



**eunethta**  
EUROPEAN NETWORK FOR HEALTH TECHNOLOGY ASSESSMENT

# **EUnetHTA WP7: Implementation report May 2019**

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## Abbreviations

AAZ: Agency for Quality and Accreditation in Health Care (now Croatian Ministry of Health)  
AEMPS: Agencia Española de Medicamentos y Productos Sanitarios  
AETSA: Andalusian Agency for Health Technology Assessment  
AETS-ISCI: Health Technology Assessment Agency-Institute of Health Carlos III  
AGENAS: The National Agency for Regional Health Services  
JAZMP: Agency for Medicinal Products and Medical Devices of the Republic of Slovenia  
AIFA: Agenzia Italiana del Farmaco  
AOTMiT: Agency for Health Technology Assessment and Tariff System  
AQuAS – Agència de Qualitat i Avaluació Sanitàries de Catalunya  
ASSR-RER: Agenzia Sanitaria e Sociale Regionale-Emilia-Romagna  
AVALIA-T – Galician Agency for Health Technology Assessment  
AWTTC: All Wales Therapeutics and Technology Centre  
CGM: Continuous glucose monitoring  
CRP POCT: C-reactive protein point of care testing  
DEFACTUM: Social & Health Services and Labour Market  
DPA: Directorate Pharmaceutical Affairs (DPA), Malta  
EC: European Commission  
EUnetHTA: European Network for Health Technology Assessment  
EU REA: EUnetHTA Relative Effectiveness Assessment  
FIMEA: Finnish Medicines Agency  
FLACS: Femtosecond laser-assisted cataract surgery  
FOPH: Federal Office of Public Health  
FUCANIS: Canary Foundation for Health Research  
GOeG: Gesundheit Österreich GmbH  
GRADE: Grading of Recommendations Assessment, Development and Evaluation  
HAS: Haute Autorité de Santé  
HIFU: High-intensity focused ultrasound  
HILA: Pharmaceuticals Pricing Board  
HIS: Healthcare Improvement Scotland  
HIQA: Health Improvement and Quality Authority  
HTA: Health Technology Assessment  
HTW: Health Technology Wales  
INFARMED: National Authority of Medicines and Health Products  
JA: Joint Action  
JA2: Joint Action 2  
JA3: Joint Action 3  
KCE: Belgian Health Care Knowledge Centre  
LBI: Ludwig Boltzmann Institute  
MOH SI: Ministry of Health, Slovenia  
NCPE: National Centre for Pharmacoeconomics  
NHS: National Health Service  
NICE: National Institute for Health and Care Excellence  
NIPHNO: Norwegian Institute of Public Health  
NIPT: Non-Invasive Perinatal Testing  
NIPN: National Institute of Pharmacy and Nutrition  
NOMA: Norwegian Medicines Agency

NSPHMPD: National School of Public Health, Management & Professional Development  
OSTEBA – Basque Office for Health Technology Assessment  
PICO: Population, Intervention, Comparator, Outcome  
PICOTS: Population, Intervention, Comparator, Outcome, Timing, Setting  
POP Database: Planning and Ongoing Projects Database  
PT: Pharmaceutical Technologies  
PTJA: Pharmaceutical Technologies Joint Assessment  
OT: Other technologies  
OTCA: Other Technologies Collaborative Assessment  
REA: Relative Effectiveness Assessment  
rTMS: Repetitive Transcranial Magnetic Stimulation  
RWD: Real World Data  
RWE: Real World Evidence  
SBU: Swedish Agency for Health Technology Assessment and Assessment of Social Services  
SHTG: Scottish Health Technologies Group  
SMC: Scottish Medicines Consortium  
SmPC: Summary of Product Characteristics  
SNHTA: Swiss Network for Health Technology Assessment  
SUKL: State Institute for Drug Control  
TAVI: Transcatheter Aortic Valve Implantation  
TLV: Dental and Pharmaceutical Benefits Agency  
UCSC: Università Cattolica del Sacro Cuore  
UNIBA: Comenius University in Bratislava  
UK: United Kingdom  
UTA: University of Tartu, Estonia  
VASPVT: State Health Care Accreditation Agency, Lithuania  
WCD: Wearable Cardioverter Defibrillator  
WP: Work Package  
ZIN: Zorginstituut Nederland

## Foreword

This is the 3<sup>rd</sup> implementation report from WP7. In this report we present data from over 150 examples of use reported by partners from 23 different countries. In addition, this report provides preliminary data from Industry about their use of EUnetHTA documents in national submissions. These data support WP7 to understand more fully the impact of EUnetHTA assessments on HTA processes in different countries and how EUnetHTA assessments are implemented across countries.

At our recent WP7 meeting partners shared their experiences of using EUnetHTA assessments reflecting on some of the benefits they identified:

- **Efficiency;** Using EUnetHTA assessments can reduce the amount of time required to carry out agency assessment work such as data extraction and critical appraisal of clinical studies. These time savings mean that more resource can be allocated to other parts of the assessment (for example non-clinical aspects) or to other health technology assessments.
- **Quality;** EUnetHTA assessments can improve the quality of national reports, by allowing agencies to draw on methodological and clinical expertise from other countries and increase local competence in HTA.
- **Credibility;** EUnetHTA assessments can strengthen the basis for agency findings about the data in Industry submissions and agency recommendations to decision makers.
- **Timeliness;** Involvement in EUnetHTA assessments may enable agencies to negotiate earlier application for reimbursement and as a consequence this can lead to earlier decision making about use of a health technology.

These types of benefits are also reflected in our case study about the use of EUnetHTA tools and guidelines where partners also report benefits from adopting and using tools across areas including efficiency, quality and credibility.

However, it is clear from the WP7 work with partners that there is variability in the benefits reported with some agencies observing more benefits than others. Variability in benefits is also seen in the data received from pharmaceutical industry partners. From the agency perspective, those reporting the most benefits are more likely to be agencies with one or more of the following characteristics: less established HTA systems, human resource scarcity or requirement to produce reports very quickly, flexibility in their processes to adjust to EUnetHTA procedures and outputs, a remit to produce HTA rather than to critique a company submission of evidence and involvement in the authoring team so that content can be aligned to national requirements and appraisal can be carried out in parallel to assessment.

The data and feedback from partners and Industry highlight the complexities of incorporating a joint HTA report into varied healthcare systems with different HTA and decision-making processes. The variation means that there is no single factor reported that prevents or limits use of EUnetHTA assessments. In addition, where single factors predominate e.g. timing of assessments, the ideal timing for agencies varies and there is no single solution to the issue. A transparent discussion across the network including stakeholders about the acceptable balance of the different elements of the HTA process (including timing, inclusiveness, comprehensiveness, content and quality) and the effect of any compromise will be an important step towards developing a future model of HTA cooperation.

The case study shows that agencies value having EUnetHTA tools and guidelines. The results suggest that currently the choices EUnetHTA makes in its methods is not a driving factor that prevents or limits uptake of EUnetHTA assessments. However, once other issues such as quantity of reports available, timing and relevance of scope and report contents have been managed, limitations created by the evidence and methodology applied may become more apparent. In subsequent reports WP7 hope to be able evaluate the effect on uptake of ongoing initiatives in EUnetHTA for topic identification, selection and prioritisation (TISP), the EUnetHTA prioritisation list (EPL), involving partners in scoping and the task group to develop a preferred approach to grading and summarising the evidence.

The case study also highlights 2 key implications for EUnetHTA as it develops the processes for joint assessments and a model of HTA cooperation:

- Development work and changes that EUnetHTA makes to its tools and methods may have a direct effect on agencies' own methods and procedures. Methods and tools development should be participatory recognising that changes to methods and tools can have important direct consequences not only to joint work, but also to national, regional and local HTA processes.
- The nature of the EUnetHTA tools and guidelines means that although not all agencies formally align to EUnetHTA tools and guidelines this doesn't mean that their procedures are not aligned nor that this necessarily affects uptake of EUnetHTA assessments. National guidelines are, as with the EUnetHTA guidelines, often based upon international best standards (e.g. Cochrane) and so are using similar methodologies to EUnetHTA.

Going forward the EUnetHTA implementation strategy aims to clarify the principles, responsibilities and activities to increase implementation. A survey sent out with the draft strategy suggests a number of priority areas for EUnetHTA to take forward including activities targeted outside of the network, activities involving all partners and activities targeted at specific agencies within the network.

## Introduction

This is the third Work Package 7 (WP7) implementation report. The report is divided into the following three sections:

- Section 1: Implementation of JA3 assessments – This section presents the latest implementation data on the uptake of joint and collaborative assessments published under JA3. Comparison is made with data from previous implementation reports and with JA2 where appropriate and feasible. The implementation data is supplemented by findings from follow-up interviews undertaken with selected agencies.
- Section 2: Industry use of EUnetHTA documents - This section presents preliminary data from Industry national affiliates about how EUnetHTA REA reports and submissions files used for EUnetHTA assessments are also used in Industry national submissions for assessment.
- Section 3: Case study on the use of EUnetHTA tools and guidelines – This section presents the findings from a case study exploring how agencies use EUnetHTA tools and guidelines in their own processes and how the methodologies used in EUnetHTA assessments affect how agencies use EUnetHTA assessments.
- Section 4: EUnetHTA implementation strategy – This section outlines the principles, approach to activities and responsibilities to increase use of joint HTA work at a European level and responses from agencies about their ability and readiness to support uptake of EUnetHTA assessments.

WP7 implementation reports are produced bi-annually. Previous WP7 implementation reports are available on the EUnetHTA website:

<https://www.eunetha.eu/national-implementation/implementation-reports>

## Section 1 – Implementation of JA3 Assessment

### *Key findings*

- Since the last implementation report was published in November 2018 no new PT assessments have been published and only 9 new uses of PT assessments have been reported. Consequently, we see little change in the implementation data for PT assessments. In contrast 4 new OT assessments have been published since the last implementation report, and we see more changes in the implementation data and issues reported.
- 159 examples of use of JA3 assessments have been reported to date (as at May 2019). There have been 54 uses of the 3 published PT assessments (rising from 45 in November 2018) and 105 uses of the 11 published OT assessments (rising from 59 in November 2018).
- Of the 159 uses, 96 uses (60%) are in assessment procedures and 63 uses (40%) are dissemination. In the last implementation report 61% of total uses were in assessment procedures and 39% were in dissemination. The majority of uses in dissemination continue to be OT assessments (n = 55).
- Uses of PT assessments under JA3 exceeds reported use under JA2. For the OT assessments published under JA3 the median number of uses in national assessments procedures is 4 (range = 7), compared with a median number of uses of 6.5 for the OT assessments published under JA2 (range = 8). However, with a longer follow-up period we can expect to see the use of OT assessments in JA3 to rise to comparable levels to JA2. The data in this report shows particularly promising results and fast adoption for OTJA08 (glucose monitoring) now at 11 uses in total (9 in national assessments).
- For PT assessments 18 countries have now reported using a JA3 assessment (as of April 2019), rising from 10 in May 2018. For OT assessments 19 countries have now reported use of a JA3 assessment, rising from 9 in May 2018.
- Despite the overall trend in rising use of assessments, some agencies continue to carry out work on the topic EUnetHTA has assessed but do not use the EUnetHTA assessment. As with the last implementation report this continues to be a particular issue for OT assessments. Of the 63 examples of non-use reported, 52 were for OT assessments.
- For OT assessments the timing of the availability of the EUnetHTA REA remains the primary factor preventing use. The extent to which timing is identified as a preventing factor has increased from 79% in the last implementation report to 90% in this implementation report.

## **Methods**

Implementation data are collected by WP7 for all published EUnetHTA joint and collaborative assessments. Agencies provide data through completion of an implementation survey (intranet version for EUnetHTA partners, internet version for non-partners). The implementation survey is sent out after the publication of each assessment. The survey is predominately multiple choice but with some free-text responses (questions ask about whether the assessment was used, if so, how it was used, and factors that prevented or limited use). Respondents are expected to revise / update responses if their status changes.

Implementation data are downloaded, 'cleaned' and analysed by WP7 every 2 to 3 months. Implementation data is included in the WP7 implementation report published bi-annually (see results). Selected survey responses are followed-up by implementation network leads for qualitative interview and findings incorporated into the implementation report. Since the last implementation report (November 2018), 7 follow-up interviews have been undertaken.

The implementation data in this report are as reported up to 21<sup>st</sup> May 2019.

## **Results**

### **Published assessments**

As at the start of April 2019, 14 joint or collaborative assessments had been published under JA3, 11 OT assessments and 3 PT assessments. Implementation data on each of these assessments are presented in this section of the report. A further two OT assessments have now been published (OTCA11 – 3D Printed Implants and OCA14 – Robotic Surgery), but the follow-up period is not long enough to include implementation data on these assessments in this implementation report. Data on these assessments will be included in the next implementation report (November 2019).

The publication date (shown in table 1 below) should be born in mind when considering the data presented. At the time of writing this report the assessments OTCA06, OTCA12 and OTCA16 have been published for less than 6 months. This is unlikely to be adequate time to fully capture implementation data on the use of the assessment. Conversely, all PT assessments have been published for 15 – 18 months and therefore, the majority of use is likely to already been captured.

## Response rates

Table 1 details the response rate by agency for all JA3 assessments<sup>1</sup>. The response rates by agency are high for PT ranging from 83% (PTJA03) to 85% (PTJA01, PTJA02). The response rates for OT are also reasonable ranging from 44% (OTCA06 and OTJA07) to 87% (OTCA03). The response rate for the most recently published assessments, OTCA06, OTCA07, OTCA12 and OTCA16) assessment can be expected to increase over time.

Table 2 below details the response rate by country for JA3 assessments<sup>2</sup>. Response rates by country for PT are very high ranging from 87% (PTJA03) to 93% (PTJA01 and PTJA02). Response rates for OT are also good ranging from 60% (OTCA07) to 92% (OTCA01, OTCA02 and OTCA05).

The data in table 3 also shows that country response rates have improved across all assessments since May 2018 (where comparable data is available).

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<sup>1</sup> Calculated based on 39 agencies currently using HTA to assess non-pharmaceutical technologies and 47 using HTA to assess pharmaceutical technologies. Data on use of HTA was collected by WP7 in their research and analysis of HTA and reimbursement processes in EUnetHTA partner countries and from partners in the implementation network. Please note these figures have been updated to include agencies in Greece, where there is now an established HTA system.

<sup>2</sup> Calculated based on 25 countries currently using HTA to assess non-pharmaceutical technologies and 30 using HTA to assess pharmaceutical technologies. Data on which countries use different types of HTA was collected by WP7 in their research and analysis of HTA and reimbursement processes in EUnetHTA partner countries and from partners in the implementation network. Please note these figures have been updated to include Greece, an HTA process has now been established.

**Table 1: Response rate by agency – JA3 assessments**

Assessment	Publication Date	Responses from expected agencies – May 2019	
		Number (N)	Percentage (%)
OTCA01 (Wearable cardioverter-defibrillator)	Nov-16	33 of 39	85 %
OTCA02 (Antibacterial-coated Sutures)	Apr-17	30 of 39	77 %
OTCA03 (NIPT)	Feb-18	34 of 39	87 %
OTCA04 (MammaPrint)	Jan-18	30 of 39	77%
OTCA05 (Magnetic stimulation)	Apr-17	31 of 39	80 %
OTCA06 (TAVI)	Dec-18	17 of 39	44%
OTCA07 (FLACS)	Oct-18	17 of 39	44%
OTJA08 (Glucose Monitoring)	Jul-18	28 of 39	72%
OTCA09 (HIFU Ablation)	Apr-18	28 of 39	72 %
OTCA12 (CRP POCT)	Jan19	20 of 39	51%
OTCA16 (Bioresorbable Stents)	Jan-19	20 of 39	51%
PTJA01 (Midostaurin)	Nov-17	40 of 47	85 %
PTJA02 (Regorafenib)	Oct-17	40 of 47	85 %
PTJA03 (Alectinib)	Jan-18	39 of 47	83 %

**Table 2: Response rate by country – JA3 assessments**

Assessment	Responses from expected countries - May 2018		Responses from expected countries – May 2019	
	Number	Percentage (%)	Number	Percentage (%)
OTCA01 (Wearable cardioverter-defibrillator)	17 of 24	71%	23 of 25	92%
OTCA02 (Antibacterial-coated Sutures)	16 of 24	66%	23 of 25	92%
OTCA03 (NIPT)	N/A	N/A	22 of 25	88%
OTCA04 (MammaPrint)	N/A	N/A	22 of 25	88%
OTCA05 (Magnetic stimulation)	17 of 24	71%	23 of 25	92%
OTCA06 (TAVI)	N/A	N/A	15 of 25	60%
OTCA07 (FLACS)	N/A	N/A	16 of 25	64%
OTJA08 (Glucose Monitoring)	N/A	N/A	22 of 25	88%
OTCA09 (HIFU Ablation)	N/A	N/A	21 of 25	84%
OTCA12 (CRP POCT)	N/A	N/A	18 of 25	72%
OTCA16 (Bioresorbable Stents)	N/A	N/A	18 of 25	72%
PTJA01 (Midostaurin)	25 of 29	86%	28 of 30	93%
PTJA02 (Regorafenib)	25 of 29	76%	28 of 30	93%
PTJA03 (Alectinib)	N/A	N/A	26 of 30	87%

## Topic relevance

As with the first 2 implementation reports (May and November 2018), the data for May 2019 continues to show that EUnetHTA is generally choosing topics that are within an agency's remit. As shown in table 3 below, agencies indicating that topics were not within remit ranged from 0% (OTJA08) to 17% (OTCA02). For all 3 PT assessments published to date 6 agencies (15%) indicated that the topic was not within their remit.

For a number of agencies, although the topic area chosen by EUnetHTA is within their remit, the agency is not currently planning to assess the technology meaning the EUnetHTA topic may not be aligned with agency priorities. The assessment topics for OT generally show higher levels of topics being within an agency remit but not in the work programme compared to PT.

