Roche Pharma Report Relating to EUnetHTA HTA Core Model® Applications for Pharmaceuticals

December 21st 2014

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1 Introduction

In October 2013, F. Hoffmann - La Roche AG (Roche Pharma) and EUnetHTA entered a mutual collaboration. The purpose of the mutual collaboration was outlined in the Terms of Reference (ToR). The main aim for Roche Pharma was to consider how the EUnetHTA HTA Core Model® (HTA Core Model) could support the HTA evidence assembling processes within Roche Pharma. In particular, Roche Pharma wanted to explore whether the EUnetHTA's HTA Core Model® could be used to guide the HTA evidence development process and/or serve as a repository for sharing HTA evidence across the company, similar to the on-line tool developed by EUnetHTA. The aim was to enable efficiency in conducting HTA submissions in the European countries as well as in other countries outside of Europe.

Roche also agreed to offer general advice to EUnetHTA on the HTA Core Model® from a pharmaceutical value proposition perspective.

Roche is considering using the HTA Core® model for evidence assembling, storing and sharing.

The first phase, which is documented in this report, is aimed at assessing the usefulness of the EUnetHTA Core model for Roche's internal HTA assembling, storing and sharing purposes.

The second phase involves adapting the HTA Core Model® for internal use. The intention is to keep as aligned and close to the EUnetHTA HTA Core Model® as possible. All the Domains and Topics in a Roche future version of the HTA model will be used, however the language may be simplified. The second phase would involve implementing the HTA Core Model® as a checklist for evidence generation for cross-functional teams, at all stages of the product lifecycle. Assessment elements will be retained and allocated "key words" to enable a shorter checklist to be developed. A third phase would enable the HTA Core Model® to become a repository, for sharing global / local evidence generation plans and experiences from HTA assessments. The Roche HTA Model adaptation plans are still in their early stages and will become clearer during 2015. Roche will remain in dialogue with EUnetHTA to ensure alignment with EUnetHTA's subsequent development of the HTA Core Model®.

Adopting the HTA Core Model® structure has the potential for Roche (and other HTA evidence contributors) to become more efficient and effective in the global and local development of HTA evidence as well as enabling the exchange and utilization of it as part of affiliate pricing and reimbursement submissions. At the same time, conducting this project and sharing its results with other HTA contributors will advance objectives of EUnetHTA i.e. to increase awareness, utilization and understanding of the usefulness of EUnetHTA tools among relevant parties.

2 The HTA Core Model®

The HTA Core Model® contains separate applications for various types of health technologies (e.g. diagnostics, interventions, screening and pharmaceuticals). Roche Pharma wished to review the HTA Core Model® developed within EUnetHTA, as a framework for assessing the value of a pharmaceutical product. The analysis focuses on the application for "full" assessment of pharmaceuticals and not the rapid relative effectiveness assessment (REA) Pharmaceutical application. The level of importance and transferability of each assessment element may vary between different technologies and applications. This report focuses upon the Pharmaceutical application of the HTA Core Model® and the value assessment of Pharmaceuticals.

The HTA Core Model® application for pharmaceuticals version 2.0 consists of nine domains and 130 Assessment Elements.

Table 1:

Domains	Number of Assessment Elements
1. Health Problem & Current Use of Technology	20
2. Description and Technical Characteristics of Technology.	15
3. Safety	13
4. Clinical Effectiveness	15
5. Costs and Economic Evaluation	8
6. Ethical Analysis	19
7. Organizational Aspects	14
8. Social Aspects	11
9. Legal Aspects	15

3 Method of Research

The key research question for the project was framed in the following way:
Is the EUnetHTA Core Model® a useful framework for assessing the value of a pharmaceutical product?

As "usefulness" is a broad term, the research question had to be further defined.

1. Two criteria were used to define the research question more precisely:
   Whether the assessment element is important for the "Payer", for example for benefit assessment for pricing/ reimbursement negotiation and/or for formulary listing.
2. Whether it is relevant for demonstrating the value proposition.

In order to obtain a broad and comprehensive representation from Roche Pharma, there was extensive involvement from Affiliates and Global teams. Six affiliates from UK, France, Germany, Italy, Netherlands and Canada reviewed the HTA Core Model ®and completed the on-line questionnaire (thirty-one affiliate team members in total). In addition, four global team members also reviewed the HTA Core Model ®and completed the on-line questionnaire from the Global Pricing and Market Access function. An additional four team-members participated in local and global workshops. All participants are directly involved either with evidence development, preparing reimbursement submissions or payer negotiations and have many years experience.

Table 2: Perspectives taken by Roche Pharma Affiliates and Global

	No of people involved (Total = 39)	Perspective
Canada	4	Payers from national and provincial levels
France	10	Payers from national and local levels. Broad*
Italy	4	Payers from national, regional and local levels. Broad*
UK	2	NICE SMC CDF
Holland	5	Payers Broad*
Germany	6	Payers (IQWIG), GBA
Global	8	Payers, across multiple EU countries. Broad*

- *The term "Broad" refers to wide internal consultation, which occurred amongst team experts in pricing, health economics, reimbursement, value strategy and policy. It also refers to taking into account the requirements for reimbursement submissions and also value to key stakeholders.
- The term "Payer " is used within this report to mean both national or local payers as well as pricing or reimbursement decision makers or providers of guidance at either a national, regional or local level.

