EUnetHTA Joint Action 3 2016-2020

IRREVERSIBLE ELECTROPORATION IN LIVER AND PANCREATIC CANCER

Project ID: ***OTCA15***

Project description and planning

Scientific Advice Unit, Avalia-t, of the Galician Agency for Health Knowledge Management (ACIS)

Ludwig Boltzmann Institute for Health Technology Assessment

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Version Log

Version number	Date	Modification	Reason for the modification
V1	05/07/2018	Preliminary version of the Project Plan	
V2	13/07/2018	First draft of the Project Plan	Comments from the internal scoping meeting included
V3	30/07/2018	Developed draft of the Project Plan	Comments from the external experts on preliminary PICO included
V4	22/10/2018	Final draft	Comments from dedicated reviewers and external experts included

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1 Project organisation

1.1 Participants

Table 1-1: Project participants

	Agency	Role in the project	Country	Distribution of work
Assessment team				
1.	Scientific Advice Unit (avalia-t) of the Galician Agency for Health Knowledge Management (ACIS)	Author	Spain	Develop the first draft of the EUnetHTA Project Plan Perform the literature search and the study selection Carry out the assessment: data extraction, analysis, synthesis and interpretation of findings Send the first draft to reviewers, compile feedback and perform the necessary changes according to reviewer's comments Send the second draft to external experts, and to manufacturers for fact check Prepare final assessment and write a final summary of the assessment
2.	Ludwig Boltzmann Institute for Health Technology Assessment (LBI-HTA)	Co-Author	Austria	Review draft of the EUnetHTA Project Plan Perform the study selection and the assessment of risk of bias Check data extraction. Discussion of conclusions. Review draft assessment, propose amendments where necessary and provide written feedback.
3.	State Health Care Accreditation Agency Under the Ministry of Health of the Republic of Lithuania (VASPVT)	Dedicated Reviewer	Lithuania	Review and comment on EUnetHTA Project Plan, propose amendments where necessary

				Review and comment on draft assessment, propose amendments where necessary
4.	National Institute of Pharmacy and Nutrition (NIPN)	Dedicated Reviewer	Hungary	Review and comment on EUnetHTA Project Plan, propose amendments where necessary Review and comment on draft assessment, propose amendments where necessary
5.	Swiss Network for Health Technology Assessment (SNHTA)	Dedicated Reviewer	Switzerland	Review and comment on EUnetHTA Project Plan, propose amendments where necessary Review and comment on draft assessment, propose amendments where necessary
Contributors				
6.	National Institute for Health and Care Excellence (NICE)	Contributor	United Kingdom	Contribute to review the first draft of the assessment, propose amendments where necessary
7.	Dr. Des Alcorn	External expert	Scotland	Review and comment on EUnetHTA Project Plan, propose amendments where necessary Review and comment on second draft assessment, propose amendments where necessary
8.	Dr. David Kay	External expert	Scotland	Review and comment on EUnetHTA Project Plan, propose amendments where necessary Review and comment on second draft assessment, propose amendments where necessary
9.	Dr.Fabio Ausania	External expert	Spain	Review and comment on EUnetHTA Project Plan, propose amendments where necessary Review and comment on second draft assessment, propose amendments where necessary
10.	TBD	Medical Editor		Medical editing

11.	Scientific Advice Unit (avalia-t) of the Galician Agency for Health Knowledge Management (ACIS)	Project Manager	Spain	Project management

1.2 Project stakeholders

Table 1-2: Project stakeholders

Organisation	**Role in the project**
Angiodynamics. United States.	Manufacturer
Spanish group of patients with cancer (GEPAC-Grupo Español de Pacientes con Cáncer). Spain	Patient representative group

Relevant competitors manufacturing the technology: None. Angiodynamics is the only manufacturer of irreversible electroporation equipment.

