Pancreatic cancer: diagnosis and management in adults
Consultation on draft guideline - Stakeholder comments table
31/07/17 to 18/09/17

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Stakeholder	Document	Page No	Line No	Comments Please insert each new comment in a new row	Developer's response **Please respond to each comment**
Boston Scientific	Short	3	10 - 11	We would like the committee to consider the utilization of Fine Needle Biopsy as follows: • If the diagnosis is still unclear, offer endoscopic ultrasound (EUS) and 10 EUS-guided tissue sampling Utilising Fine Needle Biopsy. Please find below the available evidence for this comment : • EUS-guided tissue acquisition: Do we need to shoot for a "core" to score? Sachin Wani, MD et al. Volume 84, No. 6 : 2016 GASTROINTESTINAL ENDOSCOPY 1047-1049. • EUS - Fine- Needle Aspiration Biopsy (FNAB) in the Diagnosis of Pancreatic Adenocarcinoma: A Review. Kalogeraki A et al. Rom J Intern Med. 2016 Jan-Mar;54 (1):24-30. Endoscopic ultrasound-guided fine needle core biopsy for the diagnosis of pancreatic malignant lesions: a systematic review and Meta-Analysis. Yongtao Yang et al. Scientific Nature; Report 6, Article number: 22978 (2016); doi:10.1038/srep22978.	Thank you for your comment. The committee did not recommend the utilisation of Fine Needle Biopsy for people with suspected pancreatic cancer in secondary care who have obstructive jaundice because no evidence was identified on this intervention that met the review protocol inclusion criteria. As such it was not considered appropriate to make the changes to the recommendations suggested in the comment. The references suggested in the comment were not included for the following reasons. • Wani et al. (2016) is an editorial which means that it does not meet the criteria for study design. • Kalogeraki et al (2016) is a narrative review which means that it does not meet the criteria for study design. • Yang et al. (2016) is a meta-analysis which included studies where it was unclear how the lesion was originally identified which means that it does not meet the study population criteria.

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Boston Scientific	Short	3	12-15	We would like the committee to consider the positioning of cholangioscopy as a step in the diagnostic process where endoscopic assessment is made. Please find below the evidence for this comment: • Isaac Raijman et al. 268 Digital Single Operator Cholangioscopy (DSOC): Multicenter Experience in 237 Patients. May 2016Volume 83, Issue 5, Supplement, Pages AB134–AB135. DOI: http://dx.doi.org/10.1016/j.gie.2016.03.065. • Meir Mizrahi et Al. A Leap Forward: Comparative Effectiveness of Second-Generation Digital Single Operator Vs First-Generation Single Operator Cholangioscopy. May 2016Volume 83, Issue 5, Supplement, Page AB297. DOI: http://dx.doi.org/10.1016/j.gie.2016.03.474. • Raj Shah et Al. 346 A U.S. Multi-Center First Human Use Experience Using the Fully Disposable, Digital Single-Operator Cholangiopancreatoscope (DSOCP). May 2016Volume 83, Issue 5, Supplement, Page AB141 DOI: http://dx.doi.org/10.1016/j.gie.2016.03.081. • Navaneethan U et Al. Digital, single-operator cholangiopancreatoscopy in the diagnosis	Thank you for your comment. The committee did not recommend the use of cholangioscopy for people with suspected pancreatic cancer in secondary care who have obstructive jaundice because no evidence was identified on this intervention that met the review protocol inclusion criteria. The references suggested in the comment were not included for the following reasons. • Raijman et al. (2016), Mizrahi et al. (2016), Shah et al. (2016) and Bernica et al. (2016) are not fully published studies (they are abstracts) and so there is insufficient information to include or appraise the evidence. • Navaneethan et al. (2016) is a full article, but it was excluded because the study sample included people with biliary or pancreatic disorders (those referred for evaluation of indeterminate strictures and management of difficult biliary or pancreatic stones).