The HTA Core Model® was programmed and developed into an on-line survey. The respondents assessed which domains, topics and assessment elements are important for Payers at national, regional and local levels for benefit assessment, pricing /reimbursement negotiation and formulary listing of pharmaceuticals. In addition, respondents assessed from a Roche Pharma perspective which domains, topics and assessment elements are relevant both now and in the future for demonstrating the value proposition of a health technology. They also assessed whether the information is fully or partially transferable.

Table 3:

Questions asked in on-line survey	Additional detail relating to the Questions
1. Is the assessment element important because Payers ask for it?	1: For benefit assessment, price, reimbursement negotiation, formulary listing, Select the level of payer for which it is important. (national, regional/local, both national regional and local.) Importance was ranked as either 4= very important or 3= somewhat important.
2. Is the assessment element relevant to demonstrate the value proposition?	2: Select the level of payer for which it is important. (national, regional/local, both national regional and local.) Importance was ranked as either 4= very important or 3= somewhat important.
3. Are there any other reasons why it is important?	
4. Is the assessment element of low importance?	4: Please provide reasons for low importance. Unimportance was ranked as either 2=somewhat unimportant or 1= very unimportant.
5. Which type of information is transferable between different healthcare systems?	5: Respondents ranked whether it was totally, partially or not transferable. In Appendix 3, x means fully or partially transferable and 0 means not transferable.
6. Does the assessment element duplicate information?	6: The duplicated domain and assessment was specified.
7. Are any assessment elements missing?	7: In order to assess the value of health technologies from a Roche perspective.
8. Are any assessment elements unclear?	
9. Is any assessment element redundant?	

An assessment element was ranked as " important" if it was either required for reimbursement submissions or to demonstrate the value to key stakeholders or for both reasons. The term "transferable" was defined as relating to information, which could be used beyond its original location: e.g. from other sources than local national sources. Transferability was ranked low for information, which was specific to a region, country or health care system and could not be obtained from other settings. Only Affiliates answered the question relating to transferability, as their experience was essential to determine the level of transferability.

In addition, respondents were asked to indicate if assessment elements were unclear, redundant, duplicated or if assessment elements were missing.

Following the online survey, six workshops were conducted with each affiliate to ensure that:

- The responses were well understood by Global Pricing and Market Access (GPMA).
- Uncertainties and questions could be discussed and answered.
- Feedback on the Core Model could be augmented with verbal opinions and observations.

In addition, a GPMA workshop was held to discuss results from the four global participants.

In early September 2014, representatives from participating affiliates and global team members met in a joint workshop to align around their positions, exchange opinions and observations, as well as outline advice relating to the HTA Core Model®.

4 Main Conclusions & General Advice on the Content

Main conclusions:

Roche Pharma considers that the HTA Core Model® is a useful, comprehensive framework, which provides the ability to demonstrate the value potential of a health technology. Roche believes that all domains are important, however there are opportunities to reduce the number of assessment elements for a specific compound or product by considering their relevance and prioritizing elements as core and non-core. There are also a number of missing assessment elements. These points are outlined in more detail by Domain in Section 5 of the Report and also in the Appendix 1.

There was strong agreement that Domains 1-5 (Table 1) are critical for Pricing/Reimbursement national and sub-national submissions, assessments and also to demonstrate the value of a health technology. They reflect what payers ask for today.

It was also agreed that Domains 6-9 (Table 1) are important for HTA and important in order to illustrate the value of a health technology. These domains address a number of assessment elements of value, which are often not considered sufficiently. They allow the possibility of including multiple stakeholder perspectives in the value assessment e.g. patients, caregivers and society. Many of the assessment elements in Domains 6-9 require local data and are not transferable to or from other jurisdictions.

Roche is considering using the HTA model ® for evidence assembling, storing and sharing.

The first phase, which is documented in this report, is aimed at assessing the usefulness of the EUnetHTA Core model® for Roche's internal HTA assembling, storing and sharing purposes.

The second phase involves adapting the HTA Core Model® for internal use. The intention is to keep as aligned and close to the EUnetHTA HTA Core Model® as possible. All the Domains and Topics in a Roche future version of the HTA model will be used, however the language may be simplified. The second phase would involve implementing the HTA Core Model® as a checklist for evidence generation for cross-functional teams, at all stages of the product lifecycle. Assessment elements will be retained and allocated "key words" to enable a shorter checklist to be developed.

A third phase would enable the HTA Core Model® to become a repository, for sharing global / local evidence generation plans and experiences from HTA assessments. The "Roche HTA Model" adaptation plans are still in their early stages including the name of the future model, which needs to be agreed and will become clearer during 2015. Roche will remain in dialogue with EUnetHTA to ensure alignment with EUnetHTA's subsequent development of the HTA Core Model®.