**Table 3: Work status in the topic area subject to EUnetHTA assessment**

Assessment	Work on this topic is.....			
	Not in our remit	In our remit but not currently planned	Planned but not started	Ongoing or complete
OTCA01 (Wearable cardioverter-defibrillator)	2 (6%)	21 (64%)	1 (3%)	9 (27%)
OTCA02 (Antibacterial-coated Sutures)	5 (17%)	19 (63%)	0 (0%)	6 (20%)
OTCA03 (NIPT)	3 (9%)	16 (47%)	1 (3%)	14 (41%)
OTCA04 (MammaPrint)	2 (13%)	13 (43%)	2 (13%)	13 (43%)
OTCA05 (Magnetic stimulation)	3 (10%)	19 (61%)	0 (0%)	9 (29%)
OTCA06 (TAVI)	1 (6%)	5 (29%)	3 (18%)	8 (47%)
OTCA07 (FLACS)	1 (6%)	12 (71%)	0 (0%)	4 (23%)
OTJA08 (Glucose Monitoring)	0 (0%)	10 (36%)	1 (3%)	17 (61%)
OTCA09 (HIFU)	3 (11%)	13 (46%)	1 (4%)	11 (39%)
OTCA12 (CRP POCT)	2 (10%)	9 (45%)	1 (5%)	8 (40%)
OTCA16 (Stents)	1 (5%)	16 (80%)	0 (5%)	3 (15%)
PTJA01 (Midostaurin)	6 (15%)	12 (30%)	3 (8%)	19 (47%)
PTJA02 (Regorafenib)	6 (15%)	16 (40%)	1 (3%)	17 (42%)
PTJA03 (Alectinib)	6 (15%)	8 (21%)	2 (5%)	23 (59%)

## Overview of use of EUnetHTA assessments

Table 4 and figure 1 overleaf illustrate the use of all published JA3 assessments<sup>3</sup>. As shown 159 examples of use of JA3 EUnetHTA assessments have been reported to date, 54 for the 3 published PT assessments and 105 for the 11 published OT assessments.

For the PT assessments the median number of uses is 15 (range = 5). For the OT assessments the median number of uses is 9 range (range = 6).

Data are collected about two principal types of use:

1. Support for or as an alternative to the agency's existing HTA procedures – 96 examples reported in total (46 for PT and 50 for OT).
2. Dissemination of EUnetHTA assessments to support awareness of the availability of reports and/or evidence informed decision making – 63 examples reported in total (8 for PT and 55 for OT).

There were 80 responses to the survey question on whether the use of assessments was national or regional, 73 (91%) were reported to be national and 7 (9%) were reported to be regional. The EUnetHTA assessment procedure frequently informs an agency procedure used for reimbursement, although this continues to be more likely for PT than OT.

The quotes below from recently completed follow-up interviews provide examples of how EUnetHTA joint assessments for PT have informed reimbursement decisions:

*“The EUnetHTA assessment supports a reimbursement decision and it is relevant for payers, healthcare professionals and for ministry of health. Furthermore, when the minister of health takes the final decision about the reimbursement, we publish a summary of the national assessment with the reference (and link) to the EUnetHTA assessment. Therefore, all relevant stakeholders are informed of the results of the assessment”. (PT)*

*“Effectiveness and safety affected reimbursement decision but since EUnetHTA reports do not conclude with a definite statement on relative effectiveness and safety own conclusions were drawn for the national context” (PT)*

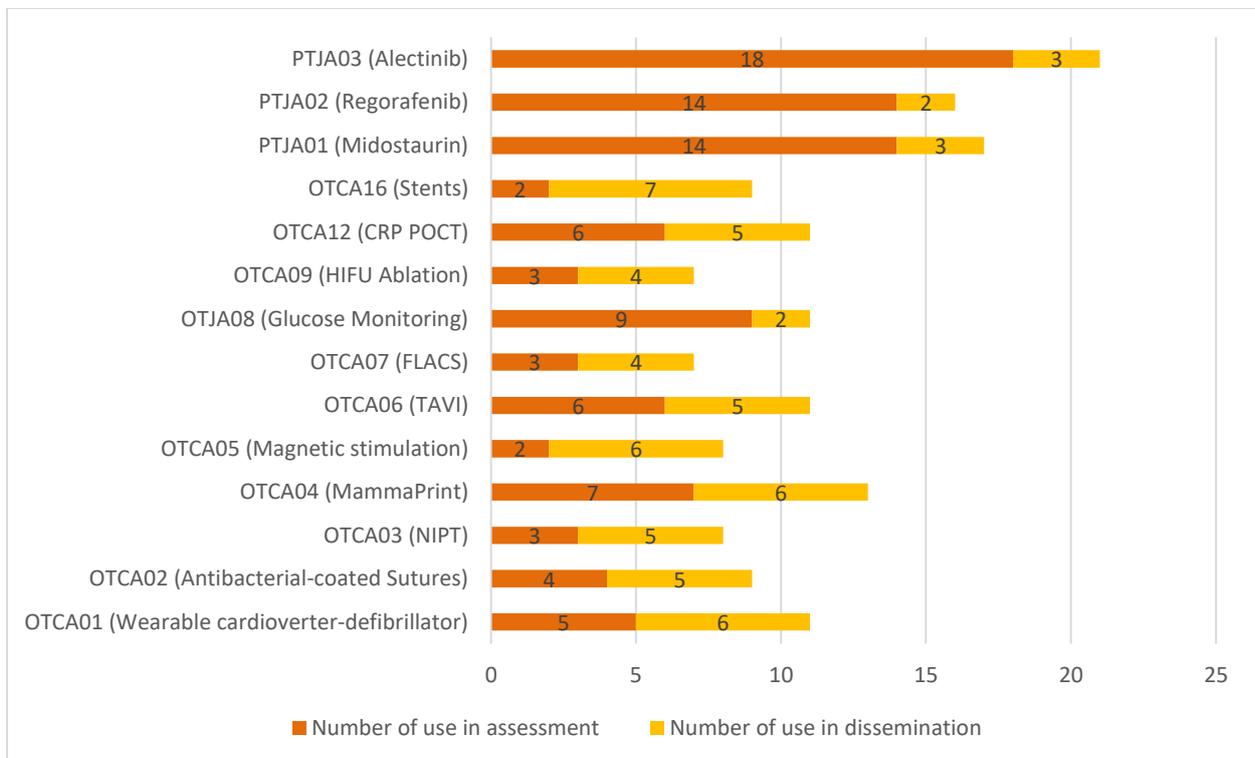
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<sup>3</sup> In the count of use each agency is only counted once for each assessment. Agencies reporting both use and dissemination for an assessment are counted once under use only.

**Table 4: Use of the EUnetHTA JA3 assessments**

	Number of uses in assessment	Number of uses in dissemination	Total number of uses of the EUnetHTA assessment
OTCA01 (Wearable cardioverter-defibrillator)	5 (45%)	6 (55%)	11
OTCA02 (Antibacterial-coated Sutures)	4 (44%)	5 (56%)	9
OTCA03 (NIPT)	3 (38%)	5 (62%)	8
OTCA04 (MammaPrint)	7 (54%)	6 (46%)	13
OTCA05 (Magnetic stimulation)	2 (25%)	6 (75%)	8
OTCA06 (TAVI)	6 (55%)	5 (45%)	11
OTCA07 (FLACS)	3 (43%)	4 (57%)	7
OTJA08 (Glucose Monitoring)	9 (82%)	2 (18%)	11
OTCA09 (HIFU Ablation)	3 (43%)	4 (57%)	7
OTCA12 (CRP POCT)	6 (55%)	5 (45%)	11
OTCA16 (Stents)	2 (29%)	7 (71%)	9
PTJA01 (Midostaurin)	14 (82%)	3 (18%)	17
PTJA02 (Regorafenib)	14 (88%)	2 (12%)	16
PTJA03 (Alectinib)	18 (86%)	3 (14%)	21
<b>Total</b>	<b>96 (60%)</b>	<b>63 (40%)</b>	<b>159</b>

**Figure 1: Use of the EUnetHTA JA3 assessments**



## Countries reporting use of EUnetHTA assessments

The maps below (figure 2 for PT assessments and figure 3 for OT assessments) illustrate the countries reporting use of JA3 assessments. Red shading represents countries that reported use in assessment activities, yellow shading represents use in dissemination activities only.

For PT assessments 18 countries reported using a JA3 assessment. All 18 reported use in assessment activities and 5 of those countries also reported use in dissemination activities. This demonstrates an increase in countries using JA3 assessments from the May 2018 implementation report when 10 countries reported using JA3 assessments (9 in assessment activities and 1 as part of dissemination only).

For OT assessments 19 countries reported using a JA3 assessment. Of those, 16 reported use in assessment activities and 6 of those countries also reported use in dissemination activities. A further 3 countries reported use in dissemination only. The countries reporting use in dissemination only are shaded yellow. Again, this demonstrates an increase in countries using JA3 assessments from the May 2018 implementation report when 9 countries reported using JA3 assessment (6 in assessment activities and 3 as part of dissemination only).

**Figure 2: Countries reporting use of at least one PT assessment**



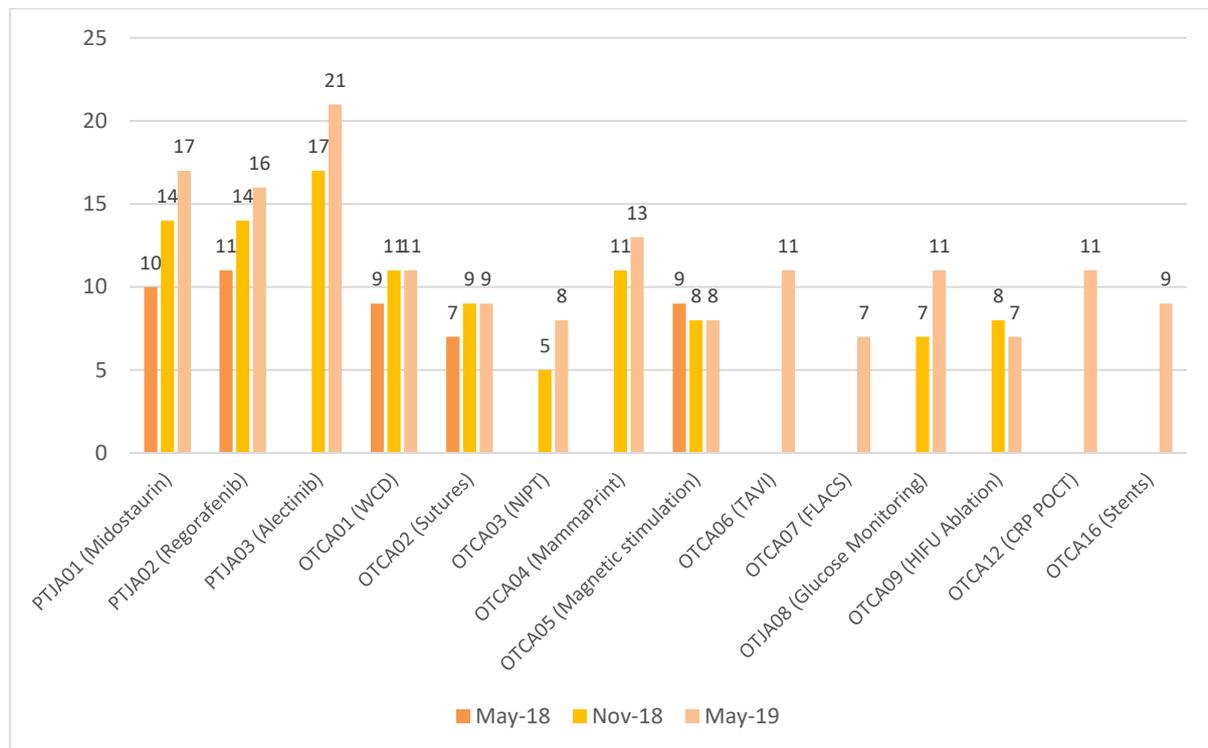
Key: Red = reported use in assessment activities, Yellow = reported use in dissemination activities only



### Comparison of use of JA3 assessments – May 2018 to May 2019

Figure 4 below details the total number of uses of JA3 assessments, comparing reported use for the 3 time points captured within the implementation reports (May 2018, November 2018 and May 2019). The graph shows that the majority of data is reported in the first year following publication of the JA3 assessment. The body of implementation data for PT assessments is largely unchanged from the November report. The publication of further OT assessments means that the volume of data about use has increased substantially.

**Figure 4: Use of JA3 assessments – May 2018 to May 2019**

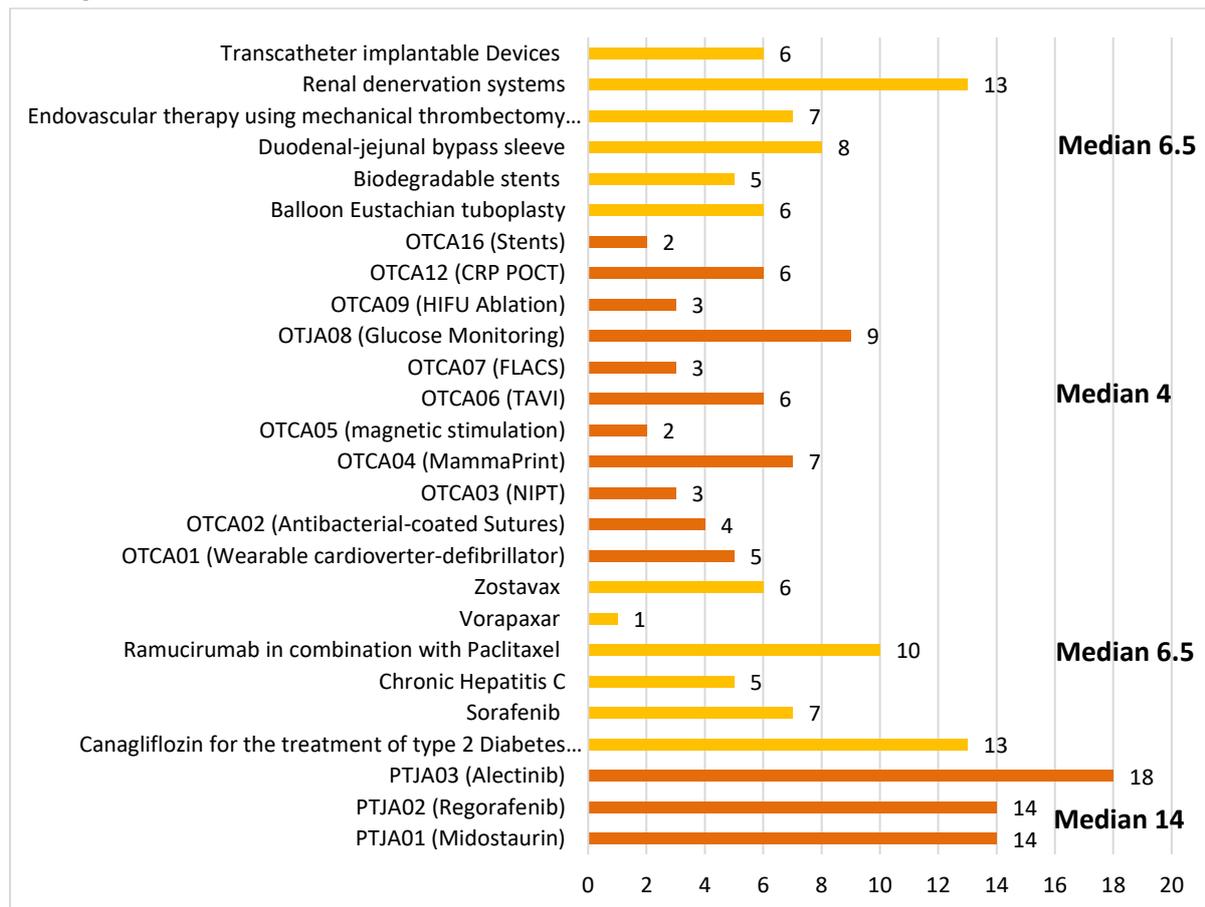


### Comparison of use of JA3 assessments in assessment procedures with JA2

Figure 5 below compares the number of reported uses of JA3 assessments in assessment procedures (dark orange) with JA2 assessments (light orange). Comparison is only made on use in assessment procedures (rather than total use) because JA2 data was predominately focussed on use in assessment procedures (not dissemination).

For the PT assessments published under JA3 the median number of uses is 14 (range = 4), compared with a median number of uses of 6.5 for the PT assessments published under JA2 (range = 12). For the OT assessments published under JA3 the median number of uses is 4 (range = 7), compared with a median number of uses of 6.5 for the OT assessments published under JA2 (range = 8). The data for some OT assessments shows that use is lower in JA3 than in JA2, but with a longer follow-up period the data is likely to show comparable use.

**Figure 5: Use of EUnetHTA assessments in national assessment procedures – Comparison between JA3 and JA2**



Key: JA3 assessments are shaded dark orange, JA2 assessments are light orange.

## Type of use of JA3 assessments

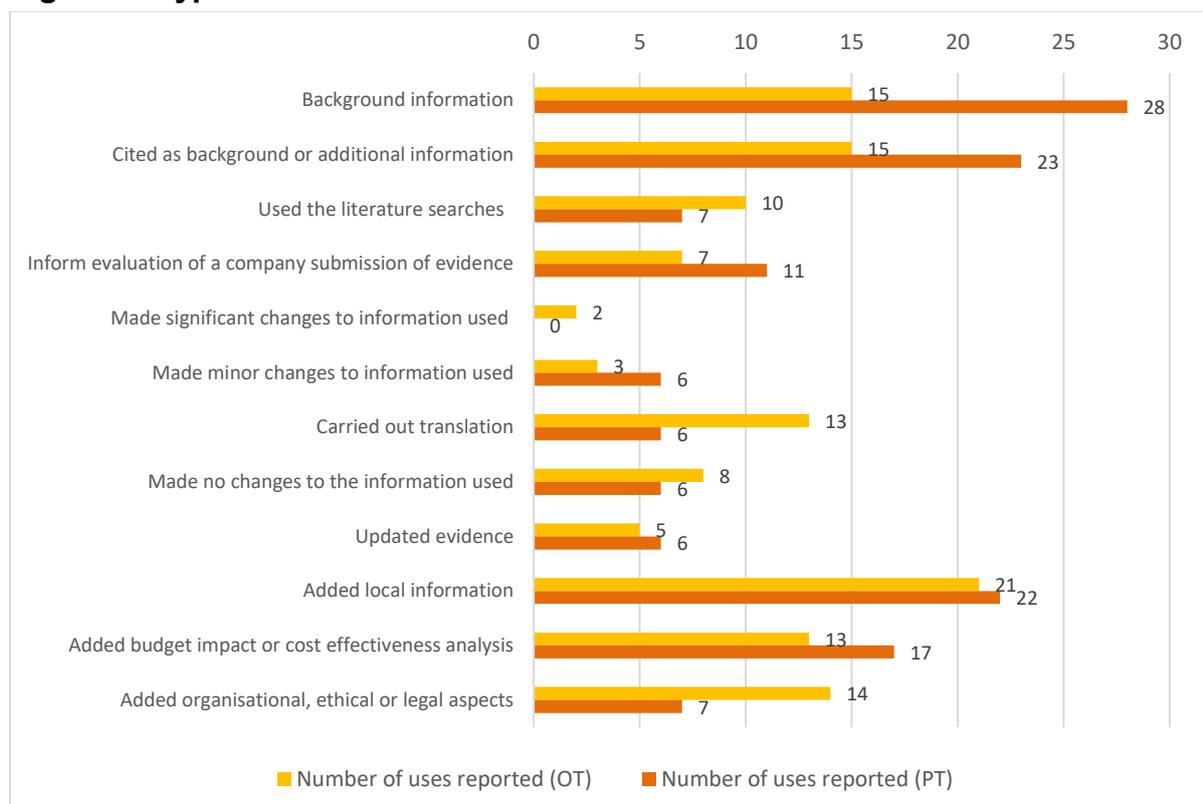
Figure 6 below details the type of use of assessments published under JA3. As with the previous implementation reports, use of PT and OT assessments varies. Most frequently the assessment is read for background information or cited in the agency report as background or additional information. Agencies also frequently reported using the assessments and adding local information, budget impact or cost-effectiveness analysis, and organisational, legal or ethical aspects. PT assessments are also frequently used to inform the evaluation of a company submission.

