National Health Care Institute

MammaPrint®

ADDED VALUE OF USING GENE-EXPRESSION SIGNATURE FOR ADJUVANT CHEMOTHERAPY DECISIONS IN EARLY BREAST CANCER

Project ID: OTCA04

Project description and planning

Contents:

A. VERSION LOG

Version number	Date	Name (Initials)	Modification	Reason for the modification
V1	20/12/2016	AL	First version of draft project plan	
V2	31/03/2017	AL		Comments from dedicated reviewers incorporated
V3	08/11/2017	YL	Final version of Project Plan	Comments from editor incorporated

B. PROJECT PLAN

1.0 PARTICIPANTS

Table 1. Project participants

#	Agency	Country	Role in the project	Individual's expertise	Distribution of work
1.	National Health Care Institute (the Netherlands) (ZIN)	The Netherlands	Authors (AL and YK)	relative effectiveness	Author of all domains of the relative effectiveness assessment, reviewer of all domains of the cost effectiveness assessment[1]
2.	Belgian Health Care Knowledge Center (KCE)	Belgium	Co-Authors	relative cost-effectiveness	Co-author of all domains in the relative effectiveness assessment report, (and in the future author of all domains in the cost effectiveness assessment report)
3.	Ludwig Boltzmann Institute for HTA (LBI-HTA)	Austria	Dedicated reviewer	Reviewer	Reviewer of all domains of the relative effectiveness assessment
4.	Haute Autorité de Santé (HAS)	France	Dedicated reviewer	Reviewer	Reviewer of all domains of the relative effectiveness assessment
5.	Nederlandse Vereniging voor Medische Oncologie (NVMO)	The Netherlands	External Expert		Reviewer of all domains of the relative effectiveness assessment
6.	Dutch Scientific Advice Committee ([WAR] committee of 20-25 medical experts and methodologist	The Netherlands	External Expert		Reviewer of all domains of the relative effectiveness assessment
7.	Nextgenediting		Medical Editor		Editor of all domains of the relative effectiveness assessment
8.	ZIN/LBI HTA	The Netherlands, Austria	Project coordinator		

1.1 PROJECT STAKEHOLDERS

[1] This will be a separate report.

Table 2. Project stakeholders

Organisation's name	**Type of organisation**
Borstkanker Vereniging Nederland (BVN)	Patient group
Nederlandse Vereniging voor Medische Oncologie (NVMO)	Professional Group of medical oncologists.
Agendia	Manufacturer MammaPrint®

2.0 PROJECT INTRODUCTION/ RATIONALE

Project introduction/ rationale
The rationale for this assessment report is to produce collaborative assessments that are fit for purpose, of high quality, of timely availability, and cover the whole range of non-pharmaceutical health technologies. In addition, the implementation of the collaborative assessment in the national/regional practice will be facilitated.

3.0 PROJECT SCOPE AND OBJECTIVES

	List of project objectives	Indicator (and target)
1.	To produce collaborative health technology assessments that are fit for purpose, of high quality, of timely availability, and cover the whole range of health technologies.	Production of 1 rapid assessment according to the research question (see Table 3). Gene-expression assay, as the 70-gene signature (MammaPrint®) potentially provide additional prognostic information to distinguish early stage breast cancer patients who are likely to remain free of distant metastasis from patients who are likely to develop distant metastasis. Studies on analytic performances show that the MammaPrint® is reproducible and precise test. [2,3] The clinical validity was then evaluated in tumour specimens derived from prospectively completed studies. [4,5] The initial validation studies indicate that MammaPrint® can potentially help identify patients at low-risk of developing distant metastasis who might be able to skip chemotherapy.[2]
2.	To compile a rapid assessment of the clinical utility of Gene Expression Signature (GES) test MammaPrint®	Production of a rapid assessment of the respective technology. Breast cancer is the most commonly diagnosed cancer in women in the Netherlands (28.6% in 2015[6]), Belgium and worldwide. In 2012, the estimated age-adjusted annual incidence of breast cancer in 40 European countries was 94.2/100,000 and the mortality 23.1/100,000 [1]. The incidence increased after the introduction of mammography screening, and continues to grow with the ageing of the population. In the Netherlands over 3,000 persons die from breast cancer every year. Although there is an increase in breast cancer incidence, breast cancer mortality is decreasing in the last decennia, caused by the introduction of breast cancer screening (although this is under debate) and the improvement of adjuvant systemic treatment. Currently, the majority (60-84%) of breast cancer patients have

