From: [redacted] (SANTE)
Sent: lundi 27 janvier 2020 10:47
To: [redacted] (SANTE)
Subject: FW: Slide deck for today's Technical Meeting
Attachments: 2019-12-02 EUNETHTA-EFPIA TECHNICAL MEETING - SLIDE DECK.pptx

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From: [redacted] (SANTE) [redacted]@ec.europa.eu>
Sent: Monday, December 2, 2019 2:12 PM
To: SANTE DL B4 HTA <SANTE-DL-B4-HTA@ec.europa.eu>
Subject: FW: Slide deck for today's Technical Meeting

The slide deck form today's meeting … quite interesting points in particular EFPIA recommendations for improvement of EUnetHTA process (and for any new system) + some interesting facts from EUnetHTA WP4

[redacted]

From: [redacted]@zinl.nl>
Sent: Monday, December 2, 2019 1:27 PM
To: [redacted] (SANTE) [redacted]@ec.europa.eu>; [redacted] (EMA) [redacted]@ema.europa.eu>
Subject: Slide deck for today's Technical Meeting

Hi [redacted] and [redacted]

Please find attached the slide deck for today's meeting. (@[redacted] – you're slides are still missing in the attached but I will add them during the break).

Do let us know if you have any questions.

[redacted]

--

2019 EUnetHTA-EFPIA Technical Meeting

Monday 2 December 2019

Haute Autorité de Santé, 5 Avenue du Stade de France, 93210 Saint-Denis

Welcome

Welcome, introductions, and adoption of the agenda

[redacted], EUnetHTA (TLV)
, EFPIA (Roche)

Update on governance changes in EUnetHTA

EUnetHTA (TLV)

Summary

In their July 2018 meeting, the Executive Board requested that the chairs of the Board, as well as the Secretariat, outline **the potential development of the Joint Action's governance structure**.

This was in attempt to:

- Address governance issues and gaps within the project.
- Improve overall transparency and accountability.

Principles of the governance changes

Decision participation

The primary role of the Executive Board and the Heads of Agencies and their function as key representatives of the project.

Quality of decisions

Decisions must be prepared by the appropriate and accredited experts.

Decision-making

Decisions must be taken by a majority vote and must be prepared by the appropriate bodies.

Decision application

The obligation of partners to implement decisions, if there has been prior commitment to do so.

Recommendations for implementation

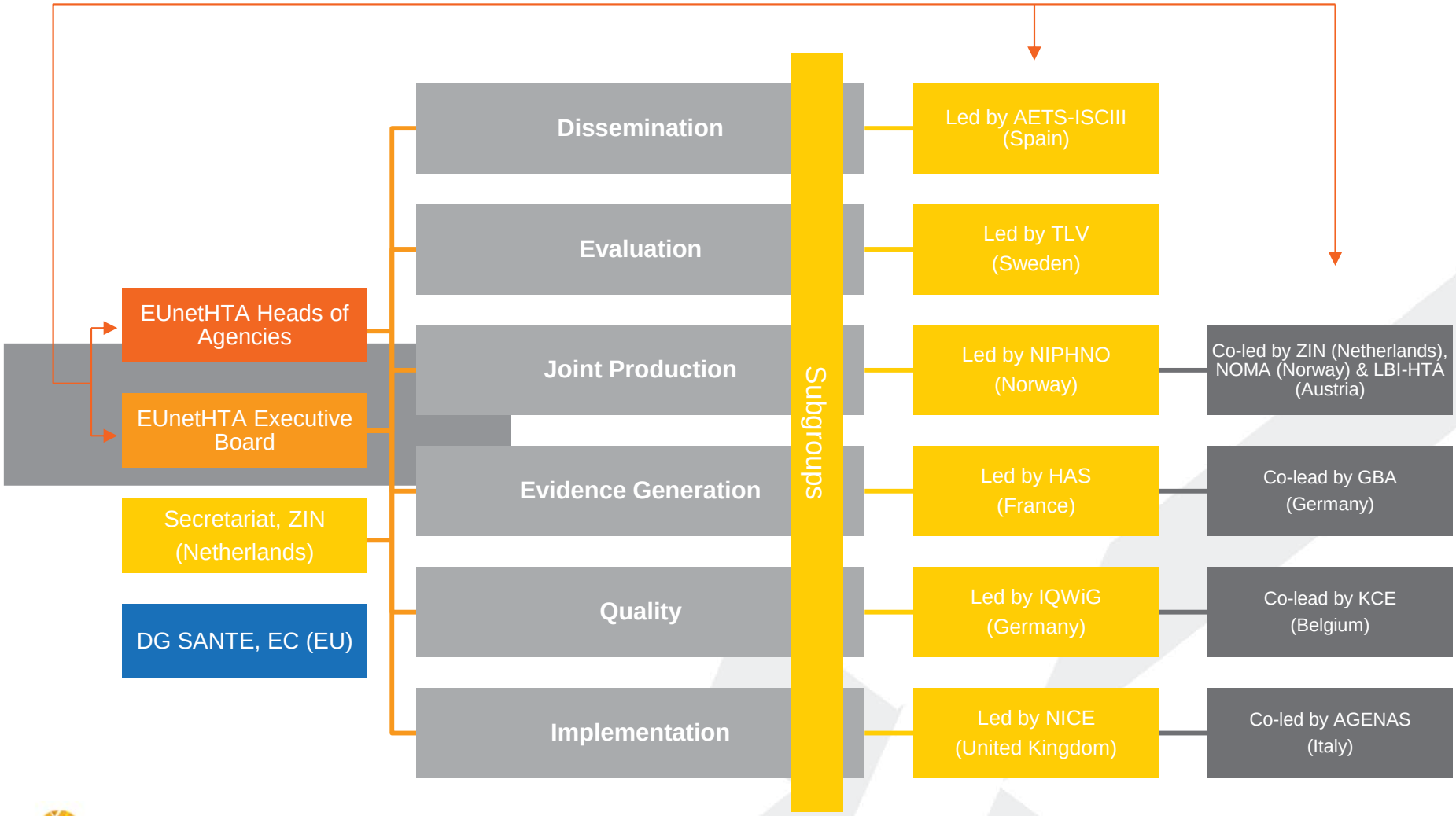
The Role of the Executive Board and the Heads of Agencies

Decisions that have **far-reaching consequences** and are of **strategic value** to the project and any future model of collaboration, should be taken by the Executive Board or the Heads of Agencies group.

The creation of subgroups

In 2018, task groups were introduced as a horizontal forum to discuss topics of cross-work package relevance. The governance development further develops this mechanism by creating subgroups that prepare decisions for the two key decision-making bodies in EUnetHTA.

Current governance structure



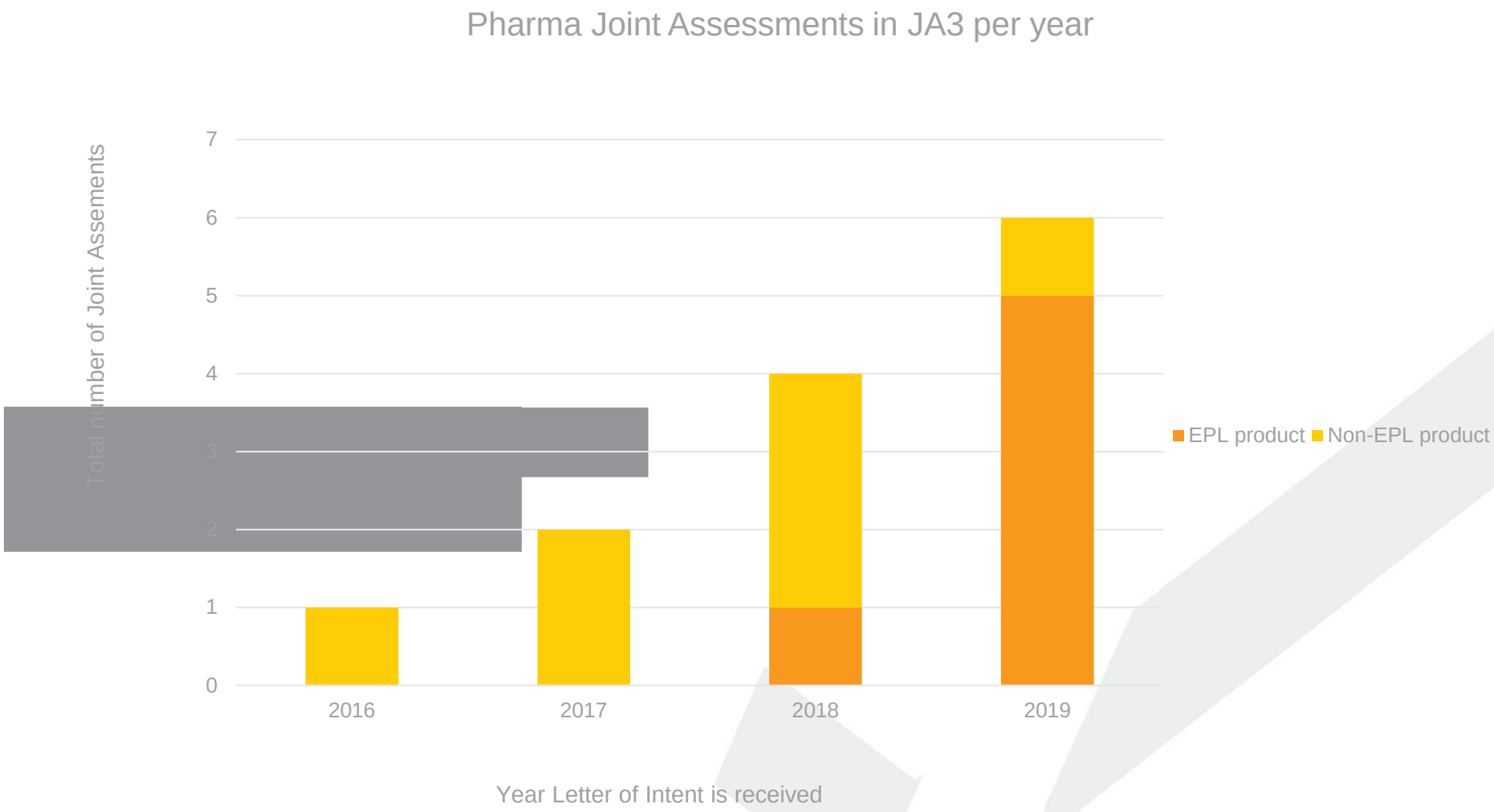
Refined Joint Assessment Production Process

- Update on outcome-feedback workshop
- Interface with EMA – Experience and fine-tuning
- General discussion

Refined Joint Assessment production process

, NIPHNO
, ZIN

Ongoing Pharmaceutical Joint Assessments and EUnetHTA Prioritisation List



Published and ongoing PTJA

No.	Status	INN	(p)MAH	Assessment Team
PTJA01	Published Nov. 2017	Midostaurin	Novartis	Finland, Norway, Sweden, Netherlands, France, UK, Spain
PTJA02	Published Oct. 2017	Regorafenib	Bayer	France, Portugal, Croatia, Switzerland, Finland, Austria, Hungary, Spain
PTJA03	Published Jan. 2018	Alectinib	Roche	Sweden, Austria, Croatia, UK, Italy, Spain, Hungary
PTJA04	Published Jun. 2019	Sotagliflozin	Sanofi	Sweden, Netherlands, Ireland, Spain, Switzerland, Latvia, Portugal, Poland
PTJA07	Published Oct. 2019	Ustekinumab	Janssen	Croatia; Sweden, Poland, Italy, Hungary, Spain, Switzerland
PTJA05		Enasidenib *	Celgene	Norway; Spain, France, Italy, Switzerland, Scotland, Malta
PTJA06		Polatuzumab	Roche	Germany; France, Czech Republic, Finland, Sweden, Portugal
PTJA08		Siponimod *	Novartis	Portugal, Ireland, Italy, Netherlands, Spain, Italy
PTJA09		Brolucizumab *	Novartis	Finland, Spain, France, Poland, Italy, Austria
PTJA10		Crizanlizumab*	Novartis	Netherlands, Spain, France, UK, Slovenia
PTJA11		Cefiderocol *	Shionogi	Italy, Norway, Spain, France, Germany
PTJA12		Glasdegib	Pfizer	Austria, Ireland, Portugal, Switzerland, France
PTJA13		Satralizumab *	Roche	Portugal, The Netherlands, Spain, Slovenia, Scotland
PTJA14		*TBC*	*TBC*	