The data show that more agencies use OT assessments with no changes or carry out translation only compared to PT assessments. This point is illustrated below by a quote below from a recent follow-up interview:

*“OTCAs HIFU & TAVI are planned to be used in English and without making any modifications to the domains included. Only a summary in our national language will be provided in order to introduce the full report”. (OT)*

In general, agencies assessing OT are more frequently able to use EUnetHTA assessments to replace agency work.

**Figure 6: Type of use of JA3 assessments**



## Sections of the assessments used

Where agencies have used EUnetHTA assessments in their assessment procedure, they are asked within the implementation survey to report which sections of the assessments they have used. In 54 cases (66%) agencies reported using all sections of the assessment and in 28 cases (34%) specific sections were used (a number of agencies did not respond to this question). The findings in this implementation report are consistent with the findings from the last implementation report, when in 65% of cases agencies also reported using all sections of the assessment and in 35% reported using specific sections.

Where agencies did use specific sections, the results are again consistent with the last implementation report. The sections reported to be used most frequently were:

- Clinical effectiveness - n = 25 (PT = 17, OT = 8)
- Safety – n = 21 (PT = 13, OT = 8)
- Health condition and use of technology – n = 12 (PT = 8, OT = 4)
- Description of technology – n = 11 (PT = 5, OT = 6)

Some examples of the specific sections used are provided in the quotes below from follow-up interviews undertaken since the last implementation report.

*“Used all parts of the assessment. We have translated and presented the results and had a clinical expert review the results in terms of if the results apply and make sense in a [national] context (especially in terms of organisational, legal and economic perspectives)”. (OT)*

*“We used the following chapters: Health problem and current use of the technology, Description and technical characteristics of the technology, Clinical effectiveness and Safety. These are the chapters that the EUnetHTA assessment has in in common with our national report model”. (PT)*

*“Quality of life section for the clinical assessment, as it was the only available published source of that evidence. Other parts of the assessment were also used to check data sources and references”. (PT)*

## Limiting Factors

Agencies that used a JA3 assessment in their assessment processes were asked whether there were any factors that had affected their ability to use the assessment (see figure 7 overleaf).

For PT assessments 75 examples limiting use of PT assessments were reported. The most frequently identified limiting factors are the same as in the last implementation report, they are:

- the requirement to prepare reports in their national language (n = 18)
- the requirement to use a specified report structure (n = 14)
- the timing of the availability of the EUnetHTA assessment (n = 12)

This is not surprising given that no PT assessments have been published since the last implementation report. However, there has been an increase in the number of agencies identifying the need for different content information as a factor limiting their use of PT assessments. Of the 9 additional uses reported since the last implementation report, 3 identified this as a limiting factor, increasing the total number of times that this has been identified as a limiting factor in the use of PT assessments to 10 (rising from 7 in November 2018).

Users of OT assessments were much less likely to identify factors limiting use than users of PT assessments (n = 26). For OT assessments the most commonly identified limiting factor was the requirement to prepare reports in their national language (n = 7, rising from n = 4 in the last implementation report). Compared with the last implementation report the following are also emerging as factors limiting use of OT assessments:

- Scope of the national assessment was different (n = 6)
- Timing of availability of EU REA (n = 3)
- Evidence included in the REA was too restrictive (n = 3)

Figure 8 (PT) and figure 9 (OT) overleaf aggregate the limiting factors reported into categories: awareness; timing; evidence and methodology; reliability; relevance; transferability; language; reporting and accountability. In this analysis the data are aggregated where an agency identified 2 or more factors as limiting use within the same category (e.g. timing or relevance) for the same assessment this was only counted once. Consequently, the numbers in figures 8 and 9 do not exactly match with those in figure 7.

Again, the grouped limiting factors identified by users of PT assessments show no significant change since the last implementation report. The most commonly identified limiting factors are: language (26%); reporting (20%); timing (20%) and relevance (18%).

The extent to which timing is a limiting factor varies by country, with the timing of EUnetHTA assessments less of an issue for countries where pharmaceuticals typically go later to market. This is illustrated by the quotes below from follow-up interviews:

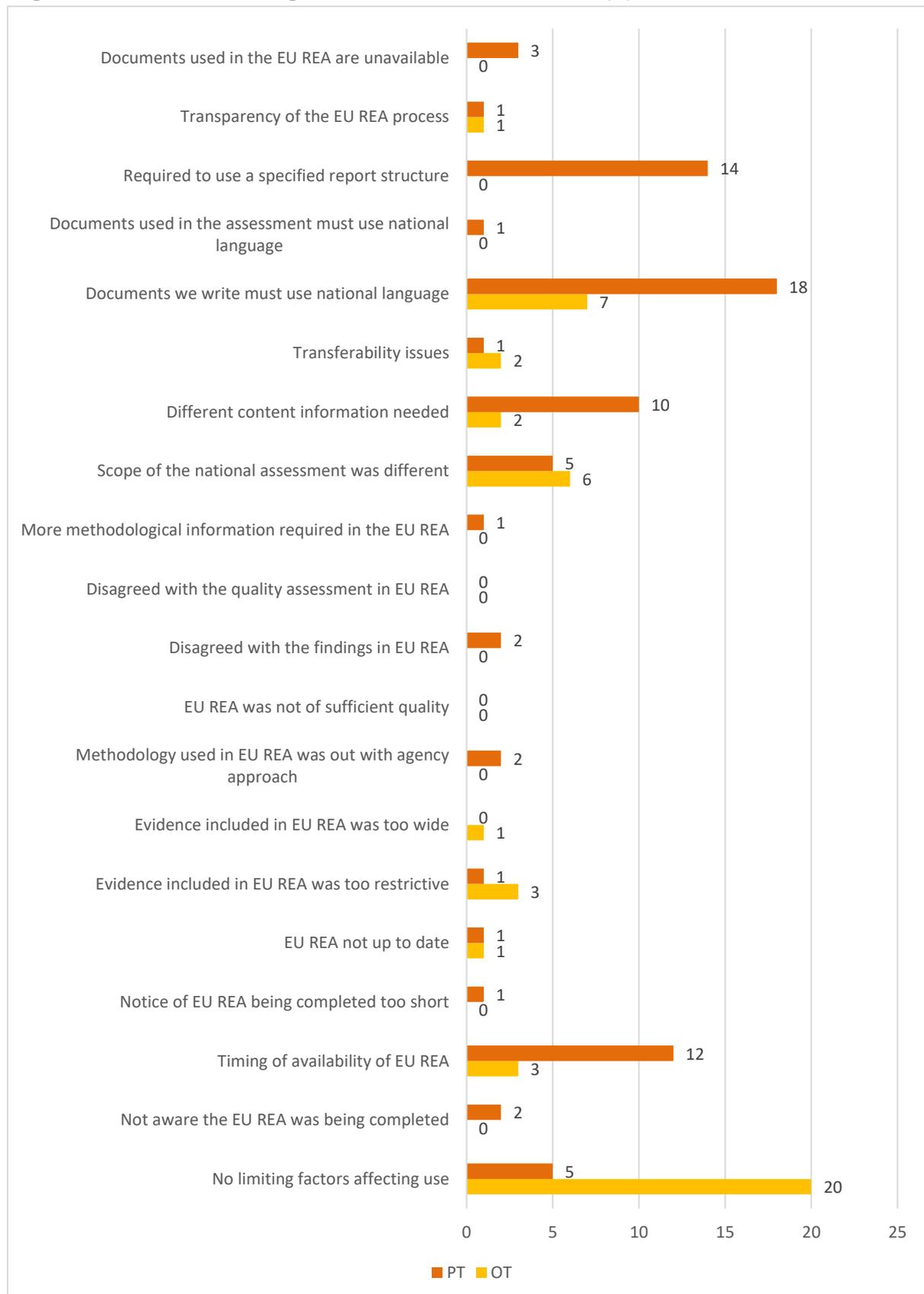
*“In this case, the EUnetHTA assessment was published in February 2018, two months after the national submission of dossier... so we had to delay our assessment in order to use the EUnetHTA assessment”.* (PT)

*“Timing of the EUnetHTA assessments is adequate due to the usually delayed reimbursement application (from pharmaceutical companies) for the [national] market”.* (PT)

*“Very often pharmaceutical companies go late to the [national] market so the timing is okay.* (PT)

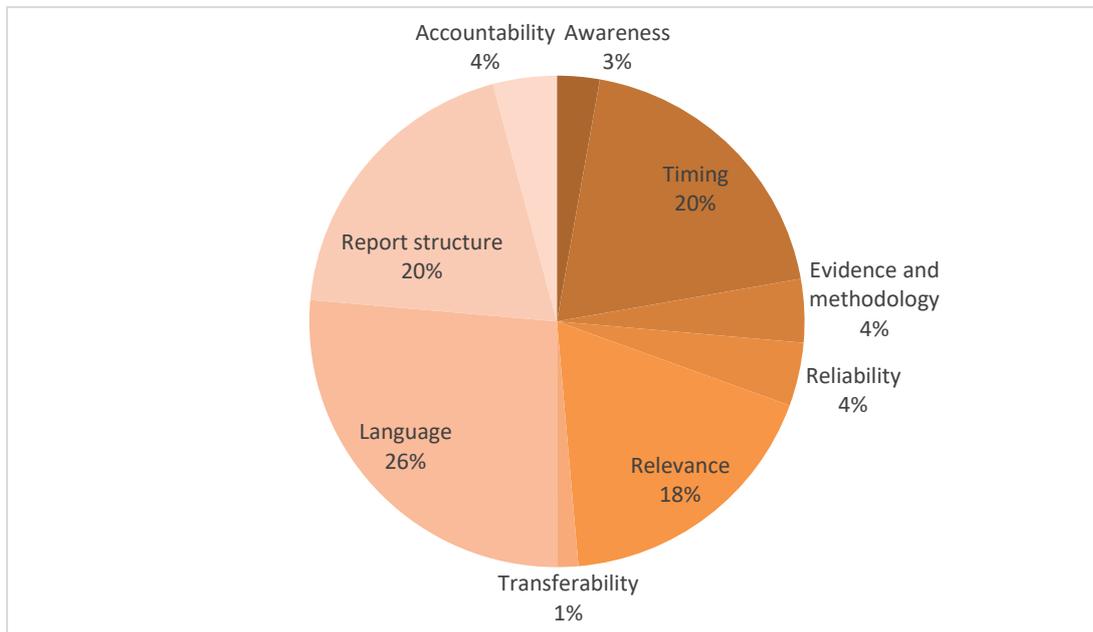
For OT the factors limiting the use of assessments show more variation in this implementation report, when compared with the last implementation report. The key factors identified as limiting use of OT assessments in this report are: language (32%), relevance (23%), timing (18%), and evidence and methodology (14%).

**Figure 7: Factors limiting use of JA3 Assessments (n)**

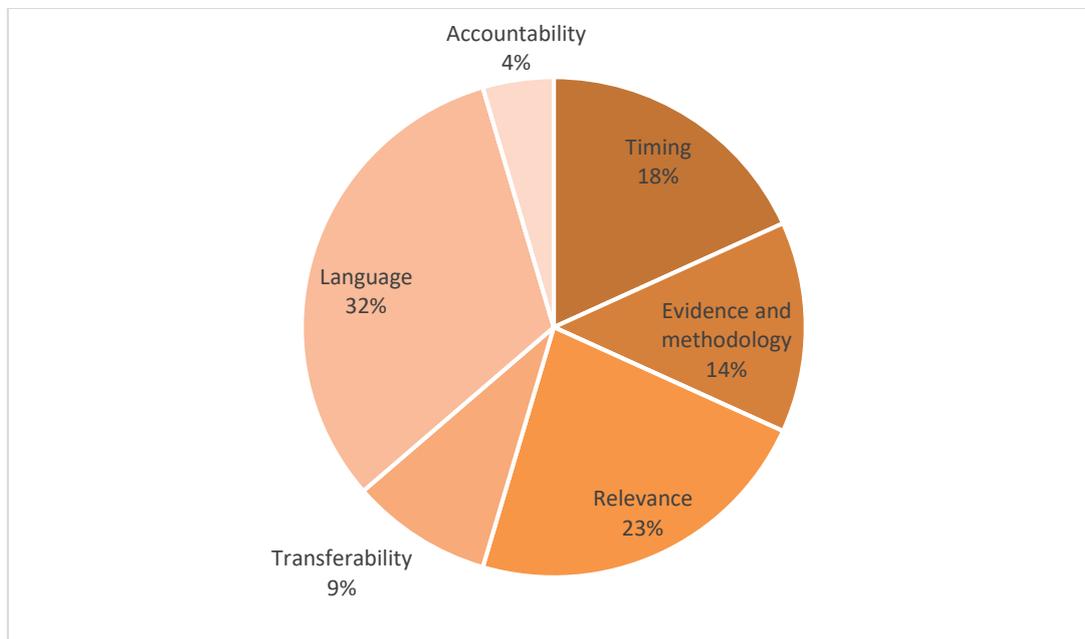


## Limiting factors (aggregated into categories)

**Figure 8: Factors that limited use of PT assessments (%)**



**Figure 9: Factors that limited use of OT assessments (%)**



### **Non-use of assessments**

As shown in table 5 below for the 11 OT assessments published to date under JA3 there have been 52 cases of an agency working on the topic but **not** using the EUnetHTA assessment, ranging from 1 example for OTCA07 (FLACS) and OTCA16 (Stents) to 11 examples for OTCA03 (NIPT).

The OT assessments with the lowest numbers of reported non-uses are generally the most recently published assessments and the assessments with the lowest response rate to the implementation survey (OTCA06 – FLACS, OTCA07 – TAVI, OTCA12 – CRP POCT, OTCA16 – Stents). The number of reported non-uses for these assessments may increase over-time with a longer follow-up period. As with the last implementation report OTCA03 (NIPT) remains the assessment with the highest number of non-uses with 11 (rising from 10 in November 2018).

For the 3 PT assessments published under JA3 there have been 11 cases of an agency working on a topic but not using the EUnetHTA assessment, ranging from 2 examples for PTJA02 (Regorafenib) to 5 examples for PTJA03 (Alectinib). This is a decrease from the last implementation report when there were 15 cases of an agency working on a topic but not using the EUnetHTA assessment. Agencies that previously reported that they had worked on the topic but not used the EUnetHTA assessment, reported that they have now used the assessment.

**Table 5: Non-use of assessments by agencies working on topic area**

	Worked on the topic but did not use the EUnetHTA assessment
OTCA01 (Wearable cardioverter-defibrillator)	4
OTCA02 (Antibacterial-coated Sutures)	2
OTCA03 (NIPT)	11
OTCA04 (MammaPrint)	6
OTCA05 (Magnetic stimulation)	7
OTCA06 (TAVI)	2
OTCA07 (FLACS)	1
OTJA08 (Glucose Monitoring)	8
OTCA09 (HIFU Ablation)	8
OTCA12 (CRP POCT)	2
OTCA16 (Stents)	1
<b>Total</b>	<b>52</b>
PTJA01 (Midostaurin)	4
PTJA02 (Regorafenib)	2
PTJA03 (Alectinib)	5
<b>Total</b>	<b>11</b>

**Preventing factors**

Agencies who didn't use the EUnetHTA assessment are asked about the factors that prevented them from using the assessment. Users of OT assessments identified 56 examples of factors preventing use of OT assessments. As shown in figure 10 below for OT assessments the timing of the availability of the EUnetHTA REA (n = 41) is, as with previous implementation reports, still clearly identified as the main factor preventing use of OT assessments.

Users of PT assessments are less likely to identify preventing factors (n = 26). For PT assessments the timing of the availability of the EUnetHTA REA was also identified as the main factor preventing use of PT assessments (n = 5).

