
- strategies for future evidence generation, by constructing a sustainable ecosystem that utilises and goes beyond the data and resources of the project.

A unifying conceptual framework may be useful when comparing findings across surveys, and mapping areas of uncertainty to evidence that we will generate. Such a framework might be implemented as (metadata) tags attached to a survey finding or a new evidence insight, and used to discover it within a database. For example, a public survey might highlight specific concerns about what impact medicines used to treat long term conditions might have on the fertility of men. These concerns could be tagged as <Continuous treatment of a chronic condition> and <Pre-conception> and <Father> and <Attitude or perception survey>. These tags could allow someone to later discover this survey finding through a search of our knowledge bank.

WP6 proposes a set of eight dimensions or tags for characterising evidence.

1. Therapeutic area and health situation for which the medication is intended to be taken
2. Role of the medication (for the condition or situation)
3. The relationship of this evidence to the relevant current labelling and treatment guidance or recommendation during pregnancy/lactation
4. Stage of pregnancy / lactation to which the evidence or evidence gap applies
5. Person to whom the evidence or gap applies
6. Kind of stakeholder decision(s) for that evidence or gap
7. Nature of the evidence generated or needed
8. Weight of the evidence (according to a rating still to be defined)

A term list is proposed for each of these tags below. Only those that are applicable need to be used to tag any particular finding.

Therapeutic area and health condition

Term list for specifying therapeutic areas [1]

- Cardiology/Vascular Diseases
- Dental and Oral Health
- Dermatology
- Endocrinology
- Gastroenterology
- Genetic Disease
- Haematology
- Hepatology (Liver, Pancreatic, Gall Bladder)
- Immunology
- Infections and Infectious Diseases
- Internal Medicine
- Medical imaging
- Musculoskeletal
- Nephrology
- Neurology
- Nutrition and Weight Loss
- Obstetrics/Gynaecology (Women's Health)
- Oncology
- Ophthalmology
- Orthopaedics/Orthopaedic Surgery
- Otolaryngology (Ear, Nose, Throat)
- Pathology
- Paediatrics/Neonatology
- Pharmacology/Toxicology
- Podiatry
- Prevention and Wellness
- Psychiatry/Psychology
- Pulmonary/Respiratory Diseases
- Rheumatology
- Sleep
- Trauma and wound care
- Urology
- Vaccines
- Other (to be specified)

Note: an alternative or additional classification could be on the basis of ATC mechanism of action

[1] This term list has been compiled from a combination of term lists including those used by the pharma industry to classify therapeutic areas.

Role of the medication

Term list for specifying the role played by the medication or therapeutic class

- Continuous treatment of a chronic condition
- Acute treatment for an exacerbation of a chronic condition (for a disease escalation)
- Treatments used for secondary prevention
- Acute treatment for health events such as infections and injuries
- Treatments used in medical (e.g. operative) procedures
- Therapies specifically targeted at health issues arising within pregnancy, including treatments for a disease occurring in the pregnancy
- Prophylaxis treatments
- Wellness products

The relationship of the new evidence to current evidence

It is still to be determined how best define to a term list of values for this.

Stage of pregnancy / lactation

Term list for specifying the lifecycle point in pregnancy

- Women of childbearing age (who plans to become, or may become, pregnant)
- Pre-conception (e.g. during fertility treatment)
- First trimester
- Second Trimester
- Third trimester
- During labour
- Immediately post-partum
- During lactation

Person to whom the evidence or gap applies

Term list for specifying the party whose health or safety was studied by the evidence or for whom a gap exists

- Mother
- Baby (including long term consequences)
- Father
- Second generation offspring

Type of stakeholder decision(s) for that the evidence or gap

Term list for specifying the kind of decision to be made using the evidence, and which stakeholders are most impacted by the evidence e.g.

