EUnetHTA Joint Action 3 WP4

Submission Dossier & Assessment Report Template Subgroup - Pharma

RECOMMENDATIONS FOR A SUBMISSION DOSSIER TEMPLATE FOR PHARMACEUTICAL RAPID REA

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V0.1	**21/10/2020**	First draft
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Disclaimer

The content of this Recommendation document represents a consolidated view based on the consensus within the Authoring Team; it cannot be considered to reflect the views of the European Network for Health Technology Assessment (EUnetHTA), EUnetHTA's participating institutions, the European Commission and/or the Consumers, Health, Agriculture and Food Executive Agency or any other body of the European Union. The European Commission and the Agency do not accept any responsibility for use that may be made of the information it contains.

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LIST OF ABBREVIATIONS

(p)MAH	(prospective) Marketing Authorisation Holder
PICO	Population, Intervention, Comparator, Outcome
PP	Project Plan
REA	Relative Effectiveness Assessment
SDAT	Sub Group on Submission Dossier and Assessment Template for pharmaceuticals

1 INTRODUCTION

Pharmaceutical rapid Relative Effectiveness Assessments (REA) are based on submissions from the (prospective) Marketing Authorisation Holder (pMAH) of the new drug under assessment. The (p)MAH provides a submission dossier, which must include all the information required to perform a robust and complete assessment according to the needs of Member States which plan to use the assessment for their national decision making. As such the submission dossier must consider the research question(s) and scope of the assessment as defined in the Project Plan of the assessment.

To develop a submission dossier template for use of pharmaceutical rapid REAs further, the Executive Board decided in May 2019 to set up a subgroup. Later (September 2019), this subgroup was extended to include the evaluation and further revision of the assessment report template as well. Within the subgroup, two smaller teams were established, one to work hands-on with the submission dossier template, and another to work hands-on with the assessment report template. This report presents the work done by the hands-on team on submission dossier template only. Early discussions in the subgroup led to an approach according to which the submission dossier template developed in Joint Action 2 should be used for the remainder of Joint Action 3 assessments and the subgroup should aim to develop general recommendations for a future submission dossier template.

2 METHODS

As a first step, draft recommendations for general principles and general content requirements were developed by the hands-on group. These draft recommendations considered experiences from the work in the assessment report template hands-on group and in the PICO subgroup.

To gather feedback from the EUnetHTA partners on the draft recommendations, an online survey was created (see Appendix 1 for the survey). The survey was available for input from partners between 17th of June till 30th of June 2020.

The survey asked the following questions:

- Per topic
    - How relevant is the topic on a scale from 1 (irrelevant) to 4 (highly relevant)
- Per content item
    - how relevant it was on a scale from 1 (irrelevant) to 4 (highly relevant)
    - How elaborate should the content be on a scale from 1 (short summary) to 4 (full detail)
    - Is there any content missing in the topic.
- Is there any topic missing.

The survey results were analysed by characterising the answers on relevance and required comprehensiveness by the median and mean scale points and the range of scale points. In addition, the explanations for the answers provided in the survey were reviewed and a summary description of the answers per item was provided. Furthermore, the survey answers were reviewed for suggestions of missing items in the draft recommendation.

After endorsement of the paper by the Executive Board, the document will be shared with EFPIA for their feedback. Their feedback will be attached as an appendix to this document, but will not lead to any revisions of the content, nor will their feedback be answered by the sub group. Please note that the lack of responses on the EFPIA feedback should not be considered as endorsement of any feedback.

3 RESULTS

7 out of 51 agencies responded to the survey, all of whom represented a EUnetHTA partner focussing on pharmaceuticals. The summary results of the survey are provided in Appendix 2, 3 and 4.

3.1 Relevance of the topics and items (see Appendix 2)

Generally, the suggested topics and items were supported by the respondents of the survey. Median and mean scale points were 3 and above (on a 1-4 point scale) for the vast majority of items. Nevertheless, the ranges of the answers showed that individual respondents considered some of the items less relevant.

3.2 Required comprehensiveness of topics and items (see Appendix 3)

Median and mean scale points on the required comprehensiveness of the presentation of topics and items were slightly below those of relevance. At the same time for most items responses covered the full range of the scale from 1 to 4 points, i.e. at least one of the respondents required an extended presentation of information on the specific item. The decision on how elaborate individual items should be presented cannot be made on the level of the general recommendations aimed for with this paper. This has to be decided when a new template will finally be developed.