**Figure 10: Factors that prevented use of assessments**

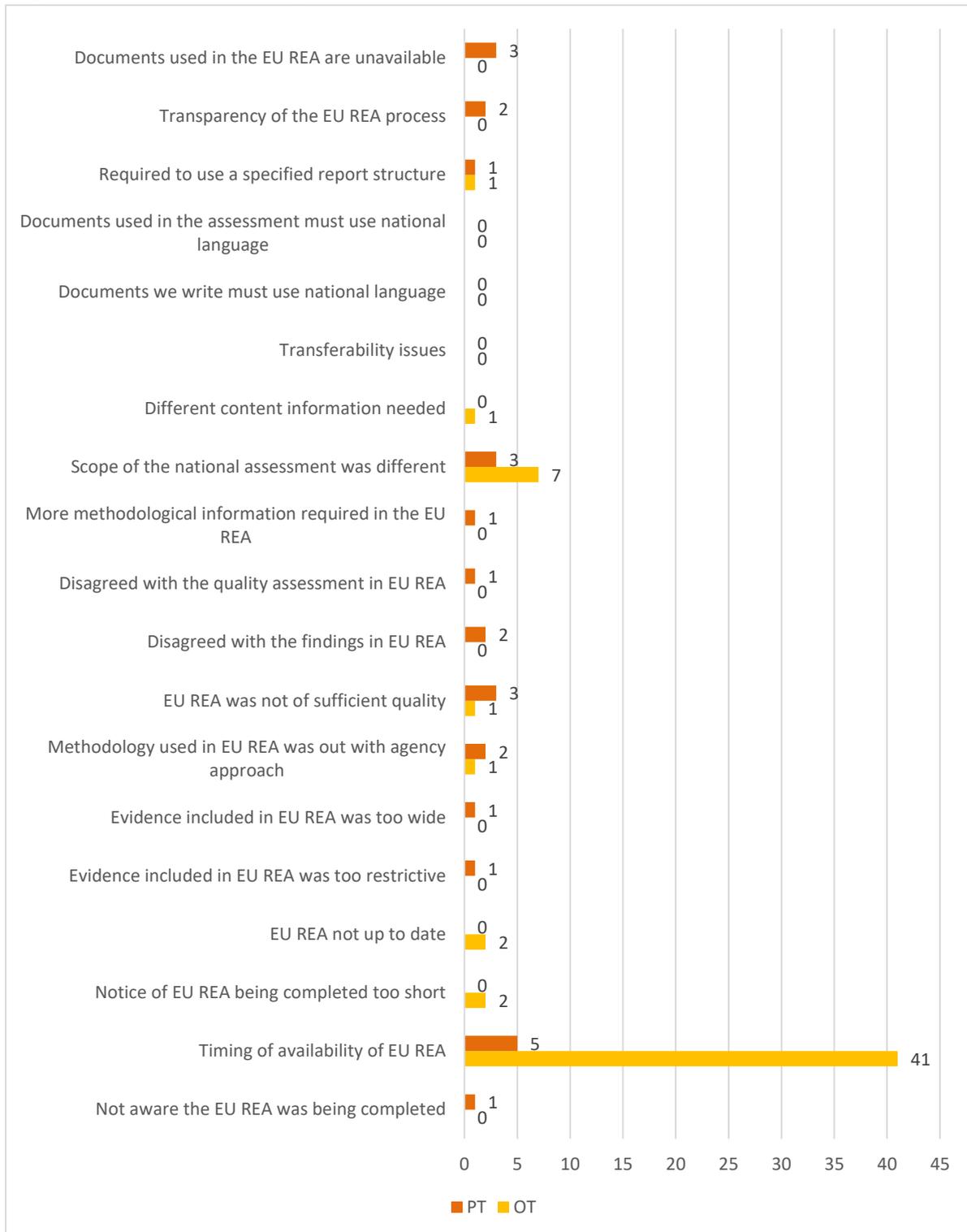


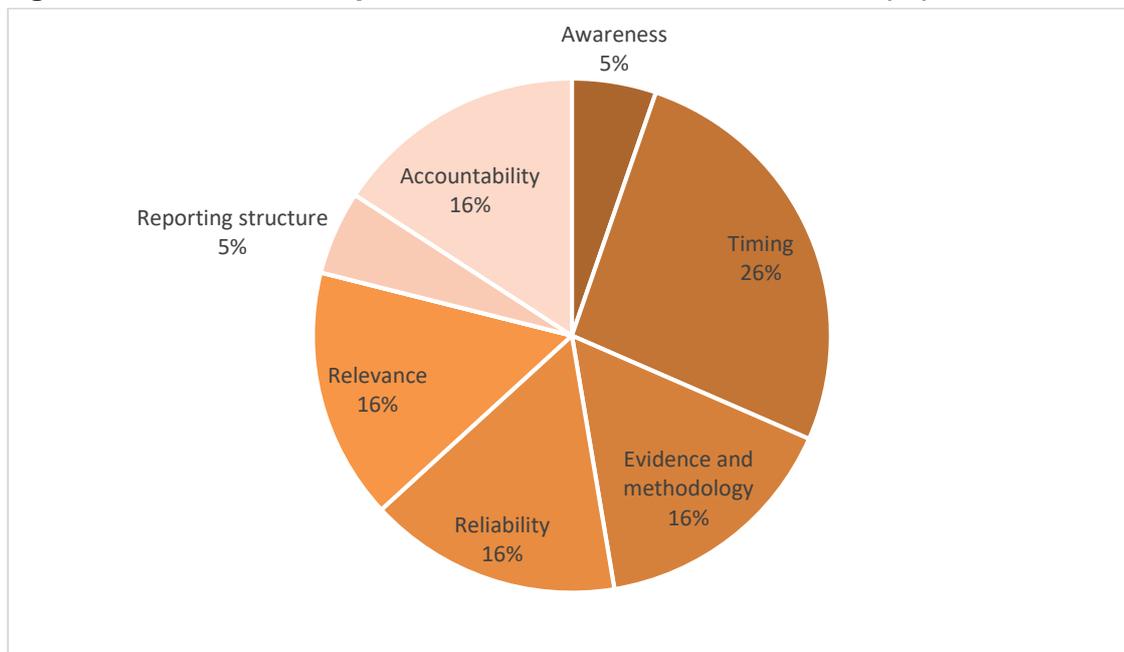
Figure 11 (PT) and figure 12 (OT) below aggregate preventing factors reported into categories and present them in percentage (%) terms. In this analysis where an agency identified 2 or more factors as limiting use within the same category (e.g. timing or relevance) for the same assessment this was only counted once. Consequently, the numbers in figures 8 and 9 do not exactly match with those in figure 7.

For PT assessments the factors identified as preventing use are varied, with the most commonly identified factor being, as with the last implementation report, timing (26%). This is followed by accountability, evidence and methodology, reliability and relevance, all with 16%.

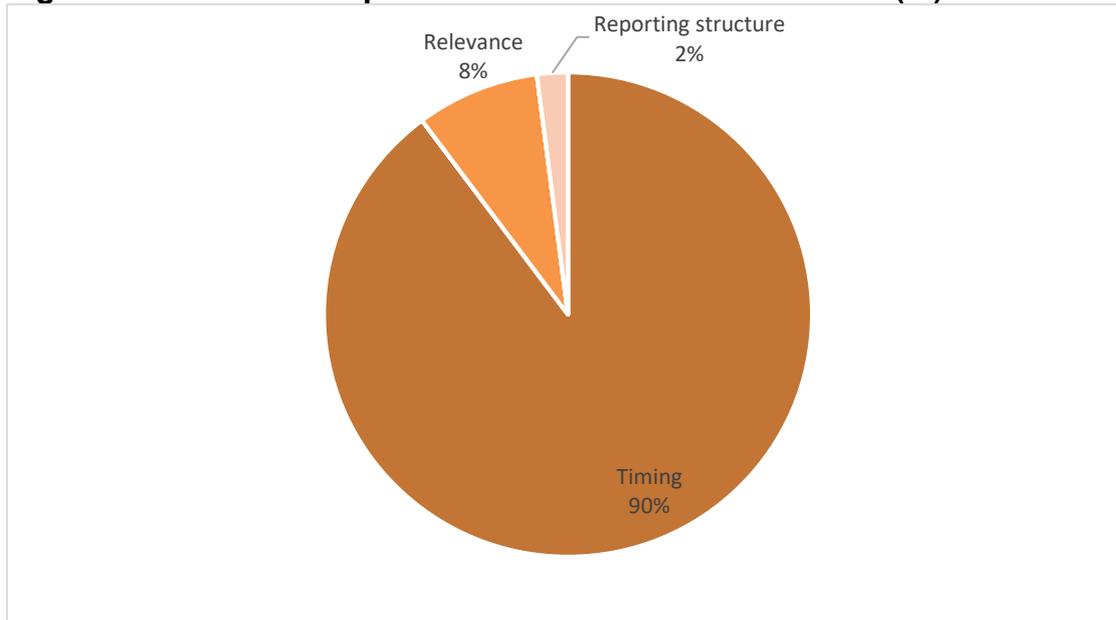
For OT assessments the main preventing factor, again as with the last implementation report, is timing (90%). Some of the challenges faced by agencies in respect of the timing are illustrated by the quote below from recently completed follow-up interviews:

*“OTCAs suffered delays and did not accomplish the expected timelines for publication. No alerts or messages explaining these delays were received so we were not aware of the report’s status. More info/alerts on these delays and new dates for publications would be very welcome. As an example, the TAVI report was published after several months of delay. Our regional health service had already asked for this report several times, and we were not able to produce a satisfactory answer regarding the new estimated dates” (OT)*

**Figure 11: Factors that prevented use of PT assessments (%)**



**Figure 12: Factors that prevented use of OT assessments (%)**



## Section 2 – Industry use of EUnetHTA Documents

### *Key findings*

- 10 of the 14 respondents (72%) reported that either the EUnetHTA submission or EUnetHTA REA report had been used by the company in their national submissions.
- In 9 instances the EUnetHTA REA report was used and in 6 instances the submission file submitted to EUnetHTA was used.
- Companies mainly incorporated EUnetHTA documents into their national submission, rather than used them as an alternative to or in addition to their national submission.
- Most companies reported making no changes to the EUnetHTA documents in the process of using them and changes that were made were often reported to be translation only.
- The main factors reported as limiting or preventing the use of EUnetHTA documents were reporting structure, language, timing and relevance.
- Use of EUnetHTA documents had a varied impact on the resources and costs of national submissions, ranging from saving time and resources, through to no impact and adding to workloads.
- Suggestions on how EUnetHTA could improve the ability of industry to use EUnetHTA documents focussed on improved timing of assessments, translation of assessments and harmonised submissions and reports.

### *Methods*

At the EUnetHTA / EFPIA technical meeting held in December 2018, companies identified that they have information on implementation of EUnetHTA pharmaceutical assessments and that their information and perspectives could be collected and presented alongside the implementation data collected from EUnetHTA partners.

Following further discussion, it was agreed that implementation data would be collected from industry on the use of EUnetHTA pharmaceutical assessments. Initially the scope of the work is limited to the 3 PT assessments published to date under JA3. However, it is intended that the data collection will remain ongoing and further data from industry on the use of PT assessments will be collected and presented in future WP7 implementation reports. WP7 is also currently considering options to collect data from industry on the use of OT assessments.

The data collection for PT assessments is being undertaken using the methods and stages described below:

### **Online survey**

- An online survey was created by WP7 to collect implementation data from industry on the use of the EUnetHTA submission file and the EUnetHTA REA assessment reports. The survey was adapted from the WP7 implementation survey used with HTA agencies and includes a mixture of multiple choice and free text responses. A draft version of the survey was reviewed by industry partners before finalising.
- The finalised survey was sent to the company global representative for the three pharmaceutical assessments published to date under JA3: PTJA01 Midostaurin – Novartis; PTJA02 - Regorafenib – Bayer; PTJA03 Alectinib – Roche. Upon receipt of the survey the company global representatives were requested to send the survey onto national affiliates in each EU member state for them to complete.
- A total of 14 survey responses has been received to date. The data has been downloaded and analysed. Key findings and themes arising from the data received so far are summarised in this section of the implementation report.

### **Interviews**

- WP7 is also undertaking follow up interviews with national affiliates from selected countries. Ideally this will include the author and co-author countries for each of the PT assessments.
- A draft interview pro-forma was drafted and reviewed by industry partners before finalising.
- The interviews are being undertaken virtually using ZOOM web conferencing. The interviews take approximately 1 hour and are being audio recorded.
- The interviews will be written up as narrative summaries and sent to each interviewee for comments and revisions, before finalising.
- 1 interview has been undertaken to date. Further interviews will be undertaken in the coming months, providing that enough survey responses are received, and industry colleagues are willing to be interviewed. The findings will then be analysed thematically for inclusion in the next implementation report.

## Results

As previously documented 14 survey responses have been received in total to date. The breakdown of responses by assessment and country is detailed in table 6 below:

**Table 6: Breakdown of responses**

Assessment	Number of responses	Countries responding
PTJA01 - Midostaurin (Novartis)	7 responses (covering 10 countries)	Spain, Nordic countries (Sweden, Denmark, Finland, Norway), Italy, Greece, Bulgaria, Poland Belgium
PTJA02 - Regorafenib (Bayer)	5	Italy, Norway, Portugal, Spain, France,
PTJA03 - Alectinib (Roche)	2	Austria, Sweden

### Use of EUnetHTA documents in national assessment procedures

Respondents to the survey were asked if EUnetHTA documents, specifically the REA report (that is the assessment report produced by EUnetHTA) and / or submission file (that is the submission of evidence prepared by companies and submitted to EUnetHTA for its assessment), were used in their national submissions. Of the 14 respondents 10 (72%) reported they had been used by the company, 3 (21%) reported use by the agency and 1 (7%) reported no use of EUnetHTA documents.

In 6 instances the company used the EUnetHTA submission file and in 9 instances they used the EUnetHTA assessment report. In most instances (table 7) companies incorporated the EUnetHTA documents into the national REA submission, rather than used them as an alternative to or as an addition to the national REA submission.

**Table 7: How companies used EUnetHTA documents**

	Submission File	REA Report	Total
Incorporated into national REA submission	6	5	11
Alternative to national REA submission	0	0	0
In addition to national REA submission	0	1	1
Other	1	3	4
<b>Total</b>	<b>7</b>	<b>9</b>	<b>16</b>

Respondents were asked which parts of the EUnetHTA documents they had used, 8 respondents reported they had used all sections. Where specific sections were used, the most commonly reported sections were clinical effectiveness (n = 7), safety (n = 6) and health condition and use of technology (n = 5).

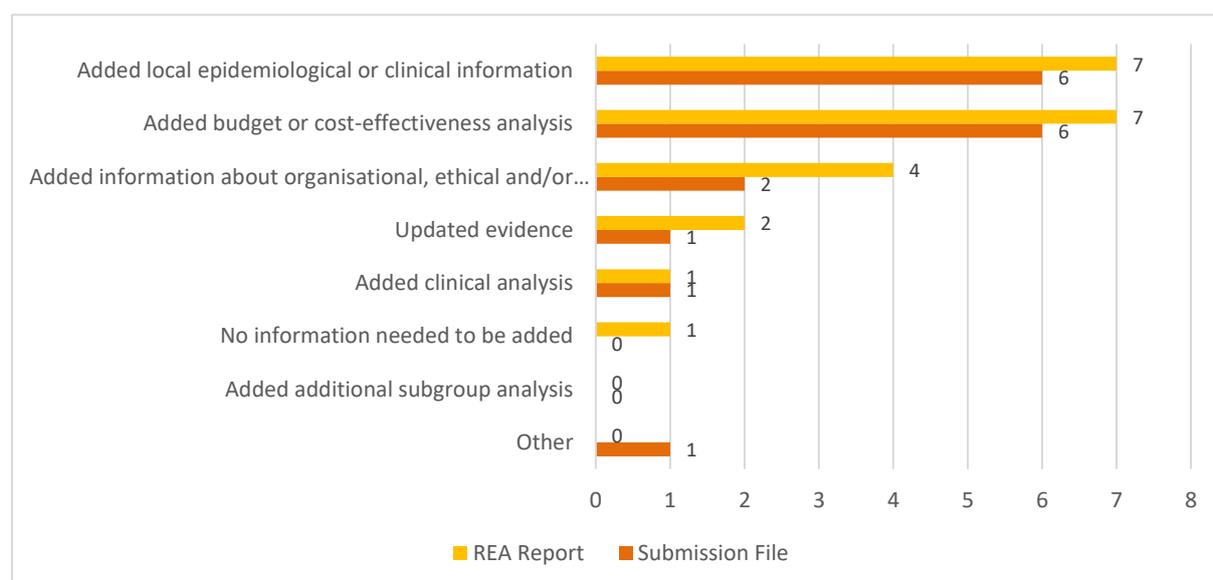
Respondents were asked to report any changes they had made to EUnetHTA documents. As can be seen in table 8 below very few changes were reported to have been made, and where changes were made this was most frequently translation.

**Table 8: Changes made to the EUnetHTA documents**

	Submission File	REA Report	Total
Carried out translation only	3	2	5
Made no changes to the information used	4	6	10
Significant changes to information used	0	1	1
Minor changes to information used	0	0	0
<b>Total</b>	<b>7</b>	<b>9</b>	<b>16</b>

In the survey, respondents were asked to detail what (if any) information they added to the EUnetHTA documents in the process of using them. As can be seen in figure 13 below companies most frequently reported that they had added local epidemiological or clinical information or budget or cost-effectiveness analysis.

**Figure 13: Information added to the EUnetHTA documents**



### Limiting and preventing factors

Respondents to the survey were asked to identify what (if any) factors had limited or prevented their ability to use EUnetHTA documents. The most frequently identified limiting and preventing factors were:

- Reporting structure: Company submission must use a specified structure (n = 5)
- Language: Company submission must be in the national language (n = 5)
- Timing: The EUnetHTA documents were not available (n = 4)
- Relevance: Different content information was needed (n = 4)

## **Impact of using EUnetHTA documents**

Respondents were asked to report what impact the use of EUnetHTA documents had on: person days and costs; the timing of national submissions, assessments and reimbursement decisions; and national decision-making processes. The results are presented in the next pages, together with illustrative quotes.

### **Person days**

The impact on person days of using EUnetHTA documents was extremely varied. Ranging from saving time, through to no impact and adding to workloads.

*“Impact was huge demonstrating comprehensiveness of centralized EUnetHTA procedure”.*

*“A couple of days (saved). Had the report been published before we more or less had completed the submission file, more time could have been saved. For example, at time of EPAR”.*

*“Added workload due to the fact that we needed to co-work on the EUnetHTA preparation, submission and review”.*

### **Costs**

Several respondents reported that there was no impact on costs. Where costs were saved this came from reduced person days. Again, respondents identified that in some instances use of the EUnetHTA documents resulted in additional work.

*“We would have not done such an analysis, so the saving comes from the reduced time of the person who worked to the document”.*

*“Small impact on the costs”.*

*“No cost impact”.*

*“No additional cost and we had additional work”.*

### **Impact on the timing of national submission**

A small number of respondents identified that use of EUnetHTA documents sped up (slightly) the time of submission. Most respondents identified that there was no impact on timing of submission, as illustrated by selected quotes below.

*“Speed up the submission process”*

*“National Submission was independent form EUnetHTA assessment”*

*“No impact because we did not use it for our national submission.”*

*“No impact in terms of submission timelines. We accomplished our company submission dates”.*

*“No impact. In [Country] reimbursement submission and evaluation occurred before EUnetHTA documents were available”*

### **Impact on the timing of assessment**

The impact of EUnetHTA documents on the timing of the national assessment was varied. As illustrated by the quotes below some felt it sped up the assessment, some felt it had no impact and some felt it resulted in delays.