[2] Delahaye LJM, Wehkamp D, Floore AN et al, Performance characteristics of the MammaPrint breast cancer diagnostic gene signature. Personalized Medicine 10(8), 801-811 (2013)
[3] Beumer I, Witteveen A, Delahaye LJM. Equivalence of MammaPrint array types in clinical trials and diagnostics. Breast Cancer Res Treat, 156(2):279-87, (2016)
[4] Van de Vijver MJ, He YD, van 't Veer LJ et al. A gene-expression signature as a predictor of survival in breast cancer. N. Engl J. Med. 347(25), 1999-2099 (2002)
[5] Buyse M, Loi 2, van 't Veer LJ et al, Validation and clinical utility of a 70-gene prognostic signature for women with node-negative breast cancer. J. Natl Cancer Inst. 98(17), 1183-1192(2006)
[6] http://www.cijfersoverkanker.nl/ en Senkus et al. (2015) Primairy breast cancer:

		early stage (stage I and II) disease at the time of diagnosis, Overall five-year survival for women with stage I and II breast cancer is 87-98%, and ten-year survival is 78%-94%. Breast cancer has a significant burden of disease. In the top ten of diseases with the highest burden of disease in women, breast cancer takes place six. Most of the burden of disease (70%) of breast cancer is caused by premature death. Distant metastases account for the majority of breast cancer deaths. The incurable nature of metastatic breast cancer at this moment emphasizes the importance of selecting patients for adjuvant systemic therapy who are at risk of developing distant metastasis. Scope We are interested in direct evidence on the clinical utility of diagnostic tests, because test accuracy alone is not a measure of clinical effectiveness and patient related outcomes. We searched clinical trials databases to identity trials or studies in which the clinical utility of GES test (MammaPrint®, Oncotype DX®, PAM50 RT-PCR 50 genes, MapQuant DX, H/I*, EndoPredict, BluePrint, Randox Breast Cancer Array, Mammostrat, NPI+, IHC4, uPA/PAI-1, Prosigna and Breast Cancer Index) was evaluated. We only found for Mammaprint® and Oncotype DX® the publication of randomized studies that evaluated the clinical utility . The current EUnetHTA assessment will focus on the MammaPrint® as currently it is the only genomic signature test of which results with regard to the direct evidence on the clinical utility of the whole early-stage breast cancer population have been published in a peer reviewed journal. In the assessment of clinical utility we consider it as important that the gene signature should be performed on the whole population of early-stage breast cancer patients in order to identify all patients who would have been treated differently by the GES test. The results of the TAILORx study (Oncotype DX®) are scheduled to be published in December 2017. The results of the RxPONDER (Oncotype DX®) are expected to be due within the next years.
3.	To refine the production processes of collaborative assessment reports based on lessons learned and experiences from JA2 and probe a stepped roll-out of additional collaborative assessments yielding timely information.	Development of sustainable production processes for collaborative assessments. Production of collaborative assessments probing a decentralized coordination process and facilitating to meet national timelines.

4.	To develop a process that facilitates the implementation of the collaborative assessment in the national/regional practice.	Production of >2 national/local reports based on the collaborative assessment.

This rapid assessment addresses the following research question:

- In patients diagnosed with early invasive breast cancer, does a stepwise risk assessment approach (i.e 1st adjuvant! Online, followed by MammaPrint®), offer added value compared to treatment decisions based on the standard risk assessment test alone (i.e.Adjuvant! online).