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				and management of pancreatobiliary disorders: a multicenter clinical experience (with video). Gastrointest Endosc. 2016 Oct;84(4):649-55. doi: 10.1016/j.gie.2016.03.789. Epub 2016 Mar 16. • Jessica Bernica et Al. Sa1193 Cholangioscopy Is Safe and Feasible in Elderly Patients. May 2016Volume 83, Issue 5, Supplement, Page AB250. DOI: http://dx.doi.org/10.1016/j.gie.2016.03.357 .	
Boston Scientific	Short	4	15 - 16	We would like the committee to consider also the utilization of Fine Needle Biopsy as follows: • Consider Fine Needle Biopsy or fine-needle aspiration during EUS if more information on the likelihood of malignancy is needed. Please find below the available evidence for this comment: • EUS-guided tissue acquisition: Do we need to shoot for a "core" to score? Sachin Wani, MD et al. Volume 84, No. 6 : 2016 GASTROINTESTINAL ENDOSCOPY 1047-1049. • EUS - Fine- Needle Aspiration Biopsy (FNAB) in the Diagnosis of Pancreatic	Thank you for your comment. The committee did not recommend the utilisation of Fine Needle Biopsy for people with suspected pancreatic cancer in secondary care who have who have pancreatic cysts because no evidence was identified on this intervention that met the review protocol inclusion criteria. As such it was not considered appropriate to make the changes to

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				Adenocarcinoma: A Review. Kalogeraki A et al. Rom J Intern Med. 2016 Jan-Mar;54 (1):24-30. Endoscopic ultrasound-guided fine needle core biopsy for the diagnosis of pancreatic malignant lesions: a systematic review and Meta-Analysis. Yongtao Yang et al. Scientific Nature; Report 6, Article number: 22978 (2016); doi:10.1038/srep22978.	the recommendations suggested in the comment. The references suggested in the comment were not included for the following reasons. • Wani et al. (2016) is an editorial which means that it does not meet the criteria for study design. • Kalogeraki et al (2016) is a narrative review which means that it does not meet the criteria for study design. • Yang et al. (2016) is a meta-analysis which included studies where it was unclear how the lesion was originally identified which means that it does not meet the study population criteria.
Boston Scientific	Short	4	17-18	We would like the committee to consider also the utilization of Fine Needle Biopsy as follows: • When using fine needle biopsy or fine-needle aspiration, perform carcinoembryonic antigen (CEA) assay in addition to cytology if there is sufficient sample. Please find below the available evidence for this comment: • EUS-guided tissue acquisition: Do we need to shoot for a "core" to score? Sachin Wani,	Thank you for your comment. The committee did not recommend the utilisation of Fine Needle Biopsy for people with suspected pancreatic cancer in secondary care who have who have pancreatic cysts because no evidence was identified on this intervention that met the review protocol inclusion criteria. As such it was not considered appropriate to make the changes to the recommendations suggested in the comment.

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				MD et al. Volume 84, No. 6 : 2016 GASTROINTESTINAL ENDOSCOPY 1047-1049. • EUS - Fine- Needle Aspiration Biopsy (FNAB) in the Diagnosis of Pancreatic Adenocarcinoma: A Review. Kalogeraki A et al. Rom J Intern Med. 2016 Jan-Mar;54 (1):24-30. • Endoscopic ultrasound-guided fine needle core biopsy for the diagnosis of pancreatic malignant lesions: a systematic review and Meta-Analysis. Yongtao Yang et al. Scientific Nature; Report 6, Article number: 22978 (2016); doi:10.1038/srep22978.	The references suggested in the comment were not included for the following reasons. • Wani et al. (2016) is an editorial which means that it does not meet the criteria for study design. • Kalogeraki et al (2016) is a narrative review which means that it does not meet the criteria for study design. • Yang et al. (2016) is a meta-analysis which included studies where it was unclear how the lesion was originally identified which means that it does not meet the study population criteria.
BRITISH DIETETIC ASSOCIATION (BDA) – Oncology Sub-group	Full	General	General	Supports the need for high quality research in nutrition support for this patient group as the evidence presented in low to moderate quality.	Thank you for your comment in support of the guideline.
BRITISH DIETETIC ASSOCIATION (BDA) – Oncology Sub-group	Full	221	34	Would it be beneficial to expand on these terms in brief as some people will be unfamiliar with the terminology mentioned? Or consider linking together to highlight the impact on the patient, e.g. '*Weight loss is extremely prevalent in patients with pancreatic cancer, both in resectable and non-*	Thank you for your comment. The committee agreed that this was useful background information and has therefore added this to the introductory text. However, we have reworded the text by changing 'anorexia leading to reduced dietary intake' to 'reduced dietary