- Medication prescription by health professional
- Medication purchase / acceptance / consumption by mother - *use/don't use during pregnancy/lactation*
- Regulatory approval: regulator, pharma - *what warnings/recommendations to include in the product labelling*
- Health Technology Assessment (HTA) (HTA body, public health agency, health professional body) - *how these recommendations affect endorsements i.e. expected usage*
- Reimbursement/coverage
- Patient information update
- Pharmacovigilance (regulator, pharma, HTA)
- Others to be determined

Type of study

Type of study that was undertaken to generate the evidence

- Interventional study: RCT
- Interventional study: Pragmatic Clinical Trial
- Observational/non-interventional study
- RWE from a pregnancy registry
- Post-authorization Safety Study
- Pharmacovigilance monitoring
- Comparative effectiveness research
- Bio-sample examination e.g. milk bio-bank
- Animal study
- In vitro study
- Attitude or perception survey

Weight of the evidence

An axis for further development, to determine if it can be objectively asserted or assessed. This would need to take into account:

- the sources, care settings, relevance and quality of the data;
- geographical and other characteristics of the study populations
- sample/population size
- time period studied
- study duration
- data set, including what outcomes were studied
- data collection or acquisition methods used
- analysis methodology used
- positive or negative findings: presence of the outcome or absence of the outcome (we will need to be more clear about the outcome, e.g. definitions of categories for the pregnancy outcome)

6. Conclusion and next steps

Given the wide aims of the project which include changing the evidence base for decision making, stakeholder engagement is critical to success. This first year has shown that engagement has to be ongoing and an iterative process, informed by each event or survey. Inevitably these findings will highlight new gaps, engagement needs and opportunities.

In year two of the project WP6 anticipates putting the content of these deliverable chapters into action, in particular through providing expert advice to other WPs on their stakeholder engagements and beginning to collect candidates for EMA advice. Future WP6 deliverables will summarise what engagements we have helped with and the outcomes of each. It will also synthesise findings from stakeholder engagements, including surveys, undertaken by other WPs which capture evidence needs and acceptance factors.

An important objective of year 2 is to collate, synthesise and analyse the anticipated WP results that may be potential candidates for Qualification Advice. Given that QA submission is resource intensive (time & financial), WP6 will play an important role in aligning proposals from the different WPs (combining, where appropriate those methodological innovations, into a single proposal). All proposed candidates will be appraised and reviewed by the Management Board to endorse prior to formal submission to the EMA. To assist this process WP6 will look to utilise the Innovation Task Force, which offers an informal forum to discuss candidate proposals with EMA identified experts before working up a QA submission.

Appendix 1: Overview of existing guidance for stakeholder engagements

Examples of stakeholder engagement guidelines used in different settings of health care/health research were collected and reviewed as part of developing the principles outlined in Section 1 of this document. All of these examples are available in the Table below. Please note that these are examples – i.e. the overview list is not meant to be complete or exhaustive.

Stakeholder Engagement - Existing Guidelines for Engagement with Patients/Patient Organisations (PO)				
Organisation	**Document Title**	**Issued (Date)**	**Content**	**Link**
EUPATI	Overarching principles for patient involvement throughout the medicines research and development process	2018	• Proposes ethical values and suggested working practices when interacting with patients • Defines "Patient" to reflect the different types of input /experience required from patients, patient advocates and POs in different collaborative processes • Includes 4 separate guidance documents (see below) to support the integration of patient involvement across the entire process of medicines research and development	https://www.eupati.eu/guidance-patient-involvement/
EUPATI	Guidance for patient involvement in ethical review of clinical trials	2018	• Gives practical recommendations for ground rules • Lists options for conditions /practices for involving patients in the work of ethics committees to enable trustful/constructive collaboration • Sets collaboration of patients in ethics committees in broader context by pointing out opportunities for patient input on ethics throughout the clinical trial process - from concept development to trial result reporting in lay summaries	https://www.eupati.eu/clinical-development-and-trials/guidance-for-patient-involvement-in-ethical-review-of-clinical-trials Klingmann I, et al. Front Med. 2018; 5:251
EUPATI	Guidance for Patient Involvement in Medicines Research and Development (R&D) Guidance for Pharmaceutical Industry-Led Medicines R&D	2018	• Covers interaction between patients and the pharmaceutical industry within all functions throughout the medicines R&D lifecycle (pre-to post-approval) involving individuals and groups of patients • Distinguishes between level of expertise in a disease area that is required and the different areas where patient involvement can take place • Aimed at pharmaceutical companies who want to engage patients in R&D activities (and beyond)	https://www.eupati.eu/patient-involvement/guidance-for-patient-involvement-in-industry-led-medicines-rd/ Warner K, et al. Front Med. 2018;5:270.
EUPATI	Guidance for patient involvement in	2018	• Covers patient involvement in the regulatory field	https://www.eupati.eu/patient-involvement/guidance-for-patient-involvement-in-regulatory-

