National Institute for Health and Care Excellence

IP1023/2 - Irreversible electroporation for treating pancreatic cancer
Consultation Comments Table

IPAC date: 9 February 2017

Com. no.	Consultee name and organisation	Sec. no.	Comments	Response Please respond to all comments
1	Consultee 1 British Society of Gastroenterology (BSG)	4&5	<u>Adequacy of the literature review:</u> Since March 2016, the following peer reviewed papers have been published: i) Hester J. Scheffer, Laurien G. P. H. Vroomen, Marcus C. de Jong, et al. Ablation of Locally Advanced Pancreatic Cancer with Percutaneous Irreversible Electroporation: Results of the Phase I/II PANFIRE Study. Published online before print 10.1148/radiol.2016152835	Thank you for your comment. This new publication has been picked up in our update search and added to table 2 in the overview. It was noted that the authors of this paper concluded that their data "support the setup of larger phase II and III clinical trials to assess the efficacy of IRE plus chemotherapy in the neoadjuvant and adjuvant or second-line setting compared with more widely adopted regimens such as chemotherapy and/or radiation therapy".

2	Consultee 1 British Society of Gastroenterology (BSG)	1	The existence of a UK wide registry.	Thank you for your comment. NICE interventional procedures Advisory Committee can make a recommendation encouraging data submission to registers where it is appropriate in its guidance if the register meets the criteria set out in NICE programme manual. IP team followed up with the UK IRE registry lead to check if the register meets NICE standards. NICE was informed that the register does not yet comply with the NICE standards and not fully operational. **IPAC added a committee comment to section 6 of the guidance as follows:** *'the committee noted that the UK IRE registry is currently underdevelopment and encourages data submission when the register becomes available.*

3	Consultee 1 British Society of Gastroenterology (BSG)	4.5, 5.11	The quality of the Specialist Adviser questionnaires: All four advisers were respected interventional radiologists, representing either the British Society of Interventional Radiology (BSIR) or British Society of Gastrointestinal and Abdominal Radiology (BSGAR). The narrow range of specialists chosen as advisors is surprising, as most clinical experience and evidence relates to IRE performed as an open surgical procedure. Of concern, in response to the question, 3.2 "What would be the comparator (standard practice) to this procedure?", four completely different modalities of treatment were offered as answers, by the respondents: •"Resection, rather than other ablative procedures, which have not been borne out for LAPC" •"Chemotherapy- Folfirinox (ACCORD 11 Trial, Conroy et al, NEJM 2011) also Gemcitabine and Gemcitabine + NabPaclitaxel depending on fitness levels etc." •"Thermal ablation (microwave ablation)" •"Chemotherapy followed by surgery" The correct answer is the second option (chemotherapy). The wide discrepancy in knowledge of the current standard of care in pancreatic cancer, exemplifies the failure of NICE to obtain a broader range of specialist advice, from medical and surgical oncologists, who take a more holistic approach to the management of PC.	Thank you for your comment. IPAC has identified and approached the following specialist societies for advice: • British Society of Interventional Radiology • The Great Britain and Ireland Hepato-Pancreato-Biliary Association • British Society of Gastrointestinal and Abdominal Radiology. The Specialist advisers who advised the IP advisory committee on this procedure are nominated or approved by their professional bodies or specialist societies. More details about the process of seeking the opinions of the specialist advisers are presented in section 10.1 of the NICE IP programme manual https://www.nice.org.uk/process/pmg28/chapter/advice-and-commentary#opinions-of-specialist-advisers Additional societies/ organisations and patient ogranisations were identified as consultees to obtain a broad range of advice for all relevant stakeholders. These include:

				• British Association of Surgical Oncology (cancer surgery) • Pancreatic Society of Great Britain and Ireland • Association of Upper Gastrointestinal Surgeons of Great Britain & Ireland • British Society of Gastroenterology • The Royal College of Radiologists
4	Consultee 1 British Society of Gastroenterology (BSG)	1.1	The 'special case' of pancreatic cancer. There has been little progress in improving outcomes in PC over the past 40 years. One reason is the lack of survivors to lobby for funding. The lack of funding is a particular problem because research is needed to develop new approaches to earlier diagnosis and treatment. Given delayed diagnosis, lengthy investigation pathways, limited treatment options and poor prognosis, this disease has a devastating impact on the patient, their family or carers. Hence, because of its rapid lethality and the current lack of treatment options, PC should receive special consideration from NICE, when new innovative treatments emerge.	Thank you for your comment. The Committee considered this comment but decided not to change the guidance.

