EUnetHTA Joint Action 3 2016-2020

Regional hyperthermia for high-risk soft tissue sarcoma treatment

Project ID: ***OTCA18***

Project description and planning

The Norwegian Institute of Public Health (NIPHNO), Norway

Regione Emilia-Romagna (RER), Italy

Version Log

Version number	Date	Modification	Reason for the modification
V1.1	18/10/18	1st version of the draft project plan sent to co-authors	
V1.2	25/01/19	New 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	07/02/19	Draft sent to dedicated reviewers	Integration of comments and suggestions from co-authors
V3	26/02/19	Draft sent to experts and manufacturers	Integration of comments and suggestions from dedicated reviewers
V4	14/05/19	Final version	Integration of comments from experts, manufacturers, and Norwegian stakeholder

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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.	Regione Emilia-Romagna (RER)	Co-Author	Italy	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.	Instituto de Salud Carlos III, AETS-ISCIII	Dedicated Reviewer	Spain	Thorough review of draft project plan and 1st draft report incl. studies + results. Review of information retrieval strategy in draft project plan by information specialist.
Contributors				
6.	Dr. Stephan Bodis, Kantonsspital Aarau	External expert	Switzerland	Clinical expert (radiotherapy and hyperthermia expert) who provides advice during the scoping phase of project and who peer reviews the draft assessment prior to publication.
7.	Dr. Frank Lohr, University University of Modena	External expert	Italy	Clinical expert (radiotherapy expert) who provides advice during the scoping

				phase of project and who peer reviews the draft assessment prior to publication.
8.	Dr. Jan Peter Poulsen, Norwegian Radiumhospital, Oslo University Hospital	External expert	Norway	Clinical expert (oncology expert) who provides advice during the scoping phase of project and who peer reviews the draft 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 identified the following manufacturers that have devices that are relevant for treatment of soft tissue sarcoma with regional hyperthermia: Pyrexar Medical, Oncotherm, Alba Hyperthermia System, Celsius 42, Synchrotherm, Andromedic. We will reach out to every manufacturer.	To provide technical device information, perform a data fact check of the project plan, to complete a submission file and to fact check the draft assessment report.
Patient/consumer or patient organization /groups (hereafter patients): We will reach out to Sarcoma Patients Euronet and Sarkomer (Norwegian patient organization) and we will publish an open call for patient involvement on the EUnetHTA website. The open call for patient involvement will be promoted through social media and through an email to European patient organisations/groups.	Patients will be invited to provide input at protocol and draft assessment stages. They will be invited to share their experiences and views with the intervention being assessed.
Healthcare organisation: Haukeland University Hospital in Bergen, Norway requested a health technology assessment on this topic through the National System for Introduction of New Health Technologies within the Specialist Health Service in Norway. We will reach out to this organisation in order to assure that this assessment covers their information needs.	To provide feedback on the scope of the project and on the project plan.

1.3 Milestones and Deliverables

The authors and co-authors, are responsible for planning realistic timelines for the assessment during the scoping phase to avoid delays during the assessment process. When planning the timelines, the complexity of the topic needs to be considered: complex assessments may need extended periods for the identification of 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. In addition, more time is likely to be needed for the assessment phase (e.g., identification, review and synthesis of the literature, writing the 1st and 2nd draft assessment). Amongst others, complex assessments may be characterised by:

- Assessment of multiple indications/interventions/comparators,
- elaboration of additional assessment elements from other domains (organisational, legal, social, etc.),

- exceptionally high amount of studies identified, screened and included and/or inclusion of various different study designs.

The project manager of the assessment is responsible for cross-checking and approving the timelines.

Table 1-3: Milestones and Deliverables

Milestones/Deliverables	Start date	End date
Project duration	**09/07/2018**	**09/09/2019**
Scoping phase	09/07/2018	29/03/2019
Identification of manufacturer(s) and external experts; *optional: identification of patients*	09/07/2018	05/11/2018
Scoping and development of draft Project Plan incl. preliminary PICO	09/07/2018	01/12/2018
Share the preliminary PICO with external experts for comments	02/12/2018	09/12/2018
Internal Scoping e-meeting with the assessment team	10/12/2018 1st meeting	21/01/2019 2nd meeting
Consultation of draft Project Plan with dedicated reviewers	07/02/2019	14/02/2019
Consultation of draft Project Plan with external experts *(and patients)* and fact check by manufacturers	26/02/2019	04/03/2019
Amendment of draft Project Plan & final Project Plan available	05/03/2019	11/03/2019
Completion of Submission file template by manufacturer(s)	11/03/2019	29/03/2019
Assessment phase	**08/04/2019**	**20/09/2019**
Writing first draft rapid assessment	12/04/2019	07/06/2019
Review by dedicated reviewer(s)	10/06/2019	19/06/2019
Writing second draft rapid assessment	19/06/2019	28/06/2019
Review by ≥ 2 external clinical experts and fact check by manufacturers	1/07/2019	26/07/2019
Writing third draft rapid assessment	29/07/2019	9/08/2019
Medical editing	12/08/2019	23/08/2019
Writing of fourth version of rapid assessment	26/08/2019]	6/09/2019
Formatting	09/09/2019	13/09/2019
Final version of rapid assessment		**week** from 16/09/2019 - to 20/09/2019

