EUnetHTA Joint Action 3 2016-2020

Biodegradable rectum spacers to reduce toxicity for prostate cancer

Project ID: ***OTCA23***

Project description and planning

The Norwegian Institute of Public Health (NIPHNO), Norway

National School of Public Health, Management and Professional Development (NSPHMPD), Romania

Version Log

Version number	Date	Modification	Reason for the modification
V1.1	22/08/19	1st version of the draft project plan sent to co-authors	Integration of comments and suggestions after internal scoping meeting and input from the external experts
V2	05/09/2019	Draft sent to dedicated reviewers	Integration of comments and suggestions from co-authors
V3	23/09/2019	Draft sent to experts (clinical expert, manufactures) and patient partner in the team	Integration of comments and suggestions from dedicated reviewers
V4	18/112019	Final version	Integration of comments from experts, integration of comments from manufacturers

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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.	The Norwegian Institute of Public Health (NIPHNO)	Author	Norway	Overall responsibility on production and quality of the assessment; develop first draft of the project plan; perform the literature search; carry out the assessment: select and answer assessment elements (for the domains EFF and SAF); fill in the checklist on potential "ethical, organisational, patient and social and legal aspects" of the HTA Core Model for rapid REA; quality check all steps of the production process for the TEC and CUR domain; send "draft versions" to reviewers for comments, compile feedback from reviewers and incorporate relevant changes to the draft; prepare all draft versions and the final assessment including an executive summary.
2.	National School of Public Health, Management and Professional Development (NSPHMPDB)	Co-Author	Romania	Review the project plan draft; select and answer assessment elements for the domains TEC and CUR. Support the production of the assessment report and quality check all steps of their production (data, information, sources); contribute in answering questions related to potential ethical, organisational, patient and social and legal aspects if needed. Approve/endorse conclusions drawn as well as all draft versions and the final assessment including the executive summary.
3.	Swiss Network for HTA (SNHTA)	Dedicated Reviewer	Switzerland	Thorough review of draft project plan and 1st draft report incl. studies + results
4.	State Health Care Accreditation Agency (VASPVT)	Dedicated Reviewer	Lithuania	Thorough review of draft project plan, and 1st draft report incl. studies + results
5.	National Institute of Care and Excellence in health, (NICE)	Dedicated Reviewer	England	Thorough review of draft project plan, and 1st draft report incl. studies + results
Contributors				
6.	Dr Torgrim Tandstad	Clinical Expert	Norway	Takes part in the scoping of the project and the review of the assessment prior to publication
7.	Dr Juliette Thariat	Clinical Expert	France	Takes part in the scoping of the project and the review of the assessment prior to publication
8.	Mr Daniel Ask	Patient partner	Norway	Takes part in the scoping of the project and the review of the assessment prior to publication

9.	TBD	Medical Editor	TBD	Text editing
10.	The Norwegian Institute of Public Health (NIPHNO)	Project Manager	Norway	Project Management

1.2 Project stakeholders

Table 1-2: Project stakeholders

Organisation	Role in the project
Manufacturers: We will identify manufacturers that have devices that are relevant for rectum protection for prostate cancer treatment. We will reach out to every manufacturer and confirm their product is CE marked.	To provide technical device information, perform a data fact check of the project plan and draft assessment report and to complete a submission file.
Prostate Scotland: “This is an Scottish charity set up to provide information, advice and help on prostate health and diseases and treatments” (retrieved from https://www.prostatescotland.org.uk/)	Provide organizational perspective to inform the scope of the assessment.

1.3 Milestones and Deliverables

When planning the timelines, we took in consideration the complexity of the topic for the identification of clinical experts, patient partners, manufacturers, for defining the PICO question (e.g., planning several e-meetings with the assessment team and/or external experts) and for the review and amendment of the project plan.

Table 1-3: Milestones and Deliverables

Milestones/Deliverables	**Start date**	**End date**
Project duration	**15/04/2019**	**27/04/2020**
Scoping phase	15/04/2019	14/10/2019
Identification of manufacturers and external experts; and patients	29/04/2019	10/09/2019
Scoping and development of draft Project Plan incl. preliminary PICO	13/05/2019	24/08/2019
Share the preliminary PICO with external experts *(and patients)* for comments	24/08/2019	06/09/2019
Internal Scoping e-meeting with the assessment team	24/06/2019	28/06/2019
**Consultation of draft Project Plan with dedicated reviewers	24/08/2019	06/09/2019
Consultation of draft Project Plan with external experts *(and patients)* and fact check by manufacturers	20/09/2019	15/10/2019
Amendment of draft Project Plan & final Project Plan available	15/10/2019	18/11/2019
Completion of Submission file template by manufacturer(s) + Clarifying further questions concerning draft Submission file)	23/10/2019	18/11/2019
Assessment phase	15/10/2019	25/05/2020
Writing first draft rapid assessment	15/11/2019	07/02/2019
Review by dedicated reviewer(s)	10/02/2020	24/02/2020
Writing second draft rapid assessment	25/02//2020	09/03/2020
**Review by ≥ 2 external clinical experts and fact check by manufacturers*	10/03/2020	30/03/2020
Writing third draft rapid assessment	31/03/2020	13/04/2020
Medical editing	14/04/2020	28/04/2020
Writing of final version of rapid assessment	29/04/2020	13/05/2020
Formatting	14/05/2020	22/05/2020
Final version of REA		**week** of 25/05/2020

