

**Input from external experts and manufacturers on 2nd draft
assessment “Irreversible electroporation in liver and pancreatic
cancer”**

(Project ID: OTCA15)



eunethta

EUROPEAN NETWORK FOR HEALTH TECHNOLOGY ASSESSMENT

EXTERNAL EXPERTS

Comments were received from:

Contributor	Helen Gallo, National Institute for Health and Care Excellence (NICE), UK
External experts	Fabio Ausania, Hospital Clinic, Barcelona

Comment from <i>Insert your name and organisation</i>	Page number <i>Insert 'general' if your comment relates to the whole document</i>	Line or section number	Comment and suggestion for rewording <i>Please insert each new comment in a new row.</i>	Character of comment <ul style="list-style-type: none"> • 'major'^a=1 • 'minor'^b= 2 • 'linguistic'^c=3 <i>Please indicate your choice by writing the according number in this field, e.g. for major choose "1".</i>	Author's reply
General comments					
Fabio Ausania, Hospital Clinic, Barcelona	General comment	-	I think the conclusion of this assessment should be changed. The quality of the evidence is very low, there are no randomized clinical trials and therefore the results of this review should be interpreted with caution. In my opinion, it should be stated that the current available evidence does not allow any definitive conclusions with regard to safety and oncological effectiveness of IRE. Randomized clinical trials are needed.	1	In the discussion section it has been highlighted that the quality of the evidence is very low, but also that appropriately designed comparative trials are needed in order to be able to determine the comparative effectiveness and safety of IRE. This

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					is in line with the conclusions, where it is indicated that there is insufficient evidence to establish the comparative effectiveness and safety of IRE in pancreatic cancer (as only one comparative trial has been included) and there is lack of data to establish the comparative effectiveness and safety of IRE in liver cancer (no comparative trials available).
Fabio Ausania, Hospital Clinic, Barcelona	General comment	-	Oncological Effectiveness: given that only one comparative series was included and its risk of bias is critical, I consider that no conclusions can be made regarding effectiveness of IRE. Furthermore, some experiences suggest that IRE can be associated to higher survival rates in very selected patients. My opinion about oncological outcomes is that this is an unexplored field and further studies are needed.	1	The conclusions can only make reference to the evidence available. For pancreatic cancer, it has been highlighted that the evidence is insufficient to establish the effectiveness of IRE. For liver cancer, no comparative trials were found, so the conclusions state that there is a lack of data to establish the effectiveness of IRE in relation to the comparators.
Fabio	General	-	Safety outcomes: the authors state that IRE is not safe because the	1	The conclusions regarding the safety of IRE is that the evidence is

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Ausania, Hospital Clinic, Barcelona	comment		procedure-related mortality is around 2%. In my opinion, this is not correct. Safety should always be compared with alternative treatments. Whichever invasive procedure has complications. Of course IRE has a higher morbidity and mortality rate if we compare it with absence of treatment. However, this complications rate would be certainly lower than aggressive surgery. The conclusions should indicate that no comparative trials were available and no definitive conclusions should be made in absence of a proper control arm receiving an alternative treatment.		insufficient to establish whether IRE is safer, or at least as safe, as the standard of care. However, the procedure related mortality for pancreatic cancer was 1.62% (4 patients) and around 10% experienced major procedure related complications, so we consider it is important to highlight, given the low quality of the evidence and the possible risk of underreporting, that there are doubts regarding the occurrence of adverse events. The population of the assessment are patients who are not candidates to surgery procedures, so our comparator would not be any invasive procedure. However, taking into account that the evidence base is low we have rephrased the conclusion to make it clearer: "there are uncertainties regarding the appearance of severe

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					adverse events", instead of "the available evidence raises serious concerns regarding the appearance of severe adverse events".
Summary					
Helen Gallo, senior analyst, NICE	9	40	'liable to supportive palliative care' could be changed to 'eligible for supportive palliative care'	3	Amended
Helen Gallo, senior analyst, NICE	11	37	There is a prospective non-randomised comparative study: Bhutiani N et al. (2016) Evaluation of tolerability and efficacy of irreversible electroporation (IRE) in the treatment of Child-Pugh B (7/8) hepatocellular carcinoma (HCC). HPB: the official journal of the International Hepato Pancreato Biliary Association 18: 593–9	2	This study has been excluded for the several reasons: <ul style="list-style-type: none"> - It compares IRE with MWA. We did not consider MWA as a comparator in our PICO - We considered that it is a retrospective study ("a prospective multinstitutional double arm treatment registry was evaluated") - IRE is applied in patients with unresectable tumours or as a