2 Project Outline

2.1 Project Objectives

The rationale of this assessment is to collaboratively produce structured (rapid) core HTA information on regional hyperthermia for high-risk soft tissue sarcoma. 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 collaboratively 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 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 oncological patients with high-risk soft tissue sarcoma, the regional application of non-invasive external hyperthermia administered in addition to chemo- and/or radiotherapy is more effective and/or safer than radio- and/or chemotherapy alone.

This topic was chosen based on a request from the National System for Introduction of New Health Technologies within the Specialist Health Service in Norway. They proposed the topic to the Norwegian Institute of Public Health. The relevance of the topic lies in the fact that the therapy is already in use for selected patients, but it is very resource demanding and not a generally accepted treatment modality. Regional hyperthermia could be especially useful for patients where it is not possible to remove the entire sarcoma surgically or when surgery would be mutilating (for example requiring amputation).

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, patient and social and legal aspects. The Core Model® for Rapid Relative Effectiveness Assessment Version 4.2 will be used as the reference framework for the selection of the assessment elements per domain. We will use the HTA report by the Ludwig Boltzmann Institute (LBI-HTA) on hyperthermia as a starting point for this assessment.[1] This report was identified through a scoping search for HTA reports by an information specialist at NIPHNO. The methods for patient involvement that we plan within this assessment are described in table 1-2 and in section 3.2. **TEC and CUR domains** For these domains, the information from the LBI-HTA report will be considered in addition to information coming from current clinical practice guidelines, information from a general literature search, the input from clinical experts 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** <u>Information sources and search</u> 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.[2, 3] In order to include 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 methodological rigour of any relevant evidence syntheses with the AMSTAR2 instrument.[4] Based on their judgement, we will decide whether and how to use findings from existing evidence syntheses.

If suitable evidence syntheses are available 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, which are described in section 2.2.2 Project scope. This process will be double-checked by the co-author team. For potentially relevant conference abstracts we will try to locate a full text and we will reach out to the first authors. In the case that no full text is available, we will exclude the study abstract.

Rating of the importance of outcomes for decision making
According to the GRADE approach (Grading of Recommendations, Assessment, Development and Evaluation), the importance of each outcome (list of included outcomes is described in section 2.2.2 Project scope) will be graded through a structured process that includes individual voting and discussion with the assessment team, health professionals and patients.[5] Each outcome can be rated as critical, important but not critical or low importance for decision making. We will use survey software to collect the individual votes. This prioritisation of outcomes will be done in the start phase of the assessment.

Data extraction
One reviewer will use a pre-established form to extract data from the studies, with a detailed revision by another reviewer. Table 2.4 provides an overview of the data elements that will be extracted. We will try to contact study authors in cases where we need information that is not reported in the published paper. Also for terminated, not published and for ongoing primary studies we will try to establish contact with the investigators.

Risk of bias in individual studies
Two reviewers will independently appraise risk of bias on study and outcome level with the Cochrane Risk of bias tool[6]. For non-randomised studies (including controlled trials and registry-based studies, we will use the ROBINS-I tool (Risk of Bias in non-randomized studies – of interventions).[7] Any disagreements will be resolved by discussion. 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.

Data Synthesis
Measures of treatment effect
We will report both on dichotomous and continuous outcomes and we plan to estimate both relative measures of effect (e.g. odds ratio, relative risk, annualized rate ratios between pair of treatments) and absolute effect measures (e.g. absolute risks and risk difference, time-to-event data) for each outcome. For continuous outcomes, we will calculate the mean difference. We will use alternative scales if appropriate (e.g., if a continuous outcome has been measured/reported in the included randomized control trials (RCTs) using different instruments/scales we may use a standardized mean difference; SMD).

Main analysis
When possible, we will perform a random effects meta-analysis comparing hyperthermia + chemo and/or radiotherapy with chemo and/or radiotherapy using techniques as described in the Cochrane Handbook, alternatively we will report the findings descriptively.[8] We will do the analysis according to intention-to-treat. The Cochrane Handbook will be followed for statistical methods to quantify and deal with heterogeneity. If studies do not report estimates of effect and imprecision, we will impute the values where possible following the Cochrane Handbook. Where possible, we will convert reported effect estimates to facilitate meta-analysis on a common scale. As to how to incorporate findings of randomized and non randomized studies, we will follow the approach as presented in the framework developed by Cuello et al.[9] This framework was developed to inform future GRADE working group guidance on this matter. We will conduct a separate meta-analysis for randomized controlled trials and one for the other study designs (including quasi-randomized controlled trials, non-randomized controlled trials and registry based studies).