2 Project Outline**Project Objectives**

The rationale of this assessment is to collaboratively produce structured (rapid) core HTA information on biodegradable rectum spacers for prostate cancer radiotherapy. 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 produce health technology assessments that are fit for purpose, of high quality, of timely availability, and cover the whole range of rectum spacers health technologies.	Production of one (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 collaboratively produced assessment.

This rapid assessment addresses the research question whether for adult oncological patients with prostate cancer receiving curative radiotherapy, the application of biodegradable rectum spacers is more effective and/or safer for rectum toxicity than no rectum spacer.

We selected this topic based on a request from the National System for Introduction of New Health Technologies within the Specialist Health Service in Norway. The relevance of the topic lies in the fact that due to the close proximity of the prostate to the rectum wall, when curative radiotherapy is indicated to patients, the rectum can be damaged and cause unwanted consequences to patients.

2.2 Project Method and Scope

2.2.1 Approach and Method

Table 2-2: Project approach and method

Project approach and method
Within this Rapid Relative Effectiveness Assessment we will describe the technical characteristics of technology (TEC) under assessment (i.e. type of device, procedure), assess health problem and current use of the technology (CUR) (i.e. target condition, target group), clinical effectiveness (EFF) (i.e. relative benefits) and safety (SAF) (i.e. unwanted or harmful effects). • In addition, we will complete the EUnetHTA Checklist for potential ethical, organisational, and social and legal aspects. We will use the Core Model® for Rapid Relative Effectiveness Assessment Version 4.2 as the reference framework for the selection of the assessment elements per domain. We will use the following reports identified through initial scoping search as a starting point for this assessment. o NICE “Interventional procedure overview of biodegradable spacer insertion to reduce rectal toxicity during radiotherapy for prostate cancer” (2017) [1] o Cancer Care Ontario “Biodegradable rectal spacers for prostate cancer radiotherapy” (2019) [2], and o CADTH Rapid Response Report “Hydrogel spacers for patients with prostate cancer: A review of clinical effectiveness and cost-effectiveness (2019) [3] **TEC and CUR domains** For these domains, the information from the above reports will be considered in addition to information coming from current clinical practice guidelines, information from a general literature search, the input from clinical experts, patient partners and organizations, and information collected through web-searches. The manufacturers (see also section 3.2 on stakeholder involvement) will be invited to complete the EUnetHTA submission file for

the chapters: 1. Description and technical characteristics of the technology, 2. Health problem and current clinical practice, 3. Current use of the technology, 4. Investments and tools required.

EFF and SAF domains

Information sources and search

For EFF and SAF domains, we will consider if it is appropriate to use the findings from any existing evidence synthesis (i.e. from systematic reviews or as part of HTA reports or clinical practice guidelines) as starting point. Using existing data syntheses prevents duplication of efforts that otherwise would be conducted de novo for this assessment. Use of findings of existing systematic reviews may include use of the results of existing searches and/or use of data extraction, study level risk of bias assessments or synthesis.[4, 5] In order to include data from a synthesis in this assessment, the scope of existing evidence syntheses needs to match the scope of this new assessment (see section 2.2.2). Two reviewers will independently appraise the PICO and search strategies, and if there is a close match to what this assessment proposes, the methodological rigour of the evidence syntheses will be evaluated with the AMSTAR2 instrument.[6] Based on these judgement, we will decide whether and how to use findings from existing evidence syntheses.

If suitable evidence syntheses are available (in addition to the above-mentioned ones) then we use these syntheses and primary studies (as described in section 2.2.2) published after the last search date of the latest evidence synthesis. If no suitable evidence syntheses are available, then we will do a complete new systematic review. Table 2-3 provides further details on the planned literature search strategy.

Selection of individual studies

Two reviewers will independently screen studies retrieved through the literature search against the predefined inclusion and exclusion criteria. We describe the criteria in section 2.2.2 We will use Covidence software to help with this process [7] This process will be double-checked by the co-author team.