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					bridge to transplantation
Helen Gallo, senior analyst, NICE	12	19-25	Inconsistencies with the number of decimal places used when quoting percentages and months.	3	Amended
Helen Gallo, senior analyst, NICE	12	41	'CI not reported' rather than 'not CI reported'.	3	Corrected
Helen Gallo, senior analyst, NICE	13	4	'44 out of 226' rather than '44 over 226'	3	Corrected
Helen Gallo, senior analyst, NICE	13	21	It could say range 0 to 17.7% rather than 'varying this frequency from 0% to 17.65%	3	Corrected
Helen Gallo, senior analyst, NICE	30	14	There is another prospective single arm study: Zeng J et al. (2017) The safety and efficacy of irreversible electroporation for large hepatocellular carcinoma. Technology in Cancer Research & Treatment 16: 120 – 124	2	After discussing this study with authors and coauthors it was considered that it was a retrospective study ("prospective search of patients undergoing IRE"). In addition, in the

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					inclusion criteria it did not state if the tumour was unresectable and contraindicated to thermal ablation
Description and technical characteristics of the technology					
Helen Gallo, senior analyst, NICE	36	13	'consists on' should say 'consists of'	3	Corrected
Helen Gallo, senior analyst, NICE	36	28	Should 'liable to' be 'eligible for'?	3	Corrected
Health problem and current use					
Helen Gallo, senior analyst, NICE	40	33	This phrase is hard to understand: 'since both of them condition therapeutic options'.	3	We agree. We have decided to delete it as it does not add important information
Helen Gallo, senior analyst, NICE	48	1	'It stablish five categories' doesn't make sense.	3	Ok. We have corrected it as "there are five caterogies"
Clinical effectiveness					

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Helen Gallo, senior analyst, NICE	52	6	Please clarify that this statement refers to all patients; 'Neoadjuvant CT was given to 23.8% of the patients'	2	Ok. It has been clarified as follows "In the IRE group, neoadjuvant CHEMO was given to 23.8% of the patients and 33.3% received CHEMO after IRE"
Safety					
Helen Gallo, senior analyst, NICE	69	27	'on' should be 'one'	3	Ok
Helen Gallo, senior analyst, NICE	67	14	'randomized non-controlled trial' should be non-randomized controlled trial	3	Ok. Corrected
Helen Gallo, senior analyst, NICE	70	1	'prostatic' should be 'prostatic'	3	Amended
Appendix					
Helen Gallo, senior analyst,	181	5	I would question the use of the word 'negative' here. The actual recommendations from 2013 state: 'Current evidence on the safety and	2	This information was provided by the manufacturer in the submission file. However, we have added the following

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NICE			efficacy of irreversible electroporation for treating primary liver cancer is inadequate in quantity and quality. Therefore, this procedure should only be used in the context of research.' I suggest removing the word 'negative' and either summarise the main recommendation as above or just say 'research context only.' It would also be helpful to say what year this guidance was published.		sentence: "research context only"

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MANUFACTURERS

Comments were received from:

Manufacturer	AngioDynamics®
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Summary					
AngioDynamics	12	11	Add line 11 at the end: With limited data from only a small single comparative trial (no participants 21 IRE/ 23 comparators) it is not possible to draw conclusions about the efficacy of IRE.	1	The manufacturer was asked to check for factual accuracy of the document. This comment is not related to a factual inaccuracy and is, therefore, outside the scope of a fact check
AngioDynamics	12	18	Add at the end: The wide variability in the survival rates and lack of 2 year data means that the currently available survival data from single-arm studies is not reliable. Further studies are required to generate more and more consistent data before any firm conclusion might be drawn.	1	The manufacturer was asked to check for factual accuracy of the document. This comment is not related to a factual inaccuracy and is, therefore, outside the scope of a fact check
AngioDynamics	12	25	Add at the end:	1	The manufacturer was asked to check for factual accuracy of the

