EUnetHTA Joint Action 3 2016-2020

High intensity focused ultrasound (HIFU) ablation in prostate cancer

Project ID: ***OTCA09***

Project description and planning

Ludwig Boltzmann Institute for Health Technology Assessment

State Health Care Accreditation Agency under the Ministry of Health

Version Log

Version number	Date	Modification	Reason for the modification
V1	11/12/17	First draft	-
V2	18/12/17	Developed draft	Comments from co-authors included
V3	10/01/18	Further developed draft	Comments from dedicated reviewers included
V4	20/02/18	Final draft	Comments from external experts included

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1 Project organisation

1.1 Participants

Table 1-1: Project participants

	Agency	Role in the project	Country	Distribution of work
Assessment team				
1.	LBI-HTA	Author	Austria	Develop first draft of EUnetHTA project plan, amend the draft if necessary. Perform the literature search Carry out the assessment: answer assessment elements, fill in checklist regarding potential "ethical, organisational, patient and social and legal aspects" of the HTA Core Model R for rapid REA (see table 6) Send "draft versions" to reviewers, compile feedback from reviewers and perform changes according to reviewers comments Prepare final assessment and write a final summary of the assessment
2.	VASPVT	Co-Author	Lithuania	Review draft EUnetHTA project plan Check and approve all steps (e.g. literature selection, data extraction, assessment of risk of bias) Review draft assessment, propose amendments where necessary (perform additional hand search of literature if needed) and provide written feedback on: • information retrieval: sources and search terms for locating domain specific information, inclusion/exclusion criteria for studies or other information, in terms of content, methods and quality. • handling the published data: do a systematic review, cite recent reviews, "screen until saturated" etc. • finding information when there is no published data: From web sites of organisations, discussion forums, registers: Other type of own research (analysis of primary data, modelling etc). • quality assessment tools or criteria planned to be used synthesis: evidence table, plan for meta-analysis or qualitative

				synthesis, use of GRADE, etc.
3.	AETS-ISCIII	Dedicated Reviewer	Spain	Guarantee quality assurance by thoroughly reviewing the project plan and the assessment drafts; •Review methods, results, and conclusions based on the original studies included; •Provide constructive comments in all the project phases
4.	OSTEBA	Dedicated Reviewer	Spain	Guarantee quality assurance by thoroughly reviewing the project plan and the assessment drafts; •Review methods, results, and conclusions based on the original studies included; •Provide constructive comments in all the project phases
5.	SNHTA	Dedicated Reviewer	Switzerland	Guarantee quality assurance by thoroughly reviewing the project plan and the assessment drafts; •Review methods, results, and conclusions based on the original studies included; •Provide constructive comments in all the project phases
6.	NSPHMPD	Observer	Romania	Observe the process
Contributors				
7.	Dr. Roberto Llarena Ibarguren, Hospital Universitario Cruces	External expert	Spain	Guarantee quality assurance by thoroughly reviewing the project plan and the assessment drafts; •Review methods, results, and conclusions based on the original studies included; •Provide constructive comments in all the project phases
8.	Dr. Rolf Muschter, Urologisches Zentrum, Lübeck	External expert	Germany	Guarantee quality assurance by thoroughly reviewing the project plan and the assessment drafts; •Review methods, results, and conclusions based on the original studies included; •Provide constructive comments in all the project phases
9.	Margaret Ryan, Compuscript Ltd.	Medical Editor		Medical editing
10.	Ludwig Boltzmann Institute for Health Technology Assessment, LBI-HTA	Project Manager	Austria	Project management