Outcome Prioritization

The team will do an initial outcome prioritization at the kick off meeting by selecting primary and secondary outcomes. The project manager will present information derived from the COMET initiative, and James Lind Alliance on core outcomes for prostate cancer.

At a later stage, and according to the GRADE approach (Grading of Recommendations, Assessment, Development and Evaluation), the team will grade the importance of each outcome (as described in section 2.2.2 Project scope).[8] The project manager will send a form via a web platform such as google docs for this process; the outcomes could be assess as the following: critical (score 9-7), important but not critical (score 6-4), or low importance (score 3-1). There will also be a “do not know” option, in case members of the team feel they do not have enough information to make a judgement. We will collect the ratings from the clinical experts and patient partner first, then members of the assessment team (one rating per organization), while using the ratings from the clinical experts as input. While clinical experts and patient will provide a clinical and patient perspective, the assessment team will take a policy-maker perspective.

Data extraction

One reviewer will use an electronic and piloted form to extract data from the studies; a second reviewer will check the extraction and a consensus meeting will take place to discuss the differences. Table 2.4 provides an overview of the data elements that we will extract. In case of missing or unclear information in the published paper, we will contact authors (once) and note the answer/no answer in the result section and additional tables. Also for trial protocols (i.e. terminated, unpublished and ongoing) found in either databases or trial registries, we will seek further information by contacting the authors. Protocols for completed and published studies will be included as companion studies and used for the assessment of risk of bias for individual studies.

Risk of bias

Two reviewers will independently appraise risk of bias of synthesis or individual studies (on study and outcome) with the appropriate tool as follows.

- Systematic Reviews: AMSTAR 2 tool [9]
- Randomized controlled trials: Cochrane Risk of bias tool [10]
- non-randomised/observational : ROBINS-I tool [11]
- Case Control: CASP Checklist [12]
- Case Series: JBI critical appraisal checklist for case series [13]

Any disagreements will be resolved by discussion or by involving a third person if we cannot solve disagreements. We will include studies with both low, high and unclear risk of bias.

We plan to perform sensitivity analyses according to the different risk of bias categories. If possible, the impact of statistical heterogeneity and methodological weaknesses (i.e. high or unclear risk of selection bias and detection bias, or attrition rates greater than 20%) will be investigated using sensitivity analyses.

Data Synthesis

If two or more (RCT or non-RCT/observational) studies report on the same outcome, we will perform meta-analysis using techniques as described in the Cochrane Handbook [14]. However, as the level of evidence available on the different spacers varies significantly, each spacer will be evaluated upon the merits of the clinical evidence aiming to minimize the chances of erroneous conclusions.

- For continuous data, we will use the group post-test means and standard deviations to calculate effect sizes. We will preferably calculate the mean difference (MDs). When different scales are used to measure the same outcome, we will calculate the standardized mean difference (SMDs). We will analyze dichotomous data as risk ratios and 95% confidence intervals.
- When possible we will generate forest plots to display the results and report 95% prediction intervals as well as 95% confidence intervals
- For dichotomous outcomes, we will calculate the absolute risk difference (RD) and we will express the result as a percentage. For continuous outcomes, we will calculate the absolute benefit as the improvement in the intervention group minus the improvement in the control group, in the original units.
- The relative percentage change for dichotomous data will be calculated as the risk ratio (RR) and expressed as a percentage. For continuous outcomes, the relative difference in the change from baseline will be calculated as the MD divided by the pooled baseline

If possible, we will perform a random effects meta-analysis comparing rectum spacers+radiotherapy (and/or hormone therapy) with no rectum spacers, alternatively we will report the findings descriptively. The rationale for a random effects meta-analysis is due to the possibility to include studies that report on a given outcome the same underlying construct, but with important differences between studies that give rise to heterogeneity.

We will be using intention to treat (ITT) data preferably. If studies do not report estimates of effect and imprecision, we will impute the values where possible following the Cochrane Handbook [15]. Where possible, we will convert reported effect estimates to facilitate meta-analysis on a common scale.

We will conduct a separate meta-analysis for randomized controlled trials and one for the other study design (including quasi-randomized controlled trials, non-randomized controlled trials/observational studies).To incorporate findings of randomized and non-randomized studies, we will follow the approach presented in the framework developed by Cuello-Garcia et al [16]. This framework was developed to inform future GRADE working group guidance on this matter. Statistical methods to deal with missing data or heterogeneity will follow the Cochrane handbook [15].

If the number of different treatments (at least one study on each treatment) are available we could do a network meta-analysis. If we choose to do network meta-analysis we will publish an addendum to the project plan.