Stakeholder	Document	Page No	Line No	Comments Please insert each new comment in a new row	Developer's response Please respond to each comment
				resectable disease. This is multifactorial but may be due to one or a combination of anorexia leading to reduced dietary intake, malabsorption, post-surgical complications affecting nutritional status, cancer associated muscle wasting (cachexia) and hyperglycaemia due to impaired glucose tolerance or undiagnosed diabetes. Weight loss can be severe and debilitating for the patient, and contribute towards the development of sarcopenia (low muscle mass) and reduced muscle function affecting quality of life.	intake' and 'is extremely prevalent' to 'is common'.
BRITISH DIETETIC ASSOCIATION (BDA) – Oncology Sub-group	Full	221	41	Is it possible to add in that patient access to an expert with knowledge and awareness of the nutritional issues in pancreas cancer may help address the variation across the country and improve consistency in the overall nutrition message?	Thank you for your comment. This section provides a brief introduction to the topic of nutritional interventions which is the focus of this evidence review. Access to an expert with knowledge and awareness of the nutritional issues in pancreatic cancer would be a matter of organisation of services. The committee agreed that the specialist pancreatic cancer multidisciplinary team which 'should decide what care is needed' (see recommendation 1.2.1) would have access to such expertise.
BRITISH DIETETIC ASSOCIATION (BDA) –	Full	255	35	Could we consider adding in 'no evidence was found on the effectiveness of glycaemic control *but consensus of opinion/expert opinion in the field would support the importance of optimising*	Thank you for your comment. Section 8.3.8 in the full guideline documents the committee's discussions about the evidence and how these resulted in the recommendations made. As

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Oncology Sub-group				*glycaemic control to prevent symptoms of hyperglycaemia and unintentional weight loss?'*	such, it is not necessary to make the amendment suggested in the comment.
BRITISH DIETETIC ASSOCIATION (BDA) – Oncology Sub-group	Full	255	41	Although acknowledged that the data from the RCT by Davidson et al cannot be used when making recommendations, can we have a statement extrapolating findings, e.g. importance of weight stability on survival and quality of life outcome measures? This may link better with the proposed research question later on.	Thank you for your comment. Davidson et al. (2004) found an association only in a post hoc analysis between weight stabilisation and survival. No causal relationship was demonstrated. Therefore, the committee did not want to base any recommendations on these data.
BRITISH DIETETIC ASSOCIATION (BDA) – Oncology Sub-group	Full	256	32	It may be worth acknowledging that there is no consensus on diagnostic testing for Pancreatic Exocrine Insufficiency (PEI). The recommendations seem to indicate that all patients with pancreas cancer should be prescribed Pancreatic Enzyme Replacement Therapy (PERT). This may mean some metastatic patients presenting with symptoms similar to PEI may be started on PERT inappropriately, especially if the cancer is not in the head of the pancreas and/or causing pancreatic duct dilatation. Although taking PERT is safe, consideration should be given to the extra burden of taking medication in quantity that may not be indicated or beneficial.	Thank you for your comment. The evidence on Pancreatic Enzyme Replacement Therapy (PERT) came from people with unresectable pancreatic cancer and showed that nutritional status was improved with the use of PERT. The committee therefore agreed to recommend the use of PERT in this patient group and recommended enteric coated pancreatin treatment as this was the type of PERT that was used in the trials. The committee also agreed that people with resectable pancreatic cancer were unlikely to produce sufficient pancreatic enzymes and would probably benefit from taking PERT. The committee therefore also recommended PERT for people with resectable disease (both before and after resection), but this was a weaker recommendation due to the lack of evidence. The committee agreed that