3.3 Suggested additions to the recommendations (see Appendix 2)

The review of the survey feedback for mentions of additional topics and items did not suggest additional items with one exception. One respondent requested inclusion of health economic content, however, as health economics are outside the remit of a joint assessment, this suggestion was not added to the recommendations.

Overall, the survey did not result in changes to the recommendations developed by the hands-on group.

3.4 Further suggestions from the discussion in the subgroup

The outcomes from the survey and the resulting recommendations were presented to the subgroup on pharmaceutical templates in a meeting. Based on the discussion in this meeting a further topic was added to the recommendations, i.e. the need for sufficient guidance for authors of a submission dossier on how to fill in the template and meet the requirements of the data submission.

4 CONCLUSION AND RECOMMENDATIONS

The recommendations for a submission dossier template based on the subgroup work are as follows:

4.1 Recommended general requirements

- The evidence submitted for assessment is complete and not selective with regard to the available studies and data that could inform the assessment.
- The data must have been analysed using appropriate methods to answer the research question(s) of the assessment.
- The data presentation must be well-structured and transparent to allow an appropriate assessment within the limited timeframes available and to support the understanding of the submission and the assessment by third parties.
- The submission dossier must include underlying documentation of the information presented to allow the assessors to check the content of the submission.

4.2 Recommended general content requirements

Table 4.1 shows the general content requirements for a submission dossier for pharmaceutical rapid REA.

Table 4.1 – General content requirements of a submission dossier for a pharmaceutical rapid REA

General content requirements of a submission dossier for a pharmaceutical rapid REA
Characterisation of the medical condition to be treated
• overview of the medical condition • characteristics of the target population
Characterisation of the drug under assessment
• technical information (ATC code, regulatory status etc.)
Research question of the dossier
• PICO(s) elaborated in the submission dossier; should reflect the PICO(s) defined in the Project Plan (PP)
Methods
• description of methods used by the (p)MAH in the development of the content of the submission dossier (including e.g. methods for information retrieval, data analysis and data synthesis) • includes specifications of general requirements for the methods to be used by the (p)MAH
Results of information retrieval
• results of individual search and study selection steps • relevant study pool(s)
Characteristics of included studies
• study design and methods of individual studies • characteristics of patient populations of included studies and analyses
Results on effectiveness and safety
• presentation of each applicable individual study • data presentation by PICO(s) defined in the PP • description of data availability, characteristics of the analyses • results for all available endpoints as specified in the PP from all (relevant) available studies and analyses
Underlying documentation (provided in annexes and appendices)
• documentation of information retrieval (e.g. search strategies, excluded studies, RIS files etc) • presentation of specific details on individual studies (e.g. detailed methods) • documentation of individual studies (clinical study reports, including study protocol and statistical analysis plans) • documentation of analyses performed for the submission dossier (e.g. reports on indirect comparisons) • documentation from the regulatory submission and regulatory procedure • full texts of references literature • other

4.3 Recommended guidance documents

The submission dossier template should be accompanied by sufficient guidance to dossier authors to support efficient development of a complete submission dossier that meets the requirements. This

guidance can be provided in the submission dossier template itself or in additional guidelines for authors. This guidance would need to consider possibly different requirements by different partners, e. g. concerning level of detail and company justification on methods.

APPENDIX 1 – SURVEY ON RECOMMENDATIONS FOR THE SUBMISSION DOSSIER TEMPLATE

Introduction

Pharmaceutical rapid REAs are based on submissions from the (prospective) Marketing Authorisation Holder (pMAH) of the new drug under assessment. The (p)MAH provides a submission dossier, which must include all the information required to perform a robust and complete assessment according to the needs of Member States which plan to use the assessment for their national decision making. As such the submission dossier must consider the research question(s) and scope of the assessment as defined in the Project Plan of the assessment.

Please note: The below table is a draft version of general requirements for a submission dossier. These suggestions are not based on any of the existing EUnetHTA submission dossier templates.

With this survey, we are asking for your feedback on this draft. A final version of these requirements could support the development of a future detailed technical submission dossier template. The suggested content is not meant to determine a specific structure of a future submission dossier template.

General requirements are the following:

- The evidence submitted for assessment is not selective but complete with regard to the available studies and data that could inform the assessment.
- The data must have been analysed using appropriate methods to answer the research question(s) of the assessment.
- The data presentation must be well-structured and transparent to allow an appropriate assessment within the limited timeframes available and to support the understanding of the submission and the assessment by third parties.
- The submission dossier must include underlying documentation of the information presented to allow the assessors to check the content of the submission.