	regulatory processes		• Draws on mature "Framework for interaction between the EMA and patients/consumers and their organizations. • Expands on EMA framework, specifically including NCAs • Sets out objectives for patient involvement in medicines regulation and recommends concrete suggested working practices • Primarily aimed at regulatory authorities wishing to interact with patients or their organizations in their activities but should also be considered by patients/patient organizations planning to collaborate with regulatory authorities	processes/ Haerry D, et al. Front Med. 2018;5:230.
EUPATI	EUPATI Guidance for Patient Involvement in Medicines Research and Development: Health Technology Assessment	2018	• Provides recommendations for activities to support patient involvement in HTA bodies and specific guidance for individual HTA processes • Seeks to improve patient involvement, using the outcomes of published research and consensus-building exercises • Draws on good practice examples from individual HTA bodies	https://www.eupati.eu/health-technology-assessment/patient-organisation-involvement-in-hta-processes/ Hunter A, et al. Front Med. 2018;5:231
EMA	European Medicines Agency Revised Framework for Interaction Between EMA and Patients Consumers and Their Organisations	2014	Aims at • Supporting EMA to access real-life experiences of diseases and their management and to obtain information on the current use of medicines • Understanding the value, as perceived by patients, of the scientific evidence provided during the evaluation process for the purposes of benefit/risk decision-making • Contributing to more efficient and targeted communication to patients and consumers, to support their role in the safe and rational use of medicines • Enhancing patients/consumers' organisations' understanding of the role of the EU medicines Regulatory Network	http://www.ema.europa.eu/docs/en_GB/document_library/Other/2009/12/WC500018013.pdf
EFPIA	Working together with patient groups	September 2017	• Provides rationale for interactions between the pharmaceutical industry and POs • Suggests principles on which these interactions should be based • Outlines points of collaboration through the life-cycle of a medicine • Discusses some of the challenges and potential solutions to interact • Provides list of resources to support meaningful/appropriate collaboration	https://www.efpia.eu/publications/downloads/efpia/working-together-with-patient-groups/
ABPI	Working with patients and POs a sourcebook for industry	June 2019	• Provides 4 guiding principles for collaborative working between industry and patient organization • Defines minimum requirements for written agreement required for collaboration between industry and patient organizations	https://www.abpi.org.uk/media/7293/abpi_workingwithpatients_webbrochure_v8.pdf

PFMD	Patient Focused Medicines Development	2018	• Patient Focused Medicines Development (PFMD) was established in October 2015 as an open, independent global coalition of health stakeholders. • Alliance of different stakeholders involved in drug development process, such as patients, patient stakeholders and the pharmaceutical industry. • Aims to transform the way in which we understand, engage, and partner with patients globally in the design and development of research and medicines by focusing on unmet patient needs. • Brings together and synergizes disparate but complementary efforts that integrate the voice of the PATIENT across the lifecycle of medicines.	https://patientfocusedmedicine.org
PFMD	Patient Engagement Quality Guidance	2018	• A practical guide to planning, developing and assessing the quality of patient engagement activities and projects throughout the development and lifecycle of medicines. • The guidance introduces 7 quality criteria to assess patient engagement practices. These have been consolidated from published PE frameworks and co-developed further by PFMD Contributors. • The tool was co-developed with a large community of stakeholders (more than 100 people from 51 organisations), representing patient associations, industry, academics, researchers and external experts.	https://patientfocusedmedicine.org/the-patient-engagement-quality-guidance/
PFMD	PFMD Governance Structure	2019	• PFMD seeks to have a balanced representation of stakeholders to ensure transparency, inclusiveness, and credibility. The purpose of this document is to explain PFMD's governance structure. It also depicts how PFMD will operate in the future, and how it makes operational and strategic decisions on a day-to-day basis. • The governance is supported by several governing principles: 1) governance for inclusion and agility. People in governing bodies do not act as representatives of their own organizations but as representatives of the consortium. 2) Commitment and expertise. Being a member of the governance requires expertise and commitment to transform the status quo, and is not just about having a seat at the table as an observer. 3) We should not compete between members and partners of the consortium.	https://patientfocusedmedicine.org/governance/
PFMD	Stakeholder Expectations Matrix		• Methodology to understand stakeholder expectations on the topic and to establish a common purpose and vision, conducted through a stakeholder mapping.	http://patientfocusedmedicine.org/wp-content/uploads/2017/10/PFMD_UnderstandingStakeholdersExpectation.pdf https://onlinelibrary.wiley.com/doi/e