Rectum Spacers are used as part of a combined intervention with radiotherapy, and/or hormone therapy, which could lead to interactions. When analyzing adverse events, we will do it first focusing on adverse events that could be attributed to rectum spacers and RT only, we will follow the literature and clinical experts advice in this regard. Secondly, we will focus on those adverse events being attributed to the other components or their combinations as assumptions of the actual biological pathways are not always correct.

In the analyses we will categorise safety outcomes according to the Common Terminology Criteria for Adverse Events v5.0 guide (CTCAE).[17]

We will distinguish between acute (during and up to three months after radiotherapy) and late (six months post-radiotherapy) toxicity according to CTAE v 5.0 for gastrointestinal and urogenital domains (e.g. hematuria, urinary frequency, incontinence, retention and urgency, diarrhea, fecal incontinence, proctitis, rectal hemorrhage, rectal ulcer)

Secondary analyses
Subgroup analysis will only be performed if the number of studies allows this.
Predefined subgroups include:

- Combination of rectum spacers with brachytherapy only versus EBRT only vs brachytherapy and EBRT.

In addition, we define the following exploratory subgroups:

- Tumor stage: Metastatic vs. non-metastatic disease;
- Tumor stage: early vs advanced (graded according TNM staging system criteria [18])
- Device characteristics: device type (hydrogel vs balloon vs hyaluronic acid).
- Fractionation and dose of radiotherapy: normo vs moderately hypo fractionated vs hypofractionated vs ultra-hypofractionation (over ≥ 5 Gy per fraction (e.g. 36.25 Gy in 5 fractions) ; standard dose vs high dose)

Dealing with missing data
When numerical data are missing, we will contact the authors of studies, and request additional data required for analysis. We will contact authors using open-ended questions to obtain the information needed to assess risk of bias or the treatment effect, or both.
When numerical data are available only in graphic form, we will use Engauge version 5.1 to extrapolate means and standard deviations by digitalizing data points on the graphs[19]. When post-test standard deviations are unavailable, we will use the standard deviations of the pre-test scores as estimates. When the variance is expressed using statistics other than standard deviation (e.g. standard error, confidence interval or P value), we will compute standard deviations according to the methods recommended in Chapter 7 of the Cochrane Handbook [20]. When missing standard deviations cannot be derived using the above methods, we will impute them (e.g, from other studies)

Certainty in the evidence for each outcome
The quality of the body of evidence will be assessed using GRADE, taking into account for each outcome the risk of bias, imprecision, inconsistency, indirectness and publication biases. Certainty will be expressed as high, moderate, low or very low as it is defined by the GRADE working group.[21, 22]

Reporting
The results will be summarized in “Summary of findings” tables (SoF tables). In these tables we will include data from the main analyses for all the outcomes that are rated as critical or important for decision making. We will present absolute effects. Outcomes that are rated as less important for decision-making will be described in the report. Within SoF table, we will present the findings from randomized and non-randomized studies (including quasi-randomized controlled trials, and non-randomized controlled trials) as described by Cuello-Garcia [16]

We will report on terminated, not published or ongoing studies in the final report.

Use of Software
We will use Covidence [7] to screen and select studies, Review Manager, R or Stata to analyze effect data and to graphically plot the risk of bias. Further, we will use freely available softwares (i.e. Google doc) to collect individual votes about the rating of the outcomes or Engauge for graphical data [19]. Finally, we will use EndNote [23] as reference management software.

Checklist for potential ethical, organisational, patient and social and legal aspects
To answer the checklist (available in appendix A), we will use information coming from the literature search, from web-searches, from patient input (see also section 3.2 on stakeholder involvement), and from the clinical experts as information sources.