Given the various possible combinations of treatments, this assessment could qualify for a network meta-analysis. However, we anticipate that we will not have enough studies to do this. If we find a sufficiently large number of primary studies or patient level data, network meta-analysis becomes an option. In that situation, we will evaluate the feasibility of a network meta-analysis with respect to project timelines. If we choose to do network meta-analysis we will publish an addendum to the project plan that includes a detailed statistical analysis plan for that work.

Hyperthermia is part of a combined intervention with radiotherapy and/or chemotherapy, which could lead to interactions. When analysing adverse events, we will focus not only on adverse events attributed to hyperthermia, but also to those attributed to the other components or their combinations as the biological pathways are not always clear or assumptions of these pathways might not be correct. In the analyses we will categorise safety outcomes into minor and major events according to the Common Terminology Criteria for

Adverse Events v5.0 guide.[10] We will evaluate procedure-related mortality separately. We will distinguish between acute and late toxicity.

Secondary analysis:
Subgroup analysis will only be performed if the number of studies allows it.

Predefined subgroups include:

- Combination of chemotherapy and radiotherapy versus chemotherapy only versus radiotherapy only.
- Dosage or frequency of applying hyperthermia.

To define the acceptable temperature range, dosage or frequency we refer to the quality assurance guidelines for regional hyperthermia recognised by the European Society for Hyperthermic Oncology (ESHO).[11] At current, we refer to the latest published quality standards from 2012. Given that these standards are being updated, we make explicit that we will consider any more recent version of these quality standards if these would become available during the duration of this assessment. For temperature range, we will also consider the Kadota Fund International Forum 2004,[12] which defined hyperthermia as a temperature elevation between 39-45 °C versus 40-44°C as defined by ESHO. Therefore, we will explore the relative effects of temperature related characteristics via a subgroup analysis including a) ESHO guideline, b) Kadota Fund Intern Forum, c) effect of studies that either did not report temperature or reported temperature outside of acceptable range. There will be overlap between a and b, so we only interpret the results of this analysis with caution.

In addition, we define the following exploratory subgroups for which we will interpret and report the results cautiously:

- Treatment characteristics: hyperthermia and preoperative radiotherapy vs. hyperthermia and postoperative radiotherapy; hyperthermia and teletherapy vs. hyperthermia and brachytherapy vs. hyperthermia and teletherapy and brachytherapy; hyperthermia and preoperative chemotherapy vs. hyperthermia and postoperative chemotherapy; hyperthermia and preoperative radiotherapy + chemotherapy vs. hyperthermia and postoperative radiotherapy + chemotherapy;
- Tumour characteristics: extremity vs. trunk vs. retroperitoneal vs. head and neck; metastatic vs. non-metastatic disease; resectable vs, non-resectable.
- Device characteristics: device age categorized based on date of the studies and based on date of marketing authorization.

From a preliminary overview of the literature, we anticipate finding a small number of studies, but if we have a large sample of studies we plan to perform meta-regression analyses to estimate the effect of the above mentioned factors. If it is feasible to do meta-regression analyses, we will treat them as exploratory analyses and their results will be interpreted and reported cautiously.

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 bias. Certainty will be expressed as high, moderate, low or very low as it was defined by the GRADE working group.[5]

Reporting
The results will be summarized in “Summary of findings”-tables (SoF table). 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. Outcomes that are rated as less important for decision-making will be described in the report. Within the SoF table, we will present the findings from randomized and non-randomized studies (including quasi-randomised controlled trials, non-randomized controlled trials and registry-based studies) as described in the guidance for presenting these types of studies by Cuello-Garcia et al.[9]

Information about any terminated, not published studies or about ongoing primary studies will be summarised in the final report.

Use of Software
We will use Covidence to screen and select studies. To collect individual votes about the rating of outcomes, we will use survey software. We will use Review Manager (RevMan 5) to analyze effect data and to graphically plot the risk of bias. Further, we will use Endnote as reference management software. If we opt to do meta-regression analyses, then we will use R and the metafor package.