				pdf/10.1111/hex.12797
PARADIGM	Patients Active in Research and Dialogues for an Improved Generation of Medicines	2018	• Public-private partnership funded by the Innovative Medicines Initiative Joint Undertaking 2. • Aim is to optimize the practical implementation of patient engagement by establishing a framework explaining who should be involved and how and at what stage in the drug development process this needs to be accomplished.	https://imi-paradigm.eu

Abbreviations: EMA= European Medicines Agency; HTA=Health Technology Assessment; NCA= national competent authorities; PO=Patient Organisations; R&D= Research & Development

Stakeholder Engagement - Existing Guidelines for Other Stakeholder Interactions/Other Forms of Public Engagement				
Organisation	**Document Title**	**Issued (Date)**	**Content**	**Link**
EFPIA	Code of Practice	June 2019	• Collection of ethical rules agreed by EFPIA members (for the Promotion of Medicinal Products to HCPs) and the interactions with HCPs, HCOs and POs, with the intent of guaranteeing that these activities are conducted, while respecting the most stringent ethical principles of professionalism and responsibility	https://www.efpia.eu/media/413022/efpia-code-2019.pdf
Centre for Development Innovation (CDI)	The MSP guide to how to design and facilitate multi-stakeholder partnerships (MSP)		• Provides 7 principles to follow that help make MSPs successful • Provides key ideas for effective facilitation of MSPs • Provides 60 participatory tools that enable people to work together constructive and creatively	https://www.wur.nl/en/Publication-details.htm?publicationId=publication-way-343931333136
Understanding Patient Data (UK)	Website		• Supports better conversations about the uses of health information. Aim is to explain how and why data can be used for care and research, what's allowed and what's not, and how personal information is kept safe. • Works with patients, charities and HCPs to champion responsible uses of data. • Devised list with simple do's and don'ts when running engagement activities	https://understandingpatientdata.org.uk/public-and-patient-engagement-activities)
Consortium academic/ public researchers (UK)	Consensus Statement on Public Involvement and Engagement with Data-Intensive Health Research	2019	• Developed 8 principles for public involvement/engagement (PI&E) in data-intensive health research • Principles are meant to inform the design, implementation and evaluation of PI&E strategies	https://ijpds.org/article/view/586/1032

			and activities and shape the mindsets of researchers, funders and other stakeholders	
UK Public Involvement Standards Development Partnership	UK Standards for Public Involvement	2019	• Formulated 6 principles ("standards) to improve public involvement for better health and social care research	https://www.invo.org.uk/wp-content/uploads/2019/11/UK-standards-for-public-involvement-v6.pdf

Legal environment for a stakeholder engagement framework

1. **Binding documents**
    a. European Law
        i. Regulation (EU) 2016/679 of the European Parliament and of the Council of 27 April 2016 on the protection of natural persons with regard to the processing of personal data and on the free movement of such data, and repealing Directive 95/46/EC (General Data Protection Regulation)
        ii. Directive 2001/83/EC of the European parliament and of the council of 6 November 2001 on the on the Community code relating to medicinal products for human use'
        iii. 'Clinical Trial Regulation EU No. 536/2014'
        iv. Regulation (EU) 2016/679, 2016
        v. Directive 2001/83/EC, 2001
        vi. Regulation (EU) No 536/2014
    b. National law