The following table gives an overview of the required content of a submission dossier for a pharmaceutical rapid REA. Please read this carefully, as the survey is based on this content.

Table A 1 –General content requirements for the survey

General content requirements of a submission dossier for a pharmaceutical rapid REA
Characterisation of the medical condition to be treated
overview of the medical condition characteristics of the target population
Characterisation of the drug under assessment
technical information (ATC code, regulatory status etc.)
Research question of the dossier
PICO(s) elaborated in the submission dossier; should reflect the PICO(s) defined in the Project Plan
Methods
description of methods used by the (p)MAH in the development of the content of the submission dossier (including e.g. methods for information retrieval, data analysis and data synthesis) includes specifications of general requirements for the methods to be used by the (p)MAH
Results of information retrieval
results of individual search and study selection steps relevant study pool(s)
Characteristics of included studies
study design and methods of individual studies characteristics of patient populations of included studies and analyses risk of bias of included studies
Results on effectiveness and safety
presentation of each relevant individual study data presentation by PICO(s) defined in the Project Plan description of data availability, characteristics of the analyses and risk of bias for each endpoint

results for all available endpoints as specified in the Project Plan from all (relevant) available studies and analyses
Underlying documentation (provided in annexes and appendices)
documentation of information retrieval (e.g. search strategies, excluded studies, RIS files etc) presentation of specific details on individual studies (e.g. detailed methods) documentation of individual studies (clinical study reports) documentation of analyses performed for the submission dossier (e.g. reports on indirect comparisons) documentation from the regulatory submission full texts of references literature other

Survey

Table A 1 shows the general submission dossier requirements that are questioned in the survey. Each title in **bold** is considered a topic, meaning there are 8 topics questioned. Under each topic, you find a few bullet points (referred to as *content*). Please read these carefully before answering the question. Please note, this is a draft document not necessarily based on any of the existing EUnetHTA Submission Dossier Templates.

To exemplify the survey sent out to EUnetHTA pharmaceutical partners, below one question is shown. All other topics and content bullet points are questioned in the same format. In the Appendix 2, 3 and 4.

Table A 2 – Example of survey question

Characterisation of the medical condition to be treated

Question on topic		**How relevant is the topic?** 1: irrelevant to 4: highly relevant		**Please explain**		
Topic	Characterisation of the medical condition to be treated	1 2 3 4 □ □ □ □				
Question on content of the topic (the bullet points)		How relevant is this content (bullet point) from your point of view 1: irrelevant to 4: highly relevant	Please explain your answer	How elaborate should the content be? 1: short summary information to 4: full detail	Please explain your answer	Is there any content missing in the topic? Please elaborate.
Content	Overview of the medical condition	1 2 3 4 □ □ □ □		1 2 3 4 □ □ □ □		
	Characteristics of the target population	1 2 3 4 □ □ □ □		1 2 3 4 □ □ □ □		

APPENDIX 2 – SURVEY RESULTS ON RELEVANCE OF THE SUGGESTED TOPICS AND ITEMS

General content requirements of a submission dossier for a pharmaceutical rapid REA	Relevance			
	Median	Average	Range	Summary
Characterisation of the medical condition to be treated	3,5	3,25	2 till 4	Relevant topic, but should be described briefly
• overview of the medical condition	3,5	3,375	2 till 4	Is considered a relevant topic. Seen mainly as a key component and basis for the assessment. Should be not too extensive, but concise and brief
• characteristics of the target population	4	3,75	3 till 4	Highly relevant for all, but deviating opinions about extensiveness of the topic. At least not too long, but as detailed as necessary.
Characterisation of the drug under assessment	3	2,875	1 till 4	Extremely deviating opinions: Some might find it highly relevant, while it is for others from minor importance.
• technical information (ATC code, regulatory status etc.)	3,5	3,125	1 till 4	Extremely deviating opinions. However, the majority of the respondents do think the content should be brief. Even the ones who rated it as high relevance.
Research question of the dossier	4	3,625	2 till 4	For everyone is this (highly) relevant, because it defines the scope of the assessment.
• PICO(s) elaborated in the submission dossier; should reflect the PICO(s) defined in the Project Plan	4	3,25	1 till 4	Extreme deviating opinions about this topics' relevance. However the overall opinion is that this topic should be not too extensive, but clear.
Methods	4	3,5	2 till 4	There is unity among the respondents about how important the methods are (highly important). In order to assure validity, quality, transparency and reproducibility.
• description of methods used by the (p)MAH in the development of the content of the submission dossier (including e.g. methods for information retrieval, data analysis and data synthesis)	4	3,375	1 till 4	Opinions deviate about the relevance, but there is agreement about the extensiveness (adequate and concise).
• includes specifications of general requirements for the methods to be used by the (p)MAH	4	3,25	1 till 4	The vast majority of the respondents thinks it is relevant, because of consensus in expectations, transparency and quality of the assessment. The opinions about the extensiveness of the topic deviate.
Results of information retrieval	4	3,375	2 till 4	All respondents do think this topic is relevant, even though they rated it differently.
• results of individual search and study selection steps	4	3,125	1 till 4	Opinions differ about the relevance. It is seen as relevant to check of the dataset is complete, however others find the pool of evidence more important than where it came from/how it was identified. In correspondence with this, the respondents do think differently about the extensiveness (detailed/short).