** EPL compound*

Ongoing activities related to the production process

- Recommendations for patient input in EUnetHTA assessments & guidance
- Recommendations for health care professional involvement
- Plain language summary template
- Topic, Identification, Selection and Prioritisation (TISP) - evaluation of pilot and final recommendations
- Subgroup on Pharma Submission Dossier and Assessment Report Templates
- Task Group on Common Phrases

Update on outcome-feedback workshop

- (Co-) author feedback workshop – October 2019
- Industry feedback workshop – November 2019

Feedback sessions

- Survey after publication Joint Assessment
  - Assessment Team
  - MAH

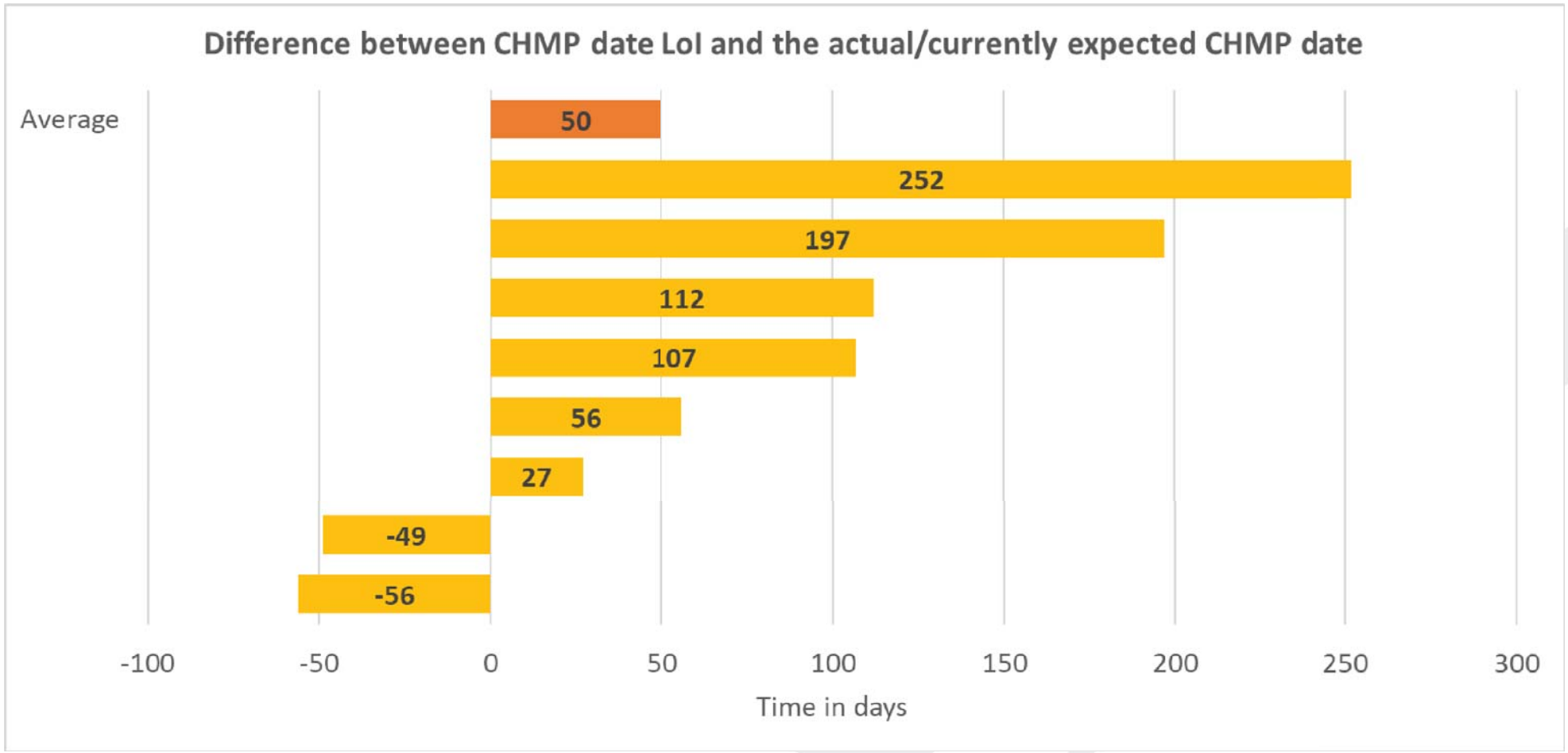
- 2nd (co-)author feedback session – October 2019, Diemen
  - Focus on scoping phase

- Industry feedback session – November 2019, Diemen
  - Discussed complete PTJA procedure

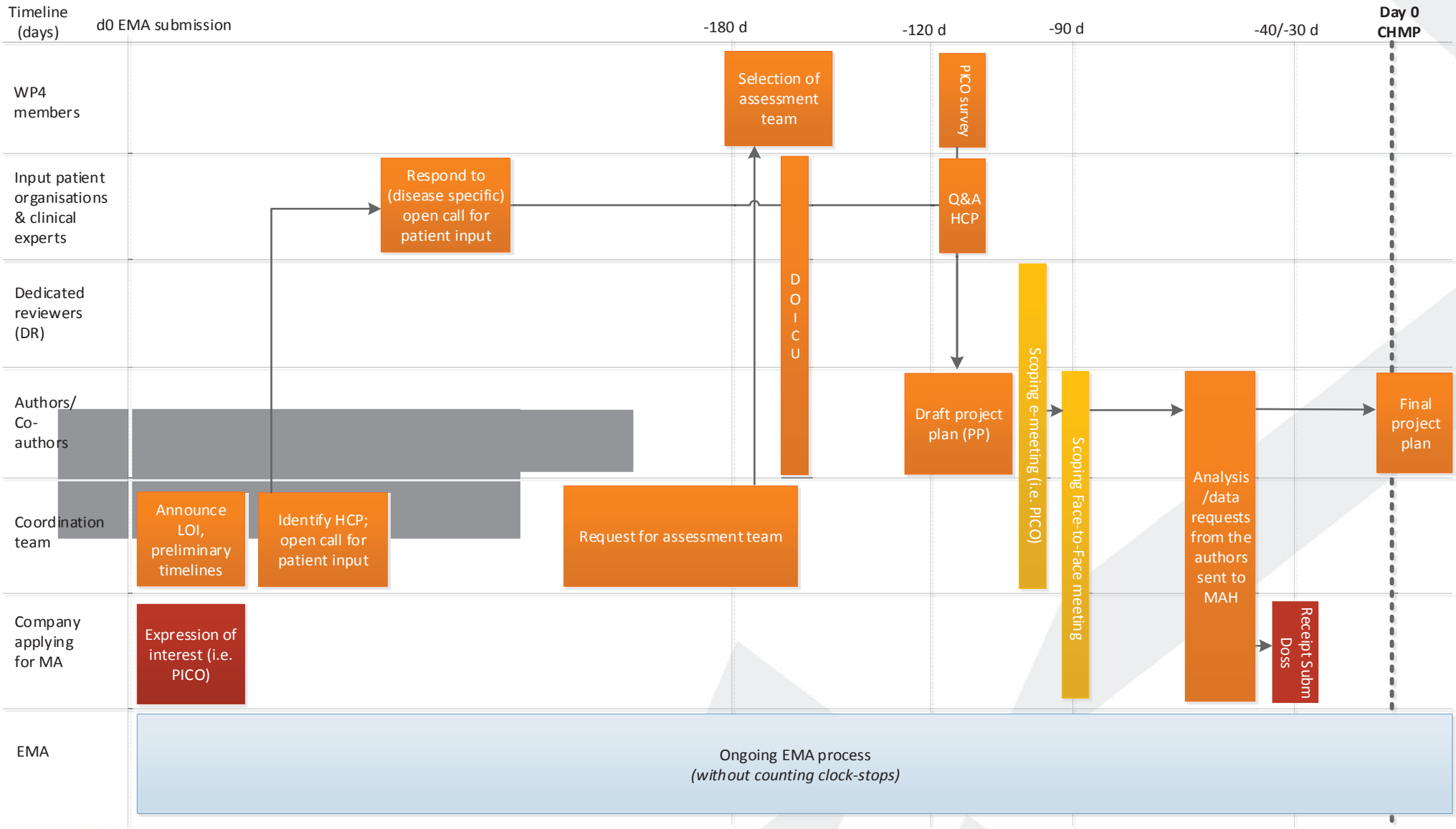
Changes to the process

Scoping – More emphasis on PICO	Letter of Intent include company PICO perspective	✓
	PICO survey among WP4 partners	✓
	Start actual scoping work later – 4 months prior to CHMP - LoI and Scoping document	✓
Project guidance	Industry Procedure Manual	✓
	Companion Guide with SOPs for the Assessment Team	✓
Submission Dossier	No more **draft** Submission Dossier	✓
	Receive one month prior to CHMP (allow grace period) - Amend dossier (clean version & track changes)	✓
	Submission requirements	✓
Implementation	EUnetHTA Prioritisation List	✓
	Scoping F2F meeting: - MAH to bring national affiliates of authoring team - Authors to present plans for re-use JA	✓
Stakeholder engagement	Open call for patient input – disease specific?	✓
	Working on process for clinical expert engagement	✓
EMA collaboration	Updates to Confidentiality Arrangement	✓

Uncertainty in expected CHMP opinion



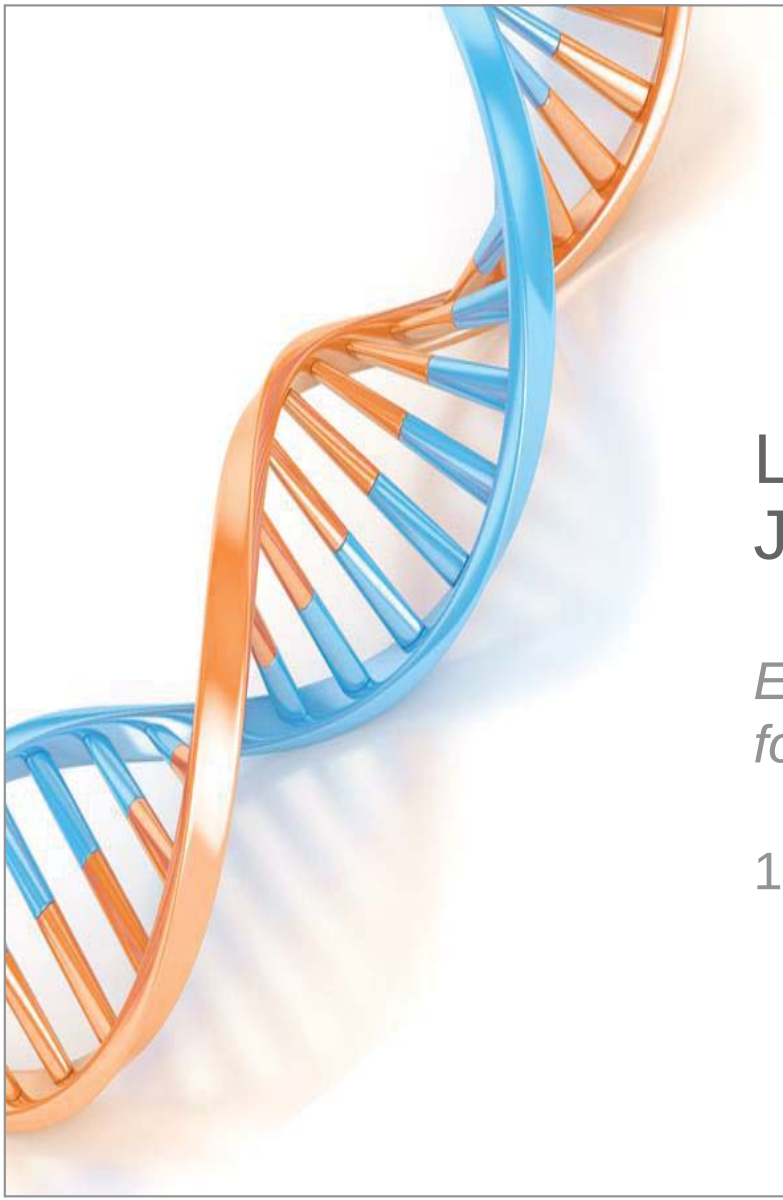
WP4 Pharma – Scoping Phase



Thank you

Any questions?