2. **Soft law (Europe)**
    a. EFPIA guidelines: multiple codes
        i. 'EFPIA Code of practice on relationships between the pharmaceutical industry and patient organisations'
        ii. 'EFPIA Code on the promotion of prescription-only medicines to, and interaction with, healthcare professionals'
        iii. 'EFPIA code on disclosure of transfers of value from pharmaceutical companies to healthcare professionals and healthcare organisations'

Appendix 2: Stakeholder engagement request form

General

Title	
Objective	
Expected output	
Linked to Task/Deliverable	
Potential alignment with other WPs	

Meeting information

Type of meeting *(please check which applies)*

☐ Face to Face

- Preferred country/city: ……...
- Is this flexible: YES/NO

☐ Webinar
☐ Teleconference
☐ Other… (please specify)

Meeting date

☐ Period:……. ☐ Date:……

- Is there room for flexibility: YES/NO

Participants

N° Internal participants	
Stakeholder engagement	YES/NO *If yes, please specify number and type of stakeholders attending the meeting*

Estimated budget (€):

Description of the meeting:

Describe in a few sentences how you envision the meeting (e.g. agenda, set-up/structure meeting)

Appendix 3: Qualification Advice WP Mapping to EMA (Regulatory) Engagement Pathways

Qualification Advice WP Mapping to EMA (Regulatory) Engagement Pathways (Expression of Interest)

Work Package Details: *Please populate with information regarding WP leads, team members etc*	*Work Package No:* *Work Package Leads:* *WP Members:*
Work Package Key Contact(s)	*Provide name(s)*
WP6 contacts	*Provide name(s)*
Proposed Timings for QA	*Please detail proposed timings for when team would be looking to go down this pathway* • *e.g. when will you have data generated from Experime to support methodology* ○ *Scientific Advice (you do not have to have data completed)* ○ *Submit topic to informal EMA Information Technology Forum / Scientific Advice Working Party meetings (these are outlined on EMA website)*
Internal Review timelines	*WP6 review* *Management Board Review*

Objectives of Request

Brief Description & aim of Method / Model *Please include details of which IMI ConcePTION project task(s) this is related too*

Need & Impact of Proposed novel methodology(ies): *What is different to current state, high level information outlining 'novelty of proposal': what is transformative for proposed methodology vs. current state?*	
Relevance to Clinical Setting (if applicable):	
Sources of Data & Proposed Findings; characteristics of proposed novel methodology(ies): *Brief description of experimental approach, technology platforms being used for the proposal*	
Review of Published Literature: *Provide outline of planned steps*	

What route is most appropriate for objective? *Provide conclusion of Work Package for review by Project Team* *Justification for seeking Qualification Advice – is this the most appropriate route?* *Innovation aspect – what is different from current state?*	To aid further discussions on expression of interest (through virtual workshops) WP6 Core Team (task 6.2)

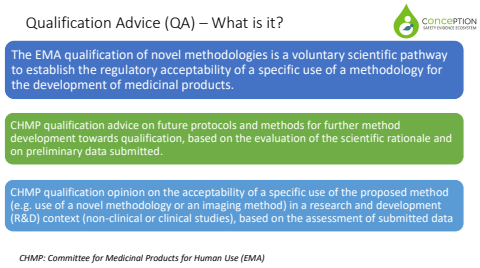
NEXT STEPS
• Collating information received from WPs (WP6 task)
  ○ Internal review by WP6
• Virtual Workshops
  ○ Preliminary tc with EMA participation (through consortium)
  ○ Deeper dive on what WPS are looking to gain from this route
  ○ ADVICE ON PATHWAY (will have input from EMA WP6 colleagues)
  ○ Further work needed (additional evidence: data, stakeholders etc)
• Bring proposal to Management Board for Review & Decision Making
	WP6 members
	Identified WP teams
	Additional Peer Review