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			The wide variability in the survival rates and lack of 2 year data means that the currently available survival data from single-arm studies is not reliable. Further studies are required to generate more and more consistent data before any firm conclusion might be drawn.		document. This comment is not related to a factual inaccuracy and is, therefore, outside the scope of a fact check
AngioDynamics	12	29	Add at the end: Again, more and more consistent data is required to draw any firm conclusions.	1	The manufacturer was asked to check for factual accuracy of the document. This comment is not related to a factual inaccuracy and is, therefore, outside the scope of a fact check
AngioDynamics	12	33	Add at the end: Again, more and more consistent data is required to draw any firm conclusions.	1	The manufacturer was asked to check for factual accuracy of the document. This comment is not related to a factual inaccuracy and is, therefore, outside the scope of a fact check
AngioDynamics	12	41	Add line 41 at the end: Comparative data would be helpful here before firm conclusions on the success of the procedure.	1	The manufacturer was asked to check for factual accuracy of the document. This comment is not related to a factual inaccuracy and is, therefore, outside the scope of a fact check
AngioDynamics	13	9	Add after "thrombosis".: Necrosis arises with chemotherapy and in particular radiotherapy. Given	1	These adverse events were classified as "IRE-related" in the

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			that patients were receiving multiple treatments, it is not possible to accurately draw conclusions about the safety of IRE from this data.		included studies
AngioDynamics	13	5	<p>20.29% not surprising for pancreas</p> <p><u>Add a new line after line 18:</u> When reviewing the safety aspects, please be aware that an important limitation of the present systematic review is the impossibility to carry out a comparative analysis to assess how the location, size of the tumour and approach could affect safety outcomes. Furthermore, the applicability of the effectiveness and safety results is also very doubtful.</p> <p><u>Comment:</u> Note that the above two sentences are draw from your own report: P17 L34 and P18 L13 Severe adverse events require a careful analysis in the clinical context of patient and procedure: Furthermore there are no randomised controlled trials included in the reviewed data sets. These are necessary to provide a more reliable perspective on safety. We would refer you to: Moris D, Machairas N, Tsilimigras DI, et al. Systematic Review of Surgical and Percutaneous Irreversible Electroporation in the Treatment of Locally Advanced Pancreatic Cancer. Ann Surg Oncol. 2019;26(6):1657-1668. In this systematic review, the authors concluded that the percutaneous approach had an major morbidity rate of 13.3% as comparted to 21.5% of</p>	1	The manufacturer was asked to check for factual accuracy of the document. This comment is not related to a factual inaccuracy and is, therefore, outside the scope of a fact check

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			surgery.		
AngioDynamics	13	20	Delete lines 26 to 28 The IFU requires that the tumour is bracketed. If the IRE is properly applied in accordance with the IFU, there will be no 26 needle tract seeding. If the technique is being wrongly applied this study (whichever it is) must be excluded from the review because it represents a completely off-label use of IRE.	1	The manufacturer was asked to check for factual accuracy of the document. This comment is not related to a factual inaccuracy and is, therefore, outside the scope of a fact check
AngioDynamics	17	27	Delete: Overall, the safety of IRE arises as an important concern. Comment: The search criteria mean that the data selection is so narrow that no inferences might be drawn from the data about safety.	1	"important" deleted according to the external expert review
AngioDynamics	18	37	Delete: The existing evidence raises doubts regarding the efficacy of IRE for achieving the complete ablation of unresectable LAPC Rationale: No such firm conclusion might be drawn from the data reviewed by EUnetHTA. This is supported by the analysis. Discussion at p17 L2 states that the evidence is not consistent and at L8 states that it is insufficient. L17 says that the "studies lack comparability" and "patients ...were treated with different CT and/or radio chemotherapy regimens...not knowing how these could have contributed to the overall survival or control rates. Therefore there is also insufficient evidence to raise "doubts regarding efficacy...". Consequently there are too many	1	The manufacturer was asked to check for factual accuracy of the document. This comment is not related to a factual inaccuracy and is, therefore, outside the scope of a fact check

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			<p>doubts about the evidence selected to support any conclusions at all about efficacy of IRE and these should be deleted. P17 L36 "...there is great uncertainty regarding how IRE compares to treatment without IRE and how the differences between the different subgroups could influence results".</p> <p>P79 L1 "The available evidence is also insufficient to establish if IRE would be effective in improving the overall survival of pancreatic and liver cancer patients when compared to the standard of care."</p>		
AngioDynamics	18	39	<p>Delete: The existing evidence raises doubts regarding the efficacy of IRE as a sole primary local treatment for LAPC. Currently, it is unclear whether it needs to be combined with chemotherapy, and if so, which regimens are optimal.</p> <p>Rationale: No such firm conclusion might be drawn from the data reviewed by EUnetHTA. This is supported by the analysis.</p> <p>See above. There is no evidence about the use of IRE as a sole primary local treatment for LAPC therefore no conclusions might be drawn. P17 L36 "...there is great uncertainty regarding how IRE compares to treatment without IRE and how the differences between the different subgroups could influence results".</p> <p>P79 L1 "The available evidence is also insufficient to establish if IRE would be effective in improving the overall survival of pancreatic and liver</p>	1	The manufacturer was asked to check for factual accuracy of the document. This comment is not related to a factual inaccuracy and is, therefore, outside the scope of a fact check