Table 4: Overall Summary Results by Domain of Important, Unimportant and Transferable assessment elements

Domain (Total number of assessment elements per domain)	**Important elements** ≥ 4 out of 5 countries*	**Unimportant elements** ≥ 3 out of 5 countries*	**Transferable elements** (fully and partially, all six countries)	**Important and transferable elements** (fully and partially) ≥ 4 out of 5 countries*	**Non-Transferable elements** (all six countries)
1. Health Problem & Current Use of Technology (20)	18		5	11	1
2. Description and technical characteristics of technology (15)	10	2	1	7	
3. Safety (13)	6	3	6	5	
4. Clinical Effectiveness (15)	13	2	7	8	
5. Costs and economic evaluation (8)	8			1	1
6. Ethical analysis (19)	5	3		2	3
7. Organizational aspects (14)	7	2			2
8. Social aspects (11)	4	4			1
9. Legal aspects (15)	3	10		1	3

* without Canada

Roche Pharma advice on Content

The suggestions and advice in Sections 4 and 5 of this report are relevant for a future Roche adaptation of the HTA Core Model®. In addition, they may be helpful for EUnetHTA when considering future revisions of the HTA Core Model®.

The respondents aligned upon a number of general suggestions.

Firstly, the HTA Core Model® could be renamed as the name was found to be very technical. In addition it was perceived that the name did not adequately reflect the full scope of the HTA Core Model®. It was therefore proposed to rename the HTA Core Model® to:

"(Pharmaceutical) Value Assessment Framework."

In addition it was advised to rename domains 4 and 8

Advice: *Rename Domain 4, calling it Clinical Evidence. Create topics on clinical efficacy and clinical effectiveness.*

Advice: *Rename Domain 8 to "Patient/Caregiver and Society", as the new name would emphasize the central importance of the Patient.*

Another suggestion relates to the timing of evidence within the HTA Core Model®.

Advice: *The HTA Core Model® could include in the introduction, a disclaimer, explaining that some of the evidence may not be available until post launch.*

In addition, it was felt that the language could be made simpler throughout the model and that the assessment elements were not always clear. Explanations sometimes did not fit with the questions. It was desired to have less technical language and instead a few clear examples to explain the content of an assessment element. (please refer to Appendix 1 for specific examples)

4.1 Overall Benefits of the HTA Core Model® from a Roche perspective

The HTA Core Model® was seen as providing a number of potential benefits both for Roche internally and for external use. They include:

- Providing a single and exhaustive framework for scoping out HTA evidence, which could lead to greater consistency and quality of evidence across products.
- It could enable a more standardized approach across European Roche affiliates as well as other Roche affiliates for evidence generation.
- It could provide a common terminology for evidence generation, sharing and communication.
- It could provide a check-list for ensuring evidence is generated more broadly and consistently across Roche pharmaceutical products.
- It could provide a repository for submissions for local affiliates.
- If used as a check- list, it could highlight where product evidence gaps exist.

4.2 Limitations of the HTA Core Model® from a Roche perspective

The main limitations of the HTA Core Model®were seen as:

- A lack of clarity relating to future use of the HTA Core Model®, which need to be made more explicit to current and potential future users. The HTA Core Model®, Handbook is helpful, however it would be useful to know if the HTA model's implementation will extend beyond current usage? Will there be future iterations of the HTA Core Model®? Will parts of the HTA Core Model®be used in pricing and reimbursement decision-making?
- The HTA Core Model® is very comprehensive, and a streamlined version would make it easier and less resource intensive to implement and maintain. The word "streamline" refers to the need to reduce areas of duplication or to reduce the number of assessment elements within an application which are ranked as low importance (please refer to Appendices 1 and 5). There are also opportunities to combine assessment elements. This activity would increase the impact of the HTA Core Model ® and make it easier for users to understand and implement.

Advice: *Clarify likely future changes of the HTA Core Model®.*

Advice: *For the purpose of value assessment of pharmaceuticals, the HTA Core model® could be streamlined according to the domain specific advice.*

5 Domain Analysis

The following section of the report will summarize by Domain, the results and conclusions relating to assessment elements, which were considered both important and important/transferable for at least four of the five Roche Affiliates (excluding Canada) for either the payer and /or for the value proposition. It is worth noting that there were low levels of agreement relating to assessment elements which were ranked as important only for the value proposition. Appendix 6 summarizes at a disaggregated level (excluding Canada) which assessment elements were ranked as important only for the value proposition and not for the pricing and reimbursement negotiations. Reference will be made to these elements during the Domain Analysis. Some of the Affiliates were unclear when answering the question relating to assessment elements, which were important only for the value proposition, thus the results in Appendix 6 are not robust.

This section includes areas of duplication, unimportant assessment elements and elements, which require further clarification for at least three affiliates. It is worth noting that there were low levels of agreement relating to duplicated, missing or unclear assessment elements. These assessment elements are listed separately, in disaggregated form, in Appendix 1.