Questions about Joint Assessments?
Please contact us via WP4_Pharmaceuticals@zinl.nl



Lessons from recent EUnetHTA JA 3 joint assessments

Emerging recommendations to EUnetHTA for future JA 3 joint assessments

15 November 2019

CRA Charles River Associates

efpia

Emerging recommendations for future JA 3 assessments

Recommendations for EUnetHTA - process of joint assessments

1. To ensure a high-level quality of the joint assessments, **an experienced author should be involved in each assessment**. This would guarantee an appropriate level of confidence and expertise in utilising the advanced REA methodologies developed by EUnetHTA. The assessment team should consistently commit adequate resources throughout the whole process

2. There should be a **consistent approach to the scoping meeting, with the possibility for the manufacturers to discuss with the authors the elements of the PICO and the best methodology for the assessment**. It should be the responsibility of the authors to ensure that the resulting PICO is supported by strong scientific evidence and any decisions taken in the scoping phase should be taken forward throughout the assessment process. **More facilitated communication** between the manufacturer and the assessment team would help to expedite the process

3. **Patient organisations and external clinical experts should systematically be involved in all the joint assessments**. Their **input should be considered in both the scoping and the assessment phase** in order to maximise the quality of the joint assessments. There should be **transparency on the criteria** for their selection and on how **their input** is considered in all the steps of the process

4. There should be **a review meeting for manufacturers, patient organisations and clinical experts to discuss the draft report with the assessment team**. The factual accuracy check process should be a standard process step in all future assessments

5. The **timeline and resource allocation for the joint assessments should allow for a high-quality report**. The industry shares the objective to have timely publication that is aligned to the regulatory process. The process timeline should automatically **adapt to changes in the timeline of the regulatory process**. There should be a facilitated discussion with the assessment team about the circumstances where flexibility in the timeline could increase the quality of the report: this would ultimately benefit the overall quality of the final assessments and support their use in national settings

Emerging recommendations for future JA 3 assessments

Recommendations for EUnetHTA - confidentiality of joint assessments

5. There should be **a comprehensive confidentiality agreement, covering all parties, establishing clarity before the assessments start**. This would ensure that the best and most relevant evidence is included in the final joint assessment, increasing their quality and reducing the need for subsequent integration of evidence (and, ultimately, maximising their use)

Recommendations for EUnetHTA - resolution of issues in the assessment phase

6. The **introduction of a systematic mechanism for issues resolution should be considered** (as last-resort) to increase the rigour of the assessment phase and its outcome whilst demonstrating that the process is impartial and that the assessment team is accountable

Emerging recommendations for future JA 3 assessments

Recommendations for EUnetHTA – overall Governance

7. A **consistent approach should be used for all the assessments**: this should be based on an agreed European approach based on EUnetHTA methodologies and not determined by the national authors involved in the assessment

8. If there is a **need to adapt approaches, this should be agreed prior to starting the assessment** based on discussions with the industry and agreed with the manufacturer participating to the assessment

9. A **clear set of rules to escalate and resolve governance issues** would be beneficial to all the stakeholders

Refined Joint Assessment Production Process

Interface with EMA

EMA

EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

Refined Joint Assessment Production Process - Interface with EMA

Experience and fine-tuning

EUnetHTA-EFPIA Technical Meeting
2 December 2019

Presented by [redacted]
[redacted] Scientific Support Department

Reminder: EUnetHTA EFPIA Technical Meeting, June 2016

Provision of regulatory assessment reports by EMA

[redacted] (EMA) presented an update of the collaboration between EMA and EUnetHTA (see slides). Specific for the topic on the provision of assessment reports, he indicated that a framework agreement is currently being finalized by EMA in collaboration with the European Commission to enable the sharing directly by the EMA of certain parts of the final CHMP assessment report (introduction, clinical aspects and benefit risk section; the quality part will not be provided) at time of CHMP opinion directly with individual HTA bodies involved in joint assessment coordinated by EUnetHTA. Such agreement cannot be entered with EUnetHTA itself as it is currently not a legal entity. The Commission clarified that this agreement is currently limited to agencies actively contributing to joint assessments.

In the Q&A round, these points were discussed:

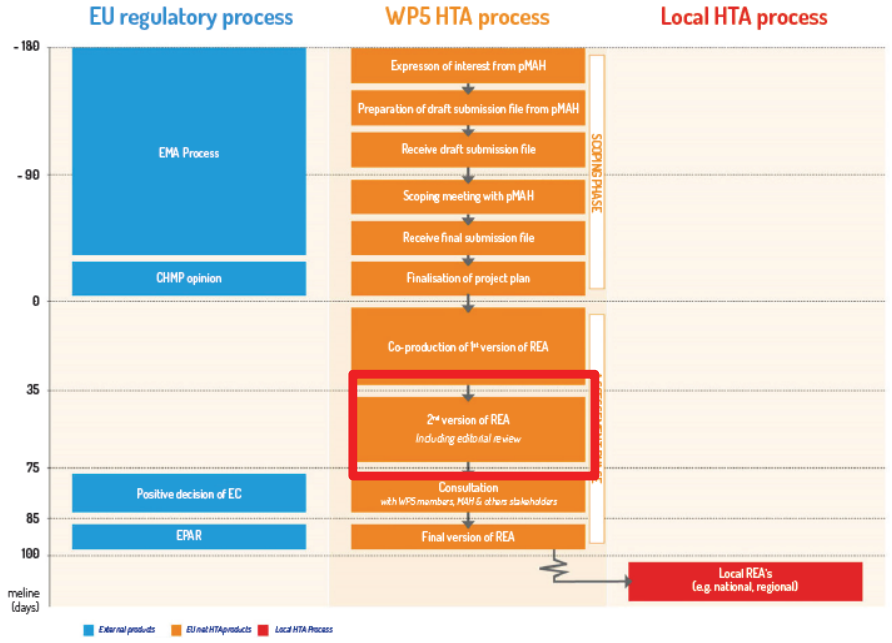
- Is the sharing of assessment reports enough? It could make more sense to initiate meetings between EMA rapporteur and co-rapporteur with EUnetHTA authors and co-authors.
- The framework agreement would be a general agreement to support JA3 activities (i.e. there would not be a need to negotiate for each individual product/assessment).
- If anything changed in the EPAR, compared to the CHMP assessment report, this will be flagged to EUnetHTA appropriately.

Minutes EUnetHTA-EFPIA technical meeting, June 2016

Bridging from regulatory opinion to relative effectiveness assessment

Collaboration between regulatory and HTA assessors in the context of joint production of relative effectiveness assessment (REA):

- make available to the HTA authoring team the outcome of the regulatory assessment based on the **final** CHMP opinion
- facilitate mutual understanding of the outcomes of each decision making
- respecting the respective **remits** and under **confidentiality** arrangements



Information of the applicant (contacts for regulatory and market access)

Dear [redacted]
Dear

This is in follow up to your submission of a Letter of Intent for joint REA production for [redacted] under EUnetHTA JA3 work package 4. As you are certainly aware an interaction between EUnetHTA and the EMA will take place to support this joint production. With the following we want to provide you with additional information on these arrangements.

In June 2016 a technical meeting was held in Paris, bringing together representatives from EUnetHTA, pharmaceutical industry, EFPIA, EMA, HTA agencies and the European Commission. The focus was on different aspects concerning joint REA production; this included the need to facilitate timely availability of the final regulatory output to the respective REA authors. Please find here meeting report: Minutes EUnetHTA EFPIA Technical Meeting. Action point 6 reads as follows: "Finalise the framework agreement for provision of final assessment reports by the European Medicines Agency (EMA) to HTA agencies in the context of rapid REA coordinated by EUnetHTA. Consider further in-person interactions beyond written arrangements for provision of final assessment reports"

Against this background EMA and EUnetHTA have been working out the technical arrangements with the following key principles: it is the final CHMP assessment report (once adopted) that will be provided; the exchange occurs under dedicated confidentiality arrangements with the recipient; the different remits of regulatory assessment and HTA are respected.

In practice this means the following:

- Once the CHMP Opinion on the marketing authorisation application has been adopted, you will be notified that elements of the final CHMP assessment report will be provided to the assigned authors of the joint production under EUnetHTA work package 4.
- The actual provision occurs once you have received the Opinion package with the final CHMP assessment report. Only the following sections of the CHMP assessment report will be provided to the REA authors as only these have been identified as being relevant for the joint production: 2.1 Problem statement; 2.4 Clinical aspects; 2.5 Clinical efficacy; 2.6 Clinical safety; 3. Benefit-risk balance; 4. Recommendations
- The recipients are exclusively the authors for the REA and the WP4 co-lead; in the case of [redacted] this concerns [redacted]. The provision occurs under dedicated confidentiality arrangements between the EMA and these organisations.
- An opportunity for these REA authors to get clarifications on the assessment report will be arranged to facilitate most optimal understanding of the regulatory decision making.

In line with previous discussions between the various stakeholders such interaction is deemed essential to support timely and robust joint REA production as part of the experience gain under work package 4. We therefore appreciate [redacted] commitment to this new process as part of the pilot. Whilst there is no particular action required from your side, we will of course be available for any clarifying questions you might have.

Best wishes.

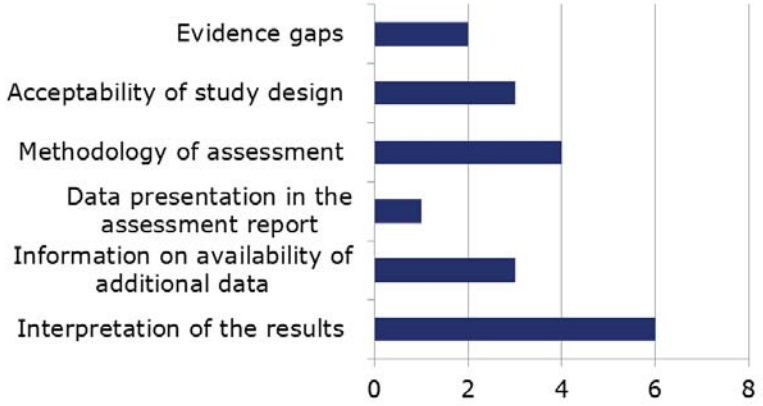
[redacted]

First experiences with product-specific discussions (in the context of five REAs)

Focus in these interactions:

1. Exchange on how the available evidence was assessed and contextualised, e.g. uncertainty of the effect size in a non-studied population
2. Mutual understanding of review principles between regulatory criteria and HTA, with the opportunity to optimise output documents
3. Possibility to share expectations for post-licensing data to be generated

Typical topics of product-specific questions in a webinar*



*based on REA-1/2/3

Review at the 17th EMA/EUnetHTA bilateral (July 2019)

The EMA/EUnetHTA bilateral meetings are the platform for oversight with the joint work plan, and reporting occurs through the published minutes (Minutes of the EMA/EUnetHTA meetings)

EMA/EUnetHTA bilateral, Diemen, July 2019

> The availability of EMA information to facilitate the preparation of REAs was then discussed. Communication between EMA and EUnetHTA Work Package 4 is indeed crucial, respecting confidentiality arrangements. Several uncertainties challenge the timeliness of REAs production, namely the lack of knowledge of the final labelling at time of CHMP opinion, possible changes of timelines of the regulatory review, uncertainty about the date of final CHMP opinion, varying time between EC decision and EPAR publication. Provision of SmPC under the confidentiality framework was also discussed. Also the need for citation of the CHMP AR in the draft Joint Assessment was discussed, as this will facilitate the quality and relevance of Joint Assessments. These issues were acknowledged and it was agreed to optimise the current arrangements to facilitate information exchanges and usability of this information in the production of Joint Assessments.