5	Consultee 1 British Society of Gastroenterology (BSG)	1	Draft recommendation. We consider that the draft recommendation, as it stands, is too restrictive. We believe that it will stifle development of a therapeutic option in the UK for locally advanced pancreatic cancer, where few options currently exist and outcomes are currently dismal. The presence of a UK wide registry enabling prospective patient data entry is noteworthy. We believe that enrolling patients onto this registry should constitute sufficient grounds for undertaking IRE in LAPC. This will facilitate assessment of the effect of this procedure on local tumour control, patient survival, pain control and quality of life. As there is no currently funded randomised controlled trial open in the UK, undertaking IRE, within the UK wide registry, provides the only current means whereby NHS patients can receive this new treatment and prevent UK patients from further falling behind other similarly developed in outcomes for cancer.	Thank you for your comment. The Committee considered this comment but decided not to change the guidance. See response to comment 2 regarding UK wide IRE registry.
6	Consultee 2 Royal College of Physicians (RCP)	1-6	The RCP is grateful for the opportunity to respond to the above consultation. We would like to endorse the response submitted by the British Society of Gastroenterology.	Thank you for your comment. See responses from comment 1 to 5.
7	Consultee 3 Pancreatic Cancer UK & Pancreatic Cancer Action joint response	General	We are grateful to the National Institute for Health and Care Excellence (NICE) for this opportunity to respond to the draft recommendations relating to irreversible electroporation (IRE) for treating pancreatic cancer. As per the interventional procedure consultation document published in October 2016, this response is divided into (i) comments on the draft recommendations, and (ii) additional relevant evidence. Bracketed paragraph numbers and page numbers refer to the consultation document.	Thank you for your comments.

8	Consultee 3 Pancreatic Cancer UK & Pancreatic Cancer Action joint response	1.1 &1.2	Whilst we appreciate that a greater 'quantity and quality' (1.1, p2) of research into IRE would help to strengthen understanding of it even further, we do not think that this would be achieved via the proposed recommendation for use only in research with a preference for randomised controlled trials (RCT) (1.2, p2). There are strong practical and ethical reasons why a recommendation for use with special arrangements would lead to better new research as well as improved patient experience and outcomes. From a practical perspective, RCTs would be difficult to conduct for two key reasons. Firstly, given the dearth of treatments currently available for pancreatic cancer patients, there is no known comparator for IRE. Indeed, palliative treatment is the typical option available to patients with stage three unresectable pancreatic cancer. Secondly, even if a comparator could be found, it would take an unfathomable amount of time to find enough patients to complete an RCT. We urge NICE to reflect on the fact that this treatment is targeted at a stage of a disease where survival rates are exceptionally poor, where participation in clinical trials by newly-diagnosed patients across different stages of the disease stands at just 4.6%[vi], and where the cancer can be markedly heterogeneous. Recommendation for use with special arrangements would enable IRE to be monitored and researched on a much-improved scale. *(vi 2014/2015 4.6% of pancreatic cancer patients were taking part in a dedicated clinical trial, National Council for Research Network. –See more at: http://www.pancreaticcancer.org.uk/our-blog/2016/june/the-trials-and-tribulations-of-clinical trials/#sthash.1Z2X859Q.dpuf)* Ethically, we feel that it would be wrong to deny patients the right to make an informed decision to try IRE, given that they currently have few other treatments available to them and IRE appears to be showing promising survival improvements. A recommendation for use with special arrangements would ensure that many more patients could give informed consent to undergo IRE if they wish to.	Thank you for your comment. The Committee considered this comment but decided not to change the guidance.