Domain 1: Health Problem and Current Use of Technology

Domain 1 was ranked of high importance because it is important from both a national and subnational payer perspective. Domain 1 considers topics including current treatment management, technology versus alternatives and unmet need. It also addresses the target population, which is critical for every aspect of health technology assessment. Eighteen out of twenty elements were considered to be important by at least four countries, excluding Canada (Appendix 4, pages 2-3). There was no consensus relating to two assessment elements, which was ranked as unimportant (Appendix 2, pages 2-3). Their low importance was due to the assessment elements not being considered by national and sub-national decision-makers for pricing/reimbursement decisions.

There were twelve assessment elements, which were both important and transferable, excluding Canada (Appendix 3, pages 2-3).

There was one assessment element, which was ranked as important only for the value proposition and not for payers (Appendix 6, page 2). It relates to the topic of Target condition.

Three affiliates highlighted that there was overlap in terms of elements A0007 (What is the target population in this current assessment of the technology?) and A0023 (How many people belong to the target population?). There were also overlaps between A0002 (What is the disease or health condition in the scope of this assessment?), A0017 (What are the difference in the management for different stages of the disease or health condition?) and A0018 (What are the other typical or common alternatives to the current technology?)

Advice: *Consider combining elements A0007 and A0023 together into one assessment element as they are focused on the same topic "target population". Outline in the assessment element the question relating to the target population and specific sub-groups. In addition, ask the question relating to the size of the target population and sub-populations. Consider combining elements A0002, A0017 and A0018 together as they are focused on the disease and current management. Each question still needs to be described as they are specific and important.*

In terms of clarity, there is a need to improve the clarification of two assessment elements.

- A0017 relating to, "What are the differences in management for different stages of the disease or health condition?"

  Advice: *to include standard of care in the clarification.*

- A0012 relating to, "What kind of variations in use are there across countries/regions and settings technology?"

  Advice: *to include alternative technologies in the clarification.*

In terms of missing assessment elements, Element A0020 "What is the marketing authorization status of the technology?" could be expanded.

Advice: *Consider listing different types of market authorization for example conditional approval and adaptive licensing.*

Advice: *Consider re-phrasing the assessment element to include the type of market authorization: "What is the market authorization status and type of market authorization?"*

Domain 2: Description and technical characteristics of technology

Domain 2 includes many important topics for example: the features of the product versus relevant alternatives, the indications and phase of development. The product administration was considered to be important if it affected costs or patient benefits. Ten out of fifteen assessment elements were considered to be important by at least four countries, excluding Canada (Appendix 4, pages 3-4).

There was agreement that the topics, "Investments and tools required to use the technology" and "Training and information needed to use the technology" were unimportant. Although, if there are changes in costs/resource use associated with implementing the new technology, then these topics could become more important.

Four Affiliates out of six (including Canada) scored the following assessment elements as unimportant (Appendix 2, pages 4-6).

- B0008, "What kind of special premises are needed to use the technology and the comparator?"
- B0014, "What kind of training and information should be provided for the patient who uses the technology, or for his family?"

Four Affiliates out of five scored the following assessment elements as unimportant, excluding Canada (Appendix 5 page 2).

- B0012 "What kind of qualification and quality assurance processes are needed for the use or maintenance of the technology?"
- B0015: "What information of the technology should be provided for patients outside the target group and the general public?"

The main reasons for the above assessment elements being scored low are that they are often not considered relevant for drug reimbursement or pricing/reimbursement decision- making. (Appendix 2 provides detailed country reasons) They are occasionally relevant, if they lead to changes in costs or resource use. They are probably more relevant for devices and diagnostics reimbursement.

Four out of five countries ranked seven assessment elements as both important and transferable (Appendix 3, pages 3-4).

There were four assessment elements, which were ranked by individual countries as important only for the value proposition and not for payers (Appendix 6, page 2). They relate to the topics of Investments and tools required to use the technology and Training and information needed to use the technology.

There was no consensus from at least three Affiliates relating to assessment elements, which are unclear, duplicated or missing (Appendix 1, summarizes individual country comments).

Advice: *Move assessment elements B0012-15 relating to the topic "Training and Information needed to use the technology" to Domain 7, as they are highly relevant for Organizational Aspects.*

Domain 3: Safety

Safety was ranked as an important domain and is well addressed within the EMA Regulatory requirements. There was recognition, that in the case of pharmaceuticals, extensive market authorization dossiers provide safety information which could be referred to. This could enable a reduction of information required to populate this domain. This point has already been made by EFPIA (ref: EFPIA response to EUnetHTA JA Public Consultation on the Core Model for Screening Technologies, 29.11.2011 points 14 and 15)

Safety elements are considered by payers and decision makers and are included within manufacturers' value messages. Domain 3 had six out of thirteen elements, which were considered to be important by at least four countries, excluding Canada (Appendix 4, pages 4-5).

Four out of five countries, excluding Canada, ranked six elements as both important and transferable (Appendix 3, page 4).