Minutes EMA-EUnetHTA bilateral meeting, July 2019

Fine-tuning in the operational arrangement between EMA and EUnetHTA

1. Provision of the final adopted SmPC together with the relevant sections of the CHMP assessment report
2. Update on timelines of the regulatory review
3. Debrief immediately after CHMP opinion
4. Citation of CHMP assessment report in the REA

Implementation: for all upcoming REAs produced on the basis of CHMP Opinions adopted from December 2019 onwards

Thank you for your attention

Further information

[redacted]@ema.europa.eu

Official address Domenico Scarlattilaan 6 ● 1083 HS Amsterdam ● The Netherlands
Address for visits and deliveries Refer to www.ema.europa.eu/how-to-find-us
Send us a question Go to www.ema.europa.eu/contact **Telephone** +31 (0)88 781 6000

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Presentation from EFPIA on EUnetHTA (22 pages) is removed as this presentation is covered by one exception under Regulation (EC) 1049/2001

Submission requirements on citations and publication policy

- Outline of requirements
- Definition & examples of Academic Confidence and Commercially Sensitive Information
- General discussion

Submission requirements on citations and publication policy

, ZIN

Submission Dossier

All to be shared with entire assessment team

- Submission Dossier Requirements published (link)
  - No redaction

- Core Submission Dossier
  - All information is subject to citation in the final JA report
  - To be published at the same time as the publication of the final assessment report

- Attachments to Core Submission Dossier: e.g. all CSR, NMA
  - Authoring team free to cite relevant information

Submission Requirements

3 APPENDIX – OVERVIEW PUBLICATION DIFFERENT PRODUCTS

Table 1: Publication of the different products

Process step	Product		Shared with*	Free to cite?	Redaction possible?	Published by EUnetHTA?
Topic selection & establish team	Letter of Intent (pMAH)		All EUnetHTA partners that assess pharmaceuticals, EMA, PM & SSO	Yes	For the call for collaboration the MA status and contact details are redacted (sections 5 and 14)	No
Scoping phase	Project Plan (EUnetHTA)		Draft version is shared with AT, pMAH, PM & SSO	NA	No	Yes, final version is published after CHMP opinion
	Scoping document (pMAH)		AT, PM & SSO	Yes	No	No
(pre-) assessment phase	Submission Dossier (pMAH)	Core Submission Dossier	AT, PM & SSO	Yes	No	Yes, at time of publication of the final Joint Assessment Report
		Attachments to Core Submission Dossier	AT, PM & SSO	Yes	No	No, unless explicitly requested by (p)MAH
	Joint Assessment Report (EUnetHTA)		Draft versions are shared with AT, external clinical experts (if without a COI), medical editor and (p)MAH for a factual accuracy check, PM & SSO	NA	No	Yes, publication after EPAR publication.

Abbreviations: AT=Assessment Team; CHMP=Committee for Medicinal Products for Human Use; COI= Conflict of Interest; EMA=European Medicines Agency; MA=Marketing Authorisation; NA=Not applicable; PM=Project Managers; pMAH=prospective Marketing Authorisation Holder; SSO=Senior Scientific Officer.

* AT consists of: Author, Co-author, Dedicated Reviewers and Observers
All involved individuals have completed and signed our Declaration of Entity and Confidentiality Undertaking (DOICU). All DOICU's have been assessed by the EUnetHTA Conflict of Interest Committee.

Definition & examples of Academic Confidence and Commercially Sensitive Information

EFPIA

Confidentiality considerations

Examples of circumstances in which a confidentiality framework is required before companies are able to supply certain types of information

Commercially sensitive

1) information that could jeopardise the commercial interests of the data owner

- **e.g. proprietary information on formulations / manufacturing processes / patents etc..**
- **e.g. regulatory filing strategies**
- **e.g. clinical data that could be used to identify directly (or via back-calculation) confidential pricing / risk share arrangements**
- **e.g. data that is not owned by the manufacturer, but is provided 'under-license' on the basis it will remain confidential**

2) information that could put patients at increased risk of harm

- **e.g. post-hoc 'methodologically limited' analyses that are subject to significant uncertainties and questionable reliability**

Academically sensitive

1) information that if published in an HTA report could jeopardise the publication preferences/rights of the investigators

- **e.g. reduced likelihood of publication the highest impact factor journals (not prohibited, but deprioritised in favour of fully unpublished material)**
- **e.g. data that is not owned by the manufacturer, and the publication rights of the data owner must be prioritised**

General discussion

The 2019 EPL

- Discussion of results
- Feedback from industry
- General discussion

EUnetHTA EPL- Topic Identification selection and prioritisation (TISP) pilot

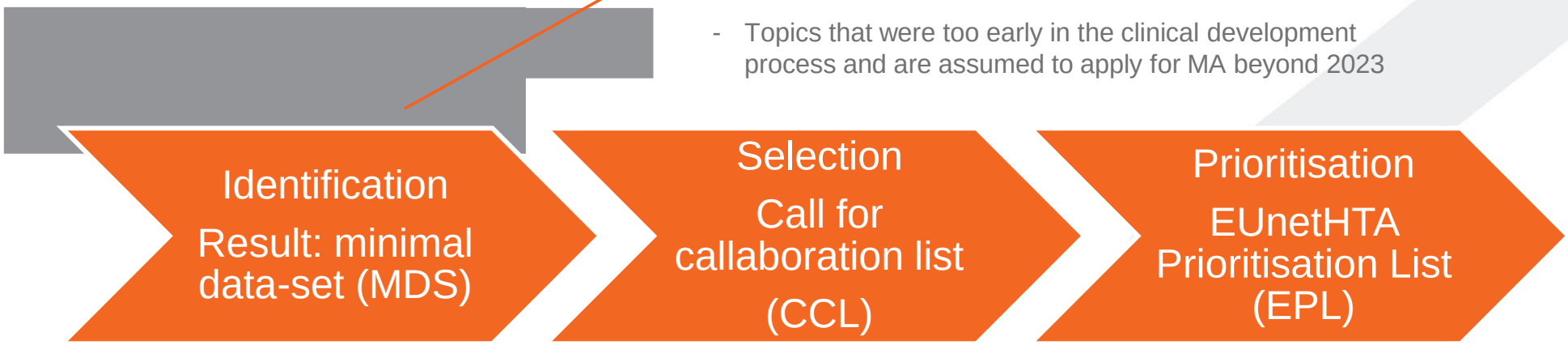
NOMA

Steps of the TISP pilot process

IDENTIFICATION:
- Partners
- EMA
- Existing horizon scanning systems

Outside scope:

- Generics
- Biosimilars
- Line extensions
- Already applied to EMA
- All Call for collaboration 2018 products
- All EPL1 products
- Some antibiotics and combination of of “old” authorised products
- Topics that were too early in the clinical development process and are assumed to apply for MA beyond 2023



Call for collaboration (CCL)

1. To all EUnetHTA partners.
   - To gather information about selection criteria:
     - Relevance (national/ regional level)
     - Interest on participating on the JA
     - Uptake of the JA
   - Predefined answers with option for comments
2. To EFPIA
   - Information about compound, proprietary name and request on provide anticipated submission to EMA date/ fact check (feasibility assessment/correct inaccuracies if needed)

143 topics

Answer % in accordance with other CCL. Good representation EU countries

Prioritisation

Prioritization process – from Call For Collaboration to EPL

1. Based on selection criteria above

2. Feasibility assessment (analysis was performed late in the process in order to secure that identified topics with a high score and anticipated EMA submission prior Q3 2020 were included)

- Topics that already have applied to EMA, have reported failure or with withdrawn studies: Discarded
- Topics with anticipated submission to EMA Q3 2020 and onwards were discarded from. from the EPL2. These topics can be included in future EPL iterations.

Results

MDS (minimal data set): 216 topics

CCL (Call for Collaboration):143 topics

EPL (EUnetHTA Prioritization List 31 products (can include several indications)

- Therapeutic areas: Cardiology, endocrinology, oncology, psychiatry, neurology, respiratory diseases, infectious diseases, immunology,
- Broad MA procedure type (orphan, prime, Extension of indication, new market authorizations, etc.)
- Variation of in and out-patients topics

Thank you

Questions

Feedback from industry

EFPIA

General discussion

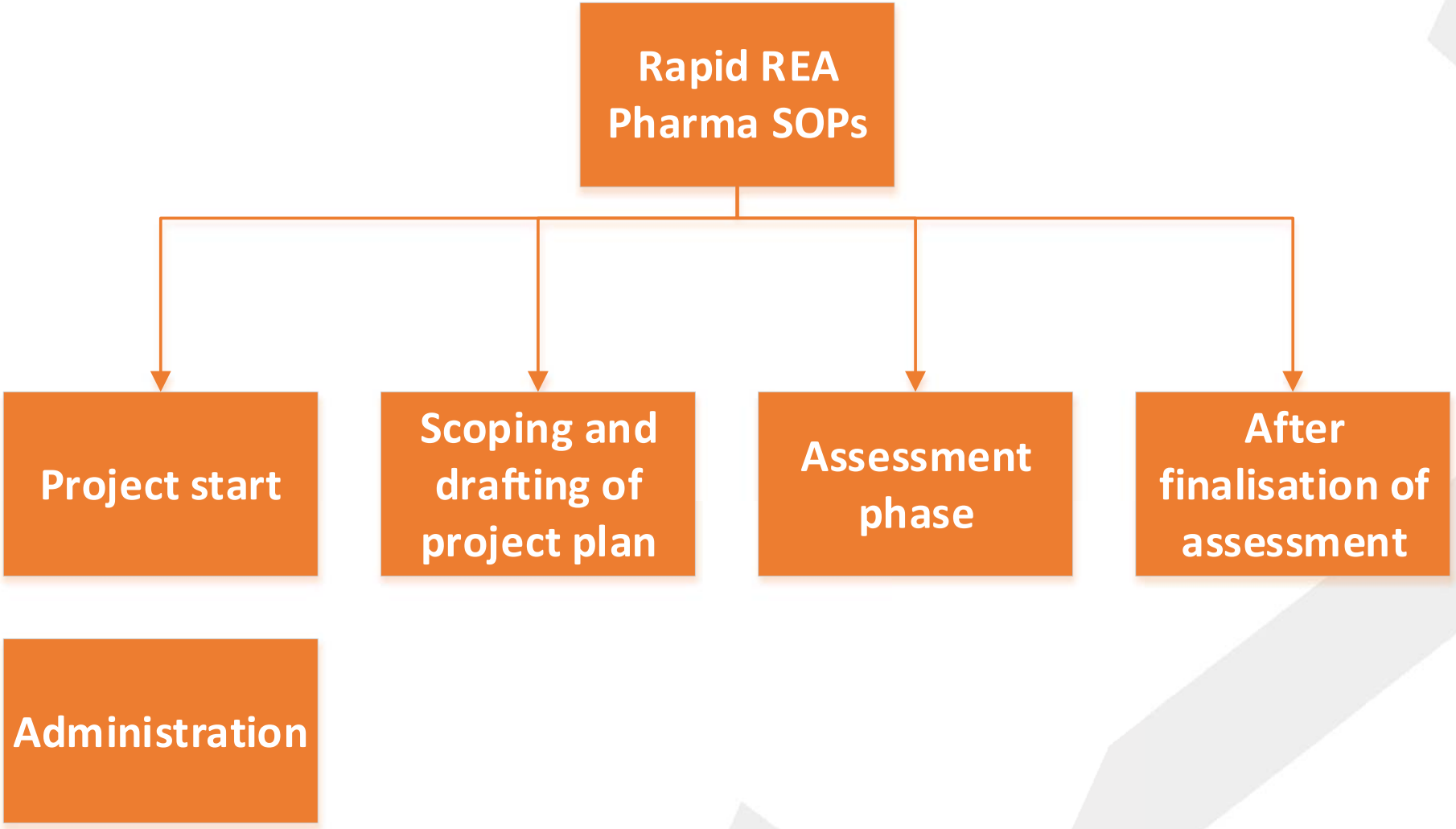
Coffee break

Guidelines and SOPs

- Update on SOPs and guidelines
- Methodological review of clinical HTA guidelines
- General discussion