*“Speeded up by over 2 months”.*

*“Accelerated the decision as our Local Committee valued outcome of REA assessment”.*

*“We expect that the independent evaluation might have shortened the evaluation process. However, we do not have evidence to confirm this”*

*“[Agency] referenced and accepted assessments made by EUnetHTA in the report, but we did not see a shortening of case handling time”.*

*“No real impact on the speed of the assessment”.*

*“It delayed the process and negotiations with the Ministry of Health because the Agency used it as a reference in their report”.*

### **Impact on timing of reimbursement decision**

Responses on the impact of EUnetHTA documents on timing of the reimbursement decision was also varied, as illustrated by the quotes below.

*“Small impact on the decision”.*

*“In general, very little. Reimbursement timing is more price driven”.*

*“The overall length of the reimbursement assessment was not shorter due to prolonged timelines for the negotiation phase in terms of setting a sales cap”.*

*“Speeded up the final decision on reimbursement”.*

### **Impact on the overall assessment and decision-making process**

Survey respondents were also asked about the impact of EUnetHTA documents on overall assessment and decision-making processes. Again, responses were varied. Some found the impact hard to define, some identified a small impact and others a more significant impact, as illustrated by the quotes.

*“Small impact on the decision”*

*“Higher quality, more fair REA assessment, cleaner from ‘price pressure’ in the clinical assessments - so more objective and better quality”*

*“EUnetHTA documents could possibly make the process smoother because it's providing an additional source of reliable information/ data summary and interpretation”.*

*“Easier as payors had to take a decision for a subject that was evaluated by EU bodies. At the time of decision there were limited capabilities for such evaluations”.*

*“For sure is better to have it as an independent assessment tool but it has a limited impact since it does not avoid/neither speed our national evaluation”.*

### **How could EUnetHTA improve the ability of Industry to use EUnetHTA documents**

In the survey respondents were asked what EUnetHTA could do to improve the ability of industry to use EUnetHTA documents. A selection of quotes from free text responses to this question are provide below. Key suggestions were the earlier publication of the EUnetHTA assessment, translation of EUnetHTA documents and harmonisation of cross-national submission requirements and templates.

*“Earlier EUnetHTA submission & assessment”.*

*“It would be good if the assessment was published earlier to make sure it can be implemented in the submissions. Submissions are usually at EMA approval date or even earlier”.*

*“Fast report after EMA approval”.*

*“The EUnetHTA report should be available some months before our local submission in order to have enough time to prepare and to be considered for national submission”.*

*“Translation into each EU member language could significantly improve the usage of REA Assessments”.*

*“Harmonize cross-national submission requirements/templates”.*

*“Pragmatic submission and report in a structured format”.*

## Section 3 – Case study on use of EUnetHTA tools and methodology guidelines

### Key findings

#### Use of EUnetHTA tools and guidelines in national processes and procedures

- The POP database was reported to be the most used EUnetHTA tool with 31 agencies reporting use (74% of the 42 case study survey respondents)
- The most used methodology guideline was the information retrieval guideline with 19 agencies reporting use (45% of respondents).
- For EUnetHTA tools (apart from the HTA Adaptation Toolkit) over 50% of reported use was formal, indicating that the tools have been incorporated into agency methods and procedures. EUnetHTA methodology guidelines were slightly more likely to be used informally (on an as required basis). For all 15 methodology guidelines, over 50% of reported uses was informal.
- The majority of agencies have not made significant changes to the EUnetHTA tools and guidelines that they use.
- Reasons for non-use often related to agencies having established national methods in place that were developed before the EUnetHTA methodology guidelines were published. Other reasons for non-use related to specific EUnetHTA guidelines not being relevant to the remit of the agency (e.g. some agencies do not undertake economic evaluation).

#### Impact of methodology guidelines on use of EUnetHTA assessments

- Agencies do not feel that EUnetHTA methodology guidelines specifically limit or support their use of EUnetHTA assessments. This finding is consistent with the data from the implementation survey.
- Notwithstanding this the agencies that participated in the case study did make suggestions on how EUnetHTA guidelines could be improved. Central to this was a proposal from a number of agencies that EUnetHTA guidelines should be more prescriptive and provide more definitive recommendations. This must be balanced with ensuring that the guidelines remain sufficiently flexible to allow agencies to extend them when required, so that being more prescriptive does not ultimately limit uptake of EUnetHTA assessments.
- Priority areas for methods development in EUnetHTA, include developing guidance on: real-world evidence; complex interventions; emerging technologies; and the use of GRADE.

## **Methods**

Case studies are being undertaken by WP7 throughout JA3. Case studies provide an opportunity to explore in detail the experiences of joint working, the use of jointly produced products and the context in which HTA cooperation will have to be implemented.

A key feature of proposals for a sustainable model of HTA collaboration is to promote the use of shared tools and procedures. The EC proposal for HTA regulation includes a specific objective to “*promote convergence in tools, procedures and methodologies*”.

In support of this objective WP7 has been working with WP6b to undertake a case study on the use of EUnetHTA tools and guidelines. The objectives of the case study are to understand:

1. How agencies use EUnetHTA tools and guidelines in their own processes
2. Whether the methodologies used in EUnetHTA assessments affect how agencies can use EUnetHTA assessments

The case study was undertaken through the methods / stages described below:

### **Survey**

- A survey was developed and sent to all WP7 partners to complete. Partners were given the option of completing either a paper or online version of the survey.
- The survey asked respondents to provide information on: which EUnetHTA tools and guidelines they use and how they use them; any changes they make to EUnetHTA tools and guidelines in national use; the impact of EUnetHTA methodology guidelines on the use of EUnetHTA assessments; and priority areas for EUnetHTA to develop new methods.
- A total of 42 responses were received to the survey. A full list of the agencies that responded is provided in appendix 1.

### **Interviews**

- A semi-structured interview pro-forma was drafted to undertake interviews with selected agencies. The purpose of the interviews was to follow up survey responses and explore in detail how agencies use EUnetHTA tools and guidelines
- 10 interviews were undertaken in total. 9 interviews were undertaken virtually using either ZOOM or SABA. All interviews took approximately 1 hour to complete and were audio recorded. One agency submitted a written response. A full list of agencies that participated in the interviews is also provided in appendix 1.

- The case study interviews were written up and sent to each participating agency for comments and changes, before finalising. A separate appendix to this implementation report provides a narrative summary for each interview conducted.

#### **Workshop session at WP7 F2F meeting**

- A workshop session on the use of EUnetHTA tools and guidelines was held at the WP7 face to face meeting (F2F) in Zagreb in March 2019.

#### **Analysis**

- The quantitative results from the survey were analysed and are presented in this report. These results are augmented by a thematic analysis of the qualitative findings from the interviews, the workshop session on EUnetHTA tools and guideline at the WP7 F2F meeting, and the free text responses to the survey.

## **Results**

In this section of the report the results of the case study are presented. The results are divided into four principal sub-sections: 1) the use of EUnetHTA tools and guidelines in agency procedures; 2) the impact of EUnetHTA methodology guidelines on the use of EUnetHTA assessments; 3) improvements in methodological guidelines; and 4) priority areas for methodological development.

### **1. The use of EUnetHTA tools and guidelines in agency procedures**

In the survey agencies were asked to indicate which (if any EUnetHTA tools and guidelines) they use. The results are summarised in table 9 and figure 14 overleaf. The POP database was the most used EUnetHTA tool with 31 agencies (74% of the 42 respondents) reporting use.

This was followed by the HTA Core Model with 22 agencies (52%) and then the HTA adaptation toolkit with 13 agencies (31%) reporting use. The EVIDENT database was only reported to be used by 6 agencies (14%), a key reason for this being that the EVIDENT database is currently offline (see further detail in subsequent sections).

Of the 15 EUnetHTA methodology guidelines that are currently published, the most frequently used guidelines were:

- Process of information retrieval for systematic reviews and HTAs on clinical effectiveness – 19 (45%) agencies
- Endpoints used for Relative Effectiveness Assessment: Clinical endpoints – 17 (40%) agencies
- Endpoints used for Relative Effectiveness Assessment: Safety – 17 (40%) agencies
- Comparators and comparisons: Direct and indirect comparisons - 17 (40%) agencies
- Comparators and Comparisons: Criteria for the choice of the most appropriate comparator(s) – 16 (38%) agencies

The least frequently used guidelines were reported to be:

- Therapeutic medical devices – 7 (17%) agencies
- Personalised medicine and co-dependent technologies – 5 (12%) agencies

Overall, the data show that there is a group of agencies who don't use the guidelines or use only 1 or 2 of them, another group who mainly use the 5 endpoints guidelines and the 2 comparisons guidelines and a third group of agencies (n = 10) that report using the vast majority or all of the EUnetHTA guidelines.

**Table 9: Use of EUnetHTA tools and guidelines**

Tool / Guideline	Number	Percentage (%)
POP database	31	74%
EVIDENT database	6	14%
HTA core model	22	52%
HTA adaptation toolkit	13	31%
Evidence submission template	10	24%
Process of information retrieval for systematic reviews and HTAs on clinical effectiveness	19	45%
Endpoints used for Relative Effectiveness Assessment: Clinical endpoints	17	40%
Endpoints used for Relative Effectiveness Assessment: Health-related quality of life and utility measures	13	31%
Endpoints used for Relative Effectiveness Assessment: Safety	17	40%
Endpoints used for Relative Effectiveness Assessment: Composite endpoints	13	31%
Endpoints used for Relative Effectiveness Assessment: Surrogate endpoints	15	36%
Comparators and comparisons: Direct and indirect comparisons	17	40%
Comparators and Comparisons: Criteria for the choice of the most appropriate comparator(s)	16	38%
Levels of evidence – Applicability of evidence for the context of a relative effectiveness assessment	13	31%
Meta-analysis of diagnostic test accuracy studies	9	21%
Methods for health economic evaluations: A guideline based on current practices in Europe	9	21%
Internal validity of non-randomised controlled studies (NRS) on interventions	10	24%
Internal validity of randomised controlled studies	10	24%
Therapeutic medical devices	7	17%
Personalised medicine and co-dependent technologies	5	12%

**Formal and informal use**

Respondents to the survey were asked whether for each of the EUnetHTA tools and guidelines that they used their use was formal or informal. Formal use indicated that the EUnetHTA tool or guideline is incorporated into agency manuals, operating procedures or guidelines. Informal use means that that EUnetHTA tool or guideline is used on an as required basis.

The results are presented in percentage (%) terms in figure 14 overleaf. For each of the EUnetHTA tools (with the exception of the HTA Adaptation Toolkit) over 50% of the reported use was formal, indicating that they have been incorporated into agency methods and procedures (POP database = 59%, EVIDENT database = 67%, HTA Core Model – 57%, Evidence Submission Template = 60%).

EUnetHTA methodology guidelines were slightly more likely to be used informally (on an as required basis). For all 15 methodology guidelines, over 50% of reported use was informal, ranging from 83% for the guideline on Therapeutic Medical Devices to 53% for the guideline on Endpoints used for Relative Effectiveness Assessment: Health-related quality of life and utility measures.

Where EUnetHTA tools and guidelines had been formally incorporated into national methods and processes agencies were asked to provide detail in the follow-up interviews on how the tools and guidelines had been incorporated, specifically in respect of what procedures the agency was required to go through (e.g. internal only, consultation or legal changes).

None of the 10 agencies interviewed reported that legal changes had been required to incorporate EUnetHTA tools and guidelines into national procedures. A small

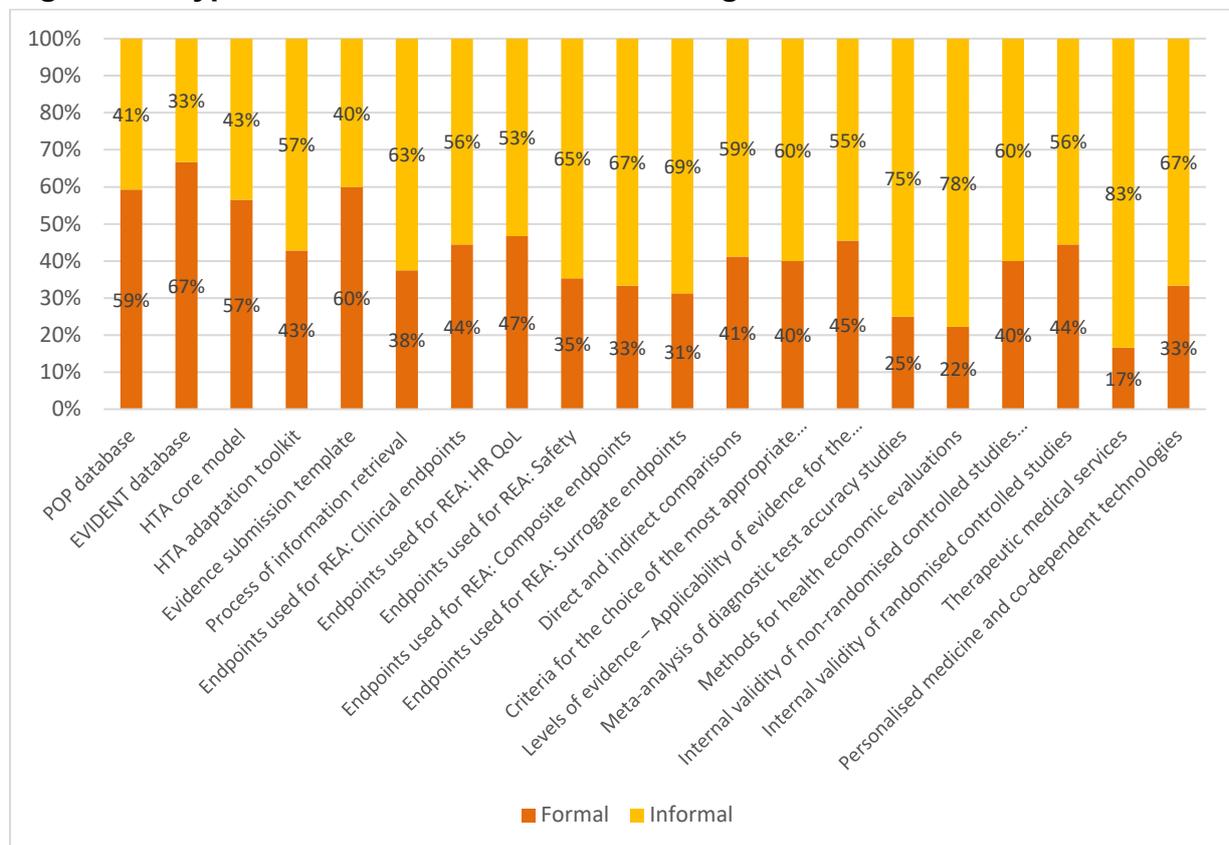
number of the agencies reported that the tools and guidelines have been incorporated through internal discussion only. The majority of agencies interviewed reported that the guidelines had been incorporated through either internal or public consultation. Illustrative quotes of examples of incorporation are provided below:

*“SOP on information retrieval outlines all regular or optional sources to be used for preliminary searches (including the POP database) and this went through an internal consultation” (PT and OT)*

*“Implemented into procedures but was not formally included in national legislation” (PT and OT)*

*“Internal decision with Ministry of Health to use EUnetHTA HTA Core Model and reporting structure” (OT)*

**Figure 14: Type of use of EUnetHTA tools and guidelines**



### Changes made to EUnetHTA tools and guidelines

Respondents to the survey were asked whether they have made any changes to EUnetHTA tools and guidelines when using them within their agency. The results are presented in table 10 below and figure 15 overleaf. The POP and EVIDENT databases were not included in this question as they are not tools to which changes can or should be made.

For the HTA Core Model, the HTA Adaptation Toolkit and the Evidence Submission Template, agencies reported they have made some changes to these tools. In most instance these changes were reported to be minor changes to enable adaptation of the tools at a national level. Examples of changes made to these tools are provided through direct quotes from survey and interview responses at the end of this section. For some tools, changes are expected when the tool is used. For example, the submission template tool guides partners that it should be adapted, likewise the HTA CORE model assessment elements used in an HTA should be chosen taking into account their relevance to the topic and national context.

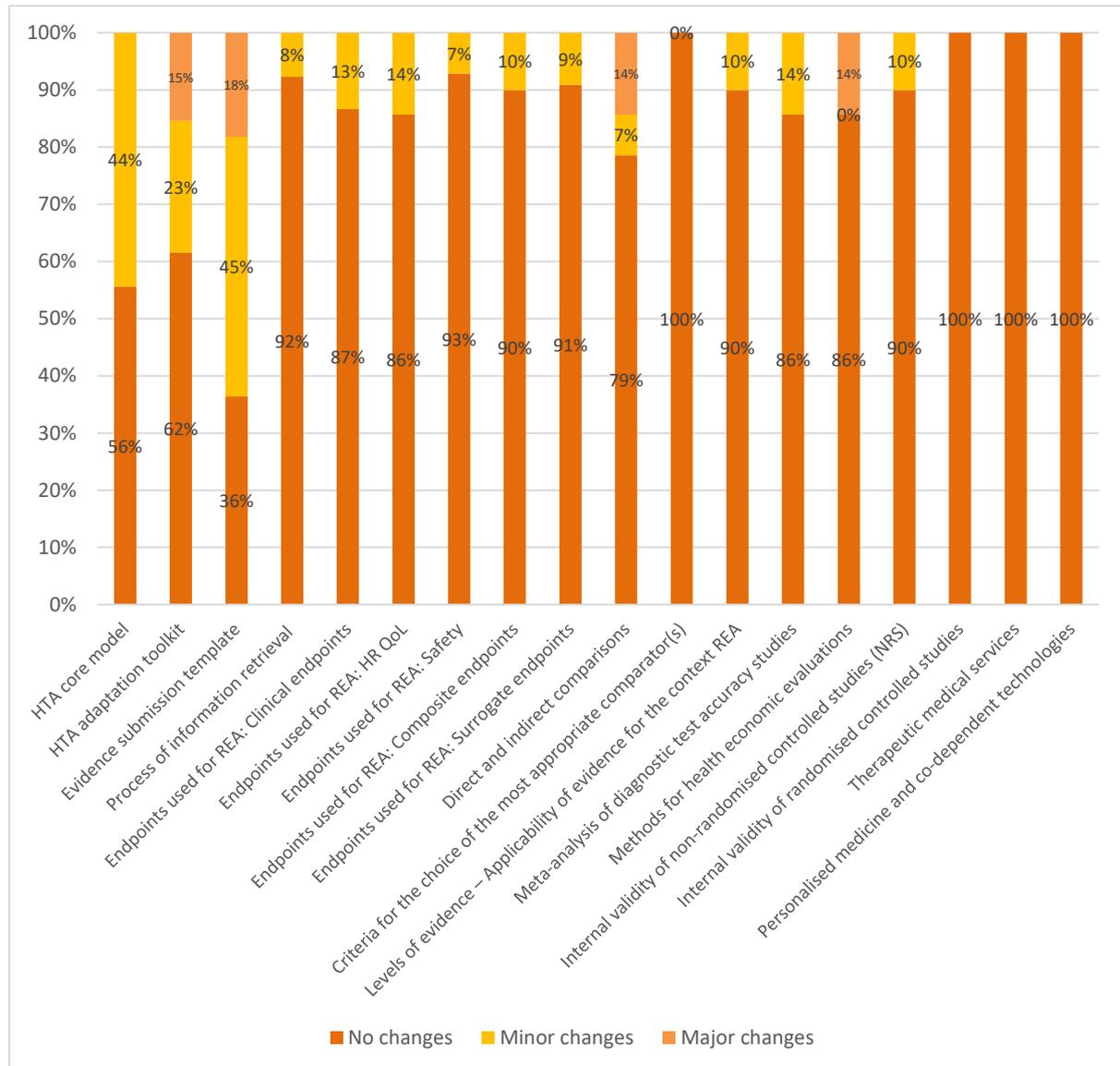
For the EUnetHTA methodology guidelines the vast majority of agencies reported that they have made no changes to the guidelines. For the EUnetHTA methodology guidelines only 12 examples of minor changes were reported and only 3 examples of major changes were reported. The relatively small number of changes agencies reported making to EUnetHTA methodology guidelines, is also likely a product of the fact that some agencies only use the EUnetHTA methodology guidelines when they are in agreement with their existing methods.