Table 2-3: Planned literature search strategy

Literature search strategy
Information specialist Ingrid Harboe (IH) will develop the search strategy with the assistance of the project manager. She will look at the search terms from the documents identified in the scoping phase as a starting point to developing the new strategy. After peer review of the strategy by information specialist Giry H Straumann (GHS) and a EUnetHTA partner (EUnetHTA information specialist network IQWiG), she will run the search. While there are previous HTAs on rectum spacers for the period 2017 to 2019, we will redo the search for the period 2010 forward. We opt to do this because of some differences in inclusion criteria for design and some changes in the search filters for study designs. Given the developments in oncological standard therapy, and some relevant publications from 2012 identified by the scoping search, we will limit the search for publications from 2010-current. We will not limit the search by language, or publication status restrictions. The search strategy will follow the selected PICO. It will contain both index-terms and text-words to identify as many relevant studies as possible. The search will be executed in the following databases: - Cochrane Database of Systematic Reviews and Protocols - CENTRAL for clinical trials - Epistemonikos - Ovid Medline - Embase (Ovid) - Cochrane Central Register of Controlled Trials - AMED (Allied and Complementary Medicine) - HTAi Vortal (HTAi: Health Technology Assessment International) - Guidelines International Network (GIN) - NICE guidance - NIHR-HTA - Devices @FDA First, will look for relevant systematic reviews, health technology assessments, and guidelines published after 2010.If we find a high quality evidence synthesis with similar PICO, we will not continue searching for primary studies. Second, if no evidence synthesis are found as stated previously we will search and screen primary studies. We will search for ongoing and planned systematic reviews in PROSPERO and the POP database, and terminated, completed and published, completed and unpublished and ongoing primary studies in ClinicalTrials.gov and WHO ICTRP. We will also search in cancer specific trial registries American Society of Clinical Oncology conference abstracts (meetinglibrary.asco.org/); and Radiation Therapy Oncology Group (RTOG) clinical trials protocols (www.rtog.org/ClinicalTrials/Welcome.aspx). The reference lists of identified systematic reviews and studies will be exported from EndNote to Covidence and screened by for inclusion and exclusion by two independent researchers (as described in section 2.2.1). In addition, we will ask manufacturers of rectum spacers devices for information about published and unpublished (but not confidential) clinical studies/clinical data for their products. Inclusion/exclusion criteria for studies or other information are described in section 2.2.2. Planned queries to study authors are described in table 2-2, in the section on data extraction. Search terms for use in Medline 1. exp Prostatic Neoplasms/ 2. (prostat* adj4 (neoplas* or cancer* or carcinom* or adenocarcinom* or tumour* or tumor* or malignan* or lump* or masses* or sarcom* or metastas*)).ti,ab,kw,kf. 3. or/1-2 4. Hydrogels/ 5. Hydrogel, Polyethylene Glycol Dimethacrylate/ 6. Hyaluronic Acid/ 7. Polyethylene Glycols/ 8.. (hydrogel* or hydrodissect* or (polyethylene adj3 glycol) or liquid-to-solid).ti,ab,kw,kf.

9..	(spacer* or spacing or spaceOAR or (separat* adj6 prostat* adj3 rect*) or ProSpace or (biodegradable or bioresorbable) adj3 polymer) or ((biodegradable or rect*) adj3 balloon*).ti,ab,kw,kf
10.	(hyaluronic adj3 acid).ti,ab,kw,kf.
11..	((perirect* or rect* or prostate-rect* or denonvillier* or transperineal*) adj4 space*).ti,ab,kw,kf.
12	or/4-11
13.	3 and 12
14.	limit 13 to yr="2010 -Current"

Overview of the most relevant studies that will be included:

NICE 2017 interventional procedure rapid review/overview [1] discusses the efficacy of the intervention based on medical literature and specialist opinion. It included 1074 patients from 1 RCT, 1 pseduo-randomised controlled trial, 6 case series, 1 prospective comparative case series, 1 retrospective comparative case series and 2 case reports.

In addition, we have identified two other potentially relevant documents: a rapid response report with critical appraisal from CADTH (2019) on Hydrogels Spacers [3] and a Recommendations Report on biodegradable rectal spacers from Cancer Care Ontario (2019) [2].

Table 2-4: Plan for data extraction

Planned data extraction
We plan to extract the following data from the included studies: • Study details: author's name, year of publication, trial protocol identification number, sponsorship source, country, setting, language, declaration of interest, contact with authors • Methods: study design, type of analysis (eg ITT), characteristics of trial design as outlined in the assessment of risk of bias • Population: Inclusion criteria, exclusion criteria, total number and number per group, baseline characteristics (age, gender ratio, tumour characteristics, comorbidities). Tumour characteristics, Disease status (primary, recurrent, prior surgery), Tumour size, Tumour grading, Tumour depth, histological subtype, WHO performance status, tumour stage • Intervention and comparator characteristics: description of procedure and comparators and concomitant treatments, • Outcome: Primary/secondary endpoints as specified in the PICO table below, type, effect measure, scale, number lost to follow-up, follow up period, treatment discontinuation with reason