Table 3. Project Scope: PICO

Description	Project scope
Population	Early stage breast cancer patients (pT1-2, operable T3, N0-3,cM0) ICD-10: C50 MESH: Breast Neoplasms
Intervention	MammaPrint® MammaPrint® is a gene-expression signature test decisive for or against receiving adjuvant chemotherapy. MammaPrint® will be assessed as add-on to standard clinical pathological criteria by Modified Adjuvant! Online (and possibly as replacement). Kind of technology: MammaPrint® is a genomic prognostic test that aims at providing a risk assessment of mamma carcinomas by giving a risk profile (i.e. low or high) of the chance of developing distant metastases. MammaPrint® is a gene expression signature test that measures the expression of 70 genes in cancerous breast tissue. MESH: Gene expression profiling
Comparison	Modified Adjuvant! Online is an online decision making tool used to decide on whether to administer adjuvant chemotherapy. Modified Adjuvant! Online was chosen as the comparator. Treatment decision-making on adjuvant chemotherapy is based on clinicopathological risk criteria (modified Adjuvant! Online): a high clinical risk means that adjuvant chemotherapy is indicated based on

	clinicopathological risk criteria , and a low clinical risk means that based on clinicopathological risk criteria no adjuvant chemotherapy is indicated.
Outcomes	Critical endpoints for relative effectiveness/safety • Ten-year overall survival (OS) • Health-related quality of life (QoL) • Short- and long-term side effects from chemotherapy such as cardiovascular and haematolo-oncological toxicity such as (sub-)clinical cardiac failure or secondary leukaemia, respectively If necessary, surrogate endpoints will be included. The relationship between the surrogate endpoint and critical endpoint will be described.
Study design	Effectiveness/safety • Randomised controlled trial (RCT) • If evidence from RCTs is limited, prospective observational studies will be considered for inclusion to provide more stable estimates of clinical utility.
Follow up time	• Follow-up time should be at least ten years and, if unavailable, shorter follow-up times where acceptable surrogate endpoints are available will be considered.

* Because the caregivers in Belgium and the Netherlands are positioning the MammaPrint® as an extra prognostic test, we decided to take this as a starting point for the PICO. When a diagnostic test is added to standard diagnostic test there has to be added value.

4.0 PROJECT APPROACH AND METHOD

Table 4a. Project approach and method

Project approach and method
Distribution of tasks among agencies: Distribution of tasks among agencies: As Author, ZIN will: • Have a leading role in both scoping and production of the relative effectiveness assessment; • Be responsible for management of the completed scientific work; • Have ultimate responsibility for quality assurance; • Be responsible for reviewing the cost effectiveness assessment report; • Answer comments.

As Co-author, KCE will:
- Be responsible for supporting the author in all project phases;
- Be responsible for reviewing all relative effectiveness domains and production of the cost effectiveness assessment;

As Dedicated reviewers, LBI and HAS will:
- Guarantee quality assurance by thoroughly reviewing the project plan and the assessment drafts and manufacturer's submission file;
- Review methods, results and conclusions based on the original studies included;
- Provide constructive comments in all the project phases.

Selection of Assessment Elements (AEs) and development of domains

A preliminary working version of the HTA Core Model® for Rapid Relative Effectiveness Assessment , based on the "HTA Core Model® for Rapid Relative Effectiveness Assessment of Pharmaceuticals 3.0", will be the primary source for selecting the assessment elements. Additionally, assessment elements from other EUnetHTA Core Model Applications will be screened and included if believed relevant to the present assessment. The REA Model Checklist will be used for potential ethical, organisational, social, and legal aspects.

The following domains will be developed within the present assessment:
- Description and technical characteristics of the technology (TEC);
- Health Problem and Current Use of Technology domains (CUR);
- Clinical effectiveness (EFF);
- Safety (SAF).

Selected assessment elements are presented in Table 5. Methods are described, per each domain, in the following sections.

TEC: This domain will be developed starting from the information provided by the manufacturer within the Manufacturer's Submission File. Whenever the Submission File has not been provided by the manufacturer or believed insufficient, information will be integrated with ad hoc PubMed and internet searches of grey literature using the Google search engine, review of the reference lists and bibliographies of studies identified through the basic systematic search, manufacturers' web sites, brochures, information for use, and regulatory bodies' databases.

CUR: This domain will be developed starting from the information provided by the manufacturer within the Manufacturer's Submission File. Whenever the Submission File has not been provided by the manufacturer or believed insufficient, information will be integrated with basic systematic searches, ad hoc PubMed and internet searches of grey literature using the Google search engine, review of the reference lists and bibliographies of studies identified through the basic systematic search, manufacturers' web sites, brochures and information for use.