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					these recommendations applied to the majority of patients based on the evidence and their experience, but that there was room for clinical judgement to not prescribe PERT to individual patients who may not benefit (i.e. it is a weaker recommendation for people with resectable disease). The committee agreed that there is no consensus on testing for Pancreatic Exocrine Insufficiency (PEI). However, based on the committee members' knowledge and experience they noted that the percentage of people with pancreatic cancer and PEI is high and that the identified evidence did not show any major adverse events associated with PERT. They therefore concluded that overall the benefit would outweigh harms.
BRITISH DIETETIC ASSOCIATION (BDA) – Oncology Sub-group	Full	257	21	Consider expanding this to investigate the most appropriate diagnostic panel/testing for PEI, thereby indicating PERT. This would help ensure that any intervention studies target appropriate patients. Clinicians need to consider other causes of gastrointestinal symptoms may need investigating (that are common especially post-pancreatic resection), e.g. bacterial overgrowth, bile salt malabsorption, etc. This would allow better targeting of nutrition intervention studies involving PERT.	Thank you for your comment. This review question investigated the effectiveness of nutritional interventions for people with pancreatic cancer. The guideline did not have a review question on the most effective diagnostic test for Pancreatic Exocrine Insufficiency (PEI). In line with NICE processes, research recommendations can only be made on topics where reviews have identified gaps or uncertainty in the evidence (see 'Research recommendation processes and methods

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					guide', 2011). Since no evidence review was conducted on diagnostic testing for PEI, we are not able to include this in the research recommendation.
BRITISH DIETETIC ASSOCIATION (BDA) – Oncology Sub-group	Full	257	29	Consideration needs to be given that the current definition of cachexia is a working definition. Research needs to focus initially on achieving a consensus of this definition, especially defining inflammation. Without this it is sometimes difficult to determine weight loss due to malnutrition (potentially reversible) vs weight loss due to cachexia (potentially irreversible). Establishing this would allow nutrition intervention studies proposed to target patients more appropriately. Sarcopenia is mentioned in the first paragraph (page 221, line 34). Achieving consensus definition of this and linking nutrition interventions with the outcomes of interest mentioned in section 8.3.9 would also be of interest.	Thank you for your comment. The committee recognised that there was currently limited agreement on how best to assess cachexia and that this was related in part to variations in definitions of cachexia. The committee therefore made a research recommendation which covered both the effectiveness of anti-cachexia interventions and also the most effective assessment method to identify this condition. Committee members were also aware that there had been a previous Delphi consensus study on definitions of cachexia related to cancer (Fearon et al. Lancet Oncol. 2011 May;12(5):489-95) and therefore did not prioritise this as a research recommendation. A reference to this has now been added to the introductory text of the research recommendation. The committee discussed the comment and agreed that further detail related to weight loss could provide useful background to readers and so the introduction to this section the full guideline (see Section 8.3.1) has been expanded.

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British Society of Gastroenterology	-	-	-	Thank you for asking the British Society of Gastroenterology to comment on the draft guidelines for pancreatic cancer. The guidelines are extremely impressive in their scope and thoroughness, and are relevant to patients, carers, clinicians and health professionals. Our comments on these are as below as related to the summary provided by the NICE group.	Thank you for your comment in support of the guideline.
British Society of Gastroenterology	-	-	-	including the opening statement patients that should be involved in the decision making process is important and well considered in the complex management of these patients.	Thank you for your comment in support of the guideline.
British Society of Gastroenterology	-	-	-	The diagnostic route for patients is thorough and appropriate. Need to clarify in the summary what PET-PANC is.	Thank you for your comment. PET PANC refers to 'PET-PANC: Multi-centre prospective diagnostic accuracy and clinical value study of PET/CT in the diagnosis and management of pancreatic cancer'. A brief description of this study has been added to Sections 5.1.2, 5.3.2.7 and 7.2 of the full guideline.
British Society of Gastroenterology	-	-	-	Characterisation, management and surveillance of pancreatic cysts is a complex and evolving area. Certainly in the summary document, a practical one page summary would be useful. Including that treatment of a cyst involves pancreatectomy, hence the importance of documenting the medical status of	Thank you for your comment. The guideline provides recommendations related to the most effective diagnostic pathway to identify cysts at high risk of pancreatic malignancy. The management or surveillance of cysts was not covered in this review and was not the focus of