• relevant study pool(s)	4	3,625	1 till 4	Except from 1 respondent, everyone thinks the relevant study pools are highly relevant for the SD. However the opinions deviate extremely about how extensive this topic should be.
Characteristics of included studies	4	3,75	2 till 4	Overall the respondents do think the topic characteristics of included studies is highly relevant. In this way the relevance, validity, restrictions and comparability can be mapped.
• study design and methods of individual studies	4	3,875	3 till 4	All the respondents do think the study design and methods of individual studies are highly relevant. Mainly for comparability among studies and the validity of study results. Preferable as extensive as necessary and as short as possible.
• characteristics of patient populations of included studies and analyses	4	4	4	Highly relevant for everyone. Need to be well documented, detailed if needed.
• risk of bias of included studies	4	3,625	1 till 4	For almost all respondents is this highly relevant, for e.g. validity, strength of the evidence, comparability. Need to be described as extensive as needed.
Results on effectiveness and safety	4	3,75	2 till 4	Almost all respondents think that the topic "results on effectiveness and safety" is the most important section, because conclusions can be extracted from that part
• presentation of each relevant individual study	4	3,75	3 till 4	Almost all respondents think that this section is highly relevant, because it is the key to extract conclusions. The respondents are divided in two groups about the extensiveness: extensive or short description.
• data presentation by PICO(s) defined in the Project Plan •	4	3,125	1 till 4	The majority of the respondents do think this section is very relevant. However, 2 out of 8 do think this section is not relevant at all. Different opinions about extensiveness.
• description of data availability, characteristics of the analyses and risk of bias for each endpoint	4	3,375	2 till 4	The majority of the respondents do think this section is very relevant. In this way conclusions can be extracted, for the validity of the results and uncertainties can be mapped. Most respondents think that this section should be detailed and clearly described.
• results for all available endpoints as specified in the Project Plan from all (relevant) available studies and analyses	4	3,25	1 till 4	This section is for the majority of the respondents highly relevant. In this way selective data presentation can be avoided and it can be important to know if there is no information in endpoints considered relevant in the PP. The overall opinion is that this section should be (even more) extensive.
Underlying documentation (provided in annexes and appendices)	3,5	3	1 till 4	This section is for some relevant (5/8) and for others not (3/8).
• documentation of information retrieval (e.g. search strategies, excluded studies, RIS files etc)	4	3,125	1 till 4	This section is for most respondents relevant. In this way reproducibility and completeness can be ensured. The vast majority do think it can be briefly stated.

• presentation of specific details on individual studies (e.g. detailed methods)	3,5	3,125	1 till 4	The relevance of this topic is high. This section should be as extensive as needed, but overall adequate.
• documentation of individual studies (clinical study reports) •	3	2,75	1 till 4	The overall opinion is that this section is relevant. The extensiveness is a topic of debate, some say it is something they cannot influence and therefore cannot respond on this.
• documentation of analyses performed for the submission dossier (e.g. reports on indirect comparisons)	4	3,5	1 till 4	The vast majority do think this topic is highly relevant, in order to support critique, evaluate methods, assess the validity of any analysis and for understanding of the AR. Should be as extensive as needed, in order to replicate, check validity and a proper evaluation should be possible.
• documentation from the regulatory submission	3,5	2,75	1 till 4	This is for most respondents relevant, in order to provide background and understanding of CHMPs considerations. The opinions about the extensiveness deviate, since it is not always requested on a national level.
• full texts of references literature	4	3,625	1 till 4	This section has an extremely high relevance, since it is used as background information and check of statements.
• other	1,5	2,125	1 till 4	The content “other” is relevant depending on the dossier
Anything missing				Ensure alignment with assessment template. Proper formatting