9	Consultee 3 Pancreatic Cancer UK & Pancreatic Cancer Action joint response	1	Patients desperately need access to new promising treatments if improvements in survival are to be delivered. 10% of pancreatic cancer patients receive surgery[vii], which is the only curative treatment, but for the remaining 90% the only NICE approved treatment currently available for pancreatic cancer is chemotherapy with gemcitabine. Pancreatic cancer has the worst survival of the 21 most common cancers and survival rates have hardly improved in the last 40 years. Although average survival for all cancers has doubled since 1970, a patient diagnosed with pancreatic cancer today has the same chance of surviving as a patient diagnosed in the 1970s.[viii] It is difficult for patients or indeed policy makers to see how pancreatic cancer survival can improve if promising new treatments are not made available subject to realistic research methods. As the All Party Parliamentary Group (APPG) on Pancreatic Cancer, stated in its 2013 inquiry report, "it is hard not to be struck by the lack of treatments that are available to pancreatic cancer patients", going on to say, "given the lack of options for curative treatment or for extending life, it is essential that any new treatments shown to be effective are made available to patients as quickly as possible".[ix] *(vii http://www.pancreaticcancer.org.uk/media/86662/every-lm_policybriefing-final.pdf, p2* *viii http://visual.ons.gov.uk/how-do-survival-estimates-compare-for-common-cancers/* *ix http://www.pancreaticcancer.org.uk/media/86665/time-to-change-the-story_a-plan-of-action-for-pancreatic-cancer.pdf, p18)* A recommendation from NICE for the use of IRE with special arrangements would create a long overdue treatment option for people with pancreatic cancer who would otherwise have no sense of hope for extending life. If treatment could be available at more centres across the UK, additional rigorous clinical research could be completed far more quickly, with many more people enabled to probably extend their life as part of the process, judging by existing research findings. We understand	Thank you for your comment. The Committee considered this comment but decided not to change the guidance.

			that training programmes are already underway at centres such as Kings College Hospital, London to ensure that clinicians are proficient in IRE procedures, so evaluations of IRE could be swiftly extended if NICE is to give the recommendation that IRE will be available to pancreatic cancer patients.	
10	Consultee 3 Pancreatic Cancer UK & Pancreatic Cancer Action joint response	6.1	NICE rightly acknowledges that its recommendations were mostly made in the light of research regarding open or laparoscopic IRE procedures (6.1, p10/11). In case NICE is not already aware, [redacted] has researched patient outcomes of IRE via percutaneous insertion, and is expected to release his findings next year after an academic review. NICE may also wish to enquire about a study underway at [redacted] by [redacted] which is trialling IRE as a method to shrink tumours enough to make them resectable.	Thank you for your comment and sharing information about relevant upcoming research. Efficacy data that have not been published or accepted for publication by peer reviewed journals are not normally selected for presentation to the committee. IPAC may review the guidance upon publication of substantive new body of evidence in peer reviewed journals.

11	Consultee 3 Pancreatic Cancer UK & Pancreatic Cancer Action joint response	7.2	NICE also rightly acknowledges that no patient commentary was taken into account in the production of the draft recommendations (7.2, p11). As soon as NICE launched this consultation, Pancreatic Cancer UK commissioned Dr [redacted] to independently survey people who have experienced IRE in the UK. Given that the population of people who have experienced IRE is so small, and that long-term survival remains low, it was only possible to gain one response before the consultation deadline. Although it is as yet unpublished, we are happy to share the following write-up of this response, written by Dr [redacted] earlier this month: The respondent was a White British female, aged between 35 and 44, living in the south east of England. She was diagnosed with a stage 3 pancreatic ductal adenocarcinoma in 2015. She has received 5-FU, 10 chemotherapy sessions, chemoradiation and IRE, all privately. She had percutaneous IRE privately at the [redacted] Hospital in September 2016. The procedure was not part of a research study. She had stage 3 pancreatic cancer when she had IRE and was receiving Gemcitabine, Abraxane and chemotherapy at the same time. She found out about IRE from the Pancreatic Cancer UK online forum but doesn't feel she has had enough information about the procedure: "Patients have to make a leap of faith rather than have an outline of treatment from the person referring.'' She decided to have IRE to try and make her pancreatic tumour operable as it had grown on vessels. IRE is the only way of removing the tumour without damaging the vessels, as chemotherapy hasn't worked. When asked how well IRE has worked, she responded, "I won't know until 2 to 3 months after Nano whether this has worked."	Thank you for your comment and sharing a response from a patient who has undergone IRE treatment for pancreatic cancer. The Committee noted the views and experiences of this patient in their deliberations.

			The respondent said she would be willing to experience side effects of IRE if there was a chance it would help her live longer – but aside from a small amount of abdominal/stomach pain on the night of the procedure, she has not experienced any side effects from IRE. When asked to rate her quality of life after IRE she responded, “don’t know”. However, she reported that there has been no negative physical impact and she is “actually doing more since [IRE]” including yoga. It has improved her ability to take on activities. She feels it is too early to say what the advantages have been but there are no disadvantages. She would recommend IRE to others: “non-invasive, fantastic option for locally advanced” and feels IRE should be available on the NHS: “This should form part of a treatment plan for stage 3 and 4 at the very least.”	