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				the patient, and if appropriate for surveillance would be useful. The group should consider whether cyst management may be included in a separate review in the context of recommendations from several societies.	the question. In line with NICE processes the committee could, therefore, not make recommendations on this matter. The 'full guideline' contains details of the methods used, the underpinning evidence as well as the recommendations, whereas the 'short guideline' lists the recommendations, context and recommendations for research in a more concise format. It is therefore not possible to add the additional information suggested to the short guideline.
British Society of Gastroenterology	-	-	-	Need to say what surveillance procedures are for those with a family history.	Thank you for your comment. The committee felt that the available evidence was not sufficient to allow them to identify a particular test that should be used for the surveillance of people with a family history of pancreatic cancer. Please see Section 5.4.8.3 of the full guideline, which elucidates the decision- making process of the committee regarding this issue. The committee agreed that the evidence on the diagnostic yield of CT, MRI and endoscopic ultrasound (EUS) for surveillance in people with an inherited high risk of pancreatic cancer had shown they were all accurate at identifying early tumours. However, from the available evidence the committee could not identify which of these

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					investigations was the most effective. The committee also noted that repeated CT scanning would expose people to harms associated with radiation and therefore did not want to recommend this as an option for people without hereditary pancreatitis in whom a larger percentage of people would have a relatively smaller risk. The committee agreed that a pancreatic protocol CT scan for pancreatic cancer surveillance should be considered for people with hereditary pancreatitis and a PRSS1 mutation who would be at higher risk of developing pancreatic cancer.
British Society of Gastroenterology	-	-	-	Need to specify the sources of psychological support available.	Thank you for your comment. The committee decided that it was not possible to specify the source of psychological support that should be made available. The committee agreed that information needed to be provided to all people with pancreatic cancer. However, the committee was aware, based on the evidence and their experience that people have individualised requirements and that information and support needs to be tailored accordingly. Such requirements can also vary when symptoms or circumstances change and it is therefore not possible to recommend specific sources. The committee was also aware that when the

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					guideline is published a selection of sources for support will be signposted via a link entitled 'Information for the public' in the web version of the guideline.
British Society of Gastroenterology	-	-	-	In the adjuvant chemotherapy section for patients with unresectable cancers state when patients assessed for response.	Thank you for your comment. The purpose of the reviews in these sections was to establish the most effective adjuvant chemotherapy for patients with unresectable cancers. When to assess for response to adjuvant chemotherapy was not prioritised for inclusion in the guideline because this would depend on many factors and would therefore have to be tailored to each person with the condition. The evidence on this has not been reviewed and the committee was unable to draft recommendations about this.
British Society of Gastroenterology	-	-	-	In the text include when venous thromboembolism prophylaxis should be used.	Thank you for your comment. The details of when to provide venous thromboembolism (VTE) prophylaxis are covered by the NICE guideline on 'Venous thromboembolism - reducing the risk' CG92. This guideline is in the process of being updated and consulted on, so we have forwarded your comment to the relevant team at NICE (please see the link provided for documents related to this update). We have provided a link to the draft VTE recommendations in the guideline. This will be updated to a cross-reference to the final VTE

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					guideline upon publication of the VTE guideline update (which is due to publish in March 2018).
Celgene UK Ltd	Full	517-523	n/a	It is unclear what the inclusion criteria for this table (176) is. For example, why is the Von Hoff et al. 2013 study not included in this table?	Thank you for your comment. The study by Von Hoff et al. 2013 was included in the network meta-analysis of Gresham et al. 2014. The text has thus been amended to make clear that the summary of characteristics of included studies are presented in two tables, one for the 15 randomised controlled trials (RCTs), and one for the 23 RCTs included in the network meta-analysis of Gresham et al. 2014.
Celgene UK Ltd	Full	514	4-6	We are concerned that the following statement is misleading: "Those interventions where there is existing NICE technology appraisal guidance will not be reviewed here, nab-paclitaxel combined with gemcitabine (TA 360)" This implies that the previous negative TA 360 guidance on nab-paclitaxel combined with gemcitabine is still applicable. A comment should be added to state 'the TA 360 guidelines will shortly be updated following a FAD that states the following: Paclitaxel as albumin-bound nanoparticles (nab-paclitaxel) with gemcitabine is recommended as an	Thank you for your comment. The NICE Technology Appraisal guidance 'Paclitaxel as albumin-bound nanoparticles with gemcitabine for untreated metastatic pancreatic cancer' TA476 (2017) was published after the pancreatic cancer guideline went out for consultation. We have now added a cross-reference to TA476 in recommendation 1.9.5.