APPENDIX 3 – SURVEY RESULTS ON REQUIRED COMPREHENSIVENESS OF THE SUGGESTED TOPICS AND CONTENT ITEMS

General content requirements of a submission dossier for a pharmaceutical rapid REA	Extensiveness			
	Median	Average	Range	Summary
Characterisation of the medical condition to be treated				
• overview of the medical condition	2	2	1 till 4	The overview of the medical condition should be not too extensive, but concise and brief
• characteristics of the target population	3	2,875	2 till 4	Deviating opinions how extensive the content of the characteristics of the target population should be. At least not too long, but as detailed as necessary
Characterisation of the drug under assessment				
• technical information (ATC code, regulatory status etc.)	2	2,25	1 till 4	The majority of the respondents thinks that extensiveness of the content "Technical information" should be brief.
Research question of the dossier				
• PICO(s) elaborated in the submission dossier; should reflect the PICO(s) defined in the Project Plan	3	2,625	1 till 4	Although the respondents have different opinions about the importance of the PICO, the overall opinion is that the PICO should not be too extensive (e.g. 1 page).
Methods				
• description of methods used by the (p)MAH in the development of the content of the submission dossier (including e.g. methods for information retrieval, data analysis and data synthesis)	2,5	2,75	1 till 4	All the respondents have the opinion that the description of the methods by the (p)MAH should be as extensive as needed, but adequate and concise.
• includes specifications of general requirements for the methods to be used by the (p)MAH	2,5	2,625	1 till 4	How extensive the content of specifications of general requirement for the methods to be used by the (p)MAH differs among the respondents.
Results of information retrieval				
• results of individual search and study selection steps	1,5	2,25	1 till 4	How extensive the results of individual search and study selection steps should be described differs within the respondents. Some say detailed enough and others prefer a short description.

• relevant study pool(s)	1,5	2,25	1 till 4	The opinions of the respondents deviate extremely about how extensive the relevant study pools should be. Ór extensively and well documented, ór kept short.
Characteristics of included studies				
• study design and methods of individual studies	3	3	2 till 4	The content "study design and methods of individual studies" should be as extensive as necessary and as short as possible.
• characteristics of patient populations of included studies and analyses	4	3,375	2 till 4	Need to be well documented, detailed if needed.
• risk of bias of included studies	3,5	3	1 till 4	The main point of view is that the content "risk of bias of included studies" should be described as extensive as necessary.
Results on effectiveness and safety				
• presentation of each relevant individual study	3,5	3	1 till 4	The respondents have deviating opinions about how extensive the "presentation of each relevant individual study" should be. The respondents are divided in two groups: extensive or short description.
• data presentation by PICO(s) defined in the Project Plan	2,5	2,625	1 till 4	The respondents differ from opinion how extensive "data presentation by PICO(s) defined in the Project Plan" should be.
• description of data availability, characteristics of the analyses and risk of bias for each endpoint	3	2,75	1 till 4	Most respondents do think that the "description of data availability, characteristics of the analyses and risk of bias for each endpoint" should be detailed and clearly described.
• results for all available endpoints as specified in the Project Plan from all (relevant) available studies and analyses	2,5	2,75	1 till 4	"Results for all available endpoints as specified in the Project Plan from all (relevant) available studies and analyses" should be extensive by most of the respondents. Could be even more extensive, said by one respondent.
Underlying documentation (provided in annexes and appendices)				
• documentation of information retrieval (e.g. search strategies, excluded studies, RIS files etc)	3	2,625	1 till 4	The content "documentation of information retrieval (e.g. search strategies, excluded studies, RIS files etc)" should be as extensive as needed. The vast majority do think it can be briefly stated.
• presentation of specific details on individual studies (e.g. detailed methods)	3,5	2,75	1 till 4	The topic "presentation of specific details on individual studies (e.g. detailed methods)" should be as extensive as needed. The ratings deviate, but overall it should be adequate
• documentation of individual studies (clinical study reports)	3	2,625	1 till 4	The opinions how extensive the CSR should be, deviate. Some say all studies must be available, others say this is for them not applicable.
• documentation of analyses performed for the submission dossier (e.g. reports on indirect comparisons)	3,5	2,875	1 till 4	The content "documentation of analyses performed for the submission dossier (e.g. reports on indirect comparisons)" should be as extensive as needed, in order to replicate, check validity and a proper evaluation should be possible