EFF and SAF:

These domains will be developed using a systematic structured search of the literature. Searches of the following databases will be performed:

- MEDLINE;
- Embase;
- Cochrane Library;

MeSH terms in Table 3 will be combined with the following terms to perform the searches: Randomized Controlled Trial, and mammaprint (non-MESH) or 70-gene or 70 gene.

All searches will be performed limiting the results to English and Dutch language sources published between June 2014 (date of KCE literature search[7]) and the time of searches (March 2017).
In addition, the following clinical trials databases will be searched to identify ongoing trials or studies:

- ClincalTrials.gov;
- Cochrane Register of Controlled T
- https://www.clinicaltrialsregister.eu/

If only one RCT is found we will use studies with a lower level of evidence as supporting evidence (whether or not the evidence of these supporting studies go in the same direction) a described in the publication of KCE of published since then[7].
The retrieved data will be cross-checked against the submission file received from the manufacturer for completeness.

If possible, we will present results for the following subgroups if the data are of added value :
* low clinical risk population
* high clinical risk population
* ER status
* HER2 status
* other subgroups which are relevant

For the TEC and CUR domains no quality assessment tool will be used, but multiple sources will be used in order to validate individual, possibly biased, sources. Descriptive analysis will be performed on different information sources.

Distribution of tasks among team members:

- The two authors will screen the records by title and abstract. Disagreements will be solved by discussion. Potentially relevant studies will be retrieved in full-text and reconsidered for actual inclusion in the present evidence review. Data extraction will be performed independently by the two researchers on pre-defined extraction tables.
    - Methodological quality of systematic reviews will be based on the ROBIS (Risk of Bias in Systematic Reviews) tool.
    - The methodological quality of RCTs will be assessed using the Cochrane risk of bias tables[8] and EUnetHTA Guidelines.

[7] https://kce.fgov.be/publication/report/gene-expression-profiling-and-immunohistochemistry-tests-for-personalised-managem#.V4S6JKKVlTE

- The GRADE approach will be used to qualitatively summarise the results from the EFF and SAF domains.
- Quantitative results based on an intention-to-treat principle will be expressed as point estimates together with associated 95% confidence intervals (95% CI) and exact p-values.
- If more than one study is included, then pooled analysis of treatment effect using forest plots and standard meta-analytic techniques will be carried out provided sufficient study data are obtained and taking account of heterogeneity between studies. An assessment of the heterogeneity of included studies will be performed. The I^2 statistic will be examined to describe the proportion of the variability in the results that reflects real differences in effect size. Chi-squared test for heterogeneity will be performed; if significant heterogeneity is detected, possible explanations will be investigated. The clinical heterogeneity of the populations in included studies will also be assessed. Asymmetry of the funnel plot based on the data for the primary outcome will be taken as an indication of publication bias. Studies will also be assessed to ensure all proposed outcomes in the methods section are reported in the results section to exclude selective outcome reporting.
- Outcomes specified in the methods that are omitted from the results will be taken as evidence that outcomes were selectively reported. If this occurs the authors of the paper will be contacted to enquire if the results are reported elsewhere.

Table 4b. Preliminary Evidence

Preliminary evidence table
Preliminary evidence table The following information will be extracted from included primary studies: **Study general information:** - Author - Year of publication - Objectives **Study characteristics**: - Study design -allocation concealment (and method), randomisation (and method), blinding (outcome, assessors), PP analysis - Country(ies) of recruitment - Sponsor - Study duration **Patients groups:** - Number of patients (total and for each comparator) - Age

[8] Higgins JPT, Green S (editors). *Cochrane Handbook for Systematic Reviews of Interventions* Version 5.1.0 [updated March 2011]. The Cochrane Collaboration, 2011. Available from http://handbook.cochrane.org.