Update on SOPs

IQWIG



Process steps for authors, co-authors, dedicated reviewers, project managers

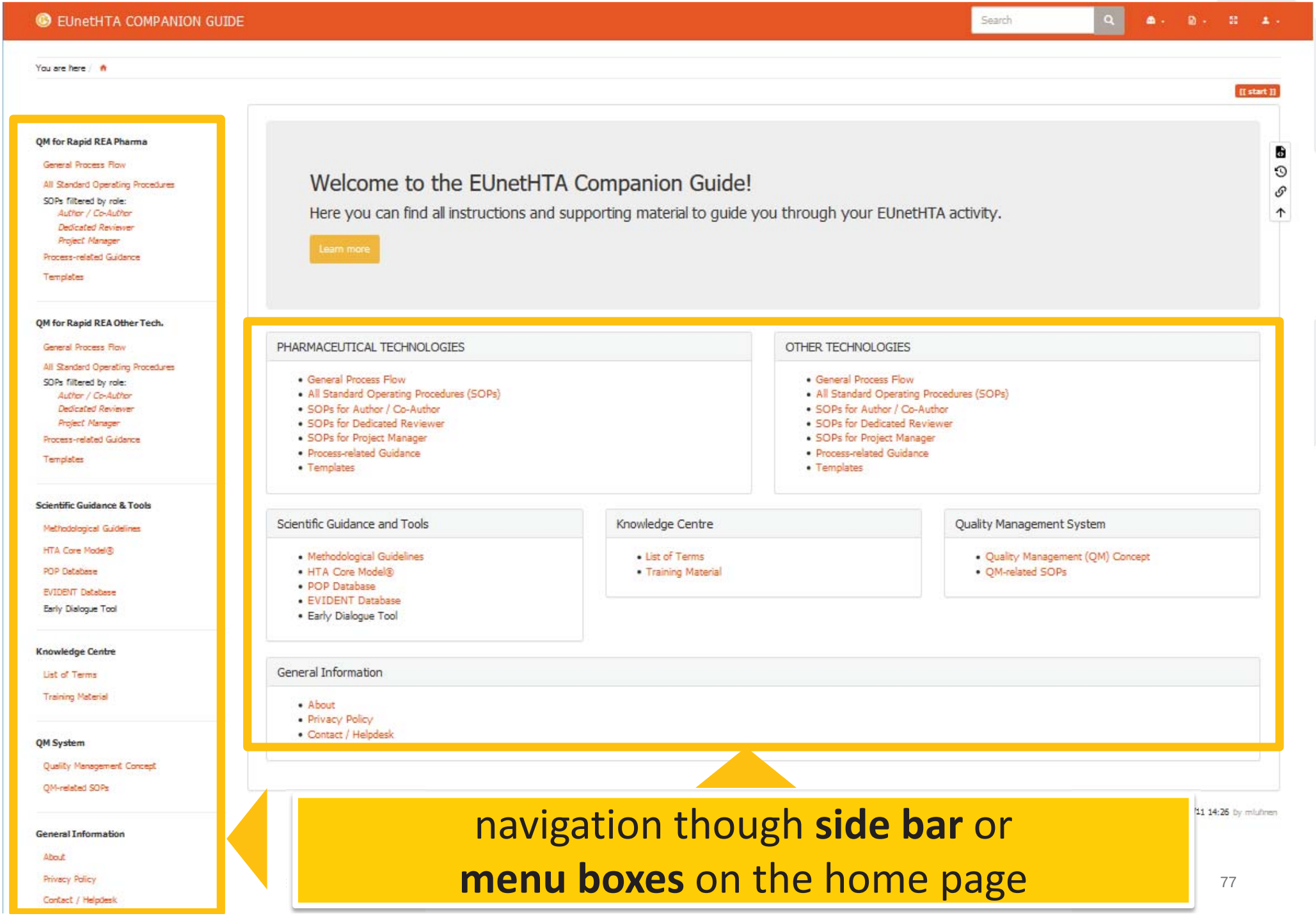
Support of EUnetHTA authors

EUnetHTA Companion Guide provides an overview of available SOPs, methodological guidelines and other guidance

Specific (online) training sessions inform new authors about available supportive documents

Feedback mechanisms ensure collection of learnings from assessments

EUnetHTA Companion Guide



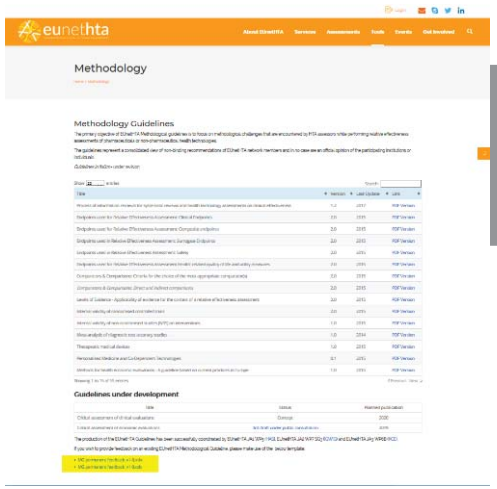
navigation though **side bar** or
menu boxes on the home page

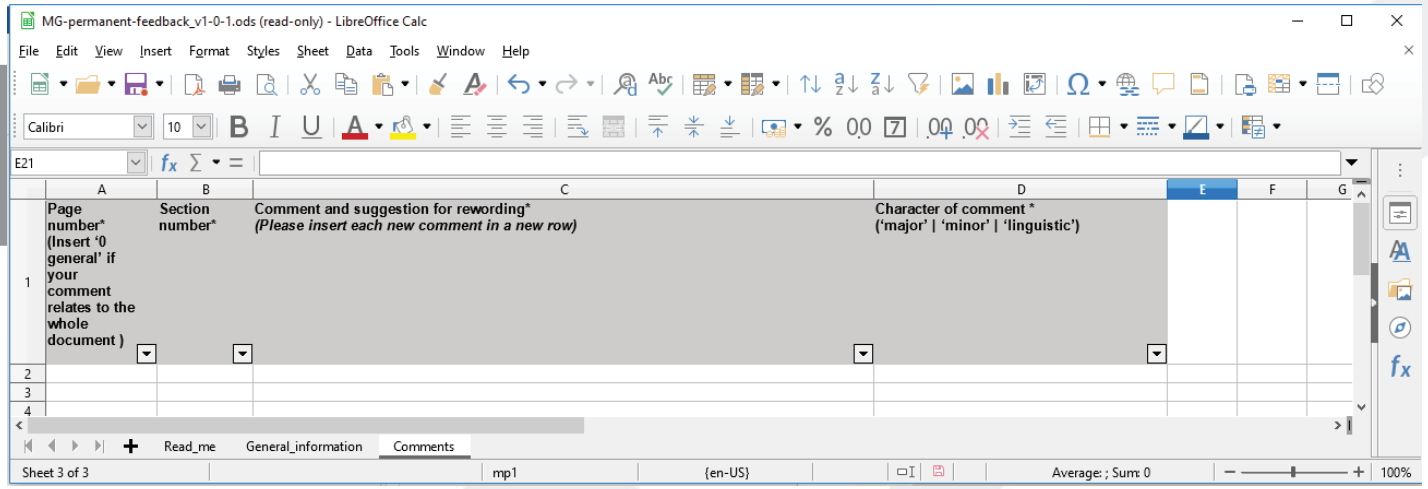
Update on guidelines

, KCE

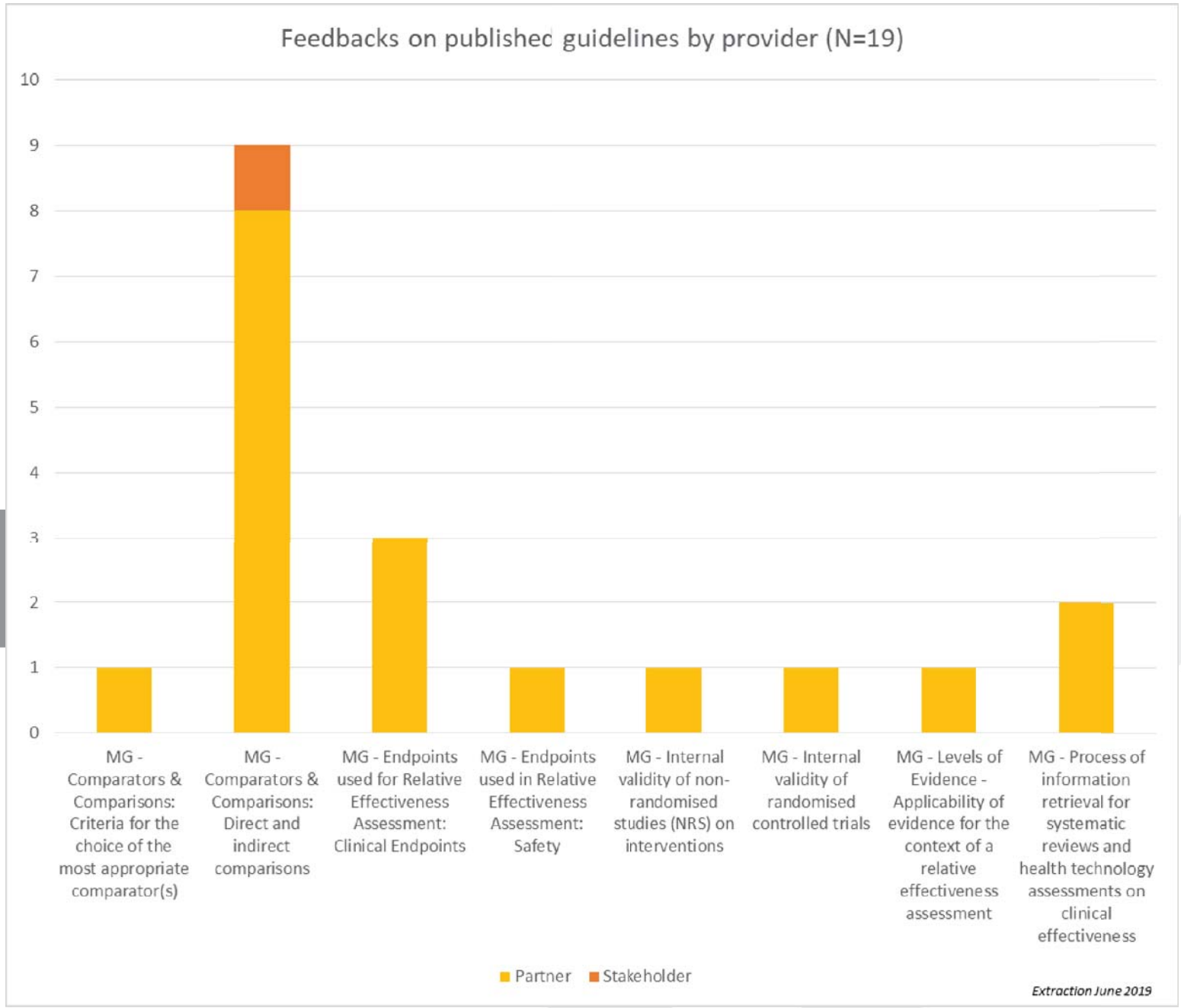
Follow up

1. Stakeholders are now informed in advance of forthcoming public consultations
2. A structured feedback form for published guidelines is available on the EUnetHTA Website