2.2.2 Project Scope

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

Description	Project Scope
Population	Adults (>18yrs) who have a prostate cancer diagnosis and receive radiotherapy with curative intent, meaning radical doses of radiotherapy, either for first time and recurrent cancer. Within this assessment, we will include cancers confined to the prostate gland (vs cancers with extracapsular growth and/or infiltrating seminal vesicles) both non-metastatic and metastatic types of cancer. The latter means where the cancer has spread from the main tumours to other areas of the body. We will include adenocarcinomas and any other types of prostate cancer requiring radiotherapy. We will include individuals undergoing curative treatment radiotherapy alone or alongside and/or hormone therapy (eg androgen deprivation therapy). • Exclusion criteria: Individuals undergoing palliative treatment as radiation dose (and therefore toxicity to the rectum) may differ from those receiving RT for curative purposes. Individuals in a postoperative stage. Intended use of the technology: Specialist health care ICD 10 codes: Malignant neoplasm of prostate C61, C79.82, Z79.81, C79.49, Z85.46, R97.21, D07.5 ICD 10 codes: Radiotherapy Z51.89, D01, D71. D81, D91, DB1, DD1, DF1, DG1, DM1, DT1, DU1, DV1, DW1 Mesh-terms: prostatic neoplasms;
Intervention	There are several treatment options for prostate cancer including radiotherapy, chemotherapy, and hormonal (i.e. androgen deprivation therapy). Other standard options include radical prostatectomy, active surveillance and watchful waiting. [24] Because the rectum anterior wall is positioned in front of the prostate it makes it vulnerable and at risk of radiotherapy adverse effects. Sparing the anterior rectal wall is an important priority. Rectum spacers may aid in that matter; spacers are inserted in the body temporarily to increase the separation between the prostate and the rectum. The main purpose is to decrease the damage delivered to the rectum during radiotherapy which can be caused due to the close proximity of the prostate to the rectum. This assessment includes CE marked technologies that have an approved indication: - spaceOAR, manufactured by Boston Scientific. Material: Synthetic polyethylene-glycol (PEG)-based hydrogel, - ProSpace System (rectal balloon) by BioProtect. Material: bioresorbable polymer - Barrigel manufactured by Galderma/Palette Life Sciences Material: Hyaluronic acid also named Non-Animal Stabilized Hyaluronic Acid (NASHA) The above technologies will be assessed when used when in combination with one or more of the following: A .Radiation therapy (or radiotherapy) is an established treatment used to slow the progression or cure the disease. External-beam radiotherapy (EBRT) from outside the body from a radiotherapy machine or brachytherapy (also called internal or interstitial radiotherapy) are common forms radiation. Brachytherapy can be given at either low or high dose rate. Low or high dose rate brachytherapy may be used alone or in combination with

	EBRT. Intensity modulated radiation therapy (IMRT) is a type of EBRT that uses CT scans to form a 3D picture of the prostate before treatment and use this information to determine how much radiation is needed. Proton (beam) therapy uses protons rather than x-rays If studies include older techniques (e.g. 3D conformal) these will also be included, with the acknowledgement that they might produce higher rectal toxicity and a benefit for spacers that cannot be transferred to modern techniques. Fractionation: using fraction sizes >2Gy per day, may be radio-biologically advantageous. There is evidence that doses beyond 80Gy can be delivered safely with image-guided intensity-modulated radiotherapy (IG-IMRT). High dose rate brachytherapy is an alternative mean of delivering hypofractionated radiation as a boost to achieve dose escalation after 45-46Gy in 1.8-2Gy daily fractions or 37.5Gy in 15 fractions. b.Hormone therapy (lowering androgens levels) is often used in combination with radiotherapy to either increase the chance of successful treatment or reduce the chances of recurrence. It can be given before, during and after radiotherapy to increase overall treatment effectiveness. c. Chemotherapy Intended Use: Therapeutic MeSH terms: Hydrogels/pd [pharmacology]; Hydrogel, Polyethylene Glycol Dimethacrylate/administration & dosage; hyaluronic acid
Comparator	Management pathway without the technology (e.g. hormone therapy and/or radiotherapy)
Outcomes	The assessment team's consensus was that late rectal toxicity was the main endpoint. Additional outcomes of interest in this report are overall quality of life, sexual quality of life, overall survival, urinary toxicity and adverse events. **Main endpoint** Toxicity **Secondary endpoints** Overall Quality of life and any sub-endpoints relating to it (e.g. sexual quality of life, bowel quality of life) Overall survival, Urinary toxicity Reduction in rectal radiation dose Increase distance between prostate and rectum Prostate specific antigen (PSA) Adverse events We will include outcomes measured at short and long follow-up times i.e. measured within one year, one to three years, more than three years after the intervention. For safety data, we will include both adverse events being attributed to radiotherapy, or hormone therapy but also to those being attributed to the other components or their combinations as interactions are possible and assumptions of the actual biological pathways are not always correct. The selection of outcomes was informed by the COMET initiative resources on core outcomes for prostate cancer [25] the James Lind Alliance [26] 10 top priorities for research, and ultimately by consensus reached by the OTCA23 assessment team (dedicated reviewers, co-authors, clinical expert and patient partner involved). For adverse events, the James Lind Alliance research priorities specify an interest in both short-term, long-term (side-effects which last for years after treatment) and late side-effects (side-effects which do not appear until years after treatment).