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				option for untreated metastatic pancreatic cancer in adults, only if: • other combination chemotherapies are unsuitable and they would otherwise have gemcitabine monotherapy and • the company provides nab-paclitaxel with the discount agreed in the patient access scheme.'	
Celgene UK Ltd	Full	515	24-27	The following statement is factually inaccurate: The majority of the studies were in a mixed population that included adults with either locally advanced or metastatic pancreatic cancer, whilst five of the studies were in adults with metastatic pancreatic cancer only (Chao et al. 2013; Fuchs et al. 2015; Gourgou-Bourgade et al. 2013; Irigoyen et al. 2017; Rougier et al. 2013). The reference 'Von Hoff et al. 2013' should be added to this list, as this study includes only patients with metastatic pancreatic cancer. Therefore, the statement should be re-worded to say: The majority of the studies were in a mixed population that included adults with either locally advanced or metastatic pancreatic cancer, whilst six of the studies were in adults with metastatic pancreatic cancer only (Chao et al. 2013; Fuchs et	Thank you for your comment. The study reported by Von Hoff et al. 2013 is one of the studies included in the network meta-analysis of Gresham et al. 2014. The guideline has been amended to make it clear that the statement you refer to relates to the 15 randomised controlled trials (RCTs) included and cited in the first line of the paragraph, and not to the 23 RCTs included in the network meta-analysis of Gresham et al. 2014. A sentence has also been added to make clear that the majority of studies included in Gresham et al. 2014 included both people with locally advanced pancreatic cancer and people with metastatic pancreatic cancer. A specific reference to Von Hoff et al. 2013 is therefore not needed.

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				al. 2015; 26 Gourgou-Bourgade et al. 2013; Irigoyen et al. 2017; Rougier et al. 2013, Von Hoff et al. 2013).	
Celgene UK Ltd	Full	515	31-35	The following statement is confusing: The NMA included a study (Von Hoff et al. 2013) that was part of a NICE TA evaluation (nab-Paclitaxel plus Gemcitabine). Therefore, this trial was considered in the NMA as a silent comparator (in order to foster the accuracy and the precision of the NMA), but it was excluded from the rest of the guideline decision-making (i.e. pairwise evidence review). A statement explaining what a 'silent comparator' means and the impact this could have on the NMA should be included. A statement explaining where the guidance regarding the Von Hoff et al. 2013 study can be found (i.e. TA360, if the TA number will remain the same)	Thank you for your comment. The text has been amended to make clear that although the results of Von Hoff et al. 2013 are included in the network meta-analysis, it was not included in the pairwise comparisons presented to the committee nor in its decision making. Reference to a 'silent comparator' was also removed to avoid confusion. A link to the NICE Technology Appraisal guidance 'Paclitaxel as albumin-bound nanoparticles with gemcitabine for untreated metastatic pancreatic cancer' TA476 (2017) which was published after the pancreatic cancer guideline went out for consultation, has also now been inserted in the fourth paragraph of Section 11.2.2 and a full reference is provided in the reference section.
Celgene UK Ltd	Full	620	22-23	This statement is misleading: 'Consider gemcitabine combination therapy5 for people who are not well enough to 22 tolerate FOLFIRINOX.' This statement does not reflect the most recent guidelines. A statement should be included here to say the following:	Thank you for your comment. The NICE Technology Appraisal guidance 'Paclitaxel as albumin-bound nanoparticles with gemcitabine for untreated metastatic pancreatic cancer' TA476 (2017) was published after the pancreatic cancer guideline went out for

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				'Please note, during the development of this guideline, a final appraisal determination was issued that states that the combination paclitaxel as albumin-bound nanoparticles (nab-paclitaxel) with gemcitabine is recommended as an option for untreated metastatic pancreatic cancer in adults, only if: • other combination chemotherapies are unsuitable and they would otherwise have gemcitabine monotherapy and • the company provides nab-paclitaxel with the discount agreed in the patient access scheme. In due course, this FAD will be translated to an update of TA 360, where further details of this guidance can be found.'	consultation. We have now added a cross-reference to TA476 in recommendation 1.9.5.
Celgene UK Ltd	Full	620	22-23	With regards to reference number 5. The following statement is factually inaccurate: Although this use is common in UK clinical practice, at the time of consultation (July 2017) gemcitabine combination therapy did not have a UK marketing authorisation for this indication. The prescriber should follow relevant professional guidance, taking full responsibility for the decision. Informed consent should be obtained and documented. See the General Medical Council's Prescribing guidance:	Thank you for your comment. We agree that the footnote is confusing because some gemcitabine combinations are licensed whilst others are not. We have now added a cross reference to the NICE Technology Appraisal guidance 'Paclitaxel as albumin-bound nanoparticles with gemcitabine for untreated metastatic pancreatic cancer' TA476 (2017) in recommendation 1.9.5. Consequently the footnote related to nab-paclitaxel is no longer needed. The footnote now reads: 'Although this