1.2 Project stakeholders

Table 1-2: Project stakeholders

Organisation	Role in the project
EDAP TMS	manufacturer

Focus Surgery	manufacturer
Insightec	manufacturer
Profound Medical	manufacturer

1.3 Milestones and Deliverables

Table 1-3: Milestones and Deliverables

Milestones/Deliverables	Start date	End date
Project duration	**27/11/2017**	**22/03/2018**
Scoping phase	27/11/2017	10/01/2018
Identification of manufacturer(s) and external experts; *optional: identification of patients*	27/11/2017	06/12/2017
Scoping and development of draft Project Plan incl. preliminary PICO	27/11/2017	06/12/2017
Share the preliminary PICO with external experts *(and patients)* for comments		
Internal Scoping e-meeting with the assessment team	*12/12/2017*	*12/12/2017*
Send the preliminary PICO for comments (in case there is no scoping meeting planned) *and the request for the completion of the Submission file template to manufacturer(s) (optional)*	*15/12/2017*	20/12/2017
Consultation of draft Project Plan with dedicated reviewers	18/12/2017	23/12/2017
Consultation of draft Project Plan with external experts *(and patients)*	11/01/2018	26/01/2018
Amendment of draft Project Plan & final Project Plan available	26/01/2018	30/01/2018
Completion of Submission file template by manufacturer(s) + Clarifying further questions concerning draft Submission file) (optional)	*29/12/2017*	*30/01/2018*
Assessment phase	02/01/2018	22/03/2018
Writing first draft rapid assessment	02/01/2018	13/02/2018
Review by dedicated reviewer(s)	14/02/2018	22/02/2018
Writing second draft rapid assessment	22/02/2018	23/02/2018
Review by ≥ 2 external clinical experts and fact check by manufacturers	23/02/2018	06/02/2018
Writing third draft rapid assessment	06/02/2018	08/03/2018
Medical editing	09/03/2018	13/03/2018
Writing of fourth version of rapid assessment	14/03/2018	15/03/2018
Formatting	16/03/2018	19/03/2018
Final version of rapid assessment		**week** from – 19/03/2018 to 22/03/2018

2 Project Outline

2.1 Project Objectives

The rationale of this assessment is to collaboratively produce structured (rapid) core HTA information on other technologies. In addition, the aim is to apply those collaboratively produced assessments in the national or regional context.

Table 2-1: Project objectives

	List of project objectives	Indicator (and target)
1.	To jointly produce 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) relative effectiveness assessment.
2.	To apply this collaboratively produced assessment into local (e.g. regional or national) context.	Production of ≥2 local (e.g. national or regional) reports based on the jointly produced assessment.

This rapid assessment addresses the research questions whether
1, whole or focal ablation of the prostate using high intensity focused ultrasound (HIFU) with trans-rectal ultrasound (TRUS) imaging guidance or with magnetic resonance imaging (MRI) guidance as first-line treatment in adult men with low-risk or intermediate-risk localised prostate cancer (T1a-T2, N0-Nx, M0) is more (or equally) effective and safer than (or equally safe as) any definitive radical prostatectomy (RP), any definitive radiation therapy (RT), active surveillance (AS) or watchful waiting (WW).

2, whole or focal ablation of the prostate using high intensity focused ultrasound (HIFU) with TRUS imaging guidance or MRI guidance as salvage therapy in adult men with locally relapsed/ recurrent low-risk or intermediate-risk prostate cancer (T1a-T2, N0-Nx, M0) after any definitive RP, any definitive RT is more (or equally) effective and safer than (or equally safe as) any salvage RP, any salvage RT, AS or WW.

This topic was chosen based on a request from a government authority who commissioned LBI-HTA to do an HTA on HIFU in men with prostate cancer. The relevance of the topic lies in the fact that it is not yet in the reimbursement catalogue and the therapy is a new minimally invasive therapy.

2.2 Project Method and Scope

2.2.1 Approach and Method

Table 2-2: Project approach and method

Project approach and method
The HTA Core Model Application for rapid Relative Effectiveness Assessment (REA) (4.2) will be the primary source for selecting assessment elements. The selected assessment element generic questions will be translated into research questions. **TEC and CUR domains** Answers to these domains will be based on • Input from manufacturers, particularly related to questions on CE mark, marketing, availability and current use. The Medical Devices Evidence Submission template will be

sent to all relevant manufacturers of the technology under assessment. Manufacturers will be asked to submit non-confidential evidence, focusing on the technical characteristics and current use of the technology.
- The evidence provided will be used in addition to the literature identified by the literature search.
- Input from clinical experts, particularly related to description of disease, current treatment, current use and best available epidemiological data. The clinical experts will be asked to verify the relevance and accuracy of the information and citations.
- Clinical guidelines. A search for the clinical guidelines will be performed by the author using G-I-N as a source.