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 involvement (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
Librarian Gyri Hval Straumann will develop the search strategy. While the LBI-HTA health technology assessment on hyperthermia conducted a systematic literature search for the period 1990-2012, we will redo the search for the period 1990 and forward.[1] 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, we will apply a year limit for the period 1990 to the date of the search without language or publication status restrictions. The search strategy will be based on the population and the intervention in the 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 Library - Epistemonikos - Medline (Ovid) - Embase (Ovid) - Cochrane Central Register of Controlled Trials - AMED - HTAi Vortal - Guidelines International Network (GIN) - NICE guidance - NIHR-HTA - Devices@FDA We will also search for ongoing and planned systematic reviews in PROSPERO and the POP database, and terminated, not published and ongoing primary studies in clinicaltrials.gov and WHO ICTRP. The reference lists of relevant systematic reviews and included studies will be screened by two persons independently (as described in section 2.2.1). In addition, we will ask manufacturers of hyperthermia devices to inform us about any published and unpublished (but not confidential) clinical studies/clinical data for their products. Before searching for primary studies we will look for relevant systematic reviews and guidelines published after January 2012. 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. To further identify relevant studies we will screen the reference lists of relevant evidence syntheses and primary studies. Search terms for use in Medline 1 exp SARCOMA/ (133169) 2 exp Soft Tissue Neoplasms/ (23595) 3 ((soft tissue* or soft part or connective tissue* or connective part) and (sarcom* or cancer* or neoplasm* or malignan* or tumor* or tumour*)).ti,ab,kw. (43803) 4 sarcom*.ti,ab,kw,kf. (103862) 5 angiosarcoma*.ti,ab,kw. (5879) 6 Angioendotheliosarcoma*.ti,ab,kw. (4) 7 Chondrosarcoma*.ti,ab,kw. (7571) 8 Chondromucosarcoma*.ti,ab,kw. (0) 9 fibrosarcoma*.ti,ab,kw. (11369) 10 Dermatofibrosarcoma*.ti,ab,kw. (1817) 11 (bednar adj (tumour or tumor)).ti,ab,kw. (68) 12 (bednar's adj (tumor or tumour)).ti,ab,kw. (5) 13 Fibroblastoma*.ti,ab,kw. (280)

14 Darrier ferrand.ti,ab,kw. (4)
15 darier ferrand.ti,ab,kw. (57)
16 darier hoffmann.ti,ab,kw. (0)
17 Endotheliosarcoma*.ti,ab,kw. (12)
18 Neurofibrosarcoma*.ti,ab,kw. (394)
19 Haemangioendothelioma*.ti,ab,kw. (403)
20 Hemangioendothelioma*.ti,ab,kw. (2769)
21 Hemangiosarcoma*.ti,ab,kw. (1025)
22 (Heart adj muscle adj (tumor* or tumour*)).ti,ab,kw. (0)
23 Haemangiosarcoma*.ti,ab,kw. (214)
24 Hemangiosarcoma*.ti,ab,kw. (1025)
25 Histiosarcoma*.ti,ab,kw. (12)
26 histiocytoma*.ti,ab,kw. (5488)
27 kaposi*.ti,ab,kw. (14382)
28 Leiomyosarcoma*.ti,ab,kw. (9745)
29 Liposarcoma*.ti,ab,kw. (6001)
30 lymphangiosarcoma*.ti,ab,kw. (304)
31 (malignant adj peripheral adj nerve adj sheath adj (tumour* or tumor*)).ti,ab,kw. (2062)
32 mpnst.ti,ab,kw. (1035)
33 Lymphangioendothelioma*.ti,ab,kw. (96)
34 Mesodermal mixed tumor*.ti,ab,kw. (84)
35 Myosarcoma*.ti,ab,kw. (178)
36 (Myocardial adj (tumour* or tumor*)).ti,ab,kw. (76)
37 (Myocardium adj (tumour* or tumor*)).ti,ab,kw. (2)
38 Rhabdomyosarcoma*.ti,ab,kw. (11335)
39 Myxosarcoma*.ti,ab,kw. (248)
40 Neurofibrosarcoma*.ti,ab,kw. (394)
41 Osteosarcoma*.ti,ab,kw. (21650)
42 Cystosarcoma*.ti,ab,kw. (628)
43 Phyllodes.ti,ab,kw. (1819)
44 Rhabdoid tumor*.ti,ab,kw. (1593)
45 (Small adj round adj cell adj (tumour* or tumor*)).ti,ab,kw. (1192)
46 Synovioma*.ti,ab,kw. (341)
47 Synoviasarcoma*.ti,ab,kw. (0)
48 Synoviosarcoma*.ti,ab,kw. (28)
49 Muscle neoplasm*.ti,ab,kw. (220)
50 Muscle cancer*.ti,ab,kw. (21)
51 Vascular neoplasm*.ti,ab,kw. (800)
52 vascular cancer*.ti,ab,kw. (47)
53 or/1-52 (238094)
54 exp Hyperthermia, Induced/ (30001)
55 hypertherm*.ti,ab. (33132)
56 thermotherap*.ti,ab. (2227)
57 fever therap*.ti,ab. (173)
58 heat therap*.ti,ab. (236)
59 diatherm*.ti,ab. (3482)
60 diatherap*.ti,ab. (1)
61 alba 4d.mp. (0)
62 celsius tcs.mp. (4)
63 synchroterm.mp. (0)
64 hydeep.mp. (0)
65 sigma-60.mp. (55)
66 bsd-2000.mp. (56)
67 bsd-500.mp. (0)
68 bsd medical.mp. (14)
69 or/54-68 (57092)
70 53 and 69 (1717)
71 limit 70 to yr="1990 -Current" (1229)