**Table 10: Changes made to EUnetHTA tools and guidelines**

Tool / Guideline	No changes	Minor changes	Major changes
HTA core model	10	8	0
HTA adaptation toolkit	8	3	2
Evidence submission template	4	5	2
Process of information retrieval for systematic reviews and HTAs on clinical effectiveness	12	1	0
Endpoints used for Relative Effectiveness Assessment: Clinical endpoints	13	2	0
Endpoints used for Relative Effectiveness Assessment: Health-related quality of life and utility measures	12	2	0
Endpoints used for Relative Effectiveness Assessment: Safety	13	1	0
Endpoints used for Relative Effectiveness Assessment: Composite endpoints	9	1	0
Endpoints used for Relative Effectiveness Assessment: Surrogate endpoints	10	1	0
Comparators & comparisons: Direct and indirect comparisons	11	1	2
Comparators & Comparisons: Criteria for the choice of the most appropriate comparator(s)	11	0	0
Levels of evidence – Applicability of evidence for the context of a relative effectiveness assessment	9	1	0
Meta-analysis of diagnostic test accuracy studies	6	1	0
Methods for health economic evaluation: A guideline based on current practices in Europe	6	0	1
Internal validity of non-randomised controlled studies (NRS) on interventions	9	1	0
Internal validity of randomised controlled studies	7	0	0
Therapeutic medical devices	5	0	0
Personalised medicine and co-dependent technologies	5	0	0
<b>Total</b>	<b>160</b>	<b>28</b>	<b>7</b>

Note - not all agencies answered this question.

**Figure 15: Changes made to EUnetHTA tools and guidelines**



## **Examples of types of use and changes made to tools and guidelines**

In the free text responses to the survey and the follow-up interviews respondents were asked to explain how they have used different EUnetHTA tools and methodology guidelines and any changes they have made to them. Examples of use for different tools and guidelines and changes made to them are provided in this section of the report, together with illustrative quotes.

### **POP database**

Over half of agencies (59%) who use the POP database reported that their use of the POP database had been incorporated in agency procedures or guidelines. One agency stated:

*“POP database is included in internal SOP on preliminary searches, as an optional source. POP database is also referenced in [agency] methods manual”. (PT and OT)*

For other agencies the use of the POP database is informal:

*“POP database is not referenced as do not have a method guide, but HTA developers in agency are aware of the database” (PT and OT)*

Agencies reported that they routinely search the POP database before starting an assessment and register planned and ongoing HTAs on the database:

*“The POP database is often/always searched before we start a new assessment. It is also a source we use for early warning on new and emerging technologies. All our planned and ongoing HTAs are registered in the database” (PT and OT)*

*“We always enter our project to the database and we always search the database before we start a new project to adapt timelines if applicable”. (OT)*

Some agencies use the POP database to identify opportunities for collaboration, but others do not:

*“We always check the POP database when embarking on a new topic, to see if anyone else is already working in this area with whom we can make contact to discuss approaches/included studies etc”. (OT)*

*“We contribute to the POP database with topics that we will be assessing but we do not use it to identify collaboration”. (PT and OT)*

### **EVIDENT database**

Limited feedback was provided on how the EVIDENT database was used, as previously discussed this is primarily because it has been offline:

*“Used until it was active, we are not aware of its current status”. (OT)*

## HTA Core Model

As with the POP database over half of the agencies who use the HTA Core Model (57%) report its use to be formal:

*“HTA Core Model was incorporated into and written into the [national] methods manual” (PT and OT)*

*“HTA Core Model [used] as a basis for our national reports. a guideline based on the HTA Core Model was elaborated and officially approved for the [national] HTA Network”. (OT)*

The primary use of the HTA Core Model at a national level was to inform national report structures for HTA domains and to guide question setting. This is illustrated by the quotes below and overleaf:

*“HTA Core Model domains structure are taken into account in our assessment report template structure. We have used Core Model questions / assessment elements (as guidance/checklist) in several assessments”. (PT and OT)*

*“It is used for the production of assessment reports, to frame the research questions by using assessment elements of the domains that are going to be evaluated” (OT)*

*“Recent HTA report structure is organised using the HTA Core Model domains as headings” (PT and OT)*

*“We use the Core Model to guide question setting in the different HTA domains” (OT)*

*“Per HTA domain, we choose the relevant questions that are applicable for our HTA topic. We do not ‘change’ the core model. We just use the model to assure all relevant questions are asked”. (PT and OT)*

Changes made to the HTA Core Model by agencies focussed on the merger / synthesis of domains and translation for national use:

*“We created our own HTA report template that makes use of the HTA Core Model structure. The effectiveness and safety domains were merged into one section (Clinical effectiveness and safety). (PT and OT)*

*“We made minor changes of the HTA Core Model for REA, the assessment elements were synthesised and translated into national language”. (OT)*

## HTA Adaptation Toolkit

Only 13 agencies reported using HTA adaptation toolkit and over half of these (57%) used it informally, indicating use on an as required basis (rather than formal incorporation of the HTA Adaptation Toolkit into national methods and procedures). Some agencies, in particular those with a remit for OT, reported limited use of the HTA Adaptation Toolkit. Others reported that they were no longer using it at all.

*“We have made very limited use of the HTA adaptation toolkit when adapting EUnetHTA reports” (OT)*

*“It was used some years ago, probably during JA1. Its use was discontinued since it was found not very helpful”. (OT)*

*“Adaptation toolkit was used for an adaptation of some assessments from JA2” (OT)*

Some agencies reported using the toolkit generally to support their adaptation process, while others reported using specific checklists from the toolkit:

*“If already published Core HTA and/or HTAs from other countries exist, they will be critically appraised for quality by INAHTA checklist for the appraisal of HTA Reports and further adapted to [national] setting according to EUnetHTA Adaptation Toolkit”. (PT and OT)*

Changes made by agencies to the HTA toolkit included adaptations to meet national requirements, further explanation of items and translation. Changes made to specific checklists from the toolkit were also reported:

*“We made changes due to national requirements to only use relevant items. Added further explanation of items where they were not sufficiently explained. We also needed to undertake translation because reports are published in national language”. (PT and OT)*

*“Adapted version of checklist from HTA Adaptation Toolkit is included in [agency] report template and states that this checklist should be used for the evaluation of the transferability of results from economic evaluations”. (PT and OT)*

## Evidence Submission Template

In the survey only 10 agencies reported use of the Evidence Submission Template, with 6 (60%) of the uses reported to be formal and 4 (40%) informal. Examples of use of the submission template reported in the case study focussed on adoption or adaptation of the template into national processes or requirements.

*“[Agency] require companies to use the EUnetHTA submission template and we use EUnetHTA guidelines to evaluate the data submitted” (PT and OT)*

*“In the future, we will possibly accept OT submissions handed in on the EUnetHTA templates (decision in 2019). We will use the submission template as source of inspiration when revising our templates in [National Language]”.* **(OT)**

*“We [agency] use the evidence submission template to inform the internal submission template”* **(PT and OT)**

Some agencies reported that they felt that the submission template was too long and have made changes to the template to shorten it and make it easier for companies to complete:

*“We use a shortened version of the submission template nationally, approximately one third of a size of the EUnetHTA version. We have shortened the submission file as the full-length version is very time consuming for companies to populate”.* **(OT)**

### **EUnetHTA Methodology Guidelines**

A wide range of uses of EUnetHTA methodology guidelines were reported. Some agencies reported formal use of EUnetHTA methodology guidelines, with referencing in their guidelines:

*“The guidelines were included in our updated methodological guidelines, both for medicine and non-pharma technologies”.* **(PT and OT)**

Some agencies reported that EUnetHTA methodology guidelines were used for staff induction and for education purposes:

*“The Methodology Guidelines of EUnetHTA are reference work for assessment. They're part of the starter's pack for every assessor”.* **(PT and OT)**

*“These guidelines are used for information and education purposes internally”.* **(PT)**

Some agencies use the EUnetHTA guidelines informally, for example in response to specific methodological issues:

*“If we have methodological issues our own guideline does not cover, we look from these guidelines”.* **(PT)**

*“Used some of the guiding principles from the guidance on direct and indirect comparisons to inform [agency] guidance”.* **(PT)**

As previously documented very few agencies reported making any changes to methodology guidelines. However, one agency reported:

*“We updated them to fit the local regulations and practices”.* **(PT and OT)**

A key theme to emerge from the findings was that EUnetHTA methodology guidelines are particularly helpful for countries with less developed HTA systems and methods.

*“EUnetHTA tools and guidelines have helped [agency] to improve quality of HTA procedures as HTA is still quite a new concept in [country]”. (PT and OT)*

### **Non-use of EUnetHTA tools and guidelines**

In the interviews undertaken for the case study we also explored the reasons why agencies do not use EUnetHTA tools and guidelines. None of the agencies interviewed reported that they have made a specific decision not to use any of the EUnetHTA tools and guidelines on the basis of their content or methodology. One of the agencies explained:

*“Will always have a look at new or updated EUnetHTA tools and guidelines. If they fit into our national guidelines, we will always consider using them or implementing them” (PT).*

Reasons for non-use often related to agencies having established national methods in place that were developed before the EUnetHTA methodology guidelines were published. This is illustrated by the quotes below:

*“Not discounted use of any guidelines. Just not had reason to use many of them. We have established methods that pre date many of the EUnetHTA methods guides. We and will consider using EUnetHTA methods as and when they think they are needed, for example when developing methods in new areas such as direct and indirect treatment comparisons” (PT)*

*“Perhaps it has something to do with habits. We have been using other guidelines for several years”. (OT)*

Other reasons for non-use related to specific EUnetHTA guidelines not being relevant to the remit of the agency. For example, some agencies do not undertake economic evaluation and so the EUnetHTA guideline on economic evaluation is not relevant to or used by these agencies.

*“We do not use EUnetHTA health economic guideline as do not undertake economic evaluation” (OT)*

*“Limited use of guideline on economic evaluation as primary economic evaluation is not mandatory nationally”. (PT and OT)*

Some agencies have not used EUnetHTA guidelines in emerging areas such as personalised medicine because they have not yet undertaken HTA on these topics.

*“Have not yet used personalised medicine guideline as have not had reason to use it”. (PT and OT)*

In relation to EUnetHTA tools, one agency reported that they do not use the POP database because they do not have the resources:

*“A decision was taken that we do not have the time and resource to input into and review the POP database”.* (PT and OT)

As previously documented a number of agencies reported non-use of the EVIDENT database because it has been offline.

## **2. Impact of EUnetHTA methodology guidelines on use of EUnetHTA assessments**

Respondents to the survey were asked whether the contents or recommendations in EUnetHTA methodology guidelines limit or support their use of EUnetHTA assessments. The results are presented in table 11 and figure 16. As can be seen EUnetHTA methodology guidelines were largely identified as neither specifically supporting nor limiting the use of EUnetHTA assessments. The reasons for this are explored later in this section of the report.

Very few examples were provided in the case study of EUnetHTA methodology guidelines limiting the ability of an agency to use a EUnetHTA assessment. None of the agencies that responded to the survey reported that any of the EUnetHTA methodology guidelines had *significantly limited* their use of EUnetHTA assessments, and only 2 examples were reported of EUnetHTA methodology guidelines *somewhat limiting* the use of EUnetHTA assessments. Some agencies felt that the guidelines limit use when they fail to provide clear instruction:

*“They limit as long as don’t provide a clear indication on how to proceed in real life HTA or ask for data usually not available”* (PT and OT)

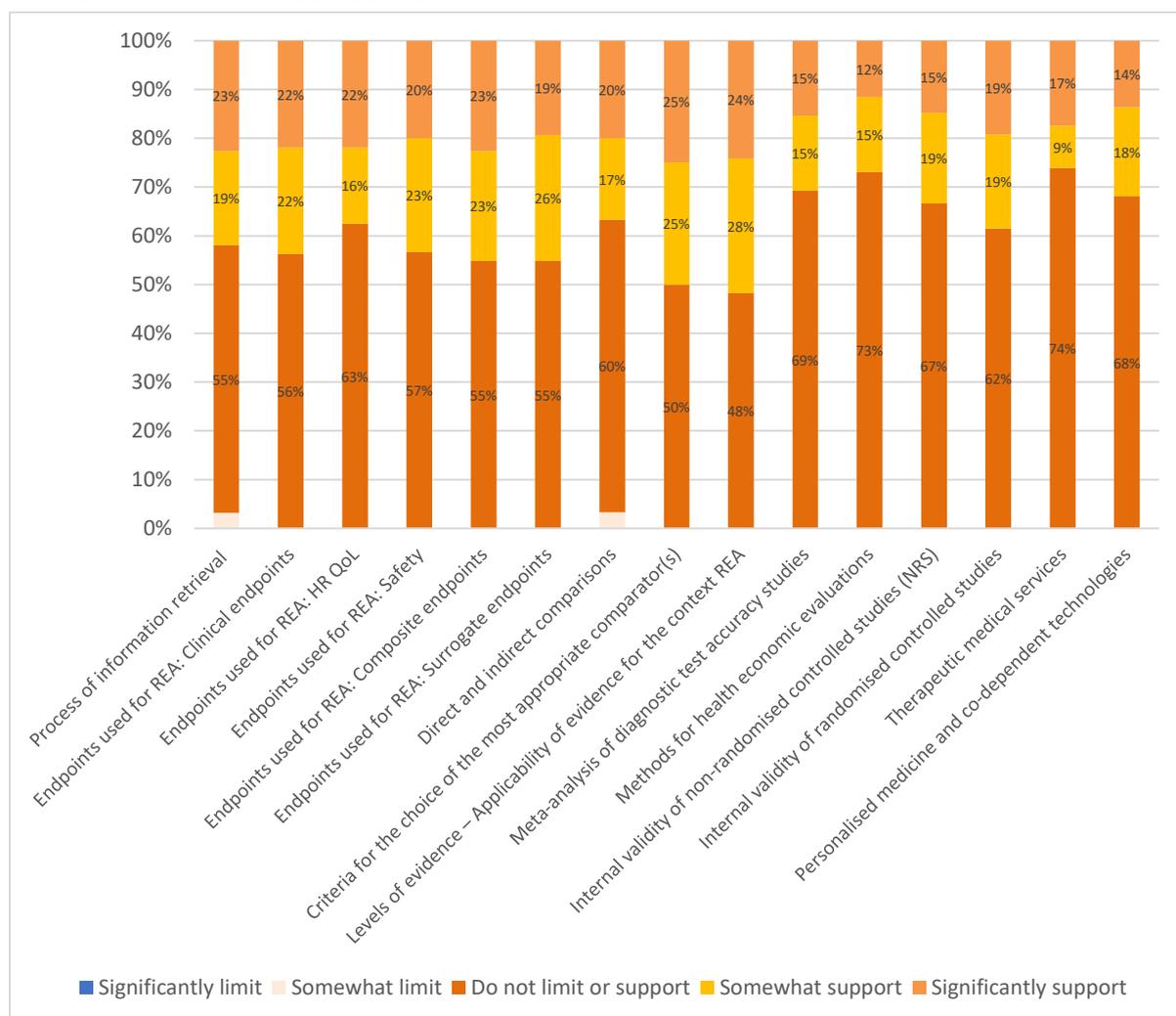
Some agencies reported that EUnetHTA methodology guidelines support their use and uptake of EUnetHTA assessments. The methodology guidelines most frequently identified as supporting use of EUnetHTA assessments were:

- Levels of evidence – Applicability of evidence for the context of a relative effectiveness assessment (28% *somewhat support*, 24% *significantly support*).
- Comparators & Comparisons: Criteria for the choice of the most appropriate comparators (25% *somewhat support*, 25% *significantly support*).
- Endpoints used for Relative Effectiveness Assessment: Composite endpoints (23% *somewhat support*, 23% *significantly support*).
- Endpoints used for Relative Effectiveness Assessment: Surrogate endpoints (26% *somewhat support*, 19% *significantly support*).
- Endpoints used for Relative Effectiveness Assessment: Clinical endpoints (22% *somewhat support*, 22% *significantly support*).
- Endpoints used for Relative Effectiveness Assessment: Safety (23% *somewhat support*, 20% *significantly support*).