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			<p>cancer patients when compared to the standard of care."</p> <p>IRE is not ever advocated as a sole primary local treatment, particularly for this type of aggressive cancer. Therefore this inference is not one that needs to be discussed: IRE is always intended to be complementary.</p>		
AngioDynamics	18	42	<p>Delete: The available evidence raises serious concerns regarding the appearance of severe adverse events when IRE is used for the treatment of unresectable LAPC.</p> <p>Comment: No such firm conclusion might be drawn from the data reviewed by EUnetHTA. This is supported by the analysis. P17 L34: "An important limitation of the present systematic review is the impossibility to carry out a comparative analysis to assess how the location, size of the tumour and approach could affect safety outcomes." P18 L13 "The applicability of the effectiveness and safety results is also very doubtful."</p> <p>Severe adverse events require a careful analysis in the clinical context of patient and procedure:</p> <p>Furthermore there are no randomised controlled trials included in the reviewed data sets. These are necessary to provide a more reliable perspective on safety.</p>	1	"Serious" deleted according to the external expert review
AngioDynamics	19	9	Delete: The existing evidence raises doubts regarding the efficacy of IRE for achieving the complete ablation of primary or secondary unresectable	1	The manufacturer was asked to check for factual accuracy of the document. This comment is not

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			<p>liver tumours that are not suitable for thermal ablation.</p> <p>Comment: No such firm conclusion might be drawn from the data reviewed by EUnetHTA. This is supported by the analysis.</p> <p>See P17 L20 regarding the limited data for liver tumours reviewed: no comparative trials and only one single arm study with long-term survival. See p17 L23 "only few studies report on QoL." P17 L36 "...there is great uncertainty regarding how IRE compares to treatment without IRE and how the differences between the different subgroups could influence results".</p> <p>P79 L1 "The available evidence is also insufficient to establish if IRE would be effective in improving the overall survival of pancreatic and liver cancer patients when compared to the standard of care."</p>		related to a factual inaccuracy and is, therefore, outside the scope of a fact check
AngioDynamics	19	11	<p>Delete: The existing evidence raises doubts regarding the efficacy of IRE as a sole primary local treatment for liver tumours that are not suitable for thermal ablation.</p> <p>Comment: No such firm conclusion might be drawn from the data reviewed by EUnetHTA. This is supported by the analysis.</p> <p>See P17 L20 regarding the limited data for liver tumours reviewed: no comparative trials and only one single arm study with long-term survival. See p17 L23 "only few studies report on QoL." P17 L36 "...there is great uncertainty regarding how IRE compares to treatment without IRE and how the differences between the different subgroups could influence</p>	1	The manufacturer was asked to check for factual accuracy of the document. This comment is not related to a factual inaccuracy and is, therefore, outside the scope of a fact check

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			<p>results".</p> <p>P79 L1 "The available evidence is also insufficient to establish if IRE would be effective in improving the overall survival of pancreatic and liver cancer patients when compared to the standard of care."</p> <p>IRE is not ever advocated as a sole primary local treatment, particularly for this type of aggressive cancer. Therefore this inference is not one that needs to be discussed: IRE is always intended to be complementary.</p>		
AngioDynamics	19	13	<p>Delete: The available evidence raises serious concerns regarding the appearance of severe adverse events when IRE is used for the treatment of liver tumours that are not suitable for thermal ablation.</p> <p>Comment: No such firm conclusion might be drawn from the data reviewed by EUnetHTA. This is supported by the analysis.</p> <p>Query how it is possible to reach the conclusion of "serious concerns" given (p13 L21) that some studies had major AE's rate of 0% and there was zero procedure related mortality and the overall statistical significance of the study data reviewed is low and quality of the data is low.</p> <p>P17 L34: "An important limitation of the present systematic review is the impossibility to carry out a comparative analysis to assess how the location, size of the tumour and approach could affect safety outcomes."</p> <p>P18 L13 "The applicability of the effectiveness and safety results is also</p>	1	The manufacturer was asked to check for factual accuracy of the document. This comment is not related to a factual inaccuracy and is, therefore, outside the scope of a fact check