Overview of the most relevant studies that will be included:

The EORTC-ESHO multi-centre trial (NCT 00003052) is a key study for the EFF domain.[13] This two-armed trial compared treatment with neo-adjuvant chemotherapy alone versus combined with regional hyperthermia. The trial enrolled 341 patients with a median follow-up period of 34 months for the primary outcome local progression-free survival. This study also published long-term outcomes (median follow-up of 11.3 years).[14]

In addition, we have identified two potentially relevant ongoing studies, i.e. the HyperTET study (NCT 02359474) and the HYPROSAR study (NCT 01904565). NIPHNO has contacted the primary investigators for these trials regarding options for synchronisation between their primary research and this OTCA18 assessment.

While completion of data collection for these studies was initially anticipated by December 2018, patient recruitment for these studies is slow and setting a date for completion of data collection is not possible. The characteristics of these trials will be summarized in this report under a section called “ongoing studies”. NIPHNO will follow-up if any intermediate results are published that could be included in the report. The HYPROSAR study published initial data for their trial which can be reported in this assessment. [15]

We anticipate that the results of these studies will only become available after publication of this assessment report. This assessment team is committed to update the report once the results for both studies are availabe. The update of the report will include searching for any other new studies and all the steps described in table 2.1 for the domains EFF and SAF.

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, clinical trial identification number, sponsorship source, country, setting, language, declaration of interest, contact with authors; • Methods: study design, type of analysis (eg. per protocol, etc.), 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 include: Tumour site (extremity, trunk and retroperitoneal), Disease status (primary, recurrent, prior surgery), Tumour size, Tumour grading, Tumour depth, Sarcoma histological subtype, WHO performance status, resection status; TNM-stage, AJCC prognostic stage group; • Intervention and comparator characteristics: description of procedure and comparators and concomitant treatments. For hyperthermia we will extract frequency, target, maximum power attained, duration of hyperthermic therapy, temperature variables (max, mean, T90). For radiotherapy we will extract data about type of radiation, dose, number of fractions, and total treatment time. For chemotherapy we will extract information about the substances, dose per course, total dose, data about any reduction in doses and about any delays due to side effects. • 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

The EUnetHTA Guidelines, available at http://www.eunethta.eu/eunethta-guidelines, need to be consulted throughout the assessment process.

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

Description	Project Scope
Population	Adults (>18yrs) who have a high-risk soft tissue sarcoma. We exclude adolescents or children since treatment in these age groups follows specific paediatric protocols. Soft tissue sarcoma represent a type of cancer that can arise in soft tissues (for example in muscles, nerves, blood vessels, fat tissues, etc.) in any part of the body. There are approximately 50 different types of soft tissue sarcoma based on the location and based on the type of soft tissue involved. Within this assessment we will include the various types of soft tissue sarcoma in different locations, i.e. extremity, trunk, head and neck, and retroperitoneal. Surgical excision of the tumour tissue is the most important part of the overall treatment for patients with soft tissue sarcoma, but achieving a clear surgical resection is not always possible. In this assessment, we will include both patients with non-resectable tumours and with tumours that can be surgically resected. High-risk soft tissue sarcomas harbour an increased risk of local recurrence and distant metastases following surgical resection, resulting in a high tumour related mortality. We will use the criteria from the European Society for Medical Oncology (ESMO) guidelines, defining high-risk sarcoma as tumours which are high-grade malignant, situated deep (located either exclusively beneath the superficial fascia, superficial to the fascia with invasion of or through the fascia, or both superficial yet beneath the fascia) to the subcutaneous fascia and large (size > 5cm).[16] This excludes studies that focus on low risk sarcoma, which do not require radiotherapy or chemotherapy, so meaning small, superficial, low-grade tumours. The two most widely used systems for grading sarcoma are the NCI (United States National Cancer Institute) system and the FNCLCC (French Fédération Nationale des Centres de Lutte Contre le Cancer) system.[17, 18] We also identified the Sarculator as a tool to predict the probability of overall survival and incidence of distant metastasis for patients with soft tissue sarcoma.[19] Given that there is no universally accepted definition of high risk sarcoma, we will also include high risk classifications by Sarculator which is based on patient age and tumour histology, size and grade. Within this assessment we will include both localized and metastatic sarcomas where the cancer has spread from the main tumours to other areas. We will include patients undergoing curative treatment and patients undergoing palliative treatment. In the event of studies including a mixed population (i.e. low and high risk), we will not include studies if less than 75% of the included patients are considered to be high-risk soft tissue sarcoma patients, unless they provide stratified results that enable to extrapolate data on high risk patients. Intended use of the technology: Specialist health care ICD 10 codes: C48, C49.0-C49.9 and organ specific ICD 10 codes (since ICD codes follow organ of origin) ICD-O-3 topography codes: C47, C48 and C49, ICD-O-3 morphology malignant behaviour codes: 880*, 881*-883*, 884*, 885*-888*, 889*-892*, 893*-899*, 904, 912*-913*, 917*[20, 21] Mesh-terms: Sarcoma[mh], Soft Tissue Neoplasms[mh]
Intervention	Regional application of non-invasive external hyperthermia to a soft tissue sarcoma and administered in addition to chemo- and/or radiotherapy and treatment as usual. Hyperthermia treatment aims to increase the temperature in target tissue to levels above normal systemic temperature. Quality assurance guidelines for regional hyperthermia recognised by the European Society for Hyperthermic Oncology (ESHO) define 40 °C as the temperature where the treatment starts, while the temperature in the target tissue should not