There were two assessment elements, which were ranked by individual countries as important only for the value proposition and not for payers (Appendix 6, pages 2-3).

The topics relate to: Patient safety and safety risk management.

The assessment elements, which were ranked as unimportant, related to safety risk management, occupational safety and environmental safety. The reasons given for their unimportance was that they were currently not required for national Payer processes, nor included within regional /local Payer decision-making.

There was agreement amongst four out of six Affiliates (including Canada) that two assessment elements were mostly unimportant (Appendix 2,page 7) relating to occupational and environmental safety. However, Roche Global does have a strong interest in environmental safety and produces an environmental safety report for regulatory purposes.

- C0040: What kind of risks for public and environment may occur when using the technology?
- C0020: What kind of occupational harms can occur when using the technology?

There was agreement amongst three out of five Affiliates (excluding Canada) that two assessment elements were unimportant (Appendix 5, page 2).

- C0063: How can one reduce safety risks for professionals?
- C0064: How can one reduce safety risks for the environment?

Advice: *Assessment elements relating to occupational and environmental safety and safety risk management, which were ranked low by at least three Affiliates could be reduced if the pharmaceutical application of the HTA Core model® is used for value assessment of pharmaceuticals.*

There was no consensus from at least three Affiliates relating to assessment elements, which are unclear, duplicated or missing (Appendix 1 summarizes individual country comments)

Domain 4: Clinical Effectiveness

In Domain 4, thirteen out of fifteen assessment elements were considered to be important by at least four countries (excluding Canada) (Appendix 4, pages 5-6).

Four out of five countries (excluding Canada) ranked eight assessment elements as both important and transferable (Appendix 3, 4-5).

The elements relating to patient satisfaction and convenience are important when they have either a positive or negative impact upon compliance and outcomes. Overall mortality is a critical issue and was ranked more highly than disease specific mortality.

There were six assessment elements, which were ranked by individual countries as important only for the value proposition and not for payers (Appendix 6, page 3). The topics relate to: Function, Morbidity, Change- in- management and Patient satisfaction.

There was agreement amongst three out of five Affiliates that two assessment elements were unimportant (Appendix 5, page 2-3).

- D0003: What is the effect of the technology on the mortality due to causes other than the target disease?
- D0017: Was the use of the technology worthwhile?
- D0003 was ranked as unimportant as it is not part of the reimbursement assessment for oncology, when overall survival is considered as the most important measure. This assessment element is already integrated within the overall survival measure.
- D0017 was ranked as unimportant as in Germany; only PRO and HRQoL are considered relevant and in the Netherlands, QoL is required.

Advice: *Consider re-labelling Domain 4, calling it Clinical Evidence. Create topics for clinical efficacy and clinical effectiveness. The rationale for the recommendation is that clinical efficacy addresses RCTs and clinical effectiveness includes real-world evidence.*

Advice: *The assessment elements, which could be included within the topic of clinical efficacy are: D0011, "What is the effect of the technology on patients' body functions?" D0015, "What is the effect of the technology on return to previous living conditions?" D0016, "How does use of the technology affect activities of daily living?" D0012, "What is the effect of the technology on generic health related quality of life?" D0013, "What is the effect of the technology on disease specific quality of life?" D0029, "What are the overall benefits and harms of the technology in health outcomes?" D0001, "What is the expected beneficial effect of the intervention on overall mortality?" D0002, "what is the expected beneficial effect on the disease-specific mortality?" D0003, "What is the effect of the technology on the mortality due to causes other than the target disease?" D0005, "How does the technology affect symptoms and findings (severity, frequency) of the target condition?" D0006, "How does the technology affect the progression (or recurrence) of the target condition?"*

Advice: *The assessment elements, which could be included within the topic of clinical effectiveness are: D0014, "What is the effect of the technology on work ability?" D0010,"How does the technology modify the need for hospitalization?" D0023, "How does the technology modify the need for other technologies and use of resources?" D0017, "Was the use of the technology worthwhile?"*

Advice: *Create a new assessment element, clarification and methodology relating to the topic of Real World Evidence. This new assessment element could be included within the topic of clinical effectiveness.*
The proposed wording for a new assessment element is: "To what extent does real world evidence (RWE) demonstrate the clinical outcomes of the technology?"
The proposed wording for a clarification is: "How does Real World Evidence provide additional evidence to the randomized clinical trials in terms of patient outcomes to either the technology or the standard of care?" The proposed methodology would be: registries, chart reviews, chart audits and prospective data collection.

Advice: *Reference EUnetHTA methodological guidelines* in the HTA Core Model ®relating to Indirect Treatment Comparisons and Mixed Treatment Comparisons, as they are important for Payers who require more detailed analysis. They can be necessary when there is only indirect evidence relating to a specific comparator in a country, which may be different from the comparator in the Phase III registration trial.*
* EUnetHTA Methodological Guidelines on "Comparators and Comparisons: Direct and Indirect Comparisons", February 2013 and also EUnetHTA Methodoligcal Guidelines for Rapid REA, Guideline 7, Direct and Indirect Comparison.*

There was no consensus from at least three Affiliates relating to assessment elements, which are unclear, duplicated or missing (Appendix 1 summarizes individual country comments).