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			very doubtful."		
Description and technical characteristics of the technology					
Angiodynamics	No comments				
Health problem and current use					
AngioDynamics	44	13	Delete: Open surgery is the standard of care and only curative option for pancreatic cancer (27,32). Replace with: For patients with resectable tumours, open surgery is the standard of care and is the only potentially curative treatment choice. Comment: The replacement suggested is taken from the source and therefore is more accurate than the original draft.	1	The manufacturer was asked to check for factual accuracy of the document. This comment is not related to a factual inaccuracy and is, therefore, outside the scope of a fact check
Effectiveness					
AngioDynamics	63	1	Add under Line 1: Note that the data reviewed by EUnetHTA is extremely limited in both the number and size of studies. In addition, for both safety and efficacy the quality of that data is "very low" according to the GRADE system. Furthermore data was narratively synthesised using descriptive statistics to summarise quantitative measures. According to the UK's National Institute for Health Research ² : "A common criticism of narrative synthesis is that it is difficult to maintain transparency in the interpretation of the data and development of conclusions. This ultimately threatens the value of the synthesis and the	1	The manufacturer was asked to check for factual accuracy of the document. This comment is not related to a factual inaccuracy and is, therefore, outside the scope of a fact check

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			<p>extent to which the conclusions can be relied upon."</p> <p>Consequently no firm conclusions (positive or negative) about the safety or efficacy of IRE might be drawn from any of the data summarised below.</p>		
AngioDynamics	64	15	<p>Add below Line 15</p> <p>Note that the data reviewed by EUnetHTA is extremely limited in both the number and size of studies. In addition, for both safety and efficacy the quality of that data is "very low" according to the GRADE system.</p> <p>Furthermore data was narratively synthesised using descriptive statistics to summarise quantitative measures. According to the UK's National Institute for Health Research³:</p> <p>"A common criticism of narrative synthesis is that it is difficult to maintain transparency in the interpretation of the data and development of conclusions. This ultimately threatens the value of the synthesis and the extent to which the conclusions can be relied upon."</p> <p>Consequently no firm conclusions (positive or negative) about the safety or efficacy of IRE might be drawn from any of the data summarised below.</p>	1	The manufacturer was asked to check for factual accuracy of the document. This comment is not related to a factual inaccuracy and is, therefore, outside the scope of a fact check
AngioDynamics	65	42	<p>Add below Line 42:</p> <p>Note that the data reviewed by EUnetHTA is extremely limited in both</p>	1	The manufacturer was asked to check for factual accuracy of the document. This comment is not

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			<p>the number and size of studies. In addition, for both safety and efficacy the quality of that data is "very low" according to the GRADE system. Furthermore data was narratively synthesised using descriptive statistics to summarise quantitative measures. According to the UK's National Institute for Health Research⁶:</p> <p>"A common criticism of narrative synthesis is that it is difficult to maintain transparency in the interpretation of the data and development of conclusions. This ultimately threatens the value of the synthesis and the extent to which the conclusions can be relied upon."</p> <p>Consequently no firm conclusions (positive or negative) about the safety or efficacy of IRE might be drawn from any of the data summarised below.</p>		related to a factual inaccuracy and is, therefore, outside the scope of a fact check
AngioDynamics	66	1	<p>Add below Line 1:</p> <p>Note that the data reviewed by EUnetHTA is extremely limited in both the number and size of studies. In addition, for both safety and efficacy the quality of that data is "very low" according to the GRADE system. Furthermore data was narratively synthesised using descriptive statistics to summarise quantitative measures. According to the UK's National Institute for Health Research⁷:</p> <p>"A common criticism of narrative synthesis is that it is difficult to maintain transparency in the interpretation of the data and development of conclusions. This ultimately threatens the value of the synthesis and the</p>	1	The manufacturer was asked to check for factual accuracy of the document. This comment is not related to a factual inaccuracy and is, therefore, outside the scope of a fact check