	exceed 44 °C.[11, 22] The Kadota Fund International Forum 2004 defines hyperthermia as a modest temperature elevation in the range of 39-45 °C.[12] We will accept the treatment temperature to be in the range of 39 to 45 °C after both ESHO and the Kadota Fund International Forum guidelines. We exclude wellness hyperthermia (low temperature hyperthermia) and ablative (high temperature hyperthermia) where tissue is burned. The technology can be described and classified by the anatomical extensiveness of the treated area (local, regional or whole body), by the methods used for hyperthermia application (invasive or non-invasive) and by the energy sources (such as microwaves, radiofrequency, ultrasound, simple radiation) used to provide the intended heating effect.[1] Superficial hyperthermia, whole body hyperthermia and invasive treatment are not included in this assessment. Hyperthermia can be used in both a neoadjuvant context (used before surgical removal of a sarcoma) and in an adjuvant context (used after surgery). In some cases, surgery is difficult or potentially mutilating. This assessment will include use of hyperthermia in both neoadjuvant and adjuvant context and in situations where hyperthermia is used without surgical resection. Product names of the involved technologies: BSD 2000 devices produced by Pyrexar Medical, EHY devices produced by Oncotherm, ALBA 4D devices produced byMed-logix srl , Celsius TCS device produced by Celsius 42, Synchrotherm devices produced by Synchrotherm, HYDEEP devices produced by Andromedic. This list is not intended to be limitative. If we identify additional devices during the assessment, then we will expand this list. However, for some of the listed devices, we have not yet received information about availability of CE approval and devices without a CE approval will be excluded from this assessment. MeSH terms: Hyperthermia, Induced [mh]
Comparison	Radio- and/or chemotherapy alone in addition to concomitant treatment as usual. We selected the standard interventions for the target population according to the clinical guidelines.[23, 24] The main treatment for soft tissue sarcoma is usually a combination of surgery, chemotherapy and radiotherapy. Radiotherapy and/or chemotherapy can be indicated as pre- or postsurgical (neo-)adjuvant treatment. MeSH terms: Chemotherapy, Adjuvant[mh]; Chemoradiotherapy [mh], Radioimmunotherapy [mh]; Radiotherapy, Adjuvant[mh]; Neoadjuvant Therapy[mh]
Outcomes	The selection of outcomes was informed by the assessment by LBI-HTA, COMET and the James Lind Alliance.[1, 25, 26] Following the LBI-HTA assessment overall survival was selected as the main endpoint because it is a clear measure of benefit that can be relatively easy obtained and which is not subject to assessment bias. Additional outcomes included in the LBI-HTA assessment and of interest in this report are disease-free survival, progression-free survival, objective response rate, health-related quality-of-life, rate of local tumour control and local tumour recurrence and adverse events. Based on the top 10 research priorities formulated by the James Lind Alliance for Living With and Beyond Cancer we selected the following additional outcomes: pain, fatigue, and outcomes related to psychological wellbeing of patients, carers and families. 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). In addition, we will include outcomes on limb preservation, patient satisfaction, procedural time and resource use. Outcomes on patient satisfaction could also include shared decision making related measures, which was also included in the top 10 priorities by the James Lind Alliance. We searched the COMET database, but did not find a core outcome set specifically for soft tissue sarcoma. We will use the standardised definitions of time-to-event outcomes for sarcomas as these are formulated by the DATECAN initiative.[27] Data from studies that apply different definitions for time-to-event outcomes will be included, but we will clearly report any differences in how the outcome was defined.