Domain 5: Costs and economic evaluation

Domain 5 was considered important by respondents. At least four out of five countries (excluding Canada) ranked all eight assessment elements in Domain 5 as important
(Appendix 4, pages 6- 7).

Germany ranked this Domain as moderately important and ranked seven elements as unimportant. (Appendix 2, pages 11-13) The reason for this ranking is that Germany currently does not consider cost effectiveness as part of their decision-making.

The Affiliates ranked transferability as moderate to low due to the need for local cost and resource use data.

Four out of five countries ranked one assessment element as both important and transferable (Appendix 3, page 5).

There was no consensus from at least three Affiliates relating to elements, which are unclear, duplicated or missing (Appendix 1 summarizes individual country comments).

Domain 6: Ethical Analysis

Domain 6 had a wide range of ranking in terms of importance. A number of topics were unfamiliar to respondents such as: vulnerable patients, autonomy, human dignity, respect for persons and required clearer examples in the clarification section. There was agreement that in the future, ethical analysis could become increasingly important for developing the value proposition.

Domain 6 was ranked as important by Netherlands and Germany. The Netherlands saw a strong link between Domain 6 and Domain 9 (legal aspects). The Netherlands believe that whilst ethical analysis is not considered today in Payer decision making, it could become increasingly important in the future, particularly the topic relating to "patient autonomy." Germany highlighted ethical considerations relating to data generation e.g. when there is a lack of data due to cross-over in trials, it is not ethical to withhold treatment and ask to generate new trial data. They would like an Ethics Committee to become involved at a European level, relating to answering questions as to when it is ethical to run additional trials or to examine the relationship between ethics and level of evidence.

At least four countries out of five (excluding Canada) ranked five assessment elements out of nineteen as important (Appendix 4, pages 8). Three assessment elements were ranked as both important and transferable (Appendix 3, page 6).

There were four assessment elements, which were ranked by individual countries as important only for the value proposition and not for payers (Appendix 6, pages 3-4). The topics relate to: Beneficence/Non-maleficence, Autonomy, Justice and Equity and Legislation.

There was agreement amongst more than three out of five Affiliates (excluding Canada) that three assessment elements were unimportant (Appendix 5, page 3).

- F0007 Autonomy: Does the implementation or withdrawal of the technology challenge or change professional values, ethics or traditional roles?
- F0009 Respect for persons: Does the implementation or use of the technology affect the user's moral, religious or cultural integrity?
- F0013 Justice and Equity: How are technologies with similar ethical issues treated in the health system?

These assessment elements were ranked as unimportant, as they are currently not considered by Payers in their decision-making. However, in the future, some of the assessment elements could be used to illustrate the value of a health care intervention.

UK, France and Italy agreed that F0101 was unclear:

- F0101 "Does the technology invade the sphere of privacy of the patient or user?

  Advice: EUnetHTA to clarify what they mean by the "sphere of the patient or user."

  Advice: EUnetHTA to consider an assessment element to address ethical arguments relating to more rapid patient access for rare diseases/orphan drugs and diseases with very high unmet medical need, which require urgent treatment.

There was low consensus relating to assessment elements, which are unclear, duplicated or missing (Appendix 1 summarizes individual country comments).

Domain 7: Organizational aspects

Italy, Netherlands, France and Germany ranked the Organizational aspects as important. The topics within this domain included: current work processes, patient flow, training and education, quality assurance, access to care, process related costs and management issues. Some of the cost elements within Organizational aspects are also captured in Domain 5.

The countries ranking this domain highly recognized the importance of considering financial elements within healthcare at a regional and local level. They also considered these topics to be important for the future pricing and reimbursement environment.

At least four out of five countries (excluding Canada) ranked seven elements out of fourteen as important (Appendix 4, pages 8- 9). There was recognition that most of the information required is non-transferable and needs to be developed at a regional and local level. Therefore, there are no elements, which are both transferable and important.

There were two assessment elements, which were ranked by individual countries as important only for the value proposition and not for payers (Appendix 6, page 4). The topics relate to: Health delivery process and Culture.

There was agreement on two unimportant assessment elements for 4 out of 5 countries. (Appendix 5, page 3-4).

- G0012 Health Delivery Process: How is the quality assurance and monitoring system of the new technology organized?
- G0005: How do decentralization or centralization requirements influence the implementation of the technology?

These assessment elements were ranked as unimportant as they do not drive payer decision-making.

Advice: *EUnetHTA to consider moving assessment element G0006 relating to the topic of process related cost elements to Domain 5.*

Advice: *EUnetHTA to consider inviting broader stakeholders to review and populate Domain 7 e.g. Clinicians.*

Domain 8: Social aspects

The Social Aspects were ranked as important by Italy, Netherlands and the UK. The topics included: patient support, resources, impact on patients' lives and broader social impact.