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			<p>extent to which the conclusions can be relied upon."</p> <p>Consequently no firm conclusions (positive or negative) about the safety or efficacy of IRE might be drawn from any of the data summarised below.</p>		
Safety					
AngioDynamics	67	1	<p>Add below Line 1:</p> <p>Note that the data reviewed by EUnetHTA is extremely limited in both the number and size of studies. In addition, for both safety and efficacy the quality of that data is "very low" according to the GRADE system. Furthermore data was narratively synthesised using descriptive statistics to summarise quantitative measures. According to the UK's National Institute for Health Research⁸:</p> <p>"A common criticism of narrative synthesis is that it is difficult to maintain transparency in the interpretation of the data and development of conclusions. This ultimately threatens the value of the synthesis and the extent to which the conclusions can be relied upon."</p> <p>Consequently no firm conclusions (positive or negative) about the safety or efficacy of IRE might be drawn from any of the data summarised below.</p>	1	The manufacturer was asked to check for factual accuracy of the document. This comment is not related to a factual inaccuracy and is, therefore, outside the scope of a fact check
AngioDynamics	68	17	Add after (4.2%):	1	The manufacturer was asked to check for factual accuracy of the

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			<p>Given that the data has been drawn from 7 trials and with a relatively small number of patients in each, and each with a different approach to reviewing mortality data, the preceding amalgamation of the data cannot be relied upon to draw any particular conclusions on patient safety.</p> <p><u>Comments:</u></p> <p>Operations on patients who are in the older age bracket (average age in 60s) will pose risks. Surgeons will need to weigh the risks inherent in surgery against the potential benefits of a last-line treatment. The complications from surgery should not be dismissed, but when looking at the risks posed by IRE itself (as opposed to surgery generally) the data does not support the conclusion that IRE is per se unsafe. Surgery on unwell patients who are on average in their 60s is a risk which must be included in the risk/ benefit analysis for IRE, but AEs arising from surgery cannot lead to the conclusion that IRE as a treatment is itself unsafe.</p>		document. This comment is not related to a factual inaccuracy and is, therefore, outside the scope of a fact check
Discussion					
AngioDynamics	78	5	<p>Delete: It is claimed</p> <p>Replace with: Studies have shown</p>	1	The manufacturer was asked to check for factual accuracy of the document. This comment is not related to a factual inaccuracy and is, therefore, outside the

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					scope of a fact check
AngioDynamics	78	11	Delete: Currently, the exact mechanism of action of IRE is unknown. Comment: The mechanism of action is well understood when used as instructed. The clinical use might though lead to a different result if IFU is not followed.	1	As explained in the assessment, some studies raised doubts regarding the exact mechanism of IRE
AngioDynamics	78	14	Delete: The two sentences starting at line 14. Comment: If the IFU is not followed, then thermal effects can be observed. This report should relate only to on-label use of IFU.	1	As explained in the assessment, some studies raised doubts regarding the exact mechanism of IRE
AngioDynamics	79	43	Delete: Overall, the safety of IRE arises as an important concern. Comment: No such firm conclusion might be drawn from the data reviewed by EUnetHTA. This is supported by the analysis. P17 L34: "An important limitation of the present systematic review is the impossibility to carry out a	1	"important" deleted according to the external expert review
AngioDynamics	79	47	Add after 25).: The previously noted limitations of the data reviewed mean that no conclusions might be drawn from these data. The applicability of the effectiveness and safety results is also very doubtful Comment:	1	The manufacturer was asked to check for factual accuracy of the document. This comment is not related to a factual inaccuracy and is, therefore, outside the scope of a fact check

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			<p>P17 L34: "An important limitation of the present systematic review is the impossibility to carry out a comparative analysis to assess how the location, size of the tumour and approach could affect safety outcomes."</p> <p>P18 L13 "The applicability of the effectiveness and safety results is also very doubtful."</p>		
AngioDynamics	80	1	<p>Delete: reinforcing the idea that IRE may have a thermal effect.</p> <p>Comment: There is no thermal effect when IRE is used in accordance with the IFU. This report should not be discussing offlabel use.</p>	1	<p>Some studies have shown a thermal effect:</p> <ul style="list-style-type: none"> • Van Gemert MJ, Wagstaff PG, de Bruin DM, van Leeuwen TG, van der Wal AC, Heger M, et al. Irreversible electroporation: just another form of thermal therapy? Prostate. 2015;75(3):332-5. 14 PubMed PMID: 25327875. • Van den Bos W, Scheffer HJ, Vogel JA, Wagstaff PG, de Bruin DM, de Jong MC, et al. Thermal. Energy during Irreversible Electroporation and the Influence of Different