Study design	Effectiveness: Inclusion criteria: If suitable evidence syntheses (i.e. recent HTAs or systematic review) are available then we will assess them for suitability and compatibility with our PICO. Then primary studies (as described in next paragraph) published after the last search date of the latest evidence synthesis. If no suitable evidence syntheses are available we will include: • Randomised controlled trials and non-randomised controlled trials or observational studies with a control group. In this assessment non-RCTs as experimental studies in which participants are allocated to different interventions using non- random methods. • Prospective studies or registry studies defined as studies that sample patients with both a specific outcome and a specific exposure, or one that samples patients with a specific outcome and includes patients regardless of whether they have specific exposures; and which does not permit calculation of an absolute risk [27] Exclusion criteria: Studies with designs different from above based on data retrieved from sources other than registries (e.g. chart reviews, electronic health records, patient surveys, case reports, retrospective designs) Safety: Inclusion criteria: Randomised controlled trials, non-randomised controlled trials or observational studies, single arm trials and single or multiple arm prospective registry based on data from national, regional or hospital level registries. Exclusion criteria: Studies with designs different from above based on data retrieved from sources other than registries (e.g. chart reviews, electronic health records, patient surveys) We will screen the literature to identify any publications on minimum important differences for the outcomes included in this assessment. We will rate the importance of each outcome for decision making as described in table 2.2
Language	We will not apply language restrictions

Appendix A provides the specific assessment elements that will be addressed for the TEC, CUR, EFF and SAF domains.

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.	12/06/2019 1st meeting	E-meeting	Author(s), co-author(s), dedicated reviewers, project manager (external experts, patients)
	Selection of outcomes Rating of importance of outcomes	12/06/2019	E-meeting	Author(s), co-author(s), dedicated reviewers, external experts
	Fact check of the draft project plan by manufacturer	11/11/2019	E-mail	Author(s), manufacturer(s), project manager
Feedback on draft project plan	To discuss comments of dedicated reviewers, clinical experts, manufacturers	TBD	E-mail or E-meetings may be planned	Author(s), co-author(s), dedicated reviewers; external experts,
Feedback on draft submission file (optional)	To point out the requirements for the final submission file by manufacturers	TBD	E-mail	Author(s), project manager, manufacturers
First draft of the rapid assessment	To discuss comments of dedicated reviewers	TBD	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	TBD	E-meetings may be planned	Author(s), co-author(s), dedicated reviewers; external experts, manufacturers

3.1 Dissemination plan

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

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

3.2 Collaboration with stakeholders

Collaboration with manufacturer(s)

We will ask manufacturers questions related to instructions for use and CE certification for their devices together with (published/unpublished) clinical data related to their product. We will aslo ask manufacturers to get involved in the assessment process. For example, they are invited to review the preliminary PICO question, do a fact check of the 2nd draft project plan, and to complete a submission file template (i.e chapters 1-4). The manufacturers are also invited to do a fact check of the 2nd draft assessment. In addition, they will receive a copy of the final report after publication on the EUnetHTA website.

Collaboration with patient/consumer representative

We will invite patient/consumer groups from the country managing the assessment or other EUnetHTA countries to inform the scoping phase of this HTA. We will invite them to share their experiences and views with the disease and intervention being assessed. We will reach out to specific patient groups and we will publish an open call for patient involvement on the EUnetHTA website. Interested patients will be asked to complete the adapted HTAi Patient Input form for HTA of health interventions (not

medicines) in a form adapted by EUnetHTA.[28] This input will be discussed in a scoping meeting of the assessment team together with external experts as to inform the PICO-question.

Collaboration with healthcare organisations

None

3.3 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.

OTCA23 Assessment was invited to be part of a pilot project for the integration of the patient partners input in the final report. The specific involvement to the team members is not defined at the time of writing this project plan.

3.4 Conflict of interest and confidentiality management

Conflicts of interest will be handled according to the EUnetHTA Procedure Guidance for handling Declaration of Interest and Confidentiality Undertaking (DOICU) (March 2019). All individuals participating in this project will sign the standardised DOICU form.

The HTA assessment project manager will distribute and collect filled and signed DOICU forms from every person involved in the assessment. The EUnetHTA secretariat will set up and maintain a database for the completed DOICU forms and overview the interest that has been declared. The secretariat will then inform the relevant individuals to update his/her DOICU when the form is expired. The form is valid for 1 year based on the signature date of the individual. Filled DOICU forms will be evaluated by the EUnetHTA COI Committee who makes a decision on the inclusion or exclusion of an individual.

Once the team is ready to start, we will work collaboratively in the development and production of the assessment; however, EUnetHTA, as the main author of the assessment, can make final decisions.