12	Consultee 4 Patient	General &7.2	I would like to feedback my experiences of Pancreatic Cancer and my treatment with Irreversible Electroporation. I was diagnosed early November 2015 with adenocarcinoma of the pancreas. I had showed symptoms from Easter 2015 but despite frequent visits to GP it wasn't diagnosed by him or under my NHS hospital. I self-referred privately and the cancer was already stage 3 with vessel involvement. This meant inoperable despite being 42 and fit with 3 children under the age of 9. I have saved my own life so far by accessing all the things that NICE seem not to be recommending for pancreatic cancer on the NHS. I have had Irinotecan chemo in combination which reduced size of tumour. I also had irreversible electroporation together with Gemcitabine / Abraxane. Unfortunately I don't get into the CT scanner until tomorrow to see if this has been effective and your deadline is today. However I can make the following comments. My Irreversible electroporation procedure was done without opening me up. I was put to sleep and had the op at about 5pm and went home 11am the next day. I had absolutely no side effects. The only thing I had was a bruise covered with dressing near my pancreas. I took antibiotics for 7 days but didn't need any pain killers to go home with. This was the least invasive and quickest procedure that I have experienced for pancreatic cancer. It is worthy of note that this must be used with appropriate chemo. I am hearing that some patients on the NHS are having the procedure but are being refused the chemo to go with it. This will make any results less effective. I can say that my experience of this procedure is overwhelmingly positive. I feel well and stable and I am alive to write this email. Out of 100 people in a room probably only 20 to 28 will be alive a year after diagnosis. These will mainly consist of those who have been operated on. The remaining few will have accessed treatments as described as above mostly by paying or going privately.	Thank you for your comment. The Committee noted your views and experiences in their deliberations.

			This procedure is necessary because it gives another course of treatment to stabalize the cancer and in some cases make the cancer operable. It is also an up to date alternative to heat ablation which can't be used near vessels. I am also in touch with a man whose pancreatic cancer was entirely killed by the IRE treatment he received in combination with chemo. In this situation IRE is a lot less invasive and expensive than the difficult Whipples surgery which uses extensive NHS resources including a bed in the intensive care unit. In itself comparatively, the machine manufactured by AngioDynamics in itself is not that expensive. The needles are more so but a price could be negotiated based on volume. The reason that Pancreatic Cancer is so ignored is because there are hardly any people alive long enough to shout about it unlike those with other cancers that receive greater funding. Frankly the statistics are an embarrassment and a disgrace. My father is already a statistic. He was diagnosed with pancreatic cancer in the summer 2016 and died recently. Pancreatic sufferers deserve more funding within the NHS system. The numbers of those being diagnosed with pancreatic cancer are on the rise including those diagnosed young. IRE is a massive opportunity to redress this balance. Trials should happen but be done by the expert (s) who have the greatest expertise and experience of the procedure.	

13	Consultee 5 Manufacturer Angiodynamics	1, 4, 5	**The draft recommendations suggest that the current evidence on the safety and efficacy on IRE for treating pancreatic cancer is inadequate in quantity and quality.** **Comment:** IRE technology is a local zone therapy which involves the application of electrical fields that create permanent nanopores in cell membranes, disrupting homeostasis, and leading to gradual cell death via the apoptosis pathway. This multi-needle zone therapy allows the clinician to customize the treatment zone to include killing the microscopic cancer cells often found in tumor and the surrounding stroma, thereby achieving R0 or negative margins, providing excellent local control as evidenced by the real world results published on both open and percutaneous IRE. IRE is an active local treatment providing clinical benefit comparable to surgery for local soft tissue tumors which are unresectable, avoiding limitations associated with standard ablative therapies, including the heat sink effect and damage to nearby critical structures and vessels. IRE also does not post the same type of toxicity associated with radiation therapy. As we examine the safety and efficacy of IRE, it should be done within the context of the current state of pancreatic cancer treatment options, the risk/benefit of those treatment options and the care pathways followed by clinicians. Today, the medical oncology community collectively believe that pancreatic cancer, by nature, is a systemic disease. This assumption is based, in part, on the fact that after curative-intent resection, early and late metastases are frequent in most tumors. Though there is a recognized Staging system for classifying pancreatic cancer into one of four stages, the general treatment paradigm separates patients into two care pathways: localized disease and metastatic disease.	Thank you for your comment. The current treatment options for pancreatic cancer have been considered while developing this guidance and a concise summary of indication and current treatments for management of the indication is provided in section 2.2.