EFF and SAF domains
We will do a systematic search of the literature, and as such update the systematic review authored by LBI-HTA in 2010 [1].
The author and co-author will independently screen the titles and abstracts and select studies according to the pre-defined inclusion and exclusion criteria. The full-text publications will be retrieved by the author and the full-text examination will be performed by the author and the co-author independently. The author will provide a list of included and excluded studies. In case of disagreement, third parties (dedicated reviewers, external experts) will be involved.

Study and outcomes validity and level of evidence will be assessed according to the EUnetHTA guidelines. The Cochrane Risk of bias tool will be used on study and outcome level. The quality of the body of evidence will be assessed using GRADE (Grading of Recommendations, Assessment, Development and Evaluation). The author will perform the risk of bias assessment and the GRADE assessment, the co-author will check it. Disagreements will be resolved by consensus.

Table 2-3: Planned literature search strategy

Literature search strategy
• Sources for locating EFF and SAF domain specific information: Embase, Medline, CRD database, Cochrane Library. • Search terms: Prostatic Neoplasms, cancer* or neoplasm* or carcinoma* or tumo*r* or adenoma* word variations, High-Intensity Focused Ultrasound Ablation with word variations, Magnetic resonance-guided focus*ed ultra*sound* with word variations, Ablatherm, Insightec, Sonablate, Exablate, Focus Surgery, EDAP • Inclusion criteria: language: English or German • Exclusion criteria: publication date before 2010.01.01, retrospective study design, less than 50 patients (low-and intermediate-risk) in prospective single-arm cohort studies, studies with all risk group patients where the number of low-and intermediate risk patients cannot be distinguished, studies in which HIFU is administered as combination therapy • Relevant ongoing RCTs will be identified by searching the following information sources: Clinicaltrials.gov, international clinical trials registry platform (ICTRP), EU Clinical Trials Register

Table 2-4: Plan for data extraction

Planned data extraction
Data to be extracted from the studies included:

- Information about the study (authors, year of publication, setting/country, funding, study design, clinical trial identification number/ registry identifier and funding source)
- Participant/patient characteristics (number of participants in the trial, age, clinical stage, risk category,)
- Intervention and control characteristics (description of procedure, comparator, name/type of the device, frequency of intervention per patient, length of follow up and loss to follow up)
- Outcomes (Effectiveness endpoints: overall survival rate, prostate cancer specific survival rate, local disease recurrence, distant disease recurrence, biochemical recurrence/failure, disease progression/pathological progression, quality of life, need for salvage treatment, ablation failure, positive surgical margin. Safety endpoints: mortality, adverse events, functional outcomes (urinary dysfunction, sexual dysfunction, bowel dysfunction)).

For missing data trial authors will be contacted by the author.

Dichotomous outcome results will be expressed as risk ratio (RR). Where continuous scales of measurement are used to assess the effects of treatment, the mean difference (MD) will be used; if different scales are used the standardised mean difference (SMD) will be used.

Relevant subgroup analyses will be performed based on the type of device and technique (HIFU with TRUS or MRI guidance; whole gland or focal lesion based ablation) if possible.

2.2.2 Project Scope

Table 2-5: Project Scope: PICO (please see HTA Core Model® for rapid REA)