• documentation from the regulatory submission	1	2,125	1 till 4	The opinions deviate extremely about the extensiveness of "documentation from the regulatory submission". Or it should be well documented, or they say it is not requested/ not applicable.
• full texts of references literature	4	3,5	1 till 4	Extensiveness of "full texts of references literature is mainly high, but elobaration is often N/A. *[Note: probably because it is or a full citation/reference or not]*
• other	1,5	2,125	1 till 4	The content “other” should be as extensive as needed and if applicable.
Anything missing				Ensure alignment with assessment template. Proper formatting

APPENDIX 4 – SURVEY RESULTS ON MISSING ITEMS IN SUGGESTED TOPICS

General content requirements of a submission dossier for a pharmaceutical rapid REA	Missing items in suggested topics
Characterisation of the medical condition to be treated	
• overview of the medical condition	The overview of the medical condition should be not too extensive, but concise and brief
• characteristics of the target population	Deviating opinions how extensive the content of the characteristics of the target population should be. At least not too long, but as detailed as necessary
Characterisation of the drug under assessment	
• technical information (ATC code, regulatory status etc.)	The majority of the respondents thinks that extensiveness of the content "Technical information" should be brief.
Research question of the dossier	
• PICO(s) elaborated in the submission dossier; should reflect the PICO(s) defined in the Project Plan	Although the respondents have different opinions about the importance of the PICO, the overall opinion is that the PICO should not be too extensive (e.g. 1 page).
Methods	
• description of methods used by the (p)MAH in the development of the content of the submission dossier (including e.g. methods for information retrieval, data analysis and data synthesis)	All the respondents have the opinion that the description of the methods by the (p)MAH should be as extensive as needed, but adequate and concise.
• includes specifications of general requirements for the methods to be used by the (p)MAH	How extensive the content of specifications of general requirement for the methods to be used by the (p)MAH differs among the respondents.
Results of information retrieval	
• results of individual search and study selection steps	How extensive the results of individual search and study selection steps should be described differs within the respondents. Some say detailed enough and others prefer a short description.
• relevant study pool(s)	The opinions of the respondents deviate extremely about how extensive the relevant study pools should be. Ór extensively and well documented, ór kept short.
Characteristics of included studies	
• study design and methods of individual studies	The the content "study design and methods of individual studies" should be as extensive as necessary and as short as possible.
• characteristics of patient populations of included studies and analyses	Need to be well documented, detailed if needed.
• risk of bias of included studies	The main point of view is that the content "risk of bias of included studies" should be described as extensive as necessary.
Results on effectiveness and safety	
• presentation of each relevant individual study	The respondents have deviating opinions about how extensive the "presentation of each relevant individual study" should be. The respondents are divided in two groups: extensive or short description.

• data presentation by PICO(s) defined in the Project Plan •	The respondents differ from opinion how extensive "data presentation by PICO(s) defined in the Project Plan" should be.
• description of data availability, characteristics of the analyses and risk of bias for each endpoint	Most respondents do think that the "description of data availability, characteristics of the analyses and risk of bias for each endpoint" should be detailed and clearly described.
• results for all available endpoints as specified in the Project Plan from all (relevant) available studies and analyses	"Results for all available endpoints as specified in the Project Plan from all (relevant) available studies and analyses" should be extensive by most of the respondents. Could be even more extensive, said by one respondent.
Underlying documentation (provided in annexes and appendices)	
• documentation of information retrieval (e.g. search strategies, excluded studies, RIS files etc)	The content "documentation of information retrieval (e.g. search strategies, excluded studies, RIS files etc)" should be as extensive as needed. The vast majority do think it can be briefly stated.
• presentation of specific details on individual studies (e.g. detailed methods)	The topic "presentation of specific details on individual studies (e.g. detailed methods)" should be as extensive as needed. The ratings deviate, but overall it should be adequate
• documentation of individual studies (clinical study reports) •	The opinions how extensive the CSR should be, deviate. Some say all studies must be available, others say this is for them not applicable.
• documentation of analyses performed for the submission dossier (e.g. reports on indirect comparisons)	The content "documentation of analyses performed for the submission dossier (e.g. reports on indirect comparisons)" should be as extensive as needed, in order to replicate, check validity and a proper evaluation should be possible
• documentation from the regulatory submission	The opinions deviate extremely about the extensiveness of "documentation from the regulatory submission". Or it should be well documented, or they say it is not requested/ not applicable.
• full texts of references literature	Extensiveness of "full texts of references literature is mainly high, but elobaration is often N/A. *[Note: probably because it is or a full citation/reference or not]*
• other	The content “other” should be as extensive as needed and if applicable.
Anything missing	Ensure alignment with assessment template. Proper formatting

APPENDIX 5 – EFPIA COMMENTS

After endorsement of the paper by the Executive Board, the document was shared with the EFPIA HTA working group for their feedback. The report was open for review by EFPIA from December 02, 2020 until January 12, 2021.