- Sex
- Inclusion criteria
- Exclusion criteria
- Diagnosis

Intervention
Comparator
Outcomes and follow-up
- Efficacy outcomes
- Safety outcomes

Conclusions
- Authors' conclusions
- Reviewers' comments

Selected assessment elements

Table 5. Assessment elements and translating research questions

ID	Topic	Topic Issue	Relevance in this assessment Yes/No	Research question(s) or reason for non-relevance of 'mandatory' elements
Description and technical characteristics of technology				
B0001	Features of the technology and comparators	What is the technology and the comparator(s)?	Yes	What is Mammaprint® and what is Adjuvant! Online?
A0020	Regulatory Status	For which indications has the technology received marketing authorisation or CE marking?	Yes	For which indications has the MammaPrint® received market authorisation or CE marking?
B0002	Features of the technology and comparators	What is the claimed benefit of the technology in relation to the comparator(s)?	Yes	What is the claimed benefit of MammaPrint® in relation to Adjuvant! Online?
B0003	Features of the technology	What is the phase of development and implementation of the technology and the comparator(s)?	No	Question = non-mandatory and not relevant for the scope of this assessment.

ID	Topic	Topic Issue	Relevance in this assessment Yes/No	Research question(s) or reason for non-relevance of 'mandatory' elements
B0004	Features of the technology	Who administers the technology and the comparator(s) and in what context and level of care are they provided?	Yes	Who is involved (prescriber, assessor) in applying the technology?
B0008	Investments and tools required to use the technology	What kind of special premises are needed to use the technology and the comparator(s)?	No	Question = non-mandatory and not relevant for the scope of this assessment.
B0009	Investments and tools required to use the technology	What equipment and supplies are needed to use the technology and the comparator(s)?	No	Question = non-mandatory and not relevant for the scope of this assessment.
A0021	Regulatory Status	What is the reimbursement status of the technology?	No	Question = non-mandatory and not relevant for the scope of this assessment.
Health problem and current use of technology				
A0002	Target Condition	What is the disease or health condition in the scope of this assessment?	Yes	What is the disease in the scope of this assessment?
A0003	Target Condition	What are the known risk factors for the disease or health condition?	No	Question = non-mandatory and there is no relevant differences between the technology and the comparator.
A0004	Target Condition	What is the natural course of the disease or health condition?	Yes	What is the natural course of the disease?
A0005	Target Condition	What are the symptoms and the burden of disease or health condition for the patient?	Yes	What are the symptoms and the burden of disease for the patient?
A0006	Target Condition	What are the consequences of the disease or health condition for the society?	Yes (non-mandatory question)	What are the consequences of the disease for the society?

ID	Topic	Topic Issue	Relevance in this assessment Yes/No	Research question(s) or reason for non-relevance of 'mandatory' elements
A0024	Current Management of the Condition	How is the disease or health condition currently diagnosed according to published guidelines and in practice?	Yes	How is breast cancer currently diagnosed and staged?
A0025	Current Management of the Condition	How is the disease or health condition currently managed according to published guidelines and in practice?	Yes	How is the breast cancer treatment and risk assessment for adjuvant systemic management according to published guidelines and in practice?
A0007	Target Population	What is the target population in this assessment?	Yes	What is the target population in this assessment?
A0023	Target Population	How many people belong to the target population?	Yes	How many people belong to the target population?
A0011	Utilisation	How much are the technologies utilised?	No	Question = non-mandatory and not relevant for the scope of this assessment.
Clinical effectiveness				
D0001	Mortality	What is the expected (beneficial) effect of the intervention on mortality?	Yes	What is the expected effect of the intervention on mortality?
D0032	Morbidity	How does the test-treatment intervention modify the magnitude and frequency of morbidity?	Yes	How does the test-treatment intervention modify the magnitude and frequency of morbidity?
D0011	Function	What is the effect of the technology on patients' body functions?	Yes	What is the effect of the MammaPrint® and treatment on patients' body functions?
D0016	Function	How does the use of technology affect activities of daily living?	Yes (non-mandatory question)	How does the use of MammaPrint® and treatment affect activities of daily living?
D0012	Health-related quality of life	What is the effect of the technology on generic health-related quality of life?	Yes	What is the effect of the MammaPrint® and treatment on generic health-related quality of life?
D0013	Health-related	What is the effect of the technology on disease-specific quality of life?	Yes	What is the effect of the MammaPrint® and treatment on disease-specific