Existing guidelines - feedbacks



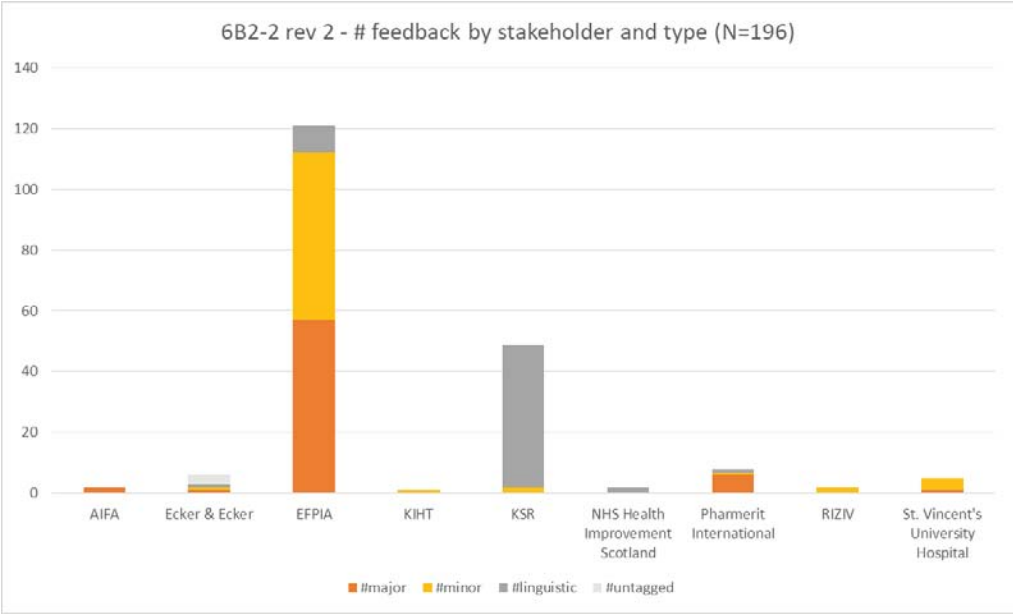
Current status of guidelines' development

nr	Title	Status	Planned publication
6B2-2	Process of information retrieval for systematic reviews and health technology assessments on clinical effectiveness	Public consultation finished, finalisation of the major update	End 2019
6B2-3	Comparators & Comparisons: Direct and indirect comparisons	Scoping of the update	End 2020*
6B2-4	Critical assessment of clinical evaluations	Concept guideline	End 2020*
6B2-5	Practical considerations when critically assessing economic evaluations	Public consultation finished, finalisation of the first version	End 2019

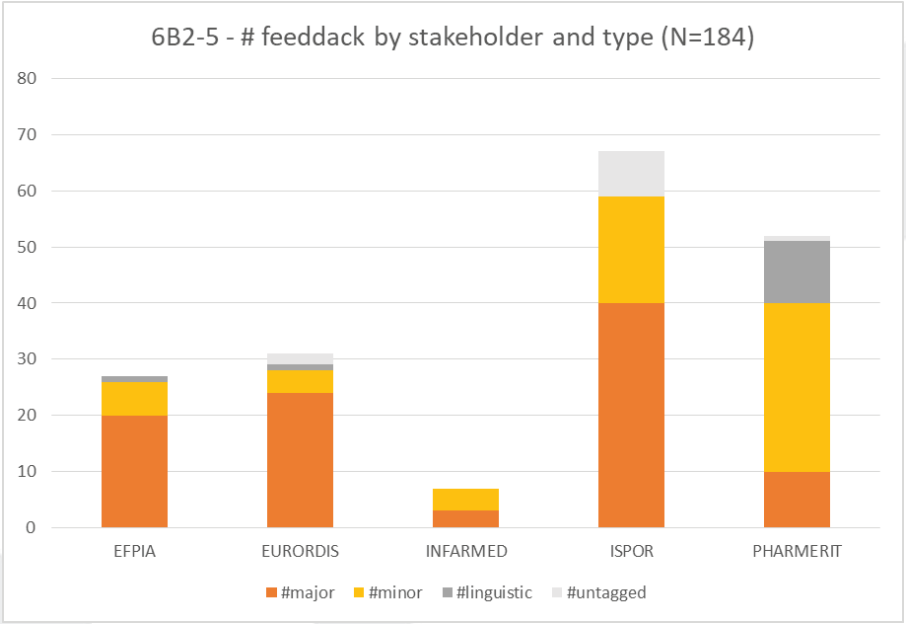
** This activity need to be validated by the Executive board as a priority for the prolongation (2020-2021)*

Public consultations - feedback from Stakeholders

6B2-2 Major revision guideline « Process of information retrieval for systematic reviews and health technology assessments on clinical effectiveness “



6B2-5 New guideline «Practical considerations when critically assessing economic evaluations”

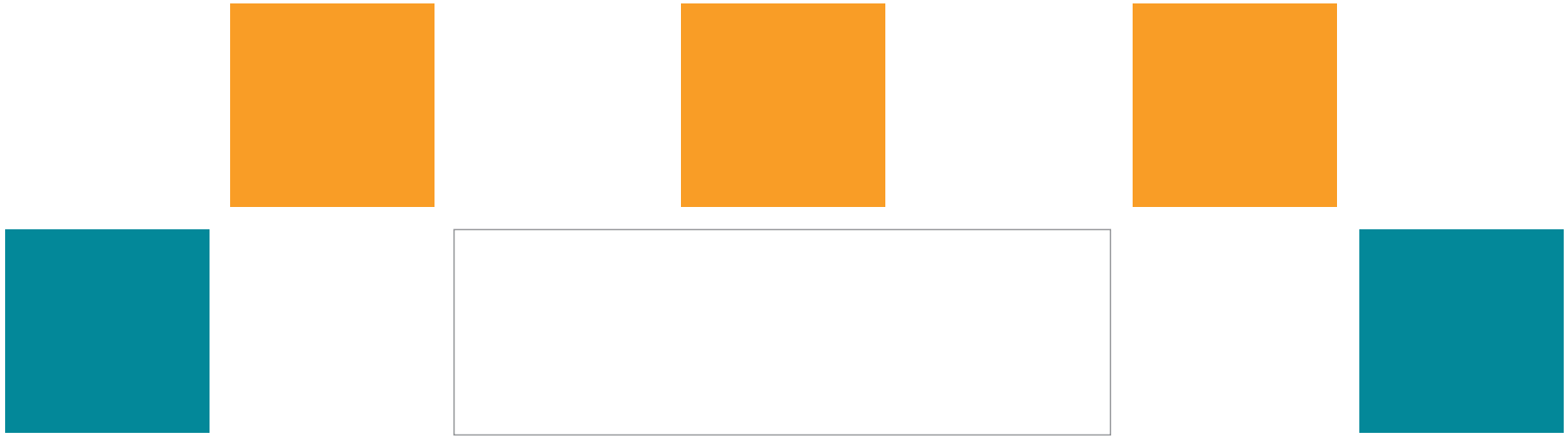


Methodological review of clinical HTA guidelines

[redacted] (EFPIA)

European Federation of Pharmaceutical Industries and Associations

Methodological standards for clinical HTA



Background & Objectives

- EFPIA believes that a future system of joint clinical assessment should build on high quality methodological framework, in line with agreed best practices and clearly building on EUnetHTA methodological guidelines.

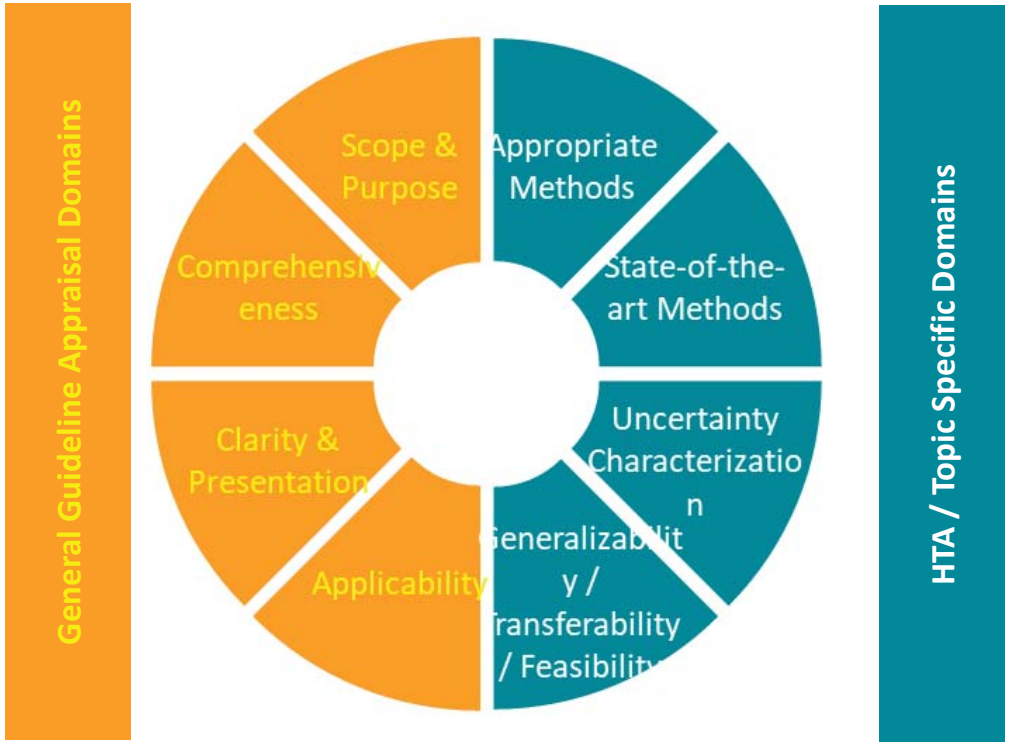
- EFPIA worked with ICON to articulate the industry view on best practice in the context of a European collaborative model of clinical HTA, using the EUnetHTA methodological guidelines as an opportunity to frame the discussion.

EU Collaboration on clinical HTA: Methodology a Critical Success Factor

- Variations in Standards of care / Treatment algorithms
- Trial Comparators (HTA vs Regulatory)
- Acceptability of endpoints
- Complex evidence networks
- Extrapolation / Modelling

Review of methodological standards in clinical HTA: Framework & Approach

- **Nine Methodological guidelines reviewed**
  - Comparators & Comparisons
  - Direct / Indirect
  - Surrogate, Composite & Clinical Endpoints
  - Validity RCTs
  - Validity NRS
  - HRQOL
- **Input from external HTA experts**
  - [redacted]



ICON Guidelines Review :

Comparators & comparisons
Direct & Indirect Comparisons
Endpoints (Surrogates)

ICON Guidelines Review : Comparators & comparisons (1)

EUnetHTA guideline sets out clearly that the relevant comparators for clinical HTA should be the EU-wide consensus standard of care according to up to date clinical guidelines, with good quality published evidence and licensed by EMA.

Key Findings & Recommendations : Comparators & comparisons
• Comparator Selection should be undertaken with **all stakeholders (**HTA agencies, industry, regulators, clinical experts and patients) and finalised at the **scoping phase** of the process.
• The **timely selection** of relevant comparators will underpin the success of a collaborative model of clinical HTA. Early dialogue and parallel advice provides opportunity to discuss relevant comparators.
• The guideline could clarify that **economic considerations should not be a criterio**n in selecting comparators. Allowing economic criteria contradicts the principle of assessing a new technology against the one most likely to be replaced in clinical practice.
• Comparator selection for joint clinical HTA must meet the **needs of different healthcare systems**, whilst at the same time remain **pragmatic.**

ICON Guidelines Review : Comparators & comparisons (2)

When there is no EU-wide reference treatment, the guideline sets out that there needs to be evidence that the chosen comparator is routinely used in the clinical population (and which data can be helpful)

Key Findings & Recommendations : Comparators & comparisons
• To maximise uptake, **consensus and agreement amongst EU MS is critical** for a collaborative model of clinical HTA.
• **Direction on how consensus on comparators can be established when there is no EU-wide reference treatment** is fundamental to the success of a collaborative model of HTA
• **Priority should be given to established licensed medicines**, with published robust clinical data, followed by those recommended in well-recognised clinical guidelines.
• Where there is no consensus, there is a need for a **robust and pragmatic process which identifies a core set of relevant comparators** that can be addressed with direct and indirect evidence.
• In cases where multiple comparators may be considered relevant, a **threshold for relevance of comparators** is needed to ensure the HTA can be delivered in a manageable, timely and robust manner.
• These considerations could extend to the recommendation on **relevant comparators for sub-groups**.