Description	Project Scope
Population	• Adult men with clinically localised prostate cancer (cT1a-T2, N0-Nx, M0) based on TNM staging, Gleason score/grade group, serum PSA o Low-risk: clinical stage cT1a-T2a, Gleason score ≤ 6, PSA < 10 ng/mL o Intermediate-risk: clinical stage T2b, Gleason score 7, PSA 10 to 20 ng/mL • Adult men with locally relapsed/ recurrent prostate cancer after failed radical prostatectomy (RP), radiation therapy (RT), or high-intensity focused ultrasound (HIFU) (cT1a-T2, N0-Nx, M0) • MeSH: prostatic neoplasms C04.588.945.440.770, C12.294.260.750, C12.294.565.625, C12.758.409.750 Intended use of the technology: <u>first-line treatment or salvage therapy</u>. Rationale: population was defined based on the EAU guideline [2], NICE guidance [3], S3 Leitlinie (German oncology guideline program) [4] and the indications of CE mark approvals.
Intervention	• ablation of the prostate gland using high-intensity focused ultrasound (HIFU) with trans-rectal ultrasound imaging (TRUS) guidance or with magnetic resonance imaging (MRI) guidance • MeSH: E02.565.280.945.399, E04.014.380 • Products/manufacturers: o Ablatherm® (company: EDAP TMS, France) ▪ Ablatherm® Integrated Imaging and its predecessors (Ablatherm® Maxis and Ablatherm® prototype) ▪ Focal One® o Sonablate® (company: Focus Surgery, Inc., USA) ▪ Sonablate® 500 and its predecessors (Sonablate® 200, Sonablate® 450) ▪ Sonatherm® ▪ Sonasource® o ExAblate® system (company: Insightec, Israel): focal therapy o TULSA-PRO® (company: Profound Medical, Canada): focal therapy
Comparison	1, Deferred treatment: • Active surveillance/monitoring • Watchful waiting 2, Radical prostatectomy (RP) with or without pelvic lymphadenectomy including: • Laparoscopic surgery • Robotic surgery

	• Open surgery 3, Definitive radiotherapy (RT) including but not restricted to: • External-beam radiation therapy (EBRT) with or without short-term androgen deprivation therapy (ADT) o 3D conformal radiotherapy o intensity modulated radiotherapy (IMRT) with or without image guided radiotherapy (IGR) • Brachytherapy: low-dose rate (LDR) or high-dose rate (HDR) • Combination of EBRT and brachytherapy Rationale: standard interventions for the target population according to the clinical guidelines (S3 Leitlinie [4], NICE [3], EAU [2]).
Outcomes	<u>Effectiveness-related:</u> • Overall survival/mortality (e.g. 5 and 10 year survival) (important) • **Prostate cancer specific survival/mortality** (critical) • **Local disease recurrence** (presence of significant PCa measured by biopsy and/or mpMRI) (critical) • Distant disease recurrence/metastases (important) • Biochemical recurrence/failure (increasing prostate-specific antigen (PSA) level according to ASTRO or Phoenix definition) (important) • Disease progression/pathological progression (increase in Gleason score or tumour volume evidenced by a larger number of positive biopsies or larger per-core tumour involvement) (important) • Quality of life (generic and/or disease specific measured by one of the following: UCLA-EPIC, EORTC-QLQ-30, FACIT (FACT-P and FACT-G), MAX-PC, PORPUS, EQ-5D) (important) • Need for salvage local therapy and need for systemic (hormonal or chemotherapeutic) therapy (important) • Ablation failure (failure of the technique to destroy the tissue in the treated zone, including targeting failure) (important) • Positive surgical margin (important) <u>Safety-related:</u> • **Intervention-specific mortality (peri-operative death)** (critical) • **Functional outcomes** (critical) o urinary (dys)function: urinary incontinence (measured by IPSS, UCLA-EPIC urinary domain or defined as urinary leakage or use of pads) o bowel (dys)function: faecal incontinence (measured by the UCLA-EPIC bowel domain, rectal discomfort, and change in stool frequency) o sexual (dys)function: impotence, erectile dysfunction (measured by IIEF-5 or IIEF-15, BMSFI, or any other author definitions) • **Procedural complications/adverse events:** including but not restricted to (critical) o urinary tract infection o acute and chronic urinary retention o lower urinary tract symptoms (LUTS) o pain

	o burn, injuries, bleeding o proctitis o anesthesia-related complications o thromboembolic disease o bladder neck obstruction, o urethral or bladder neck stenosis o stricture o rectal fistula Rationale: we have chosen the outcomes based on the recommended core outcome set for localised prostate cancer [5], Consensus paper on the standardization of definitions on focal therapy of prostate cancer [6], (EUnetHTA guidelines on clinical endpoints and safety [7-9], EAU guideline [2].
Study design	Effectiveness: randomized controlled trials, prospective non-randomized controlled trials Safety: randomized controlled trials, prospective non-randomized controlled trials, single-arm prospective cohort studies with at least 50 patients