1.3 Milestones and Deliverables

Table 1-3: Milestones and Deliverables

Milestones/Deliverables	**Start date**	**End date**
Project duration	**04/06/2018**	**17/05/2019**
Scoping phase	04/06/2018	22/10/2018
Identification of manufacturers and external experts; *optional: identification of patients*	04/06/2018	29/06/2018
Scoping and development of draft Project Plan incl. preliminary PICO	04/06/2018	04/07/2018
Share the preliminary PICO with dedicated reviewers	05/07/2018	11/07/2018
Share the preliminary PICO with external experts *(and patients)* for comments	16/07/2018	26/07/2018
Internal Scoping e-meeting with the assessment team	12/07/2018	
Request for the completion of the Submission file template to manufacturer(s)	16/10/2018	
Amendment of draft Project Plan	27/07/2018	30/07/2018
Consultation of draft Project Plan with dedicated reviewers	31/07/2018	07/08/2018
Consultation of draft Project Plan with external experts *(and patients)* and fact check by manufacturers	08/08/2018	05/10/2018
Amendment of draft Project Plan & final Project Plan available	08/10/2018	22/10/2018
Completion of Submission file template by manufacturer(s) + Clarifying further questions concerning draft Submission file)	17/10/2018	30/11/2018
Assessment phase	01/10/2018	17/05/2019
Writing first draft rapid assessment	01/10/2018	11/01/2019
Review by dedicated reviewer(s)	14/01/2019	25/01/2019
Writing second draft rapid assessment	28/01/2019	15/02/2019
Review by ≥ 2 external clinical experts and fact check by manufacturers	18/02/2019	08/03/2019
Writing third draft rapid assessment	11/03/2019	29/03/2019
Medical editing	01/04/2019	12/04/2019
Writing of final version of rapid assessment	15/04/2019	03/05/2019
Formatting	06/05/2019	10/05/2019
Final version of REA		**week** from 13/05/2019 - to 17/05/2019

2 Project Outline

2.1 Project Objectives

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

Table 2-1: Project objectives

	List of project objectives	Indicator (and target)
1.	To jointly produce health technology assessments that are fit for purpose, of high quality, of timely availability, and cover the whole range of health technologies.	Production of 1 (rapid) relative effectiveness assessment.
2.	To apply this collaboratively produced assessment into local (e.g. regional or national) context.	Production of ≥2 local (e.g. national or regional) reports based on the jointly produced assessment.

This rapid assessment addresses the following research questions:

1. Ablation of pancreatic tumors with irreversible electroporation (IRE) by any approach (percutaneous, laparoscopic or open surgical) in patients with unresectable locally advanced pancreatic cancer (LAPC) is more effective and safer than the standard clinical practice or any palliative care.

2. Ablation of a liver tumors with irreversible electroporation (IRE) by any approach (percutaneous, laparoscopic or open surgical) in patients with unresectable primary or secondary liver cancer and contraindicated for thermal ablation is more effective and safer than the standard clinical practice or any other palliative care.

This topic, requested by two regional health authorities, was prioritised by the Spanish National Ministry of Health, who commissioned Avalia-t to do a HTA on IRE in inoperable pancreatic and liver cancer. The assessment is part of the Spanish Network of HTA agencies and Services 2018 annual work plan. The relevance of the topic lies in the fact that this is a non-thermal minimally invasive technique that can be applied for the treatment of patients that have no other available alternatives, so it could have a high impact in the outcomes of these patients. This technique is not yet in the Spanish common services portfolio of the National Health System.

2.2 Project Method and Scope

2.2.1 Approach and Method

Table 2-2: Project approach and method

Project approach and method
The HTA Core Mode Applications for Rapid Relative Effectiveness Assessment Version 4.2. will be the primary source for selecting assessment elements. Description and technical characteristics of technology (**TEC**) and health problem and current use (**CUR**) domains: • Information from the manufacturers: the Medical Devices Evidence Submission template will be sent to the manufacturer of the technology under assessment. The manufacturer will be asked to submit non-confidential evidence, focusing on the technical characteristics and current use of the technology • The evidence provided will be used in addition to the literature identified by a literature search, scanning multiple data sources for additional information • IRE will be analyzed and discussed at the light of the found evidence and the information from the clinical experts and manufacturers Clinical effectiveness (**EFF**) and safety (**SAF**) domains A systematic search will be performed. In addition, we are aiming to include patients in order to know their expectations and to incorporate their views and perspectives regarding the clinical condition and the treatment. Participation would be open to patients with pancreatic or liver cancer who have undergone electroporation or other ablative methods, as the experiences with the disease and ablative methods will generally be shared. Information from patient involvement will be used as additional information for answering research questions related to patient aspects (mainly assessment elements D0016, D0012, D0013 and D0017). The authoring team will carry out the selection of relevant articles, independently, by screening the titles and abstracts of the retrieved studies, in accordance with the inclusion / exclusion criteria established according to the previously defined PICO question. Potentially eligible studies will be obtained and read at full-text. Reasons for exclusion will be recorded. Disagreement will be discussed and resolved between the authoring team. Study and outcomes validity and level of evidence will be assessed according to the EUnetHTA guidelines: • The importance of each outcome will be graded by the assessment team, external experts and the patient representative, according to GRADE (Grading of Recommendations, Assessment, Development and Evaluation). • Risk of Bias: the “Revised Cochrane Risk of bias tool” (RoB 2.0 tool) will be used for randomized controlled trials, the “Risk of Bias in non-randomized studies of Interventions” (ROBINS-I tool) for non randomized studies and the “IHE 20-Criteria checklist” for single-arm studies. • The quality of the body of evidence will be assessed using GRADE.