ICON Guidelines Review: Direct and Indirect Comparisons

Key Findings & Recommendations: Indirect Comparisons
• Indirect treatment comparisons are a **necessary and appropriate analytical technique for a collaborative model of clinical HTA**, where standards of care and relevant comparators may differ.
• C**larification of the range of alternative methods** that are available and necessary to analyse complex evidence networks would assist companies and agencies to align on how to approach joint assessments.
• Guidance is needed on the-strengths and weaknesses of the evidence network and the **relevance of comparators with weak evidence networks** where the output would be uninformative and/or result in erroneous conclusions
• Guidance is needed on the use and interpretation of indirect comparisons as well as commentary on **advanced and emerging techniques e.g. Matching Adjusted Indirect Comparison (MAICs) and Simulated Treatment Comparison (STCs)**
• Indirect treatment comparisons should only be conducted against relevant comparators agreed at the final scope

ICON Guidelines Review: Surrogate, Composite and Clinical Endpoints

Key Findings & Recommendations: Surrogate, Composite and Clinical Endpoints
• Endpoints (clinical, surrogate and composites) accepted as the basis for regulatory approval should used by HTA agencies as valid clinical outcome measures.
• Guidance on endpoint selection for clinical development and HTA should be informed by their value to patients and healthcare systems
• Early dialogues and parallel consultation should be used to establish the suitability and rationale for the use of a surrogate and composite endpoint as the basis for the clinical development of a new medicine

ICON Guidelines Review: Surrogate, Composite and Clinical Endpoints

Key Findings & Recommendations: Surrogate Endpoints
• The guideline on surrogate endpoints classifies PFS as an intermediate endpoint which differs from the CHMP's guideline on the evaluation of cancer medicines.
• Clarification on whether endpoints that are considered by regulators, clinical experts and patients as demonstrating patient benefit should be classified and treated as surrogate endpoints will assist companies and agencies to align on joint assessments
• The guideline recommendations on the criteria for the validation and the threshold for adequacy of surrogate endpoints need to be pragmatic and realistic especially for new technologies with innovative modes of action
• Guidance on how to estimate the impact on final outcomes for therapies that provide long term clinical benefit but which use surrogate endpoints for first assessments will assist companies and agencies to align on joint assessments

ICON Guidelines Review : Gaps Identified

ICON Guidelines Review : Methodological Gaps

Areas of Clinical HTA methodology not covered by the current guidelines
• The guidelines do not take account of the frequency of cross-over or treatment switching in clinical trials. Post-study treatment patterns have also been recognised by HTA agencies as a source of confounding for survival benefit estimates. The guidelines on the validity of RCTs or Clinical Endpoints could be relevant guidelines
• Extrapolation from clinical studies to broader populations (external validity) is not accounted for in the guidelines. Where the population covered by the regulatory indication is broader than the trial population, HTA guidelines could help clarify how results can be generalised.
• The guidelines do not address how to extrapolate from short-term endpoints to long term patient outcomes.
• The guidelines do not address the role of mean versus median survival and extrapolation techniques relevant to the estimation of clinical benefit
• The guideline do not address cure models and the potential for heterogenous patient responses over a long duration of time.

General discussion

Evidence Generation (WP5)

- Update on Early Dialogues and PLEG projects
- General discussion

WP5A: Early Dialogues

HAS

Early Dialogues May 2017 – November 2019

Requests	Therapeutic field
30	Cancer
8	Neurodegenerative
6	Autoimmune
2	Metabolic disorders
4	Viral disease
41	Other fields

30 Individual Parallel Consultations (PCI)

Including 1 vaccine
and 2 PLEG

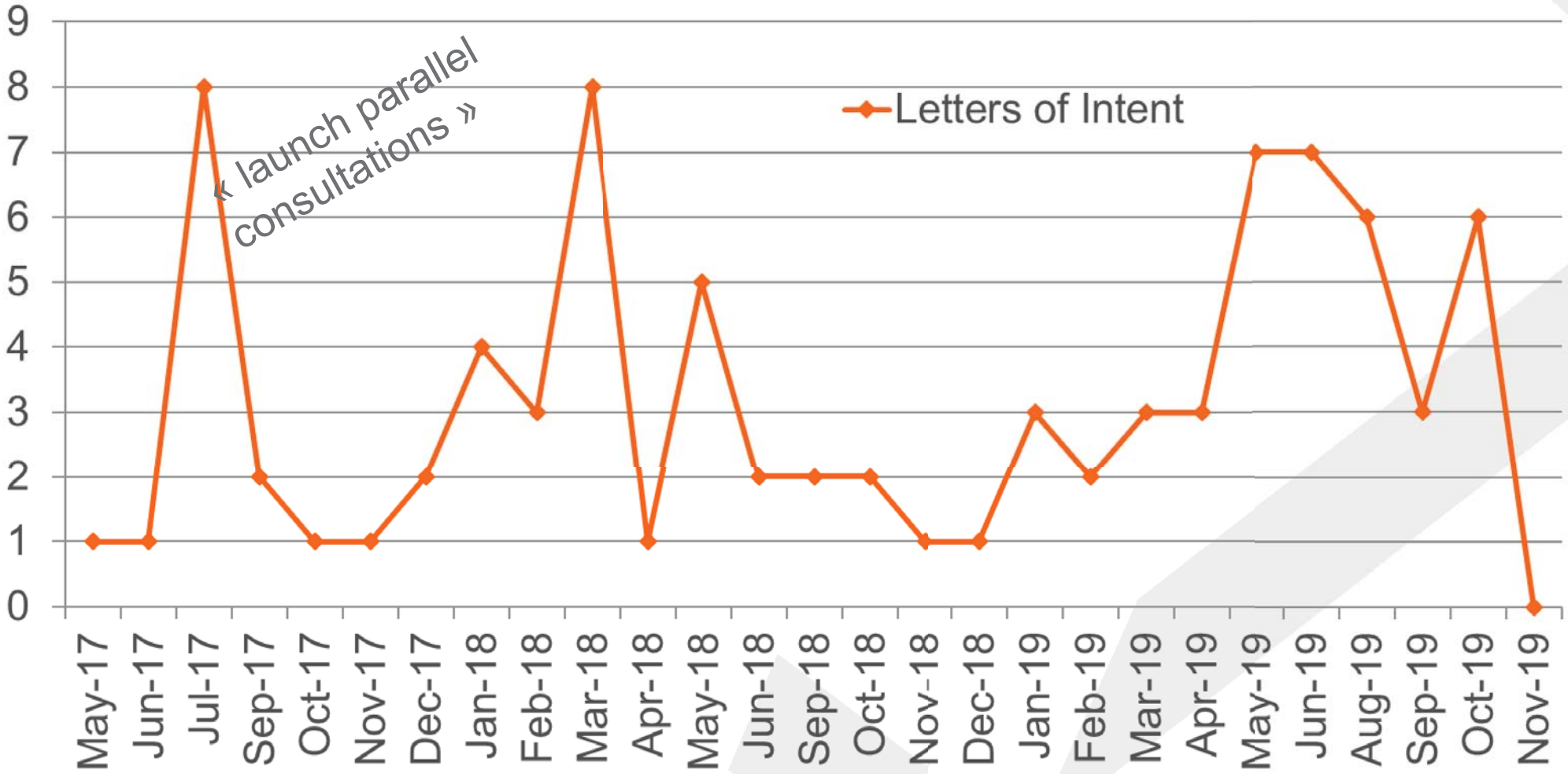
32 EUnetHTA EDs
(4 Multi-HTA + 27Consolidated Parallel Consultations (PCC))

11 Cancer
4 Neurodegenerative
1 Viral disease
16 Other fields

7 SME applicants (13 LoI)
14 Orphan designations (30 LoI)
10 ATMP; 10 biologics, 11 chemicals

6 withdrawn
15 PCI non eligible (less 3 HTAb)
7 declined (procedure not followed; did not meet eligibility criteria for multi-HTA)
1 EDMD on hold by applicant

ED Requests since May 2017



EUnetHTA Early Dialogues Financing Mechanism (EDFM)

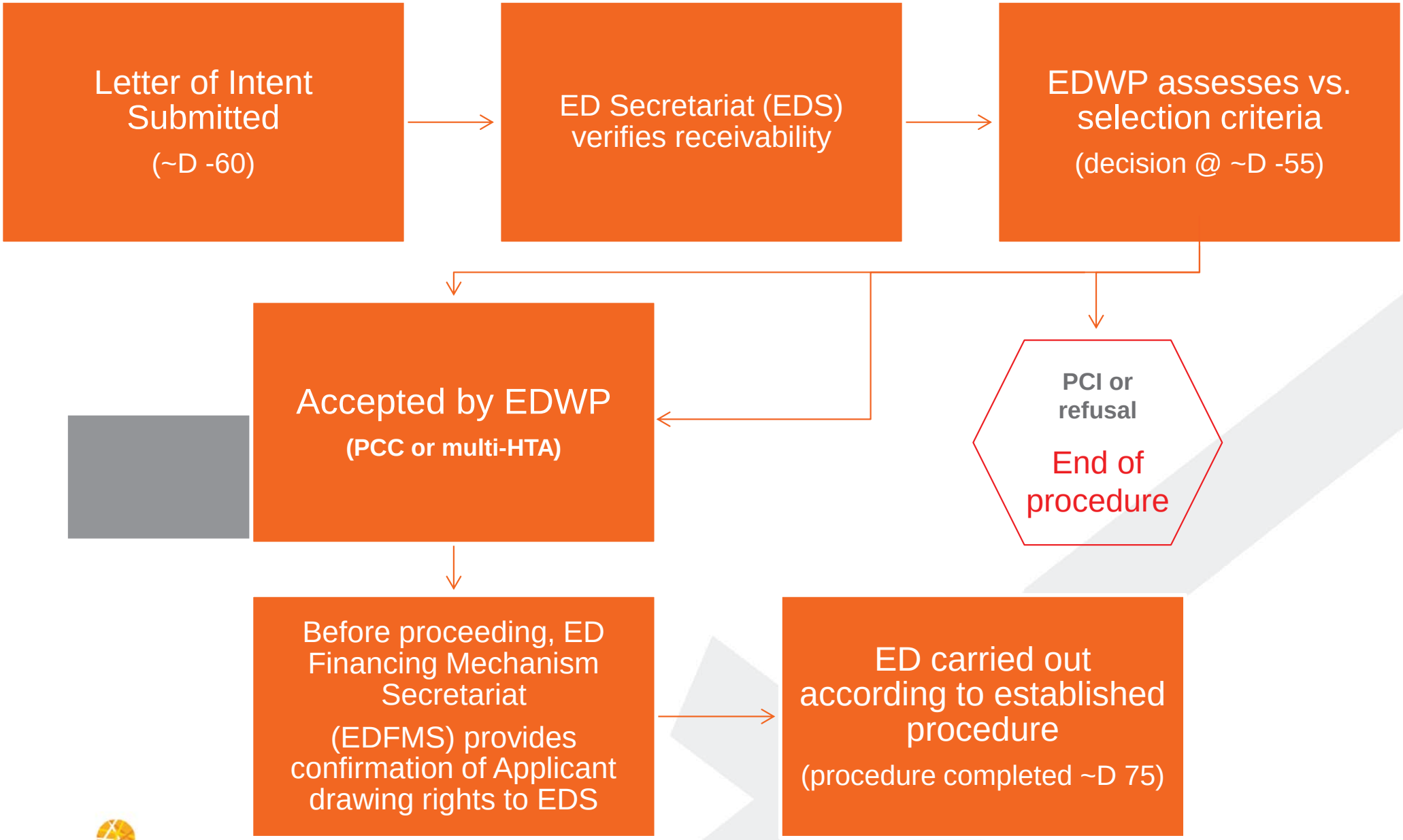
EDFM Participation and Principles

- EDWP participation in EDFM:

  Agreement signatories: AEMPS (confirmation of participating regional agencies to come), G-BA, HAS, NIPN, NOMA, AIFA/RER;

  TLV to participate at their cost
- Agreement to carry out 10-12 EDs per year
- 100% recovery of costs
- Flat rate fee that takes into account production and management costs
- Cost estimates will be established based either on currently accepted fees (ex, G-BA) or by costs from JA3.