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					Ablation Parameters. Journal of vascular and interventional radiology : JVIR. 2016;27(3):433-43. PubMed PMID: 18 26703782.
AngioDynamics	80	21	<p>Delete:</p> <p>Nonetheless, it might be important to note that some authors referred abandoning the percutaneous approach due to the discouraging complications (11)</p> <p>Comment:</p> <p>Low sample size: According to the original source, the author stated: "Although percutaneous IRE of pancreatic carcinoma is reportedly a safe procedure, our experience with two patients both of whom had complications was discouraging and was therefore abandoned." (Lambert, 2016). The exceptionally high 100% (2/2) complication rate for percutaneous approach very surprising, and maybe due to exceptionally low-sample size in the percutaneous approach arm. There was only 2 patients undergoing percutaneous approach, both of whom experienced complications. This exemplifies the fact that inappropriate conclusions were drawn from a low-sample size of patient population, which is a consistent theme throughout the literature report. It is</p>	1	The manufacturer was asked to check for factual accuracy of the document. This comment is not related to a factual inaccuracy and is, therefore, outside the scope of a fact check

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			<p>important to note that in the same quotation above, Lambert, 2016 himself admitted that percutaneous approach is a reportedly safe procedure, and cited a retrospective study (n=14) that percutaneous pancreatic IRE procedure was well tolerated with low complication rate of 14% (2/14). (Narayanan, 2012) This retrospective study is not included as part of the EUnetHTA literature search.</p> <p>References:</p> <ul style="list-style-type: none"> • Lambert, L., et al. "Treatment of locally advanced pancreatic cancer by percutaneous and intraoperative irreversible electroporation: general hospital cancer center experience." Neoplasma 63.2 (2016): 269-273. • Narayanan, Govindarajan, et al. "Percutaneous irreversible electroporation for downstaging and control of unresectable pancreatic adenocarcinoma." Journal of Vascular and Interventional. Radiology 23.12 (2012): 1613-1621. 		
AngioDynamics	Page 81 (Discussion:	16-21	<p>Add in each location:</p> <p>On May 13, 2019, Angiodynamics has announced the enrollment of the</p>	1	These trials will be mentioned in the assessment

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	Ongoing studies)		first patient in its DIRECT study and has begun recruiting patients now. <ul style="list-style-type: none"> • NCT03899636 Randomized clinical trial • NCT03899649 Registry study Comment: Existence of the new DIRECT study for pancreatic cancer The DIRECT Study is an new and ongoing clinical trial comprising of two parts 1) a Randomized Controlled Trial at up to 15 sites, and 2) a Real-World Evidence, nextgeneration registry at up to 30 sites. Both study will include a NanoKnife System treatment arm and a control arm. AngioDynamics expects each NanoKnife arm to consist of approximately 250 patients with an equal number of control patients. The primary endpoint of the study is overall survival.		
Conclusions					
AngioDynamics	82	10	Delete: The existing evidence raises doubts regarding the efficacy of IRE for achieving the complete ablation of unresectable LAPC Rationale:	1	The manufacturer was asked to check for factual accuracy of the document. This comment is not related to a factual inaccuracy and is, therefore, outside the

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			<p>No such firm conclusion might be drawn from the data reviewed by EUnetHTA. This is supported by the analysis.</p> <p>Discussion at p17 L2 states that the evidence is not consistent and at L8 states that it is insufficient. L17 says that the "studies lack comparability" and "patients ...were treated with different CT and/or radio chemotherapy regimens...not knowing how these could have contributed to the overall survival or control rates. Therefore there is also insufficient evidence to raise "doubts regarding efficacy....".</p> <p>Consequently there are too many doubts about the evidence selected to support any conclusions at all about efficacy of IRE and these should be deleted. P17 L36 "...there is great uncertainty regarding how IRE compares to treatment without IRE and how the differences between the different subgroups could influence results".</p> <p>P79 L1 "The available evidence is also insufficient to establish if IRE would be effective in improving the overall survival of pancreatic and liver cancer</p>		scope of a fact check
AngioDynamics	82	12	<p>Delete:</p> <p>The existing evidence raises doubts regarding the efficacy of IRE as a sole primary local treatment for LAPC. Currently, it is unclear whether it needs to be combined with chemotherapy, and if so, which regimens are optimal.</p>	1	The manufacturer was asked to check for factual accuracy of the document. This comment is not related to a factual inaccuracy and is, therefore, outside the scope of a fact check