The risk of bias and the GRADE quality rating will be independently assessed by two members of the authoring team. Disagreements will be resolved by consensus, consulting a third part in case of discrepancies. Relevant subgroup analyses will be assessed for the critical outcomes. The benefit and risk of IRE will be assessed.

Table 2-3: Planned literature search strategy

Literature search strategy
EFF and SAF domains: a systematic search will be performed in the following databases: Centre for Reviews and Dissemination (CRD) Databases, Cochrane Library (Wiley), Medline (PubMed), Embase (OVID), Web of Science (Web of Knowledge) and Scopus. Search of ongoing clinical trials and research projects: Clinicaltrials.gov, Cochrane Central EU clinical trials, International ClinicalTrials Registry Platform (ICTRP) and UK Clinical Trails gateway. Search terms related to irreversible electroporation and Nanoknife will be used, combined with terms related to liver and pancreatic cancer. Mesh terms and free text words will be included in the search strategy. The bibliographic research will be restricted to studies written in English, Spanish, Portuguese, French or Italian language. The following publication types will be excluded: case reports, letters, congresses or editorials. No other restrictions will be considered. The search will be completed with a manual revision of the bibliographic references cited in the selected papers and a general internet search. When the same institution had published sequential studies, in order to avoid overlap, the study with the largest number of cases will be chosen.

Table 2-4: Plan for data extraction

Planned data extraction
The relevant data will be extracted and recorded in evidence tables by one author from avalia-t and reviewed by another. This process will be checked by the co-author. Evidence tables for data extraction will be created according to The Cochrane Handbook for Systematic Reviews for Interventions. The data extracted from the studies will include: • Study characteristics (authors, year of publication, study design, setting/country, funding, study's registration number in clinical trial database, data collection period) • Population characteristics (number of participants, age, gender, tumor type, tumor size clinical stage, treatments before the intervention, simultaneous treatments, treatments after the intervention) • Intervention and control characteristics (description of the procedure, approach of the procedure, name of the device, number and length of the interventions, comparator, length of follow-up) • Outcomes:

- Effectiveness endpoints: success of the procedure, overall survival, cancer specific survival, disease free survival, time to recurrence, time to progression, time to local recurrence, health related quality of life and pain.
- Safety endpoints: procedure related complications, adverse events, intervention specific mortality

2.2.2 Project Scope

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

Description	Project Scope
Population	The diseases of interest are: • Pancreatic neoplasm MeSH-term: C04.588.274.761, C04.588.322.475, C06.301.761, C06.689.667, C19.344.421; Malignant neoplasm of pancreas ICD-10:C25 • Liver neoplasms MeSH-term: C04.588.274.623, C06.301.623, C06.552.697). Malignant neoplasm of liver ICD-10: C22; malignant neoplasm metastasis in liver ICD-10: C78-7. The target populations are: • Patients with histologically proven, primary or recurrent unresectable locally advanced pancreatic cancer (LAPC) / stage III. The following subgroups will be considered: ○ Patients who have already received chemotherapy and/or radiotherapy and the tumor does not progress *versus,* ○ Patients who have already received chemotherapy and/or radiotherapy and the tumor becomes resectable; IRE is applied for margin accentuation v*ersus,* ○ Patients who have not received chemotherapy or radiotherapy • Patients with unresectable primary or secondary liver cancer and contraindicated for thermal ablation The following subgroups will be considered: ○ Patients with primary liver cancer *versus*, ○ Patients with secondary liver cancer, differentiating by origin/histology The intended use of the technology is an ablative treatment. Rationale: population was defined according to: • European Guidelines (ESMO-Cancer of Pancreas: Clinical Practice Guideline for diagnosis, treatment and follow-up(1); EASL Clinical Practice Guideline: Management of hepatocellular carcinoma.(2). • American Guidelines: NCCN Clinical Practice Guidelines in Oncology (Pancreatic Adenocarcinoma Guideline and Hepatobiliary cancers guidelines)(3, 4) • American Joint Committee on Cancer (AJCC): Cancer Staging Manual: Pancreas and Hepatobiliary Cancers (5)
Intervention	• Tumor resection by irreversible electroporation (IRE) with Nanoknife®. The following subanalysis will be considered, depending on the approach: percutaneous, laparoscopic or open surgery • MESH: Electroporation E05.200.500.454, E05.242.448, E05.301.500 • Manufacturers:

	• Nanoknife® (Company: AngioDynamics®, USA)
Comparison	• Pancreatic cancer - Standard of care therapy: ▪ chemotherapy (CT) ▪ radiotherapy (RT) ▪ chemo-radiotherapy (CRT) ▪ palliative care ▪ not doing anything (watchful waiting) • Liver cancer - Standard of care therapy: ▪ chemotherapy (CT) ▪ radiotherapy (RT) ▪ chemo-radiotherapy (CRT) ▪ chemoembolization ▪ kinase inhibitor: Sorafenib or others ▪ palliative care ▪ not doing anything (watchful waiting) Rationale: the standard therapy was established according to: • European guidelines: ESMO-Cancer of Pancreas: Clinical Practice Guideline for diagnosis, treatment and follow-up;(1) and EASL Clinical Practice Guideline: Management of hepatocellular carcinoma. J Hepatol. 2018.(2) • NICE guideline: Pancreatic cancer in adults: diagnosis and management.(6) • American Society of Clinical Oncology- Clinical Practice Guideline: Locally Advanced, Unresectable Pancreatic Cancer.2016 (7) • EUnetHTA guideline: Comparators & Comparisons: Criteria for the choice of the most appropriate comparator(s) (8)
Outcomes	<u>Effectiveness-related:</u> • Success of the procedure (defined as the ability to complete the IRE procedure as planned and absence of any residual tumor (using imaging techniques)) • Overall survival (at 3, 6, 12, 18 and 24 months) • Cancer specific survival • Disease free survival • Time to Recurrence (TTR) • Time to progression: radiological progression, by computed tomography (CT) scan or magnetic resonance imaging (MRI) at 6 weeks, 3, 6, 12, 18 and 24 months • Time to local recurrence: local radiological progression, at 6 weeks, 3, 6, 12, 18 and 24 months • Health-related quality of life (measured by EORTC QLQ-C30 , QLQ-PAN26, FACT-Hep, EQ-5D or others, at baseline, 6 weeks, 3 months and 6 months, 12 months after IRE) • Pain <u>Safety-related:</u> • Procedure related complications (e.g. needle tract seeding) • Adverse events: type, graded as CTCAE (Common Terminology Criteria for Adverse Events), the Dindo-Clavien Classification, the SIR (Society of Interventional Radiology) grading system or others • Intervention specific mortality

	Rationale: The outcomes have been chosen based on the following guides: • Design and endpoints of clinical trials in hepatocellular carcinoma (9). • Guidelines for time to event and endpoint definitions in trial for pancreatic cancer: DATECAN(10). • EUnetHTA guidelines: endpoints used in Relative Effectiveness Assessment: clinical endpoints, safety and health-related quality of life and utility measures (11-13).
Study design	Effectiveness: randomized controlled trials, prospective non-randomized controlled trials and single-arm prospective studies with at least 10 patients. Safety: randomized controlled trials, prospective non-randomized controlled trials and single-arm prospective studies with at least 10 patients.

3 Communication and collaboration

Table 3-1: Communication

Communication Type	Description	Date	Format	Participants/ Distribution
Scoping	To discuss the preliminary PICO and draft project plan	12/07/2018	E-meeting	Author(s), co-author(s), dedicated reviewers, project manager
	To discuss the preliminary PICO with external experts	19/07/2018	*Face to face meeting/ e-meeting*	*Author(s), external experts*
		[DD/MM/YYYY]	*Additional e-meetings may be planned whenever needed*	*Author(s), Co-author(s), dedicated reviewer(s), project manager*
Feedback on draft submission file (optional)	*To point out the requirements for the final submission file by manufacturers*	*[DD/MM/YYYY]*	*E-mail*	*Author(s), project manager, manufacturers*
First draft of the rapid assessment	*To discuss comments of dedicated reviewers*	*[DD/MM/YYYY]*	*E-meetings may be planned*	*Author(s), co-author(s), dedicated reviewers*
Second draft of the rapid assessment	*To discuss comments from ≥ 2 external clinical experts and manufacturers*	*[DD/MM/YYYY]*	*E-meetings may be planned*	*Author(s), co-author(s), dedicated reviewers; external experts, manufacturers*