3 Communication and collaboration

Table 3-1: Communication

Communication Type	Description	Date	Format	Participants/ Distribution
Scoping	To internally discuss and reach consensus on the scoping.	12/12/2017	E-meeting	Author(s), co-author(s), dedicated reviewers, observers, project manager
	To discuss the preliminary PICO and draft project plan with manufacturer(s) – optional	[DD/MM/YYYY]	*Face to face or e-meeting*	*Author(s), co-author(s), manufacturer(s), project manager*
		[DD/MM/YYYY]	*Additional e-meetings may be planned whenever needed*	*Author(s), Co-author(s), dedicated reviewer(s), project manager*
Feedback on draft submission file (optional)	*To point out the requirements for the final submission file by manufacturers*	*[DD/MM/YYYY]*	*E-mail*	*Author(s), project manager, manufacturers*
First draft of the rapid assessment	*To discuss comments of dedicated reviewers*	*[DD/MM/YYYY]*	*E-meetings may be planned*	*Author(s), co-author(s), dedicated reviewers*
Second draft of the rapid assessment	*To discuss comments from ≥ 2 external clinical experts and manufacturers*	*[DD/MM/YYYY]*	*E-meetings may be planned*	*Author(s), co-author(s), dedicated reviewers; external experts, manufacturers*

3.3 Dissemination plan

The final rapid assessment will be published on the EUnetHTA website: http://www.eunethta.eu/joint-assessments.

All stakeholders and contributors are informed about the publication of the final assessment by the project manager.

3.4 Collaboration with stakeholders

Collaboration with manufacturer(s)

There will be a review of the preliminary PICO and a fact check of the 2nd draft project plan and the 2nd draft assessment by the manufacturer(s). Furthermore authors will ask the manufacturers to complete the submission file.

Collaboration with other stakeholders

None is planned.

3.5 Collaboration with EUnetHTA WPs

For the individual rapid assessment, some collaboration with other WPs is planned: WP7 [Implementation] will be informed of the project, in order to prepare activities to improve national uptake of the final assessment. Feedback on the WP4 REA process will be asked from the involved parties by WP6 [Quality Management], and this information will be processed by WP6 to improve the quality of the process and output.

3.6 Conflict of interest and confidentiality management

Conflicts of interest will be handled according to the EUnetHTA Conflict of Interest Policy. All individuals participating in this project will sign the standardised “Declaration of Interest and Confidentiality Undertaking” (DOICU) statement.

Authors, co-authors and dedicated reviewers who declare a conflict of interest will be excluded from parts of or the whole work under this specific topic. However they still may be included in other assessments.

For external experts, patients or other stakeholders involved, conflict of interest declarations are collected regarding the topic. External experts or patients who declare conflict of interest will be excluded from parts of or the whole work under this specific topic. However they still may be included in other assessments.

Manufacturer(s) will sign a Confidentiality Undertaking (CU) form regarding the specific project.

4 References

1. Warmuth M, Johansson T. Hochintensiver fokussierter Ultraschall (HIFU) zur Behandlung des Prostatakarzinoms. Systematic Review Decision Support Document Nr 037. Wien: Ludwig Boltzmann Institut für Health Technology Assessment (LBI-HTA); 2010.
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4. Leitlinienprogramm Onkologie (Deutsche Krebsgesellschaft DK, AWMF),. Interdisziplinäre Leitlinie der Qualität S3 zur Früherkennung, Diagnose und Therapie der verschiedenen Stadien des Prostatakarzinoms. 2016.
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7. EUnetHTA. Guideline - Endpoints used in Relative Effectiveness Assessment - SAFETY. 2015 [cited 2017 30.11.2017]; Available from: http://www.eunethta.eu/outputs/endpoints-used-relative-effectiveness-assessment-safety-amended-ja1-guideline-final-nov-2015.
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