

Comments from external experts:

Comment from	Page number	Line/section number	Comment and suggestion for rewording	Character of comment • 'major' <sup>a</sup> = 1 • 'minor' <sup>b</sup> = 2 • 'linguistic' <sup>c</sup> = 3	Author's reply
Fabio Ausania, Hospital Clinic Barcelona	10	146 - PICO	"Patients with histologically proven, unresectable locally advanced pancreatic cancer (LAPC)" IRE is sometimes applied in recurrent local advanced pancreatic cancer. It could be considered in the assessment	2	We agree and we will include the specification "primary or recurrent" locally advanced pancreatic cancer.
Fabio Ausania, Hospital Clinic Barcelona	10	146 - PICO	"Patients with histologically proven, unresectable primary or secondary liver cancer and contraindicated for thermal ablation" There are patients who are candidates for ablation but they do not have a biopsy (not histologically proven). It is not always necessary because there are some typical radiological and biological hallmarks.	1	We agree so the term "histologically proven" will be deleted in the final version of Project Plan
Fabio Ausania, Hospital Clinic Barcelona	10	146 - PICO	What classification has been used to define the locally advanced tumor? It should be specified	2	"Unresectable locally advanced pancreatic cancer" has been defined according to the NCCN (National Comprehensive Cancer Network) staging system. This information will be added in the final version of the Project Plan. We will also consider stage III pancreatic cancer (defined according to the AJCC (American Joint Committee on Cancer) Staging system.
David Kay, Gartnavel Hospital					<i>Failed to provide comments</i>
Des Alcorn, Gartnavel Hospital					<i>Failed to provide comments</i>

<sup>a</sup> "major": the comment points to a highly relevant aspect and a thorough answer is expected from the author(s)

<sup>b</sup> "minor": the comment does not necessarily have to be answered in a detailed manner

<sup>c</sup>"linguistic": grammar, wording, spelling or comprehensibility

Comments from manufacturer:

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AngioDynamics	General		The project plan looks very thorough and well described	2	Thanks for your comments
AngioDynamics	General		IRE is used to spare critical structures as it is a non thermal alternative. The literature review should evaluate data and author's insight regarding the critical structure sparing nature of IRE.	2	Advantages and disadvantages of IRE will be discussed according to the scientific evidence and the information provided by the manufacturer. A new sentence has been added to the Project Plan: IRE will be analyzed and discussed at the light of the found evidence and the information from the clinical experts and manufacturers.
AngioDynamics	12		<p>The use of RECIST criteria, especially in Pancreatic cancer post IRE needs special attention. Pancreatic cancer is desmoplastic neoplasm, hypo-vascularised and rich in fibrous tissue, making it is difficult to distinguish between residual/recurrent tumor and simple fibrotic tissue</p> <p>In RECIST 1.1 a spherical shape of the tumor is assumed; PDAC usually presents with ill defined and irregular margins, and very rarely a spherical shape.</p> <p>IRE in pancreatic cancer does not make the tumor disappear which would mean that the best response that IRE would accomplish would be a partial response.</p>	1	We agree, so RECIST criteria will be deleted from the Project Plan

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EUnetHTA JA3 WP4 - Other technologies, OTCA15

Review by external experts and fact check by manufacturer of the 2<sup>nd</sup> draft Project Plan for Irreversible electroporation in liver and pancreatic cancer



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			(Example citation: Response of Borderline Resectable Pancreatic Cancer to Neoadjuvant Therapy Is Not Reflected by Radiographic Indicators. <i>Matthew H. Cancer</i> 2012;118:5749-56.)		
AngioDynamics	General		A clinical risk/benefit assessment should be paramount in the analysis.	2	The following sentence will be added to the Project Plan: The benefit and risk of IRE will be assessed.
AngioDynamics	9		Level of evidence: the review should appreciate the practical and ethical limitations of randomizing subjects who have received chemotherapy and are deemed eligible for additional therapy (IRE). Not providing additional therapy that has a significant amount of clinical evidence in support has proven difficult for ethic committees to approve and for subjects to enroll in trials.	2	This has been already taken into account. Non-randomized studies will be included for effectiveness and safety domains

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