3.1 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)

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

Collaboration with other stakeholders

There will be a review of the preliminary PICO and the draft Project Plan by the patient representative. Individual patients will be included, as explained in the EFF and SAF domains.

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 will sign the standardised “Declaration of Interest and Confidentiality Undertaking” (DOICU) statement.

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

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

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

4 References

1. Ducreux M, Cuhna AS, Caramella C, Hollebecque A, Burtin P, Goere D, et al. Cancer of the pancreas: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. Ann Oncol. 2015;26 Suppl 5:v56-68.
2. European Association for the Study of the Liver. Electronic address eee, European Association for the Study of the L. EASL Clinical Practice Guidelines: Management of hepatocellular carcinoma. J Hepatol. 2018;69(1):182-236.
3. Benson AB, 3rd, D'Angelica MI, Abbott DE, Abrams TA, Alberts SR, Saenz DA, et al. NCCN Guidelines Insights: Hepatobiliary Cancers, Version 1.2017. J Natl Compr Canc Netw. 2017;15(5):563-73.
4. Tempero MA, Malafa MP, Al-Hawary M, Asbun H, Bain A, Behrman SW, et al. Pancreatic Adenocarcinoma, Version 2.2017, NCCN Clinical Practice Guidelines in Oncology. J Natl Compr Canc Netw. 2017;15(8):1028-61.
5. Chun YS, Pawlik TM, Vauthey JN. 8th Edition of the AJCC Cancer Staging Manual: Pancreas and Hepatobiliary Cancers. Ann Surg Oncol. 2018;25(4):845-7.
6. Pancreatic cancer in adults: diagnosis and management. National Institute for Health and Care Excellence: Clinical Guidelines. London2018.
7. Balaban EP, Mangu PB, Yee NS. Locally Advanced Unresectable Pancreatic Cancer: American Society of Clinical Oncology Clinical Practice Guideline Summary. J Oncol Pract. 2017;13(4):265-9.
8. EUnetHTA. Comparators & Comparisons: Criteria for the choice of the most appropriate comparator(s). 2015.
9. Di Maio M, Daniele B, Gallo C, Perrone F. Re: Design and endpoints of clinical trials in hepatocellular carcinoma. J Natl Cancer Inst. 2008;100(21):1557; author reply -8.
10. Bonnetain F, Bonsing B, Conroy T, Dousseau A, Glimelius B, Haustermans K, et al. Guidelines for time-to-event end-point definitions in trials for pancreatic cancer. Results of the DATECAN initiative (Definition for the Assessment of Time-to-event End-points in CANcer trials). Eur J Cancer. 2014;50(17):2983-93.
11. EUnetHTA. Guideline - Endpoints used in Relative Effectiveness Assessment - SAFETY. 2015.
12. EUnetHTA. Guideline - Endpoints used for Relative Effectiveness Assessment Clinical Endpoints. 2015.
13. EUnetHTA. Guideline - Endpoints used for Relative Effectiveness Assessment Health related quality of life and utility measures 2015. 2015.

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 irreversible electroporation (IRE) ablation [with a percutaneous, laparoscopic or open surgical approach]?
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]	Yes-Critical	M	For which indications has IRE 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 IRE in relation to the comparators?
B0003	Features of the technology	What is the phase of development and implementation of the technology and the comparator(s)?	Yes	NM	What is the phase of development and implementation of IRE?
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	M	Who administers IRE? In what context and level of care is IRE 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	NM	What kind of special premises are needed to use IRE?
B0009	Investments and tools required to use the technology	What equipment and supplies are needed to use the technology and the comparator(s)?	Yes	NM	What equipment and supplies are needed to use IRE?
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	NM	What is the reimbursement status of IRE?
Health problem and current use of technology					
A0002	Target Condition	What is the disease or health condition in the	Critical	M	What is pancreatic cancer?