			Staging for Pancreatic Cancer Resectable (Stage I and II) o No vascular Involvement Borderline Resectable (Stage IIb) o Moderate vascular Involvement Locally advanced – Unresectable o Significant vascular involvement Metastatic Localized Disease → Curative Intent treatment Surgery ± radiation (prevent local relapse) ± chemotherapy (prevent distant relapse) Metastatic Disease→ Palliative-intent treatment (usually chemotherapy ± radiation) Locally Advanced Pancreatic Cancer (Stage III) presents a unique challenge. Though, LAPC or Stage III is non-metastatic, it is inoperable and therefore, generally, treated like metastatic disease. The palliative-intent treatment regime, generally, results in death from locally advanced pancreatic cancer within 6 months of diagnosis. In 2013, 95% of patients died from their cancer (8524) 3, with the expected survival from diagnosis ranging from 4 to 6 months. Today, it is estimated that one person dies every hour from pancreatic cancer in the UK. Forty years of research in pancreatic cancer confirm that tumor involvement of vascular structures determine “resectability” and therefore survival. IRE technology now offers patients diagnosed with LAPC to be treated under the localized disease care pathway, enabling them to receive both systemic and local treatment resulting in significant improvement in overall survival. Treating patients with chemo followed by IRE demonstrates significant clinical benefit with OS comparable to patients with resectable disease. **The safety and effectiveness of IRE in the treatment of borderline and locally advanced pancreatic cancer is supported with evidence of safety, real world effectiveness and improved overall survival.**	The committee has reached its ‘research only’ recommendation based on all the on the published evidence on efficacy and safety (see section 4 and 5 of the guidance). Th aim of IP programme is not to describe comparative effectiveness or safety with other procedures but whether it safety and efficacy are adequately understood.

			SAFETY and EFFICACY Each new therapeutic option to be used in patients must be examined for safety. Safety, like efficacy, is a relative concept: no technology is ever completely safe, or completely efficacious. A critical property of the concept of safety: that safety represents a value judgment of the acceptability of risk. Risk can be thought of as “a measure of the probability and severity of harm to human health”. This definition of risk implies that investigators and policymakers should be concerned with both the nature of the risk and the probability of its occurrence. For example, a low but measurable probability of death can be more significant than a high probability of experiencing pain, discomfort, or other minor impairments. Thus, if the risks of using a medical technology are acceptable (to the patient, physician, society, or other appropriate decision maker), the technology may be considered “safe” in that instance. Safety can then be defined as a judgment of the acceptability of the risk associated with a medical technology. The medical problem for which the technology being evaluated is applied must be specified, not only because the medical problem or condition of the patient will often affect the action of the technology and thus the associated risks, but also because the judgment of acceptable risk depends on the type and severity of the medical problem. These risks, however, must be compared to the benefits of current options and a normal life span, which is very often the direct result of treatment. **Treatments for Pancreatic Cancer by Care Pathway (presented in the attached document in pages 4-9)**  NICE comments for pancreatic cancer fir	

14	Consultee 5 Manufacturer Angiodynamics	1, 4, 5	**IRREVERSIBLE ELECTROPORATION** IRE has been studied in locally advanced and borderline pancreatic cancer. The body of clinical evidence is a combination of retrospective case series, prospective case series and a large multi-center registry conducted at University of Louisville, Cleveland Clinic, Stoney Brook University, Henry Ford, Swedish, and Piedmont Medical Center. Observational studies can be used to address questions pertaining to safety surveillance, risk management, and efficacy. Correct study choice and effective execution are paramount to achieving the desired goals. The purpose of a disease/treatment registry is to gather uniform clinical data that will be used to evaluate the outcomes for a population defined by a particular disease, condition and exposure (treatment). The longitudinal nature of registries allows for the examination of patterns of co-morbidities, course of the disease, physician's diagnosis, and treatment concerns and overall practice patterns. They also serve to inform correct patient selection, multimodal approach, and patient reported outcomes. The registry information can be used to determine ways to optimize measures of disease impact, clinical benefit and to understand the space where product will be used and the potential impact of the product on patient survival and experience. **Safety of IRE** IRE is a targeted, tissue-sparing technique that delivers a series of short, low energy, direct current electrical pulses via electrode probes placed around the lesion. IRE allows for local elimination of cancer cells that make up local and advanced soft tissue tumors and the surrounding stroma in pancreatic cancer, avoiding limitations associated with standard therapies, including heat sink effect and damage to nearby critical structures and vessels. All cells are surrounded by a cell membrane that protects the cell from the outside environment and helps to regulate the movement of molecules both into and out of the	Thank you for your comment. The committee has reached its 'research only' recommendation based on the published evidence (see section 4 and 5 of the guidance).