	For safety data, we will include both adverse events being attributed to hyperthermia, but also to those being attributed to the other components or their combinations as interactions are possible and biological pathways may not be clear or assumptions of the actual biological pathways may not be correct. We will include outcomes measured at short and long follow-up times. If follow-up times are very diverse, we will synthesize the data in categories for a follow-up time, i.e. measured at 3 months, 6 months, within one year, one to three years, more than three years after the intervention. 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. Summary of included outcomes: • overall survival (main endpoint) • disease-free survival • progression-free survival • objective response rate • health-related quality-of-life • rate of local tumour control • local tumour recurrence • pain • fatigue • limb preservation • outcomes related to psychological wellbeing of patients, carers and families • patient satisfaction (including shared decision making related measures) • procedural time • resource use • adverse events
Study design	<u>Effectiveness:</u> Inclusion criteria: Randomised controlled trials and non randomised prospective controlled trials . We define the latter as experimental prospective studies in which participants are allocated to different interventions using methods that are not random. In case the certainty of the evidence is rated as very low, low or moderate, we will also include multiple arm prospective registry studies, provided they are based on data from national, regional or hospital level registries.[9] Exclusion criteria Studies with designs different from the above based on data retrieved from sources other than registries (e.g. chart reviews, electronic health record studies, patient surveys). If suitable evidence syntheses of above described studies are available (i.e. HTA report, guideline or systematic review) we will use data from such syntheses plus primary studies published after the last search date of the most recent evidence synthesis. <u>Safety:</u> Inclusion criteria: Randomised controlled trials, non-randomised controlled trials, single arm trials and single or multiple arm prospective registry studies based on data from national, regional or hospital level registries. Exclusion criteria Studies with designs different from the above based on data retrieved from sources other than registries (e.g. chart reviews, electronic health record studies, patient surveys). If suitable evidence syntheses of above described studies are available (i.e. HTA report, guideline or systematic review) we will use data from such syntheses plus primary studies published after the last search date of the most recent evidence synthesis.

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.	10/12/2018 1st meeting 21/01/2019 2nd meeting	E-meeting	Author(s), co-author(s), dedicated reviewers, observers, project manager (external experts, patients)
	Selection of outcomes and rating of importance of outcomes	13/03/2019	Survey tool	Author(s), co-author(s), dedicated reviewers, external experts
	Fact check of the draft project plan by manufacturer	26/02/2019	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 manufacturers

Manufacturers will be asked questions related to instructions for use and CE certification for their devices together with (published/unpublished) clinical data related to their product. Manufacturers will be also invited 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

Patient/consumer representative groups from the country managing the assessment or other EUnetHTA countries will be invited to inform the scoping phase of this HTA. They will be invited 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 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

We will invite Haukeland University Hospital to provide feedback on the scope of the project and on the project plan.

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.

3.4 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 have signed the standardised “Declaration of Interest and Confidentiality Undertaking” (DOICU) statement.

Authors, co-authors and dedicated reviewers had no relevant conflict of interest to disclose.

Among the three external experts, one person had no relevant conflicts of interest to disclose (Dr. Jan Peter Poulsen) and two experts have conflicts to disclose. Dr. S. Bodis is involved in an ongoing study (not industry sponsored) that is potentially relevant for the EFF domain. The study is ongoing and data might not be available for inclusion in this assessment. Dr. F. Lohr
has been employed by company C-Rad (member of the board of directors) that produces devices for radiotherapy. In our assessment radiotherapy is part of both the intervention (in combination with hyperthermia) and comparator group. We are not doing a head-to-head comparison of hyperthermia versus radiotherapy. Experts with conflicts of interests are allowed to provide input for all aspects of the assessment, but the decision-making throughout the production process is reserved to the assessment team (authors, co-authors and dedicated reviewers) that have no conflicts of interest.

For patients or other stakeholders involved, conflict of interest declarations will be collected regarding the topic. Any such conflict of interest declared will be evaluated and disclosed in the final assessment.

Manufacturers 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	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)?	Yes - critical	M	What is non-invasive regional hyperthermia and what are standard treatments for high-risk soft tissue sarcoma?
A0020	Regulatory Status	For which indications has the technology received marketing authorisation or CE marking?	Yes - critical	M	For which indications have non-invasive regional hyperthermia devices received marketing 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 - critical	M	What is the claimed benefit of non-invasive regional hyperthermia in addition to chemo- and/or radiotherapy in relation to chemo- and/or radiotherapy alone for high-risk soft tissue sarcoma?
B0003	Features of the technology	What is the phase of development and implementation of the technology and the comparator(s)?	Yes – not critical	NM	What is the phase of development and implementation of non-invasive regional hyperthermia and chemo- and/or radiotherapy for high-risk soft tissue sarcoma?
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 – consider later whether critical	M	Who administers non-invasive regional hyperthermia and chemo- and/or radiotherapy for high-risk soft tissue sarcoma and in what context and level of care are they provided?
B0008	Investments and tools required to use the technology	What kind of special premises are needed to use the technology and the comparator(s)?	Yes – consider later whether critical	NM	What kind of special premises are needed to use non-invasive regional hyperthermia in addition to chemo- and/or radiotherapy, and chemo- and/or radiotherapy alone for high-risk soft tissue sarcoma?
B0009	Investments and tools required to use the technology	What equipment and supplies are needed to use the technology and the comparator(s)?	Yes – not critical	NM	What equipment and supplies are needed to use non-invasive regional hyperthermia in addition to chemo- and/or radiotherapy, and chemo- and/or radiotherapy alone for high-risk soft tissue sarcoma?
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]	Yes – not critical	NM	What is the reimbursement status of non-invasive regional hyperthermia?
Health problem and current use of technology					
A0002	Target Condition	What is the disease or health condition in the	Yes - critical	M	What kind of sarcoma is in the scope of this assessment?