**Table 11: Extent to which EUnetHTA methodology guidelines limit or support use of EUnetHTA assessments**

	Significantly limit	Somewhat limit	Do not limit or support	Somewhat support	Significantly support
Process of information retrieval for systematic reviews and HTAs on clinical effectiveness	0	1	17	6	7
Endpoints used for Relative Effectiveness Assessment: Clinical endpoints	0	0	18	7	7
Endpoints used for Relative Effectiveness Assessment: Health-related quality of life and utility measures	0	0	20	5	7
Endpoints used for Relative Effectiveness Assessment: Safety	0	0	17	7	6
Endpoints used for Relative Effectiveness Assessment: Composite endpoints	0	0	17	7	7
Endpoints used for Relative Effectiveness Assessment: Surrogate endpoints	0	0	17	8	6
Comparators & comparisons: Direct and indirect comparisons	0	1	18	5	6
Comparators & Comparisons: Criteria for the choice of the most appropriate comparators	0	0	14	7	7
Levels of evidence – Applicability of evidence for the context of a relative effectiveness assessment	0	0	14	8	7
Meta-analysis of diagnostic test accuracy studies	0	0	18	4	4
Methods for health economic evaluations	0	0	19	4	3
Internal validity of non-randomised controlled studies (NRS) on interventions	0	0	18	5	4
Internal validity of randomised controlled studies	0	0	16	5	5
Therapeutic medical devices	0	0	17	2	4
Personalised medicine and co-dependent technologies	0	0	15	4	3
<b>Total</b>	<b>0</b>	<b>2</b>	<b>255</b>	<b>84</b>	<b>83</b>

**Figure 16: Extent to which EUnetHTA methodology guidelines limit or support use of EUnetHTA assessments**



## **Guidelines do not limit or support use**

The reasons agencies do not feel that EUnetHTA methodology guidelines specifically limit or support their use of EUnetHTA assessments were explored in the free text responses to the survey and the follow-up interviews. As with the implementation survey, key factors identified as limiting use of EUnetHTA assessments in the case study was the timing, relevance and availability of EUnetHTA assessments, not the methods used in undertaking them. This is illustrated by the quotes below:

*“The majority of the guidelines don’t limit or support out use of EUnetHTA assessments, as the main factor for use of an assessment is its timeliness and relevance. While these guidelines need to be in place, we assume that authors are adhering to them and therefore don’t specifically consider this when adapting”. (OT)*

*“Methodological guidelines itself do not limit our use of EUnetHTA assessments. The main limitation is the lack of timely availability of EUnetHTA assessments”. (PT)*

*“Methods do not limit use...the principal factor limiting use of EUnetHTA assessments is timing. We look to publish advice as soon as possible after marketing authorisation, and often the timing of EUnetHTA assessments is too late for national use”. (PT)*

Where agencies reported that EUnetHTA methodology guidelines have supported the use of EUnetHTA assessments at national level this was primarily because of the confidence and assurance given to national HTA agencies and decision-makers when using or adapting a EUnetHTA assessment. This is illustrated by the quotes below:

*“The EUnetHTA guidelines support the use of the assessments because they ensure a certain quality that must be met in order to be able to use the report in the national setting”. (OT)*

*“The benefit is the clarity and transparency that they give in terms of the methods used and the reasons why. National adaptation is easier when methods are clear” (PT and OT)*

*“The EUnetHTA guidelines improve quality of assessments and give more confidence to decision-makers”. (PT)*

*“We have used nationally the EUnetHTA assessments on Midostaurin. The use of EUnetHTA methodology in the EUnetHTA Midostaurin assessment, made it easier to use the assessment in a national report”. (PT and OT)*

Some agencies did identify methodology as limiting use of EUnetHTA assessments, but this related to methodology not currently included in a guideline. Some agencies proposed that GRADE should be used as standard by EUnetHTA to improve uptake of assessments. This is illustrated by the quote below:

*“Use of GRADE as standard EUnetHTA practice would improve uptake as we use GRADE in the agency. Where a EUnetHTA assessment does not use GRADE, then we have to undertake evidence grading when using the EUnetHTA assessment nationally”. (OT)*

Overall the results of the case study indicate that even if agencies do not formally align with EUnetHTA tools and guidelines, it does not seem to limit particularly their ability to use EUnetHTA assessments. As previously documented, the main factors limiting use of EUnetHTA continue to relate to the timing, relevance and availability of EUnetHTA assessments, not the methods used within them.

It should also be noted that just because an agency does not use a EUnetHTA guideline it does not mean that the agency methods are inconsistent with EUnetHTA. Many agencies, particularly those with developed HTA systems, are working to long established methods and procedures that pre date the publication of EUnetHTA guidelines. These national guidelines are, as with the EUnetHTA guidelines, often based upon international best standards (e.g. Cochrane) and so are using the same or very similar methodologies to EUnetHTA.

Notwithstanding the above, participants in the case study did identify a number of key benefits to aligning their procedures with EUnetHTA tools and guidelines. These included: improvements in the quality and efficiency of agency procedures; reduced duplication of work; and improvements in the credibility of and confidence in national methods and procedures knowing that they are based on and in line with European methods and procedures developed to a known high quality.

Agencies also feel that alignment with EUnetHTA procedures and tools does and will further improve uptake of EUnetHTA assessments in the future:

*“[Agency] has very good alignment with EUnetHTA. The adoption of the HTA core and EUnetHTA templates will make the use of EUnetHTA assessments easier in the future as they will be using the same report structures and templates”. (OT)*

### **3. Improvements to EUnetHTA methodology guidelines**

In the follow-up interviews respondents were asked to make suggestions on how EUnetHTA methodology guidelines could be improved.

#### **Prescriptive guidelines with practical recommendations**

A key theme to emerge was that some agencies feel that EUnetHTA guidelines focus too much on the discussion of methods and do not provide practical examples of how

to apply the methods in practice. A number of agencies stated that EUnetHTA methodology guidelines need to be more prescriptive and provide definitive recommendations on methods. This is illustrated by the quotes below:

*“As a general comment, if methodological guidelines focus on the discussion of methods and they do not provide you with practical recommendations or specific points of action then different agencies could interpret and use the methods guidelines in different ways. This may impact on uptake in the future”. (OT)*

*“The recommendations in the guidelines are quite ‘soft’ and not prescriptive. Some of the EUnetHTA guidelines are useful to introduce a topic but they are not really a guideline and do not provide practical guidance or recommendations”. (PT and OT)*

*“The methodology guidelines should be more specific on how to address the topics. They are too general and do not address in depth specific methods”. (PT)*

It should be noted, however, that there is a risk that if EUnetHTA guidelines are made more prescriptive the guidelines might then start to limit use of EUnetHTA assessments, because they will be in conflict with established methods for some agencies. A key theme to emerge from the workshop session on EUnetHTA tools and guidelines held at the WP7 F2F meeting was that whilst there is a need to provide more direction in EUnetHTA methodology guidelines, at the same time agencies still need to have the capability to apply methods that extend the guidelines.

### **Length, format and standardisation of guidelines**

There was also a view from agencies that some of the EUnetHTA guidelines can be too long, and that they could be improved by being more concise and through having a more standardised format.

*“Making the guidelines as clear and short as possible would be beneficial in increasing uptake” (OT)*

*“It would also be helpful for the guidelines to have a more standardised format and structure” (PT and OT)*

### **Translation of guidelines**

Some agencies felt that it would be helpful for EUnetHTA to translate methodology guidelines into EU languages to promote their use. One agency stated:

*“EUnetHTA tools and methodology guidelines could be translated into all EU languages; it would encourage their implementation into national legislation”. (OT)*

## Dissemination of guidelines

Some agencies also felt that there should be better dissemination of EUnetHTA methodology guidelines to promote awareness and use:

*“Although the EUnetHTA tools and methodology guidelines have been developed for the members of the network, we recommend a greater dissemination” (PT and OT)*

*“A greater publicity around these would be good to encourage their use beyond key EUnetHTA partners”. (OT)*

## Review and update of guidelines

In order to improve EUnetHTA methodology guidelines a number of agencies highlighted a need for them to be regularly reviewed and updated to ensure they remain up to date, particularly in fast moving and emerging methodological areas. The need for a flexible approach to updating guidelines was identified to ensure EUnetHTA guidelines remain credible and relevant. Agencies stated:

*“Methods in some areas are fast moving, so guidance needs to be regularly reviewed and updated with new guidance developed as appropriate existing guidance updated in a timely manner”. (PT)*

*“EUnetHTA must make sure that the methodology guidelines are kept up-to-date”. (OT)*

*“It would be very helpful to have a permanent methodology working party (with methods experts) responsible for monitoring the need for update of existing EUnetHTA methods and identifying priority areas for new methods development and methods guidelines”. (PT and OT)*

Some agencies provided specific examples of methodological guidelines that they felt need updating:

*“The guideline on indirect comparisons is somewhat marginal (what method should be used in which situation?) Maybe include a reference to academics with expertise; so, the guideline is not outdated so fast; especially in the field of indirect comparisons). I think indirect comparisons are important for EUnetHTA, where the reference treatment is not always the one that is used in the studies for registration, and therefore a more detailed guideline may be helpful” (PT and OT)*

*“Some methods guides are out of date and need updating e.g. the safety guideline and the guideline on indirect comparisons need to be updated” (PT and OT)*

Another agency highlighted the need for EUnetHTA guidelines to be reviewed and the need for some to be considered for decommissioning:

*“The currency of guidelines needs to be reviewed with some updated and consideration given to decommissioning others”. (OT)*

#### **4. Priority areas for new methods development**

Respondents to the survey and the agencies interviewed for the case study also identified a number of priority areas where they think it would be helpful for EUnetHTA to develop new methods or methodology guidelines. These are detailed below, together with some illustrative quotes.

- **Real-World Data (RWD) and Real-World Evidence (RWE)**

*“It would be very important to have a Working Group focused on the production of a clear and shared EUnetHTA position on the use of Real-World Data (RWD) in the assessment of other technologies and in particular medical devices” (OT)*

*“RWE is increasingly important and could also benefit from EUnetHTA work”. (PT and OT)*

- **Complex interventions / technologies**

*“Guidance would be helpful on HTA of complex technologies, for example medical devices combined with pharmaceuticals and digital health” (PT and OT)*

*“Interventions other than devices and pharmaceutical products are difficult to assess and a guideline, protocol, standard, or methodology, could be very helpful (e.g. intermediate interventions, health programs, elements that are part of larger processes where components have the potential for interactions between them). The agency is seeing an increasing demand to assess complex interventions that are often part of complex care pathways”. (OT)*

- **Emerging technologies**

*“We would welcome EUnetHTA guidance around undertaking appraisal of emerging ‘one and done’ technologies (e.g. CAR-T therapy, ATMPs) and tissue agnostic therapies. These will be challenging areas for undertaking HTA” (PT)*

- **Critical assessment of clinical evaluations (guideline in development)**

*“The critical assessment of clinical evaluations guideline is very much needed” (OT)*

*“This guideline is important because there are different approaches on how to review evidence from different types of studies / evidence”. (PT and OT)*

- **Diagnostic tests**

*“Assessment of diagnostic tests seems to be a growing area and therefore guidance on assessing tests beyond meta-analysis would be helpful”. (OT)*

Other key areas identified as priorities for methods development were:

- HTA topic selection procedures **(PT and OT)**
- Defining the PICO and research questions for HTA **(PT and OT)**
- Incorporating patient experience into HTA **(PT and OT)**
- Comparison methods for single arm trials **(PT and OT)**
- Detecting and handling selective reporting bias **(PT and OT)**
- Guidance on how to undertake organisational analysis **(OT)**

## Section 4 – EUnetHTA Implementation Strategy

### *Key findings*

- The EUnetHTA implementation strategy outlines the principles, approach to activities and responsibilities to increase use of joint HTA work.
- The strategy is underpinned by 5 key principles:
  1. EUnetHTA outputs should be fit for user needs
  2. Users of EUnetHTA outputs should be aware of the outputs available
  3. Practical support to use EUnetHTA outputs
  4. Implementation activities must have appropriate regard to proposals for a permanent model of HTA cooperation
  5. Uptake is regularly monitored and evaluated
- The activities in the strategy include drivers designed to help create an environment where EUnetHTA outputs are visible and enablers that help prospective users use EUnetHTA outputs.
- Activities are divided into those for which EUnetHTA has a main responsibility and those for which EUnetHTA partners are responsible.
- A partner survey identified the following areas of the implementation strategy as priorities to support increased implementation:
  - Wider promotion of EUnetHTA outside of the network and greater visibility of resources available to promote EUnetHTA outputs
  - A review of alignment of EUnetHTA activities and outputs to agency priorities and needs
  - A cross work package document outlining key expectations for agencies participating in EUnetHTA activities
  - Targeted implementation activities with a small number of agencies perceiving difficulties
  - Ongoing updates about proposals for permanent HTA cooperation and specifically about implications for HTA agencies

## **Methods**

One of the principal objectives of EUnetHTA JA3 is to:

“increase the use, quality and efficiency of joint HTA work at European level to support evidence-based, sustainable and equitable choices in healthcare and health technologies and ensure re-use in regional and national HTA reports and activities, in order notably to avoid duplication of assessments, in accordance with Article 15((2)(d) of the Directive with an aim of defining and implementing a sustainable model for the scientific and technical cooperation on HTA in Europe”<sup>4</sup>.

To help meet this objective WP7 have created an implementation strategy. The strategy is informed by WP7 data from: the implementation feedback survey; interviews carried out by the implementation network; case studies; and the outputs of focus groups to support development of a model of HTA cooperation.

In addition, in order to understand the areas and activities in the implementation strategy that required specific focus from EUnetHTA, WP7 carried out a short survey with partners to capture their perceptions about the extent to which key drivers and enablers were in place to support increased implementation.

The survey included 13 statements that are analysed in 4 themes:

1. the extent to which there is an environment that promotes EUnetHTA outputs
2. the extent to which EUnetHTA is perceived to be focussing on the issues that are important to EUnetHTA partners and other relevant users
3. the extent to which EUnetHTA partners and other relevant users feel knowledgeable about EUnetHTA outputs and engaged in EUnetHTA activities
4. the extent to which EUnetHTA partners and other relevant agencies feel they understand and would be able to respond to proposals for a permanent model of HTA cooperation

Respondents were asked to agree or disagree with each statement on a scale of 1-5. For the analysis responses 1 and 2 were considered agreement, 3 neither agreement not disagreement and 4 and 5 disagreement.

The survey was sent out to all agencies who are part of the implementation network (both EUnetHTA partners and other agencies who are potential users of EUnetHTA assessments) as part of consultation on the draft implementation strategy.

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<sup>4</sup> Objective one of the JA3 Grant Agreement

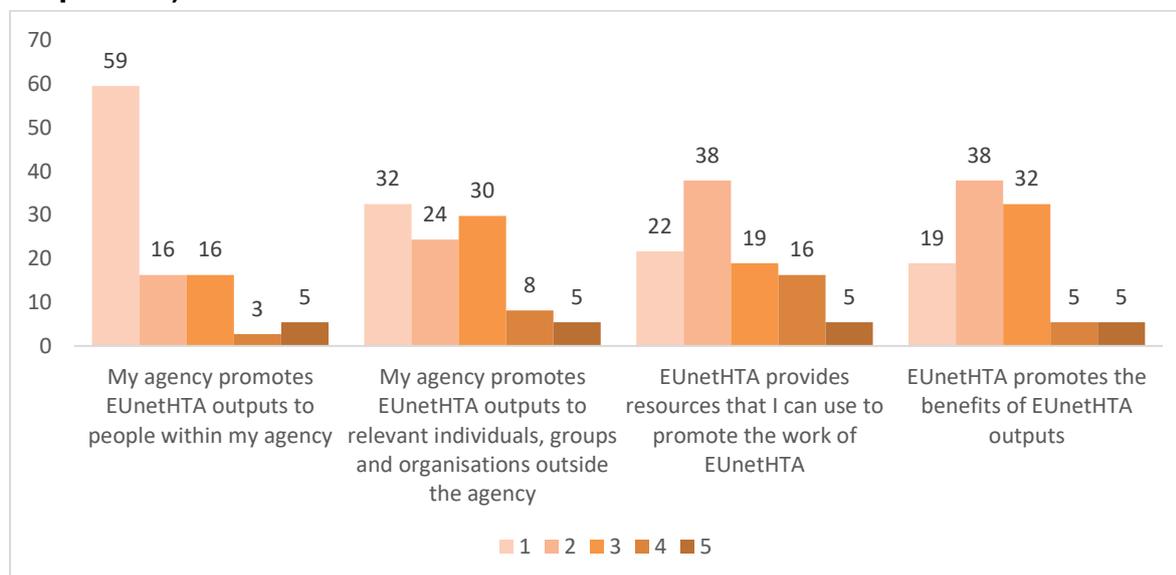
## Results of the implementation strategy survey

Thirty-eight responses were received of which 37 could be included in the graphical analysis<sup>5</sup>. The 38 responses covered 21 of the 29 EUnetHTA partner countries and included 3 responses from agencies involved in HTA and reimbursement who are relevant users of EUnetHTA outputs but who are not formally EUnetHTA partners.

### Promotion of EUnetHTA outputs

Implementation requires an environment where the outputs to be used are visible. For the most part respondents agreed that EUnetHTA outputs are promoted within their agencies (75%) but were less likely to agree that outputs are promoted to relevant users outside of their agencies (56%). Reflecting on the role that EUnetHTA plays in promoting EUnetHTA outputs, partners provided mixed responses about the extent to which they perceive EUnetHTA as providing resources to support them to promote its outputs and the extent to which EUnetHTA itself promotes the benefits of its outputs. While the majority of partners did not disagree with the statements, responses about whether EUnetHTA promotes the benefits of its outputs were more neutral with 32% of partners neither agreeing nor disagreeing, and 21% of partners disagreeing with the statement that EUnetHTA provides resources to partners to help promote EUnetHTA outputs.

**Figure 17: Survey responses about the promotion of EUnetHTA outputs (% responses)**



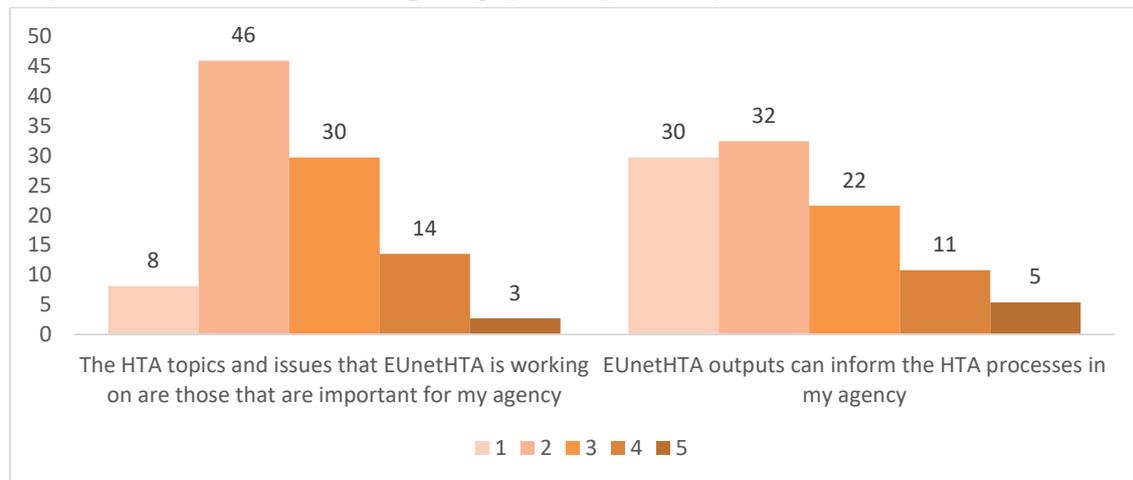
Key: Responses on a scale where 1 = agency agrees with the statement and 5 = agency disagrees with the statement

<sup>5</sup> one partner responded yes and no to the questions rather than using the scale

## Activity alignment

Implementation is more likely to be successful if the outputs produced address issues that are relevant and important to the agencies expected to use them. Sixty-two percent of respondents agreed that EUnetHTA outputs can inform the HTA processes in their agency, a smaller proportion agreed with the statement that the topics and issues that EUnetHTA work on are important to the agency (54%). The proportions disagreeing with these statements were small, but particularly for the statement about whether EUnetHTA dealt with issues important to the agency a significant minority (30%) gave neutral response.