			cell. Cell membranes are composed of a phospholipid bilayer, including hydrophilic “heads” and hydrophobic “tails”. The phospholipid bilayer works in conjunction with embedded ion transporters to maintain an electric potential between the interior and exterior of the cell. IRE exploits this electric potential gradient. **IRE mechanism for cell death, effects of IRE and unique benefits of IRE have been reported in detail in pages 10-12 in the attached summary document**  NICE comments for pancreatic cancer fir Clinical studies evaluating IRE safety demonstrate Grade 3-4 adverse events of reported complication rates ranging from 6-45%. IRE is a treatment that is used in both open and percutaneous procedures providing significantly different adverse event profiles. In percutaneous cases, the majority of adverse events are transient and insignificant Grade 1-2. Open IRE cases have many more Grade 3-4 complications which are generally related to the surgical nature of the procedures. It is, however, important to note that the IRE open procedure provides no greater complications for patients than complications found in surgical resection and palliative resection while percutaneous IRE provides much low complication rates. **See table on page 13 (in attached document above) regarding IRE clinical studies reporting complications rates.**	Section 5 of the guidance reports evidence on safety. All the studies reported in table on page 13 have been considered while developing the overview and guidance.

15	Consultee 5 Manufacturer Angiodynamics	1, 4, 5	**IRE and Patient Survival** As part of a Multimodal care pathway for treating LAPC and Borderline pancreatic cancer, IRE is proven to improve overall patient survival. While most therapies used today in advanced pancreatic cancer provide palliative care, IRE provides a clear clinical benefit with proven significant improvement in overall survival. **STAR REGISTRY 200 Unresectable Patients** When combined with standard of care, IRE demonstrates excellent local control and a significant improvement in overall survival. To date, there is a growing body of evidence establishing longer life span for patients diagnosed with LAPC and treated with a multimodal care pathway that includes IRE. The seminal multi-center registry with 200 pts, of which 150 pts received in situ IRE and 50 borderline pts received IRE and resection provided a combined median overall survival of 24.6 months more than doubling folfirinox alone. The significance of the Star Registry is that for the first time ever, a significant cohort of LAPC patients achieved median overall survival benefit comparable to resected patients. The findings in this multi-center registry only confirmed an earlier single center 2009-2010, study of 54 patients where overall survival for IRE + Chem/rad was 20 months v. 13 months for Chemo/rad alone. **For further details see figure on page 14 in the attached document**  NICE comments for pancreatic cancer fir	Thank you for your comment. Evidence from the STAR registry (Martin 2015) has been included in table 2 in the overview and the guidance.

			Two very recent clinical trials in percutaneous IRE treatment for LAPC have been accepted for publications. The Panfire Study with evaluated 25 pts with LAPC and tumors <5cm in CT guided percutaneous IRE after induction chemotherapy. The results were as follows: o Event free survival: 8mos o Local progression: 12 mos o Overall survival for IRE: 11 mos o Overall survival for DX: 17 mos The lead researchers for the second trial which as accepted by JVIR in late October 2016 was conducted by Chief of Interventional Radiology at the University of Miami Govindarajan Narayanan, M.D. and Oncologist Peter J Hosein, MD. The study was a retrospective of 50 patients treated at the University of Miami under CT guidance following induction chemotherapy and/or chemoradiation. The abstract follows: **Abstract:** Purpose: To describe safety and effectiveness of percutaneous irreversible electroporation (IRE) for the treatment of unresectable, locally advanced pancreatic adenocarcinoma (LAPC). **Patients and methods:** Fifty patients (23 females and 27 males aged 46-91 years, median age 62.5 years) with biopsy-proven, unresectable LAPC, who received percutaneous computed tomography (CT)-guided IRE were included in a retrospective study. The primary objective was to assess the safety profile of the procedure, the secondary objective to determine overall survival (OS). All patients had prior chemotherapy (1-5 lines, median 2) and 30 (60%) of 50 had prior radiation therapy. Follow-up included CT at 1 month and at 3-month intervals thereafter.	The Panfire study has been picked up in our update search and added to table 2 in the overview. The team included this publication in appendix A of the overview (Narayanan G et al 2016. Percutaneous image-guided irreversible electroporation for the treatment of unresectable, locally advanced pancreatic adenocarcinoma. Journal of Vascular and Interventional Radiology. Article in press, published online: December 16 2016) as the efficacy data and adverse events have already been covered in the guidance.