ID	Topic	Topic Issue	Relevance in this assessment Yes/No	Research question(s) or reason for non-relevance of 'mandatory' elements
	quality of life			quality of life?
D0017	Patient satisfaction	Were patients satisfied with the technology?	Yes (non-mandatory question)	How many patients follow the treatment advice based on the MammaPrint® result?
Safety				
C0008	Patient safety	How safe is the technology in relation to the comparator(s)?	Yes	How safe is the technology in relation to the comparator(s)?
C0002	Patient safety	Are the harms related to dosage or frequency of applying the technology?	No	Question = non-mandatory and there are no relevant differences between the technology and the comparator.
C0004	Patient safety	How does the frequency or severity of harms change over time or in different settings?	Yes	What are the advantages of not receiving chemotherapy (what harms were prevented)?
C0005	Patient safety	What are the susceptible patient groups that are more likely to be harmed through the use of the technology?	Yes	What are the susceptible patient groups that are more likely to be harmed through the use of the MammaPrint®*?
C0006	Patient safety	What are the consequences of false-positive, false-negative and incidental findings generated by using the technology from the viewpoint of patient safety?	Yes	What are the consequences of false-positive, false-negative and incidental findings generated by using the technology from the viewpoint of patient safety viewpoint?
C0007	Patient safety	Are the technology and comparator(s) associated with user-dependent harms?	No	Question = non-mandatory
B0010	Safety risk management	What kind of data/records and/or registry is needed to monitor the use of the technology and the comparator(s)?	No	Question = non-mandatory and there are no safety issues in using the MammaPrint®, it will be necessary to register the long term effects of patients: overall survival and harms of chemotherapy (toxicity).
Further assessment elements for diagnostic and screening technologies only				
D1001	Test accuracy	What is the accuracy of the test against reference standard?	No	We focus only on available studies in which test-treatment effects are randomly researched.

ID	Topic	Topic Issue	Relevance in this assessment Yes/No	Research question(s) or reason for non-relevance of 'mandatory' elements
D1005	Test accuracy	What is the optimal threshold value in this context?	No	We focus only on available studies in which test-treatment effects are randomly researched.

Checklist for patient and social aspects

Table 6. Checklist for potential ethical, organisational, patient and social and legal aspects.

1. Ethical	
1.1. Does the introduction of the new technology and its potential use/non-use instead of the defined, existing comparator(s) give rise to any new ethical issues?	No
If answered with 'yes', please provide a short statement explaining why. *Example:* Routine introduction of prenatal genetic screening tests, which could lead to pregnancy termination, may cause ethical issues for the couple as well as for the health-care provider.	
1.2. Does comparing the new technology to the defined, existing comparators point to any differences that may be ethically relevant?	No
If answered with 'yes', please provide a short statement explaining why. *Example:* The marketing authorisation holder claims that its product is superior, but has decided to limit the amount of the new medicine, which means that it has to be rationed and not all patients who need it can receive it. The comparator is freely available.	
2. Organisational	
2.1. Does the introduction of the new technology and its potential use/non-use instead of the defined, existing comparator(s) require organisational changes?	No
If answered with 'yes', please provide a short statement explaining why. *Example:* The new intervention requires the establishment of specialised centres for administration.	
2.2. Does comparing the new technology to the defined, existing comparator(s) point to any differences that may be organisationally relevant?	No
If answered with 'yes', please provide a short statement explaining why. *Example:* The new technology will replace a surgical intervention, which may lead to excess capacity in relevant areas.	

3. **Social**	
3.1. Does the introduction of the new technology and its potential use/non-use instead of the defined, existing comparator(s) give rise to any new social issues?	Yes, if a patient safely can omit chemotherapy she probably will be able to keep working like she normally did.
If answered with 'yes', please provide a short statement explaining why. *Example:* A new technology allows patients to return to the workplace, but since the technology can be seen by co-workers, it may lead to stigmatisation.	
3.2. Does comparing the new technology to the defined, existing comparator(s) point to any differences that may be socially relevant?	No
If answered with 'yes', please provide a short statement explaining why. *Example:* A technology, which is widely used by persons with abuse problems, colours the tongue blue, thus, immediately identifying the user. Comparators do not have this property.	
4. **Legal**	
4.1. Does the introduction of the new technology and its potential use/non-use instead of the defined, existing comparator(s) give rise to any legal issues?	No
If answered with 'yes', please provide a short statement explaining why. *Example:* The comparator for the new technology is a pharmaceutical that is not licensed for the indication of concern, but is widely in use.	
4.2. Does comparing the new technology to the defined, existing comparator(s) point to any differences that may be legally relevant?	No

If answered with ‘yes’, please provide a short statement explaining why.