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

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5 Appendix A

5.1 Selected Assessment Elements

The table shows the assessment elements and the translated research questions that will be addressed in the assessment. They are based on the assessment elements contained in the 'Model for Rapid Relative Effectiveness Assessment'. Additionally, assessment elements from other HTA Core Model Applications (for medical and surgical interventions, for diagnostic technologies or for screening) have been screened and included/ merged with the existing questions if deemed relevant.

Table 5-1: Selected Assessment Elements

ID	Topic	Topic Issue	Relevance in this assessment [**Yes – critical**, **Yes** or **No**]	Mandatory (M) or non-mandatory (NM)	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)?		M	[If selected, translate the generic issue into actual research question(s). If you selected "no" and the element is labelled as a 'mandatory' element, provide an explanation why you deemed this element as not relevant]
A0020	Regulatory Status	For which indications has the technology received marketing authorisation or CE marking?	Yes - critical	M	
B0002	Features of the technology	What is the claimed benefit of the technology in relation to the comparator(s)? [This assessment element can be placed either in the TEC OR in the CUR domain]		M	
B0003	Features of the technology	What is the phase of development and implementation of the technology and the comparator(s)?		NM	
B0004	Features of the technology	Who administers the technology and the comparator(s) and in what context and level of care are they provided?		M	
B0008	Investments and tools required to use the technology	What kind of special premises are needed to use the technology and the comparator(s)?		NM	
B0009	Investments and tools required to use the technology	What equipment and supplies are needed to use the technology and the comparator(s)?		NM	
A0021	Regulatory Status	What is the reimbursement status of the technology? [This assessment element can be		NM	

ID	Topic	Topic Issue	Relevance in this assessment [Yes – critical, Yes or No]	Mandatory (M) or non-mandatory (NM)	Research question(s) or reason for non-relevance of 'mandatory' elements
		placed either in the TEC OR in the CUR domain]			
Health problem and current use of technology					
A0002	Target Condition	What is the disease or health condition in the scope of this assessment?		M	
A0003	Target Condition	What are the known risk factors for the disease or health condition?		NM	
A0004	Target Condition	What is the natural course of the disease or health condition?		M	
A0005	Target Condition	What are the symptoms and the burden of disease or health condition for the patient?		M	
A0006	Target Condition	What are the consequences of the disease or health condition for the society?		NM	
A0020	Regulatory status	For which indications has the technology received marketing authorisation or CE marking? This assessment element can be placed either in the TEC OR in the CUR domain]			
A0021	Regulatory status	What is the reimbursement status of the technology? [This assessment element can be placed either in the TEC OR in the CUR domain]		M	
A0024	Current Management of the Condition	How is the disease or health condition currently managed according to published guidelines and in practice?		M	
A0025	Current Management of the Condition	How is the disease or health condition currently managed according to published guidelines and in practice?			
A0007	Target Population	What is the target population in this assessment?		M	
A0023	Target Population	How many people belong to the target population?		M	
A0011	Utilisation	How much are the technologies utilised?		M	
Clinical effectiveness					
D0001	Mortality	What is the expected beneficial effect of the	Yes	M	

ID	Topic	Topic Issue	Relevance in this assessment [Yes – critical, Yes or No]	Mandatory (M) or non-mandatory (NM)	Research question(s) or reason for non-relevance of 'mandatory' elements
		technology on mortality?			
D0005	Morbidity	How does the technology affect symptoms and findings (severity, frequency) of the disease or health condition?	Yes	M	
D0006	Morbidity	How does the technology affect progression (or recurrence) of the disease or health condition?	Yes	M	
D0011	Function	What is the effect of the technology on patient's body functions?	Yes	M	
D0016	Function	How does the use of the technology affect activities of daily living?	No	NM	
D0012	Health-related quality of life	What is the effect of the technology on generic health-related quality of life?	Yes	M	
D0013	Health-related quality of life	What is the effect of the technology on disease-specific quality of life?	Yes	M	
D0017	Patient satisfaction	Were patients satisfied with the technology?	Yes	NM	
Safety					
C0008	Patient safety	How safe is the technology in relation to the comparator(s)?	Yes	M	
C0002	Patient safety	Are the harms related to dosage or frequency of applying the technology?	Yes	NM	
C0004	Patient safety	How does the frequency or severity of harms change over time or in different settings?	Yes	M	
C0005	Patient safety	What are the susceptible patient groups that are more likely to be harmed through the use of the technology?	Yes	M	
C0007	Patient safety	Are the technology and comparators associated with user-dependent harms?	No	NM	
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)?	Yes	M	

5.2 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?	[Yes]
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?	[Yes/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?	[Yes/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?	[Yes/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/No]
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?	[Yes/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?	[Yes/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?	[Yes/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.*	