ID	Topic	Topic Issue	Relevance in this assessment	Mandatory (M) or non-mandatory (NM)	Research question(s) or reason for non-relevance of 'mandatory' elements
		scope of this assessment?			
A0003	Target Condition	What are the known risk factors for the disease or health condition?	Yes – not critical	NM	What are the known risk factors for high-risk soft tissue sarcoma?
A0004	Target Condition	What is the natural course of the disease or health condition?	Yes - critical	M	What is the natural course of high-risk soft tissue sarcoma?
A0005	Target Condition	What are the symptoms and the burden of disease or health condition for the patient?	Yes - critical	M	What are the symptoms and the burden of high-risk soft tissue sarcoma for the patient?
A0006	Target Condition	What are the consequences of the disease or health condition for the society?	Yes – critical	NM	What are the consequences of high-risk soft tissue sarcoma for the society?
A0024	Current Management of the Condition	How is the disease or health condition currently diagnosed according to published guidelines and in practice?	Yes - critical	M	How is high-risk soft tissue sarcoma currently diagnosed according to published guidelines and in practice?
A0025	Current Management of the Condition	How is the disease or health condition currently managed according to published guidelines and in practice?	Yes - critical	M	How is high-risk soft tissue sarcoma currently managed according to published guidelines and in practice?
A0007	Target Population	What is the target population in this assessment?	Yes - critical	M	What is the target population in this assessment?
A0023	Target Population	How many people belong to the target population?	Yes - critical	M	How many people belong to the target population?
A0011	Utilisation	How much are the technologies utilised?	Yes – not critical	M	How much is non-invasive regional hyperthermia in addition to chemo- and or radiotherapy and chemo- and or radiotherapy alone for high-risk soft tissue sarcoma utilised?
Clinical effectiveness					
D0001	Mortality	What is the expected beneficial effect of the intervention on mortality?	Yes - critical	M	What is the expected beneficial effect of the non-invasive regional hyperthermia in addition to chemo- and or radiotherapy on mortality?
D0005	Morbidity	How does the technology affect symptoms and findings (severity, frequency) of the disease or health condition?	Yes - critical	M	How does non-invasive regional hyperthermia affect symptoms and findings (severity, frequency) of soft-tissue sarcoma?
D0006	Morbidity	How does the technology affect progression (or recurrence) of the disease or health condition?	Yes – not critical	M	How does non-invasive regional hyperthermia affect progression (or recurrence) of soft-tissue sarcoma?
D0011	Function	What is the effect of the technology on patients' body functions?	Yes – not critical	M	What is the effect non-invasive regional hyperthermia on patients' body functions?
D0016	Function	How does the use of technology affect activities of daily living?	No	NM	Not addressed

ID	Topic	Topic Issue	Relevance in this assessment	Mandatory (M) or non-mandatory (NM)	Research question(s) or reason for non-relevance of 'mandatory' elements
D0012	Health-related quality of life	What is the effect of the technology on generic health-related quality of life?	Yes – not critical	M	What is the effect of non-invasive regional hyperthermia on generic health-related quality of life?
D0013	Health-related quality of life	What is the effect of the technology on disease-specific quality of life?	Yes – not critical	M	What is the effect of non-invasive regional hyperthermia on disease-specific quality of life?
D0017	Patient satisfaction	Were patients satisfied with the technology?	Yes – not critical	NM	Were patients satisfied non-invasive regional hyperthermia?
Safety					
C0008	Patient safety	How safe is the technology in relation to the comparator(s)?	Yes - critical	M	How safe is non-invasive regional hyperthermia in addition to chemo- and/or radiotherapy, and chemo- and/or radiotherapy alone?
C0002	Patient safety	Are the harms related to dosage or frequency of applying the technology?	Yes – not critical	NM	Are the harms related to dosage or frequency of applying non-invasive regional hyperthermia?
C0004	Patient safety	How does the frequency or severity of harms change over time or in different settings?	Yes – not critical	M	How does the frequency or severity of harms change over time or in different settings?
C0005	Patient safety	What are the susceptible patient groups that are more likely to be harmed through the use of the technology?	Yes – not critical	M	What are the susceptible patient groups that are more likely to be harmed through the use of non-invasive regional hyperthermia?
C0007	Patient safety	Are the technology and comparator(s) associated with user-dependent harms?	No	NM	Not addressed
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 – not critical	M	What kind of data/records and/or registry is needed to monitor the use of non-invasive regional hyperthermia in addition to chemo- and/or radiotherapy, and chemo- and/or radiotherapy alone?

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/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?	[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.*	