			Results: There was no treatment-related death and no 30-day mortality. Serious adverse events occurred in 10 (20%) of 50 patients and included abdominal pain (n=7), pancreatitis (n=1), sepsis (n=1), and gastric leak (n=1). Median OS was 27.0 months (95% confidence interval [CI], 22.7-32.5 months) from the time of diagnosis and 14.2 months (95% CI, 9.7-16.2 months) from the time of IRE. Patients with tumors ≤3 cm (n=24) had significantly longer median OS than those with tumors >3 cm (n=26): 33.8 vs 22.7 months from the time of diagnosis (p=0.002) and 16.2 vs 9.9 months from the time of IRE (p=0.031). Tumor size was confirmed as the only independent predictor of OS at multivariate analysis. **Conclusions:** Percutaneous image-guided IRE of unresectable LAPC is associated with an acceptable safety profile. Survival of treated patients exceed the reported figures for standard chemotherapy and radiation therapy in this patient population.	

16	Consultee 5 Manufacturer Angiodynamics	1.2	***The Draft recommendations suggest that further research, preferably in the format of RCTs should assess the effect of the IRE procedure on local tumor control, patient survival, pain control and QoL.*** Comment: The question of randomized controlled trials has surfaced a number of times by international regulatory bodies with respect to the use of IRE in LAPC. Simply stated, Angiodynamics nor any of international regulatory bodies have been able to resolve the significant issue of clinical equipoise when researching IRE in LAPC. The standard of care in LAPC is palliative chemotherapy and/or chemoradiation. In the UK, under the standard of care, five and ten year survival rates have not improved since the early 1970s. Clinical equipoise stipulates that a randomized controlled trial is only ethical insofar as there exists, at the outset, a state of genuine uncertainly in the community of medical experts about the relative therapeutic merits of every arm in the trial. The standard of care chemotherapy, gemicitabine, consistently provides survival benefits for LAPC of 4-6 months. For metastatic disease, Folfirinox alone provides 11 months of median overall survival. To date, there has been no head to head trial of Folfirinox and Gemicitabine in LAPC because the community of experts accept no genuine uncertainty remains, folfirinox provides a greater clinical benefit when patients can tolerate the regime. The trials with combination chemotherapy provide OS of 6-11 months. IRE has been researched as part of a multimodal approach to treating LAPC. To properly randomize IRE after patients received induction chemotherapy there would need to be a standard of care therapy with a proven clinical benefit of which to randomize against. Radiation is often used but LAP07 demonstrated that chemoradiation proivded no clinical benefit beyond chem alone. Therefore no genuine uncertainty exists for which to randomize against IRE after induction chemotherapy. To date, there is not other local therapy proven to work in IRE after Induction chemotherapy. Surgery is not an option in LAPC.	Thank you for your comment. See response to comment 2 regarding UK IRE registry.

			Thermal ablative devices are ineffective because heat sink and thermal damage to vital structures. At present, the most feasible option for providing access to patients while continuing to collect effectiveness data is a well developed medical society controlled and operated registry. This disruptive and differentiated therapy should be accessible to patients with no viable clinical options and are facing sudden death. The benefit of the IRE treatment after chemo and/or chemoradiation is significant while the risk is no greater than the current therapeutic options available today to Stage I, II and IV patients. IRE with neoadjuvant chemotherapy consistently doubles and triples the OS of Chemo alone. Clinical equipoise says if sufficiently robust evidence exists to rule out the possibility that the two treatments are clinically equivalent, then the trial is unethical. There is more than sufficient data to suggest that an RCT of Chemo alone vs. Chemo w/IRE would provide a clinical benefit and a statistically significant improvement in overall survival. Additionally, recent research demonstrates that patients with pancreatic adenocarcinoma enrolled in clinical trials have “profoundly improved survival” compared with patients in the general population, according to research presented at the 2016 Gastrointestinal Cancers Symposium. In the analysis, there was as much as a 92 percent difference in medial overall survival (OS) seen between patients treated in RCTs and “real world” data from the US Surveillance, Epidemiology and End Results (SEER) database. Addiitonally, patients with mixed metastatic/locally advanced unresectable pancreatic caner, there was a 3.23-month median increase in OS between the clinical trial and the SEER database, representing a 92 percent improvement. In the unresectable locally advanced group, OS was improved by 41 percent in the clinical trial versus SEER, a median improvement of 2.96 months. In the resectable group, median survival was 6.1 months bettwe in the clinical trial arm versus SEER group, a 36 percent improvement. The results of this study suggest the RWD may provide a clearer picture on the effect size of these	