Their feedback can be found below. Please note that their feedback will not lead to any revisions of the content, nor will their feedback be answered by the sub group. Please note that the lack of responses on the EFPIA feedback should not be considered as endorsement of any feedback.

Comment from ***Insert your name and organisation***	**Page number** ***Insert 'general' if your comment relates to the whole document***	**Section number**	**Comment and suggestion for rewording** ***Please insert each new comment in a new row.***	**Character of comment** • **'major'[a] =1** • **'minor'[b] = 2** • **'linguistic'[c] =3** ***Please indicate your choice by writing the according number in this field, e.g. for major choose "1".***
EFPIA	General	General	It should be highlighted more preeminently that only 7 out of 51 agencies have responded to the survey which forms the basis of these recommendations. Furthermore, consideration should be given to achieve broader engagement and endorsement from other EUnetHTA partners of the template and guiding document at a later stage. Furthermore, it should be made clear in the guiding documents that the individual preferences of the assessors who provided input into the survey with regards to comprehensiveness of items and points, particularly when they diverge from the final EUnetHTA recommendations, should be put aside when reviewing a REA submission dossier from the (p)MAH.	2
EFPIA	General	General	In some sections it is mentioned "Relative Effectiveness Assessment" and in other it is mentioned "Joint Assessment''. As these two terms are synonyms, and for consistency, only one of them should be used throughout the document with a note when the term is introduced the first time [e.g. Relative Effectiveness Assessment (also known as joint clinical assessment)].	3
EFPIA	General	General	A reference should be added in the recommendations that the submission template is part of the evidence and assessment continuum (early dialogue and its outcome, scoping meeting, joint clinical assessment up to post licencing evidence generation) and, as such, consideration should be given to the need to maintain predictability across the continuum.	2

Comment from ***Insert your name and organisation***	**Page number** ***Insert 'general' if your comment relates to the whole document***	**Section number**	**Comment and suggestion for rewording** ***Please insert each new comment in a new row.***	**Character of comment** • **'major'[a] =1** • **'minor'[b] = 2** • **'linguistic'[c] =3** ***Please indicate your choice by writing the according number in this field, e.g. for major choose "1".***
EFPIA	7	2	It should be specified in this section that the survey was sent out to 51 agencies (EUnetHTA partners) and a clarification on this number should be provided, given that EUnetHTA has more than 80 partner agencies across Europe.	2
EFPIA	7	2	Current text: 'After endorsement of the paper by the Executive Board, the document will be shared with EFPIA for their feedback.' Proposed text: After endorsement of the **draft recommendations** by the Executive Board, the document will be shared with EFPIA for their feedback.	3
EFPIA	7	2	The current version says, that "after endorsement of the paper by the Executive Board, the document will be shared with EFPIA for their feedback. Their feedback will be attached as an appendix to this document, but will not lead to any revisions of the content". Feedback from EFPIA should be analysed and implemented accordingly, documentation should be attached to the document, why specific comments and suggestions were not implemented.	1
EFPIA	8	3	Actual or potential reasons for the low response rate (i.e. only 7 out of 51 responded to the survey) should be provided, if available (e.g. short timeframe to respond to the survey).	2
EFPIA	8	3	If possible, the name of the 7 responder HTA agencies should be disclosed.	1

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EFPIA	8	3.1-3.3	A summary table for the results of the survey presented upfront or at least within the respective sections would help with the context and understanding.	1
EFPIA	8	3.2	It should be made clearer that the responses to the survey with regards to the required comprehensiveness of the presentation of topics and items will be taken into consideration by the subgroup who will work on the pharmaceuticals REA dossier template.	1
EFPIA	9	4	It should be highlighted more preeminently that these recommendations are based on very limited feedback collected from only 7 out of 51 agencies.	2
EFPIA	9	4.1	EFPIA considers that the focus of a joint clinical assessment report is on EU-wide aspects of clinical effectiveness and safety where there is currently duplication of effort, the submission dossier template should reflect this as it complements but does not duplicate information already generated in the marketing authorization process. As national context-specific reviews will be conducted by the individual Member States based on tailored national HTA submissions, JCAs do not need to contain country-specific data (understood as data pertaining to broader HTA domains outside of clinical data, such as, for example, economic modeling data)	1
EFPIA	9	4.1	EFPIA considers that the time taken to conduct the rapid JCA is very short and therefore this needs to be considered in terms of the data volume being processed and expected to be included in the submission dossier rather than being invested in the verification of information that is not needed for a high-quality JCA.	1
EFPIA	9	4.1	There should be a recommendation highlighting that the submission dossier template should allow the applicant to mark commercial or academic in confidence information/data in the submission (directly in the template or a specific annex).	1