		scope of this assessment?			What is liver cancer (primary or secondary)?
A0003	Target Condition	What are the known risk factors for the disease or health condition?	No	NM	
A0004	Target Condition	What is the natural course of the disease or health condition?	Yes-Critical	M	What is the natural course of the pancreatic cancer? What is the natural course of the liver cancer (primary or secondary)?
A0005	Target Condition	What are the symptoms and the burden of disease or health condition for the patient?	Yes	M	What are the symptoms and the burden of disease for patients with pancreatic cancer? What are the symptoms and the burden of disease for patients with liver cancer (primary or secondary)?
A0006	Target Condition	What are the consequences of the disease or health condition for the society?	No	NM	
A0024	Current Management of the Condition	How is the disease or health condition currently diagnosed according to published guidelines and in practice?	Yes	M	How pancreatic cancer is currently diagnosed according to published guidelines and in practice? How liver cancer (primary or secondary) is 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 pancreatic cancer is currently managed according to published guidelines and in practice? How liver cancer (primary or secondary) is 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 unresectable locally advanced pancreatic cancer (LAPC)? What is unresectable liver cancer (primary or secondary) contraindicated for thermal ablation?
A0023	Target Population	How many people belong to the target population?	Yes	M	How many patients belong to the unresecatble locally advanced pancreatic cancer (LAPC) group? How many patients belong to the unresectable liver cancer (primary or secondary) contraindicated for thermal ablation group?
A0011	Utilisation	How much are the technologies utilised?	Yes	M (NM for diagnostics)	How much is IRE utilised?
Clinical effectiveness					
D0001	Mortality	What is the expected beneficial effect of the intervention on mortality?	Yes-Critical	M	What is the expected beneficial of IRE 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 IRE affect symptoms and findings (severity, frequency) of pancreatic cancer? How does IRE affect symptoms findings (severity, frequency) of liver cancer (primary or secondary)?
D0006	Morbidity	How does the technology affect progression (or recurrence) of the	Yes-Critical	M	How does IRE affect progression (or recurrence) of pancreatic cancer?

		disease or health condition?			How does IRE affect progression (or recurrence) of liver cancer (primary or secondary)?
D0011	Function	What is the effect of the technology on patients' body functions?	Yes	M	What is the effect of IRE on patients' body functions?
D0016	Function	How does the use of 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-Critical	M	How does the effect of IRE 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-Critical	M	What is the effect of IRE on disease-specific quality of life?
D0017	Patient satisfaction	Were patients satisfied with the technology?	Yes	NM	Were patients satisfied with the technology?
Safety					
C0008	Patient safety	How safe is the technology in relation to the comparator(s)?	Yes-Critical	M	How safe is IRE ?
C0002	Patient safety	Are the harms related to dosage or frequency of applying the technology?	Yes	NM	Are the harms related to dosage or frequency of applying IRE?
C0004	Patient safety	How does the frequency or severity of harms change over time or in different settings?	Yes	M	How does the frequency or severity of harms change over the 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	M	What are the susceptible patient groups that are more likely to be harmed through the use of IRE?
C0007	Patient safety	Are the technology and comparator(s) 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 for medical devices NM for screening and diagnostics	What kind of data/records and/or registry is needed to monitor the use of IRE?
Organisational aspects					
G0003	Servicios en salud	What kind of process ensures proper education and training of staff?	Yes	NM	What kind of process ensures proper education and training of staff?
G0006	Process-related costs	What are the costs of processes related to acquisition and setting up the new technology?	Yes	NM	What are the costs of processes related to acquisition and setting up IRE?
G0007	Process-related costs	What are the likely budget impacts of implementing the technologies being compared?	Yes	NM	What are the likely budget impacts of implementing IRE?

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?	No
1.2. Does comparing the new technology to the defined, existing comparators point to any differences that may be ethically relevant?	No
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
Introduction of IRE could require some organisational changes as it is required the device and the training for the staff, and leads to increased costs	
2.2. Does comparing the new technology to the defined, existing comparator(s) point to any differences that may be organisationally relevant?	No
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?	No
3.2. Does comparing the new technology to the defined, existing comparator(s) point to any differences that may be socially relevant?	No
4. Legal	
4.1. Does the introduction of the new technology and its potential use/non-use instead of the defined, existing comparator(s) give rise to any legal issues?	No
4.2. Does comparing the new technology to the defined, existing comparator(s) point to any differences that may be legally relevant?	No