			treatments in actual clinical settings. Registries provide the opportunity for clinicians to determine how and under what circumstances different care pathways provide a clinical benefit to patients in actual clinical practice. AngioDynamics agrees that IRE in Pancreatic cancer should be continuously researched, though in a more real world setting. AngioDynamics provided a research grant to AHPBA in support of a global registry. This prospective registry will continue to increase the body of evidence of IRE in pancreatic cancer demonstrating its safety and effectiveness. Effectiveness refers to how well a device performs as intended in the general population of patients and the general chaos of clinical practice.	

17	Consultee 5 Manufacturer Angiodynamics	1.2	**UK Registry and Training** The UK IRE registry group is headed by [redacted]. It is currently planned for 8-10 regional centers with expertise in treating Pancreatic cancer to join the registry. The UK training site is centrally located at King's College. The IRE training program will consist of classroom, animal lab, CT and ultrasound imaging techniques. Physician training will include technique, patient selection and case proctoring. The percutaneous course will be taught by [redacted], whose research in IRE is the most searched in SCOTUS. Proper training is key to patient outcomes and AngioDynamics is committed to clinicians have access to the best possible training. In a study examining the learning curve associated with the IRE procedure for over 150 patients, the total time for electrode placement decreased from the first 50 patients (mean of 40 minutes), to the second 50 (mean of 25 minutes), and the final group of patients (mean of 20 minutes) *(P* = 0.01). The "key break point" to observe a significant decrease in electrode placement time at each institution was 7 patients (OR = 2.9, *P* = 0.01). In contrast, a Whipple procedure requires 4–7 hours to complete. Irreversible electroporation varies from other ablative procedures in that it requires very specific anesthetic protocols dictating the depth of neuromuscular blockade, as well as intraprocedural pain and hypertension management. Any significant retroperitoneal or diaphragmatic excitation during an IRE procedure can lead to several centimeters of movement in the pancreas. Therefore, a deep level of neuromuscular blockade is required to safely deliver IRE and minimize needle trauma. Additionally, electrocardiogram synchronization is required to minimize risks of arrhythmias during IRE. The Nanoknife training program reviews all reported complications and currently instituted protocols to minimize clinical risks including IRE treatment in the presence of metallic stents. Clinicians are also	Thank you for your comment. See response to comment 2 regarding UK IRE registry. As this is a 'research only' recommendation, training (on technique and patient selection) is more correctly covered by research governance and management committees and are outside the remit of the NICE IP programme.

			trained on patient selection, tumor size, complete current delivery for cellular apoptosis and needle alignment.	
18	Consultee 5 Manufacturer Angiodynamics	1& 6.1	**Conclusion,** AngioDynamics believes current evidence on the safety and effectiveness of IRE for the treatment of pancreatic cancer appears adequate in the context of treating unresectable patients with no curative options and whose condition has such a poor prognosis. We acknowledge that the majority of our clinical effectiveness data is with an open approach while the UK is adopting the percutaneous method predominantly. The amount of effectiveness data for the percutaneous approach is limited, particularly in the UK. Therefore, AngioDynamic proposes IRE for the treatment of unresectable pancreatic cancer should be used under very specific conditions: o Specialized centers o Training certification o Mandatory auditing and reporting to the UK registry group Similar to the guidance on Cryotherapy for the treatment of liver metastases', Clinicians wishing to undertake IRE for the treatment of unresectable pancreatic cancer should take the following actions: □ Inform the clinical governance leads in the Trusts □ Ensure that patients and their carers understand the risks/benefits of IRE and provide them with clear written information. □ Report/audit all cases to the UK IRE registry. Review clinical outcomes of all patients having IRE for unresectable pancreatic cancer. □ Patient selection and treatment should be carried out by a hepatobiliary multidisciplinary team with expertise in ablative techniques.	Thank you for your comment. The Committee considered this comment but decided not to change the guidance. Section 6.1 clearly states that 'most of the evidence was from open or laparoscopic irreversible electroporation procedures'. It also states that 'the committee was informed that there is increasing use of percutaneous approach'.