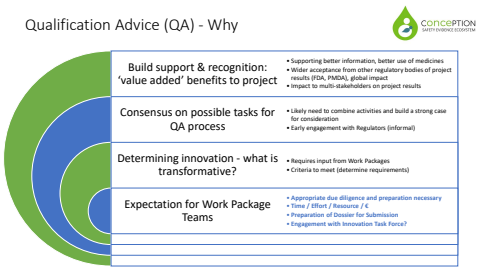
MANAGEMENT BOARD RECOMMENDATION • **THIS WILL ALLOW MB & MT AWARENESS OF HOW MANY PROPOSED QA ARE BEING PUT FORWARD** • **INFORMATION WILL BE PRESENTED TO MANAGEMENT BOARD REVIEW & DECISION**	Agreement on Proposal(s) to be sought

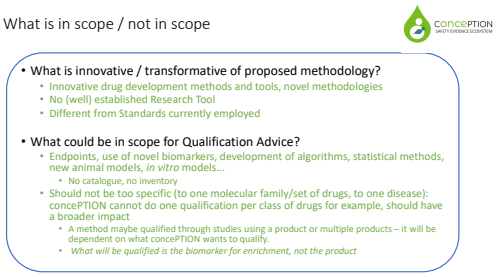
Appendix 4: Presentations giving an introduction to Qualification Advice

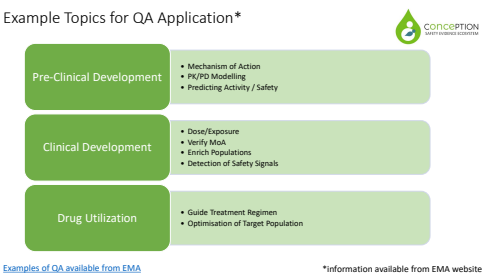
The webinar presentation explained the EMA publication: "Qualification of novel methodologies for drug development: guidance to applicants", EMA/CHMP/SAWP/72894/2008, published on 10th November 2014, and available from: https://www.ema.europa.eu/en/documents/regulatory-procedural-guideline/qualification-novel-methodologies-drug-development-guidance-applicants_en.pdf

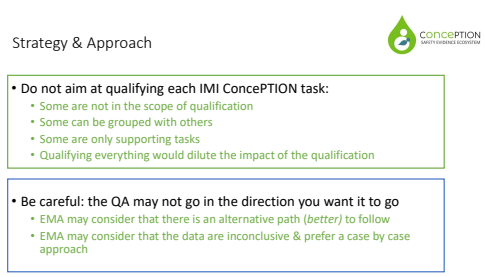
The webinar slides developed by WP6, that were delivered to the consortium members are reproduced below.



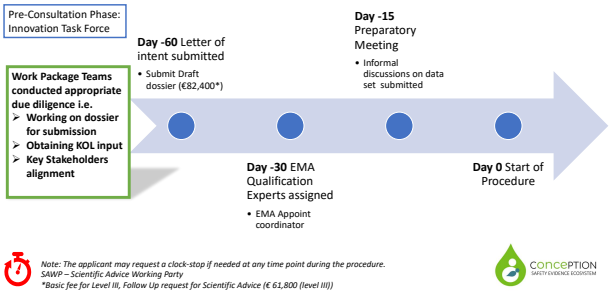




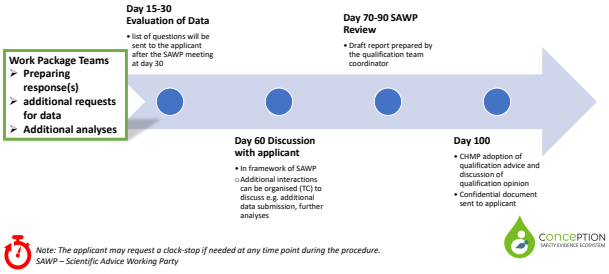




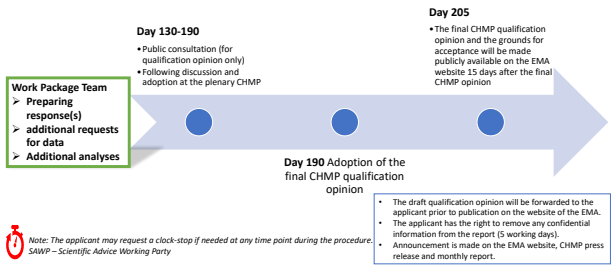
Timeline for Qualification Advice & Qualification Opinion: (1 of 3)