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EFPIA	9	4.2	In table 4.1, it should be made clear that only studies need to be presented for which the (p)MAH has data access.	1
EFPIA	9	4.2	In table 4.1, section "Characterization of the medical condition to be treated" is to be supplemented by description of the unmet medical need	1
EFPIA	9	4.2	In table 4.1, section "Research question of the dossier", additional clarification should be provided as the submission template should be the natural next step following the scoping phase, which should include at the very least a meeting with the developer/applicant to discuss and agree on the most scientifically appropriate PICO needed for the assessment at hand. This will support the manufacturer in the development of a submission where the evidence requested is available and robust to address the specific questions.	2
EFPIA	9	4.2	In table 4.1, section "Research question of the dossier", additional clarification should be provided that, beyond the PICO(s) agreed during the scoping phase should additional information on additional comparators, not selected during the scoping phase, be required in very specific national circumstances, such information can be submitted in a national complimentary submission. EFPIA believes that the selection of comparators should follow a structured approach ensuring a final list of comparators that is reasonable and concise. Under ideal circumstances, the priority should be given to established licensed medicines with published robust clinical data, followed by those recommended in European clinical guidelines. If this is not possible, routinely used comparators in established clinical practice should be considered as long as the evidence submission and assessment of the resulting set of comparators is compatible with the targeted timeline for a high-quality assessment.	1

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EFPIA	9	4.2	In table 4.1, section "Research question of the dossier", there should be a recommendation for an additional section where the (p)MAH can provide context on the evidence included in the submission dossier, if needed, namely any deviation from the assessment scope defined in the PP and respective rationale/justification.	1
EFPIA	9	4.1	In table 4.1, section "Methods", statistical analysis should include predefined (per protocol) analysis but additionally post-hoc defined analysis should be accepted as valuable evidence as pre-specified analysis.	1
EFPIA	9	4.2	In table 4.1, section "Methods" the methods which are to be used by (p)MAH should follow scientific standards and should be developed with inclusion of all relevant stakeholders (including industry)	1
EFPIA	9	4.2	Current text (table 4.1) 'Underlying documentation (provided in annexes and appendices)' Proposed text: **Supportive** documentation (provided in annexes and**/or** appendices)	3
EFPIA	9	4.2	In table 4.1, section "Underlying documentation" should clarify that CSRs should be provided without appendices with patient-individual data.	1
EFPIA	9	4.2	In table 4.1, section "Underlying documentation" the recommendation should provide more clarity as to which elements fall under 'documentation from the regulatory submission and regulatory procedure' and also clarify whether this duplicates the information exchange with EMA/CHMP.	

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			It is EFPIA's view that a clarification that only documentation from the regulatory submission and regulatory procedure (final CHMP opinion) should be included into the dossier, which might be of relevance for the assessment question and to allow an appropriate assessment within the limited timeframes available: summary of product characteristics (SmpC) and European public assessment report (EPAR). Submission of additional documents in order to achieve the goal to provide background and understanding of CHMPs considerations (as per Appendix 2 of the document) is not needed nor advisable as interim stages of the EMA assessments and answers to various list of questions provided by the manufacturer can be quite misleading in comparison to the final result at CHMP opinion stage.	
EFPIA	9	4.2	There should be a recommendation for the applicant how to handle patient individual information/data in the submission (directly in the template or a specific annex) in line with data protection rights for the patient and the pharmaceutical manufacturer. The requirements and the handling of patient individual data differ between the European HTA bodies.	1
EFPIA	9-10	4.3	The guidance documents should clarify the distinction between appendices and annexes, give examples and explain respective implications (e.g. published vs unpublished).	2
EFPIA	9-10	4.3	Examples within the guidance documents or template itself (as hidden text) to illustrate how assessors may prefer certain data presentation (brief vs comprehensive) within sections of the submission dossier template may be of use to the (p)MAH.	2