At least four countries out of five ranked four assessment elements out of eleven as important (Appendix 4, pages 9- 10). There were no assessment elements, which were ranked as both important and transferable.

There were four assessment elements, which were ranked by individual countries as important only for the value proposition and not for payers (Appendix 6, pages 4-5). The topics relate to: Individual and Major life areas.

There were four unimportant assessment elements for 4 out of 5 countries (Appendix 5 page 4).

- H0011 Major life areas: What kinds of reactions and consequences can the introduction of technology cause at the overall society level?
- H0100: What kind of changes do patients or citizens expect?
- H0007: Information exchange: What is the knowledge and understanding of the technology in patients and citizens?
- H0013: Information exchange: What are the social obstacles or prospects in the communication about technology?

The reasons for these assessment elements being ranked as unimportant are that they do not drive current HTA decision-making and are not assessed.

Advice: *EUnetHTA to consider renaming Domain 8 to: Patient/Caregiver and Society, as the new name would emphasize the central importance of the Patient.*

Advice: *Consider including all patient elements in Domain 8, recognizing that some assessment elements may need to be in a number of Domains.*
For example H0003,"What kind of support and resources are needed for the patient or citizen as the technology is introduced" could be in Domain 5 and 8.
The following assessment elements in Domain 4 could also be in Domain 8 as they relate to the patient. D00012," What is the effect of the technology on generic health-related quality of life?" D0013 "What is the effect of the technology on disease specific quality of life?" D0014, "What is the effect of the technology on work ability?" and D0017 "Was the use of the technology worthwhile?"

Advice: *Include the impact of the disease and technology on both patients and caregivers in assessment element H0100 by re-phrasing it to, "What kind of changes do patients and caregivers expect?" and in H0004, "What kind of changes may the use of technology generate in the individual's and caregiver's role in the major life-areas." Consider changing the word "citizen" to caregiver in assessment elements H0003, H0006 and H0009.*

Domain 9: Legal Aspects

The legal aspects were ranked as important by Netherlands and Germany, and moderately important by Italy. The topics include: patient consent, privacy, equality in healthcare, ownership and liability, market regulation and intellectual property. There is recognition that the legal aspects form the boundaries under which countries operate and are part of the constitution.

It is not clear how the legal elements fit into current payer decision-making and how to include these topics into a model to demonstrate value of a new technology.

There were two important assessment elements out of fifteen for 4 out of 5 countries (Appendix 4 page 10).

There was one important and transferable assessment element for 4 out of 5 countries (Appendix 3 page 6).

There was one assessment element, which was ranked by individual countries as important only for the value proposition and not for payers (Appendix 6, page 5). UK ranked one assessment elements as important. The topic relates to: Regulation of the market.

There were ten unimportant assessment elements from a value demonstration perspective out of fifteen for 4 out of 5 countries. They related to autonomy of the patient, privacy, ownership, liability and regulations of the market (Appendix 5, pages 4-5).

- I0002: What kind of legal requirements are there for providing appropriate information to the user or patient?
- I0005: What kind of legal requirements are there to obtain informed consent from the user or patient?
- I0034: Who is allowed to give consent for minors and incompetent persons?
- I0009: What do laws/binding rules require from appropriate measures for securing patient data?
- I0019: What should be known about the intellectual property rights and potential licensing fees?
- I0021: What should be known of the legal or binding rules about the width, depth and length of manufacturers guarantee?
- I0024: What kind of regulations are there for acquisition and use of the technology?
- I0025: What legal restrictions are there for marketing the technology to the patients?
- I0026: What should be known about the legal issues in cases of new technologies where the current legislation is not directly applicable?
- I0027: Are there relevant concerns of conflicts of interest concerning the preparation of binding rules and implementation?

The individual country reasons are outlined in Appendix 2 pages 22-24, however the main reason is that these assessment elements do not actively inform current decision-making.

Advice: *EUnetHTA to consider explaining in more detail in the clarification section of the assessment elements which were ranked as unimportant by Roche, how these elements are used either in current or future decision-making at national, regional or local level. Clarification is needed because of the mixture of international health law and value demonstration.*

6 Conclusion

Roche Pharma considers the HTA Core Model ®to be a meaningful, useful and comprehensive framework as it allows a broad view on the implications and consequences of a health technology. It fully addresses the range of domains and elements that inform value assessments of health technologies in the diverse environment across stakeholders in Europe. It is encouraging to see that broader domains, such as social, ethical, organizational and legal aspects are being considered as part of a health technology assessment. We welcome the opportunity to understand and consult on how the HTA Core Model® approach could be further refined and applied in the future.

Roche Pharma considers the HTA Core Model® to be a meaningful tool to help guide HTA evidence generation within the company, to inform internal decisions as well as external decision-making entities. Roche Pharma intends to apply the framework to its own internal processes in the future.