Examples:

- The comparator for the new technology is a controlled, restricted substance, but the new medicine is not.
- The most appropriate comparator for the new technology is available as a pharmacy-compounded medicine, but not as a finished product with marketing authorisation.

Note: The assessment should not address patent-related issues.

5.0 ORGANISATION OF THE WORK

5.1 MILESTONES AND DELIVERABLE(S)

Table 7. Milestones and Deliverables

Milestones/Deliverables	**Start date**	**End date**
Project duration	**01/12/2016**	**01/01/2018**
Scoping phase	01/12/2016	01/04/2017
Identification of manufacturers		
Scoping and development of draft Project Plan	01/12/2016	01/04/2017
Internal Scoping e-meeting (optional)	*09/03/2017*	*09/03/2-17*
Scoping (e-) meeting with manufacturer(s) (optional)	*20/12/2016*	*20/12/2016*
Consultation of draft Project Plan with dedicated reviewers	13/02/2017	24/02/2017
Amendment of draft Project Plan & final Project Plan available	27/02/2017	01/04/2017
Assessment phase	15/05/2017	18/12/2017
Writing first draft rapid assessment	15/05/2017	18/07/2017
Review by dedicated reviewer(s)	18/07/2017	17/08/2017
Writing second draft rapid assessment+medical editing +e-meeting with dedicated reviewers	17/08/2017	29/09/2017
Review by ≥ 2 external clinical experts (and by other potential stakeholders) + manufacturer (Agendia)	29/09/2017	20/10/2017
Medical editing	29/09/2017	20/10/2017
Writing of final version of rapid assessment	20/10/2017	24/11/2017
Formatting	24/11/2017	08/12/2017
Final version of REA		*22/12/2017*
Local Reports (if applicable)		

5.2 MEETINGS

An e-meeting may be held with the pilot team during the Scoping phase. Whenever needed, further e-meetings can be scheduled.

6.0 COMMUNICATION

We will set up meetings with relevant parties, whenever needed.

6.1 DISSEMINATION PLAN

The final rapid assessment will be distributed as laid-out in the Work Plan of WP4.

7.0 COLLABORATION WITH STAKEHOLDERS

The 2nd draft version of the assessment will be reviewed by external experts (and other potential stakeholders).

Collaboration with other stakeholders

8.0 COLLABORATION WITH EUnetHTA WPs

For the individual rapid assessment, no collaboration with other WPs is planned.

9.0 RESOURCE PLANNING

9.1 HUMAN RESOURCES

Table 9. Human resources

Role	**Total number of person days**	**Source**	
		Staff of participating organisations	**Subcontracting**
Author	60 person days	60 person days	-
Co-Author	20 person days	20 person days	-
Dedicated Reviewer	3 person days each	3 person days each	-
External reviewer	10 person days	-	10 person days
Medical Editor	10 person days	-	10 person days
Layout	5 person days	-	5 person days

10.0 CONFLICT OF INTEREST MANAGEMENT

Conflicts of interest will be handled according to EUnetHTA JA2 Conflict of Interest Policy. As conflict of interest may be topic dependent, conflict of interest declarations will be collected from authors and reviewers involved in a specific assessment via the Declaration of interest and

confidentiality undertaking (DOICU) form. Authors and reviewers who declare a conflict of interest will be excluded from parts of, or the whole work under this specific topic. However, they may still be included in other assessments.
If external experts are involved in WP4 a conflict of interest declaration will be collected from them regarding the topic. External experts who declare a conflict of interest will be excluded from parts of, or the whole work under this specific topic. However, they may still be included in other assessments.

11.0 EXPECTED OUTCOME(S)

Project outcome(s)
Collaborative assessments that are fit for purpose, of high quality, of timely availability, and cover the whole range of non-pharmaceutical health technologies will have been produced. These assessments will have been used in the national/local context. Production processes for collaborative assessment reports will have been refined based on lessons learned and experiences from JA2. The decentralized approach for producing collaborative assessments will have been probed. The implementation of collaborative assessments in the national/local context will have been facilitated.

C. REFERENCES

Please see footnotes.