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			<p>Comment:</p> <p>No such firm conclusion might be drawn from the data reviewed by EUnetHTA. This is supported by the analysis.</p> <p>See above. There is no evidence about the use of IRE as a sole primary local treatment for LAPC therefore no conclusions might be drawn. P17 L36 "...there is great uncertainty regarding how IRE compares to treatment without IRE and how the differences between the different subgroups could influence results".</p> <p>P79 L1 "The available evidence is also insufficient to establish if IRE would be effective in improving the overall survival of pancreatic and liver cancer patients when compared to the standard of care."</p>		
AngioDynamics	82	15	<p>Delete: The available evidence raises serious concerns regarding the appearance of severe adverse events when IRE is used for the treatment of unresectable LAPC.</p> <p>Comment:</p> <p>No such firm conclusion might be drawn from the data reviewed by EUnetHTA. This is supported by the analysis.</p> <p>P17 L34: "An important limitation of the present systematic review is the impossibility to carry out a comparative analysis to assess how the location, size of the tumour and approach could affect safety outcomes."</p>	1	The manufacturer was asked to check for factual accuracy of the document. This comment is not related to a factual inaccuracy and is, therefore, outside the scope of a fact check

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			P18 L13 "The applicability of the effectiveness and safety results is also very doubtful."		
AngioDynamics	82	25	<p>Delete:</p> <p>The existing evidence raises doubts regarding the efficacy of IRE for achieving the complete ablation of primary or secondary unresectable liver tumours that are not suitable for thermal ablation.</p> <p>Comment:</p> <p>No such firm conclusion might be drawn from the data reviewed by EUnetHTA. This is supported by the analysis.</p> <p>See P17 L20 regarding the limited data for liver tumours reviewed: no comparative trials and only one single arm study with long-term survival. See p17 L23 "only few studies report on QoL." P17 L36 "...there is great uncertainty regarding how IRE compares to treatment without IRE and how the differences between the different subgroups could influence results".</p> <p>P79 L1 "The available evidence is also insufficient to establish if IRE would be effective in improving the overall survival of pancreatic and liver cancer patients when compared to the standard of care."</p>	1	The manufacturer was asked to check for factual accuracy of the document. This comment is not related to a factual inaccuracy and is, therefore, outside the scope of a fact check
AngioDynamics	82	27	<p>Delete:</p> <p>The existing evidence raises doubts regarding the efficacy of IRE as a</p>	1	The manufacturer was asked to check for factual accuracy of the document. This comment is not

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			<p>sole primary local treatment for liver tumours that are not suitable for thermal ablation.</p> <p>Comment:</p> <p>No such firm conclusion might be drawn from the data reviewed by EUnetHTA. This is supported by the analysis.</p> <p>See P17 L20 regarding the limited data for liver tumours reviewed: no comparative trials and only one single arm study with long-term survival. See p17 L23 "only few studies report on QoL." P17 L36 "...there is great uncertainty regarding how IRE compares to treatment without IRE and how the differences between the different subgroups could influence results".</p> <p>P79 L1 "The available evidence is also insufficient to establish if IRE would be effective in improving the overall survival of pancreatic and liver cancer patients when compared to the standard of care."</p>		related to a factual inaccuracy and is, therefore, outside the scope of a fact check
AngioDynamics	82	29	<p>Delete:</p> <p>The available evidence raises serious concerns regarding the appearance of severe adverse events when IRE is used for the treatment of liver tumours that are not suitable for thermal ablation.</p> <p>Comment</p> <p>No such firm conclusion might be drawn from the data reviewed by</p>	1	The manufacturer was asked to check for factual accuracy of the document. This comment is not related to a factual inaccuracy and is, therefore, outside the scope of a fact check

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			<p>EUnetHTA. This is supported by the analysis.</p> <p>Query how it is possible to reach the conclusion of "serious concerns" given (p13 L21) that some studies had major AE's rate of 0% and there was zero procedure related mortality and the overall statistical significance of the study data reviewed is low and quality of the data is low.</p> <p>P17 L34: "An important limitation of the present systematic review is the impossibility to carry out a comparative analysis to assess how the location, size of the tumour and approach could affect safety outcomes."</p> <p>P18 L13 "The applicability of the effectiveness and safety results is also very doubtful."</p>		

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