**Figure 18: Survey responses about alignment of EUnetHTA activities to important issues for the agency (% responses)**

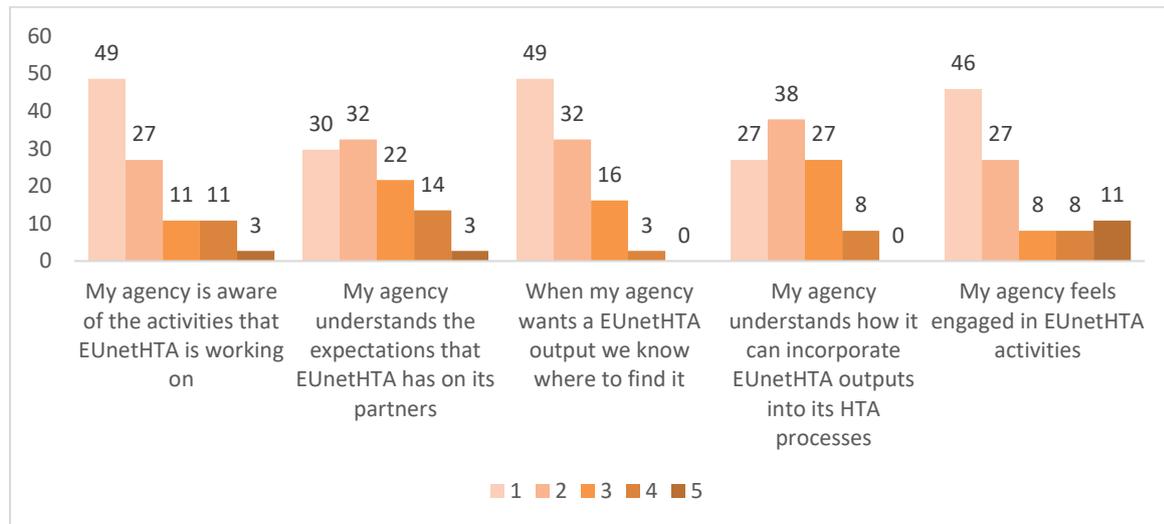


Key: Responses on a scale where 1 = agency agrees with the statement and 5 = agency disagrees with the statement

## Understanding and awareness

Implementation requires awareness of the outputs that can be used and how these can or should be used. The majority of respondents agreed that their agency is aware of EUnetHTA activities (76%), knows how to find EUnetHTA outputs (81%) and feels engaged in EUnetHTA activities (73%). Although a majority of respondents agreed with the statement that they understood the expectations EUnetHTA has on partners (62%) and how to incorporate EUnetHTA outputs into its processes (65%), respondents were less clear about this than other elements of awareness suggesting that targeted work with small groups of agencies may be needed.

**Figure 19: survey response about agency understanding and awareness of EUnetHTA outputs (% responses)**

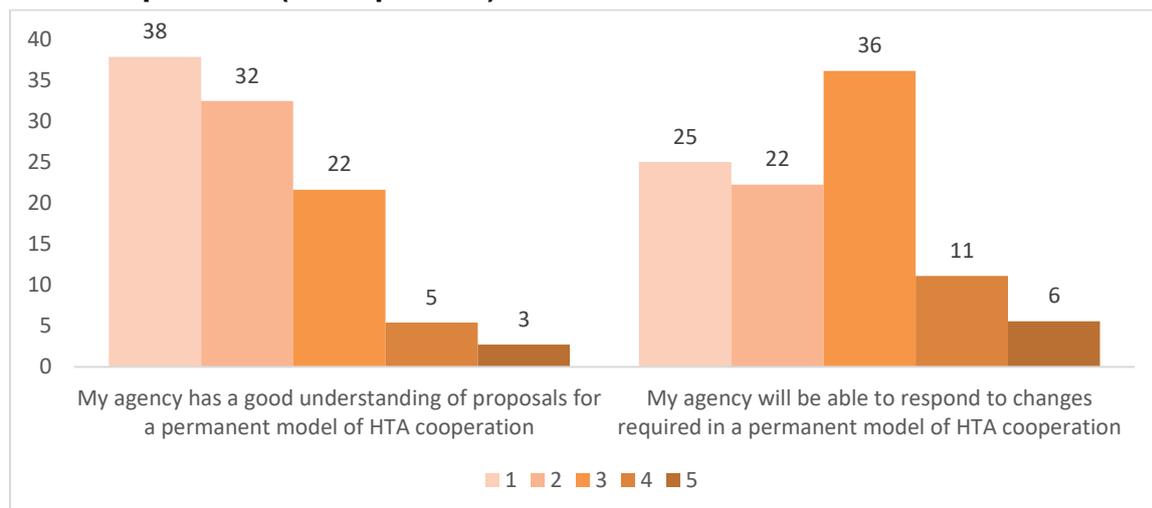


Key: Responses on a scale where 1 = agency agrees with the statement and 5 = agency disagrees with the statement

### Future readiness

Implementation in the context of EUnetHTA JA3 must also have regard for future proposals for permanent HTA cooperation. The majority of respondents (70%) agreed that they had a good understanding of proposals for a permanent model of HTA cooperation but fewer (47%) agreed they would be able to respond to any changes required. In part this was due to uncertainty in the proposals, but also uncertainties and restrictions in HTA systems in the countries.

**Figure 20: survey responses about future readiness for a permanent model of HTA cooperation (% responses)**



Key: Responses on a scale where 1 = agency agrees with the statement and 5 = agency disagrees with the statement

## **The EUnetHTA implementation strategy**

The EUnetHTA implementation strategy outlines the principles, approach to activities and responsibilities to increase use of joint HTA work at a European level. The activities in the strategy include drivers designed to help create an environment where EUnetHTA outputs are visible and enablers that help prospective users use EUnetHTA outputs. Activities are divided into those for which EUnetHTA has a main responsibility and those for which EUnetHTA partners are responsible. These responsibilities and activities are summarised in figure 21.

The EUnetHTA implementation strategy is underpinned by 5 key principles:

1. EUnetHTA outputs should be fit for user needs
2. Users of EUnetHTA outputs should be aware of the outputs available
3. Practical support to use EUnetHTA outputs
4. Implementation activities must have appropriate regard to proposals for a permanent model of HTA cooperation
5. Uptake is regularly monitored and evaluated

### ***1. EUnetHTA outputs should be fit for user needs***

Production of an output that is fit for user needs is fundamental to enabling implementation, improving resource benefits associated with using joint HTA outputs and reducing duplication of effort between HTA organisations.

### **Responsibilities of EUnetHTA**

The following areas of production activities require opportunities for broad user involvement because of their importance to successful implementation:

- Topic identification, selection and prioritisation (Other Technology priority)
- Scoping of assessments and defining the relevant research questions
- Timing of assessments
- Defining and standardising the content of joint assessments
- Development of assessment report structures

Users should have opportunities to engage in activities affecting the likely outputs of a permanent model of HTA cooperation regardless of their status in any particular EUnetHTA work package.

## **Responsibilities of EUnetHTA partners**

Individual EUnetHTA partners have a responsibility to:

- (1) identify prospective users of EUnetHTA outputs
- (2) facilitate access of prospective users to EUnetHTA activities so that user feedback is integrated into the development of EUnetHTA outputs

## **2. Users of EUnetHTA outputs should be aware of the outputs available**

To use a EUnetHTA output efficiently users require timely notification of availability.

### **Responsibilities of EUnetHTA**

Communication about EUnetHTA outputs starts as part of a broader communication strategy that promotes the value of EUnetHTA outputs to users, decision makers and stakeholders. EUnetHTA can engage and influence these groups directly to create an environment where EUnetHTA outputs are valued, and indirectly by creating resources that agencies can use to promote these messages.

Communication responsibilities for individual EUnetHTA outputs rest in all work packages and work packages need to work collaboratively with the EUnetHTA Communications Officer to support communication to all potential users. EUnetHTA is responsible for:

- Timely communication about planned, initiated and completed joint HTA outputs and timelines (and timeline changes) for these
- Communication through a variety of channels including direct communication based on the needs of target communication groups
- Access to assessments in a way that is easy to find and accessible
- Ongoing evaluation and feedback about communication and appropriate modalities of communication through advisory or liaison groups

## **Responsibilities of EUnetHTA partners**

EUnetHTA partners have a responsibility to promote EUnetHTA and its outputs to relevant users within their organisation and with other organisations within their area to disseminate awareness of EUnetHTA outputs and promote uptake.

## **3. Practical support to use EUnetHTA outputs**

Practical support to implement EUnetHTA outputs helps agencies understand how they can be used in agency processes and improve resource benefits of uptake.

## **Responsibilities of EUnetHTA**

Involvement in EUnetHTA production and development processes supports subsequent implementation of the joint HTA outputs by developing familiarity and trust with the procedures and outputs. The following production activities are specifically identified by partners as supporting uptake:

- Increase the number of assessments prepared (pharmaceutical priority)
- Broad involvement of partners in production processes and procedure development
- Coordination of topic selection so that all agencies will have had the opportunity to use an assessment in a topic of national relevance by the end of JA3

In addition, the following implementation activities support uptake

- Review existing resources to support implementation
- Shared examples of successful uptake initiatives.

## **Responsibilities of EUnetHTA partners**

EUnetHTA partners have a responsibility to promote participation in the production of EUnetHTA outputs and support their uptake. Where relevant, EUnetHTA partners should be involved in the production of assessments and use published assessments in agency procedures. EUnetHTA partners should encourage other agencies within their country to use EUnetHTA assessments where relevant.

### ***4. Implementation activities must have appropriate regard to proposals for a permanent model of HTA cooperation***

EUnetHTA JA3 supports the development of a permanent model of HTA cooperation. Implementation activities requiring changes in agency processes must be consistent with both the short term aims of increasing implementation in JA3 but also the longer-term proposals for a permanent model of HTA cooperation. In order to be able to make permanent changes to processes agencies require an understanding of what will be expected in the future.

## **Responsibilities of EUnetHTA**

- Provide support for EUnetHTA partners to understand how joint assessment products can fit into their wider decision-making processes (pharmaceutical priority).
- Undertake in-depth case studies and interviews with partners to analyse their uptake processes and changes that would be required with implementation of a permanent model of HTA cooperation

- Establish definitions and indicators of ‘acceptable’ use within the context of developing a permanent model of HTA cooperation

### **Responsibilities of EUnetHTA partners**

EUnetHTA partners are responsible for:

1. Analysing the impact of introducing EUnetHTA outputs into their processes and starting to develop plans for how EUnetHTA outputs could be incorporated into agency processes.
2. Participating in case studies and interviews to support EUnetHTA to analyse uptake processes and ensure that implementation issues are addressed both in the remainder of JA3 and in a permanent model of HTA cooperation.

### ***5. Uptake is regularly monitored and evaluated***

Accurate and timely data about uptake is critical to increasing the visibility of the impact of using EUnetHTA outputs, evaluating the success of the outputs and HTA cooperation and ensuring the EUnetHTA outputs produced remain relevant to changes in the HTA environment.

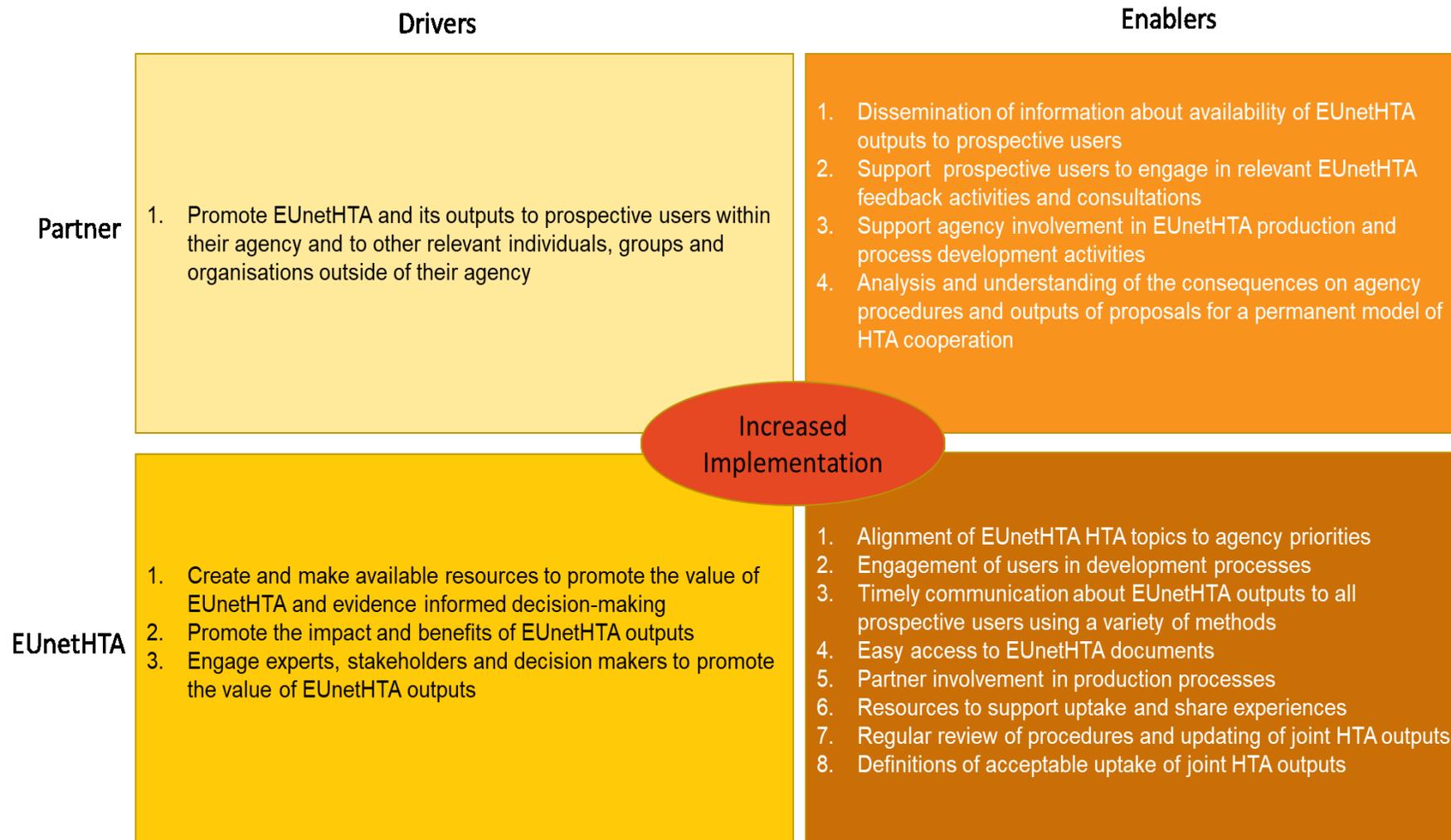
### **Responsibilities of EUnetHTA**

- Regularly review the implementation strategy and amend as requirements for HTA cooperation change
- Collate and publish information about uptake of joint HTA outputs

### **Responsibilities of EUnetHTA partners**

To provide EUnetHTA with timely feedback about the use of EUnetHTA outputs. To facilitate feedback from other relevant users within their organisation or in other organisations within the country on the use of EUnetHTA outputs.

**Figure 21: Summary of activities to promote increased implementation**



## Appendix 1: Agencies that participated in the case study

The table lists all the agencies that completed the survey. The agencies that participated in follow-up interviews are denoted in the final column with a Y.

Agency	Country	Interview
LBI-HTA	Austria	Y
GÖG	Austria	
RIZIV-INAMI	Belgium	Y
KCE (Belgian Health Care Knowledge Centre)	Belgium	
Croatian Ministry of Health - Former Agency for Quality and Accreditation in health Care and Social Welfare (AAZ)	Croatia	Y
State Institute for Drug Control (SUKL)	Czech Republic	
DEFACTUM	Denmark	Y
UTA	Estonia	
Finnish Medicines Agency (FIMEA)	Finland	
HAS	France	
IQWIG	Germany	Y
G-BA	Germany	
NIPN	Hungary	
HIQA	Ireland	
NCPE - Ireland	Ireland	
UCSC/Gemelli	Italy	Y
Agenas	Italy	
RER	Italy	
NHS of Latvia	Latvia	
VASPVT, Lithuania	Lithuania	
Directorate Pharmaceutical Affairs (DPA), Ministry for Health Malta	Malta	
Zorginstituut Nederland (ZIN)	Netherlands	
The Norwegian Medicines Agency (NOMA)	Norway	Y
Norwegian Institute of Public Health (NIPHNO)	Norway	
Agency for Health Technology Assessment and Tariff System (AOTMiT)	Poland	
INFARMED	Portugal	
National School of Public Health, Management and Professional Development Bucharest	Romania	
UNIBA-FoF	Slovakia	Y
Agency for Medicinal Products and Medical Devices of the Republic of Slovenia (JAZMP)	Slovenia	
MOH SI	Slovenia	
AQUAS	Spain	
Osteba - Basque Country's HTA Office	Spain	
SESCS-FUNCANIS (SPAIN)	Spain	
AETS-ISCIII	Spain	Y
AETSA	Spain	
SBU	Sweden	
The Dental and Pharmaceutical Benefits Agency (TLV)	Sweden	
SNHTA	Switzerland	
NICE	United Kingdom – England	
Scottish Medicines Consortium (SMC)	United Kingdom - Scotland	Y
Healthcare Improvement Scotland (SHTG)	United Kingdom - Scotland	
All Wales Therapeutics and Technology Centre (AWTTC)	United Kingdom - Wales	