Timeline for Qualification Advice & Qualification Opinion: (2 of 3)



Timeline for Qualification Advice & Qualification Opinion: (3 of 3)



Dossier for Qualification Advice / Opinion (1 of 4)

- Letter of intent*
- Briefing document:

1. Table of contents

2. Executive summary

3. Statement of the need for and impact of the proposed novel methodologies in (non)clinical drug development

- General introduction to the novel methodology followed by:
- The intended application(s) in (non)clinical drug development (context in which the qualification of the novel methodology(ies) is pursued)
- The disease/condition/experimental setting in which the novel methodology(ies) will be applied
- Currently available tools (e.g. in patient care and clinical drug development)
- Characteristics of the proposed novel methodology

*Templates are available from EMA website

Dossier for Qualification Advice / Opinion (2 of 4)

4. Methodology and results

- Detailed overview and critical analysis/interpretation of the novel methodology development programme (including relevant (non-)clinical data):
- Methods
- Results
- Remaining gaps
- Evidence from published literature

5. Conclusions

- Key findings from all your evidence sources and how they fulfil the objectives

6. References and appendices

- Protocols and reports of individual studies, meta-analyses, and systematic literature reviews performed

Dossier for Qualification Advice / Opinion (3 of 4)

Context of use, objective, studies, methods, and protocols are key to obtain advice

- Questions and applicant's position
- Background information e.g.
  - Product profile
  - Investigators' brochure
  - Relevant study protocols or draft study protocols or study outlines
  - Bibliographical data (references)
  - Content or previous requests received
  - Relevant guidelines (other than CHMP guidance documents)
  - Contract agreement if the request is submitted by a consultant/CRO on behalf of the company
- Sections/subheadings may be added or omitted as appropriate;
  - ***discuss content/format with EMA prior to submission***

Dossier for Qualification Advice / Opinion (4 of 4)

Essential considerations for successful qualification of novel methodologies :

- Definition of the Context(s) of Use
- Selection of Endpoint(s)
- Statistical Analysis Plan
- Demonstration of clinical utility
- Standard of truth / surrogate standard of truth
- Appropriateness of the analytical platform
- Other considerations with available regulatory guidance

Other pathways / other routes (1 of 2)

EMA Innovation Task Force	Scientific Advice / Parallel SA with the FDA
• Platform for informal exchange of information/early dialogue between innovators and regulators, for the benefit of public health. • Contributes to preparing for regulatory processes.	• EMA advice on the appropriate tests and studies in the development of a medicine • Aim to facilitate the development and availability of high-quality, effective and acceptably safe medicines, for the benefit of patients.

Other pathways / other routes (2 of 2)

Innovation Task Force	FDA	Multi-stakeholder workshop leading to drafting a guideline	ICH (longer timelines, beyond IMI but global scope)	Scientific Publication(s)	European Innovation network
		• Could include FDA	• Advocacy activities to push it to ICH agenda	• Ability to communicate to broader communities	• Aims to facilitate the creation of innovative methods and technologies in academic environments, and translation of basic research into the medicine-development process • Working informally with the EMA's Innovation Task Force (ITF) • One of the aim of the network is promoting Heads of Medicines Agencies (HMAs) **collaboration in the IMI projects**

Next Steps

Work Package 6 members will be reaching out to Work Package Leads & teams

Time with teams to:	To Consider

• Hold In-depth discussions on outputs from your Work Package
• What question(s) are you seeking Regulatory Endorsement of?
  • How is this new & different from current state? What is innovative?
  • What value QA will bring to WP outputs?
  • Will this add to sustainability?
  • Is Qualification Advice the most appropriate route to deliver Project results?
  • Value added effect of combining WPs results for combined submission
  • strengthening case to present to EMA
	• Understand Governance within Consortium:
	  • Decision to be presented to Management Board
	• Roles & Responsibilities within WP Team for QA Dossier (who will be doing what)
	• Timing: when will teams have enough evidence to support submission for QA advice
	• Support to WP teams from WP6: *templates, navigation of process, etc*

Questions