Current proposed EDFM workflow



Proposed workflow between the Applicant and the two Secretariats (EDS+EDFMS)

Every month, for every ED accepted

Company submits Letter of Intent to EDS/EDS+EMA

AND

Company informs EDFMS they have submitted a request

→

Request accepted by EDWP

→

EDS informs EDFMS that “company” has an accepted request

EDFMS provides copy of DDR certificate

→

ED carried out.

Every 6 Months

EDS provides report to EDFMS re: ED participation

→

EDFMS pays HTAb according to

1. EDS report

2. preset amount per role

→

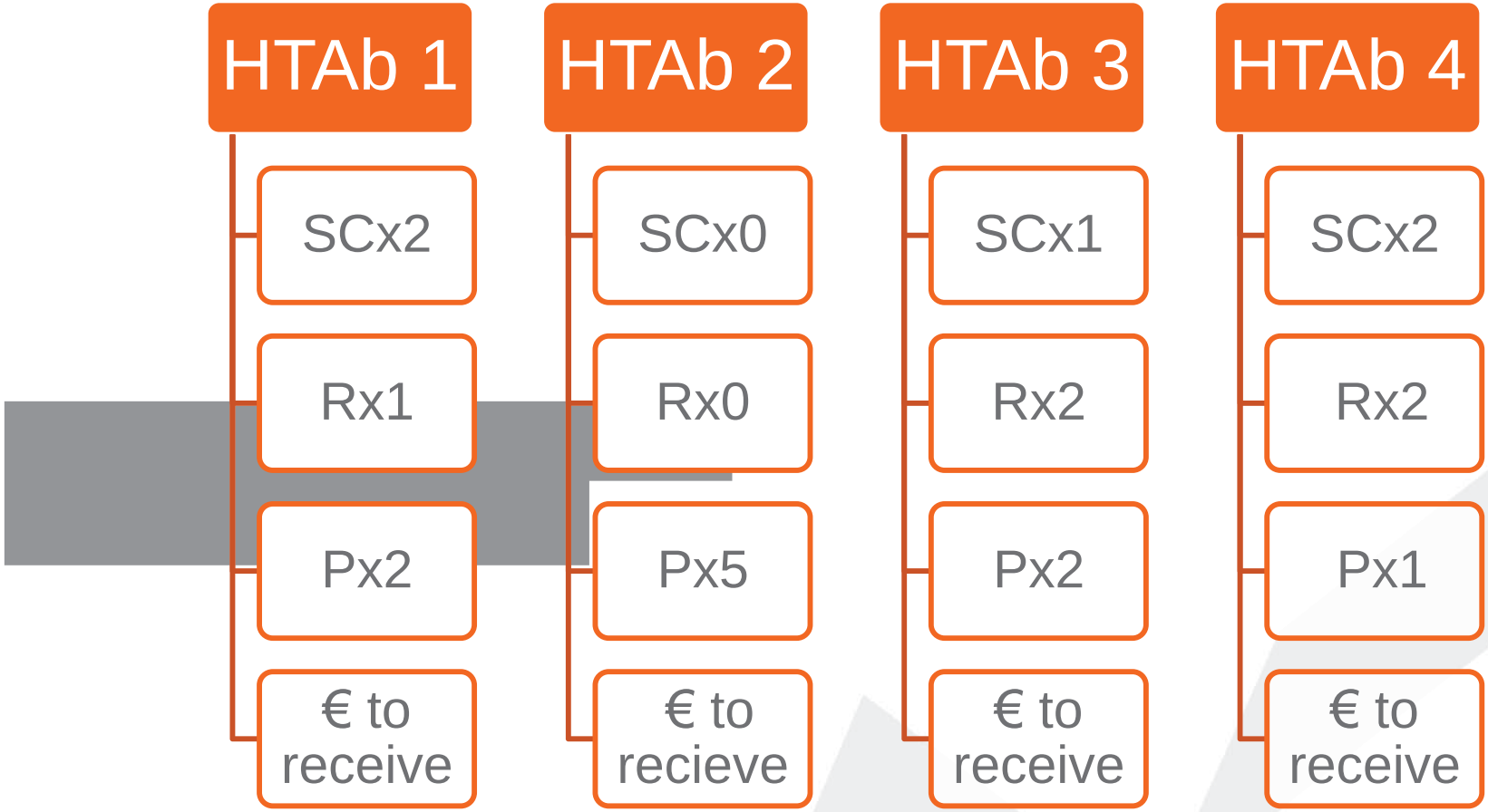
EDFMS confirms to EDS that payments executed; procedure fully closed

Many EDs in One Report

Report sent to EDFMS

Payment to partners based on EDS Report

Example of bi-annual report to EDFMS corresponding to proposal



Next Steps

1. Collaborating with business case and legal consultants to develop the framework
2. First draft to be internally reviewed in December-January
3. Update to industry in January 2020
4. Targeted implementation February 2020

JA3 WP5B – Post Launch Evidence Generation and registries

HAS

EUnetHTA work on PLEG (WP5B): background and objectives

- **PLEG** refers to **evidence generated after the launch** of a health technology within the approved or intended indication(s), and populations that could benefit under those indications.

- **JA3 WP5B objective:** confirm possible levels of cross-border collaboration on PLEG, develop/complement standards and procedures

- **Deliverables:**

  1) **PLEG pilots**: two types of pilots

     a) product specific pilots arising from HTA reports (national or joint)

     - Definition of the **common evidence gaps** and the **minimum data set** to be generated ; advice on methodology for data collection
     - Compilation and analyses of data generated in different countries, whenever possible

     b) registry/disease specific pilots consisting in qualifying existing data sources

     - HTA **advice** on variables (data set) and data quality in a specific data source

  2) **Standards Tool for Registries in HTA (REQueST®)**

     - Practical tool to guide or assess the quality of registry data

EUnetHTA work on PLEG: 2019 achievements

- Final version of REQueST® published

  https://www.eunethta.eu/request-tool-and-its-vision-paper/
- One registry specific pilot ongoing: qualification of EBMT registry for CAR T therapies

  - quality check performed against REQueST® standards
- Three product specific pilots ongoing (Spinraza, Ibrance, LVAD)

  - all three based on evidence gaps from **national** assessments (of agencies launching the call)
- Specific table templates developped in collaboration with WP4 LP and CoLP, to link WP4 and WP5B work (for product specific PLEG pilots arising from **joint** assessments)

  - to be presented today

PLEG arising from joint assessments

- Specific tables to present needs for additional evidence arising from WP4 assessments, in a **structured** and **harmonized** way
- Adaptation of tables from EUnetHTA JA2 Position paper on research recommendations arising from HTA

  https://eunethta.eu/methodology-guidelines/
- Table consists of three sections:

  1) Evidence profile of the technology

  2) Assessments results where evidence currently lacking or considered insufficient

  3) Additional evidence generation needs (in the EPICOT format)

Section 1: Evidence profile of the technology - Summary of the assessment topic, rationale and PICO

1. EVIDENCE PROFILE OF THE TECHNOLOGY	
Topic and rationale	
Title of the assessment	*[Title of the assessment]*
Research question	*[Structured research question]*
Rationale	*[Clear statement on rationale supporting the use of technology explaining how its intrinsic characteristics can lead to improvement on patient-important outcomes compared to current management, potential of the technology to cover unmet health care need (if applicable), and information on burden of disease]*
PICO	
Population	*[Health status, disease, inclusion/ exclusion criteria]*
Intervention	*[Technology and setting of use]*
Comparator(s)	*[Relevant comparator(s) and setting of use]*
The most important / critical outcomes (based on discussions with clinical experts)	*[Name of the outcome, measurement tool and desired effect size]* *[Name of the outcome, measurement tool and desired effect size]* *[Name of the outcome, measurement tool and desired effect size]* *[Name of the outcome, measurement tool and desired effect size]* *[Name of the outcome, measurement tool and desired effect size]* *(Make copies of the lines above, if needed)*
Study design(s)	*[Study design(s) which can produce robust and transferable results; may differ between outcomes]*

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Section 2: Assessment results for outcomes where evidence currently lacking or considered insufficient

2. ASSESSMENT RESULTS				
Most important/critical outcomes where evidence currently lacking or considered insufficient *[Please see Summary of findings table (if applicable)]*	**No. of studies**	**Type of studies**	**Estimate of effect size** *1	**Certainty of the evidence** *2
[Outcome 1]	*[No. of studies]*	*[Study design(s)]*	*[Estimate of effect size]*	*[Level of certainty]*
[Outcome 2]	*[No. of studies]*	*[Study design(s)]*	*[Estimate of effect size]*	*[Level of certainty]*
[Outcome 3]	*[No. of studies]*	*[Study design(s)]*	*[Estimate of effect size]*	*[Level of certainty]*
[Outcome 4]	*[No. of studies]*	*[Study design(s)]*	*[Estimate of effect size]*	*[Level of certainty]*
[Outcome 5]	*[No. of studies]*	*[Study design(s)]*	*[Estimate of effect size]*	*[Level of certainty]*

(Make copies of the lines above, if needed)

*1 If differences in results for different sub-populations, please adapt the table in order to allow reporting of these differences

*2 If no evidence grading system is used, please provide a short narrative statement about the certainty of the evidence

Section 3: Additional evidence generation needs

3. ADDITIONAL EVIDENCE GENERATION NEEDS	
Research question 1: *[Structured research question]*	
Evidence	*[Current state of the evidence available / reasons for uncertainty]*
Population	*[Population and any sub-population(s) of interest]*
Intervention	*[The technology/ intervention and setting of use]*
Comparator	*[Relevant comparator and setting of use]*
Outcome(s)	*[Outcome(s) of interest]*
Time stamp	*[Date of recommendation]*
Study design	*[Appropriate study design]*
Ongoing studies	*[Study registry numbers of relevant ongoing studies, with the date when the search (of ongoing studies) was performed]*
Research question 2: *[Structured research question]*	
Evidence	*[Current state of the evidence available / reasons for uncertainty]*
Population	*[Population and any sub-population(s)of interest]*
Intervention	*[The technology/ intervention and setting of use]*
Comparator	*[Relevant comparator and setting of use]*
Outcome(s)	*[Outcome(s) of interest]*
Time stamp	*[Date of recommendation]*
Study design	*[Appropriate study design]*
Ongoing studies	*[Study registry numbers of relevant ongoing studies, with the date when the search (of ongoing studies) was performed]* Please delete the row if no ongoing studies have been identified
Research question 3: *[Structured research question]* *(Make copies of the lines above, if needed)*	

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Suggestion for piloting in upcoming assessments

WP4

- Complete the entire table (section 1, 2 and 3) and send to WP5B
- Include the last part of the table (section 3 – additional evidence generation needs) in the assessment report templates

WP5B

- Use the table as the starting point of the WP5B PLEG pilot (common evidence gaps)
- Continue the pilot, by defining the minimum data set and quality requirements for PLEG

In conclusion

- REQueST tool available: to help improve the quality and transferability of registry data
- PLEG pilots arising from national HTA: challenges in the conduct because of the differencies in timing, organization and data access among participants
- Plans for next period: PLEG pilots arising from joint HTA
  - should further facilitate collaboration on PLEG (pilot organisation, convergence of requests)

General discussion

Update from DG SANTE, European Commission

DG SANTE (EC)

Update on EMA-EUnetHTA collaboration

[redacted], EMA

Summary of decisions, actions, and closing remarks

[redacted], EUnetHTA (TLV)
, EFPIA (Roche)

2019 EUnetHTA-EFPIA Technical Meeting

Monday 2 December 2019

Haute Autorité de Santé, 5 Avenue du Stade de France, 93210 Saint-Denis

End of session