Acknowledgements

The following people within Roche Pharma have contributed to the HTA Core Model Project®. They include:

From Roche UK: Scott Goulden, Jamie Garside and Irwin Tran. **From Roche Germany:** Alexander Neuhof, Joerg Ruof, Jutta Scherer, Anne-Eve Roske, Giovanna Macchia, Olivier Flückiger. **From Roche Netherlands:** Ad van den Heuvel, Ronald Moers, Annet van Abeelen, Eelko de Breejen, Robin de Vries. **From Roche Italy:** Jan Weinreich, Giovanni Giulani, Massimiliano Sana, Matteo Ferrario. **From Roche France:** Claudine Sapede, Caroline Klawatsch, Mathilde Roussel, Catherine Kerting. **From Roche Canada:** David Shum, Michael Duong, Bridget Maturi, Simon Yunger. **From Global Pricing and Market Access:** Marlene Gyldmark, Ricarda Windisch, Fred Jost, Fred Dejonckheere, Joshua Ray, Guido Papa, Wolfgang Berger, Jens Grueger, Ansgar Hebborn, Wolfgang Schleich and external consultant, Susie Ursell.
With comments from Karsten Berndt, Roche Diabetes Care, EDMA Chair of HTA Task Force.

Appendix 1

Disaggregated information relating to elements which are unclear, duplicated or missing

Domain 1: Health Problem and Current Use of Technology

Missing;

- Different types of market authorization (France)

Duplication:

- A007 and A002 and A0018 are quite similar and should be merged into one question. (UK)
- A004 and A005 are quite similar and should be merged. (UK)

Domain 2: Description and Technical characteristics of technology

Duplication

- B0003 and B0003b are duplicated (Italy and Canada)
- B0009 and B0007 (Global)
- Merge B0011,B0010,B0013 and B0012(Global)
- What is the difference between the question "what is the phase of development and implementation of the technology and the comparator(s)?" in the first two parts? (France)
- The questions relating to the training requirements are confusing and are duplicated. (UK)

Domain 3 Safety:

Duplication

- Cluster elements C0020,40,60,61 together. (UK)
- Cluster elements C0062-64 together.(UK)
- Merge C0002 with C0001(Global)
- C0060 and C0061 ask the same question as C0004(Canada)
- C0005 and C0060 ask for similar information. (Germany)
- The patient safety elements C0001-8 could be reduced and clustered together.(Germany)
- The assessment elements C0060-C0064 relating to safety risk management are considered to be important for Italy, as they are considered at local level.

Domain 4: Clinical Effectiveness

Unclear

- D0017: Include patient preferences and PROs within this assessment element (Italy)

Delete:

- D0003 is unclear and is unimportant (France)
- D0029 can be deleted as benefits and harms are analyzed in depth in Domains 3 and 4(Italy)

Move:

- D0023 should be moved to Domain 7(Italy)

Duplication:

- Combine D0015 and D0016 as they both relate to patients QoL(NL)
- Combine D0003 and D0001(NL)
- Combine D0017 and D0012(NL)

Domain 5: Costs and economic evaluation

Duplication:

- Combine assessment elements E0012 and E0010 which relate to characterizing uncertainty and the validity of the model.(UK)
- E0001 and E0002 are similar assessment elements and are duplicated (UK)

Domain 6: Ethical Analysis

Unclear:

A number of elements were unclear and required examples to be given in the clarification section:

- F0014 “basic human rights” are not well defined (France)
- F0101 “Does the technology invade the sphere of privacy of the patient or user.?”(France and UK)
- F0011,F0003 F0007,F0013,F0102, F0103 need to be more clearly described with examples in the clarification section(Italy)
- F0005 and F0010: How often and to what extent does a vulnerable population impact decision-making and which sub-populations are included in this term.(UK)

Duplication:

- This section could be reduced to a smaller number of elements.
- Ethical elements relating to HTA could be captured with sufficient detail in 2 or 3 questions. (UK)
- Cluster F0008, F0009, F0101 into one element and call it “respect for individuals.”
- Cluster E0012 and E0010(Global)
- F0004 is already addressed in Domain 4, D0016, D0012 and D001

Missing:

- Add an element which addresses non-acceptability, from an ethical standpoint, of conducting a second trial if a first trial had a cross-over.(Germany)
- Include within element F0010 a point which addresses the appropriateness of extrapolation, to a larger patient group. (Germany)

Domain 7: Organizational Aspects

Unclear:

- Please clarify G0010,"How is the technology accepted?" The clarification section needs to include some examples relating to which aspects would be culturally relevant.(Global)

Domain 8: Social Aspects

Unclear:

- Please clarify H0004: it is not clear which "major life areas" are being considered.

Domain 9: Legal Aspects

General Comment:

- Most legal issues do not determine the outcome of HTA assessment - the relevance of this domain is questionable.(UK)

Unclear:

- I0027: Regulation of market: Are there relevant concerns of conflicts of interest concerning the preparation of binding rules and their implementation? Please provide an example.

Move:

- Move to Domain 2: "What authorizations and register listings does the technology have? "(I0015) "What are the legal requirements for the safety of the technology and are they fulfilled in practice"(I0017)