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				prescribing unlicensed medicines for further information. The statement should be re-worded to state the following: At the time of consultation (July 2017) nab-paclitaxel in combination with gemcitabine has a UK marketing authorization for the first-line treatment of adult patients with metastatic adenocarcinoma of the pancreas. Additionally, erlotinib in combination with gemcitabine has a UK marketing authorisation for the treatment of patients with metastatic pancreatic cancer. Although use of other combination therapy is common in clinical practice, at the time of consultation (July 2017) no other gemcitabine combination therapy has UK marketing authorisation for this indication. The prescriber should follow relevant professional guidance, taking full responsibility for the decision. Informed consent should be obtained and documented. See the General Medical Council's Prescribing guidance: prescribing unlicensed medicines for further information.	use is common in UK clinical practice, at the time of publication (January 2018) many gemcitabine combination therapies did not have a UK marketing authorisation covering the first-line treatment of adults with metastatic pancreatic cancer. The prescriber should follow relevant professional guidance, taking full responsibility for the decision to prescribe. Informed consent should be obtained and documented. See the General Medical Council's Prescribing guidance: prescribing unlicensed medicines for further information.' The committee decided not to provide a comprehensive list of all combinations since there are a number that can be used and the choice depends on clinical judgement and local provision. As highlighted in the comment, erlotinib has a licence for this indication and by adding 'many' to the footnote the inaccuracy has been removed.
Celgene UK Ltd	Short	10	5-6	This statement is misleading and does not reflect the most recent guidelines. A statement should be included here to say the following:	Thank you for your comment. The NICE Technology Appraisal guidance 'Paclitaxel as albumin-bound nanoparticles with gemcitabine

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				'Please note, during the development of this guideline, a final appraisal document was issued that states that the combination paclitaxel as albumin-bound nanoparticles (nab-paclitaxel) with gemcitabine is recommended as an option for untreated metastatic pancreatic cancer in adults, only if: • other combination chemotherapies are unsuitable and they would otherwise have gemcitabine monotherapy and • the company provides nab-paclitaxel with the discount agreed in the patient access scheme. In due course, this FAD will be translated to an update of TA 360, where further details of this guidance can be found.'	for untreated metastatic pancreatic cancer' TA476 (2017) was published after the pancreatic cancer guideline went out for consultation. We have now added a cross-reference to TA476 in recommendation 1.9.5.
Celgene UK Ltd	Short	10	5-6	With regards to reference number 5. The following statement is factually inaccurate: Although this use is common in UK clinical practice, at the time of consultation (July 2017) gemcitabine combination therapy did not have a UK marketing authorisation for this indication. The prescriber should follow relevant professional guidance, taking full responsibility for the decision. Informed consent should be obtained and documented. See the	Thank you for your comment. We agree that the footnote is confusing because some gemcitabine combinations are licensed whilst others are not. We have now added a cross reference to the NICE Technology Appraisal guidance 'Paclitaxel as albumin-bound nanoparticles with gemcitabine for untreated metastatic pancreatic cancer' TA476 (2017) in recommendation 1.9.5. Consequently the footnote related to nab-paclitaxel is no longer

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				General Medical Council's Prescribing guidance: prescribing unlicensed medicines for further information. The statement should be re-worded to state the following: At the time of consultation (July 2017) nab-paclitaxel in combination with gemcitabine has a UK marketing authorization for the first-line treatment of adult patients with metastatic adenocarcinoma of the pancreas. Additionally, erlotinib in combination with gemcitabine has a UK marketing authorisation for the treatment of patients with metastatic pancreatic cancer. Although use of other combination therapy is common in clinical practice, at the time of consultation (July 2017) no other gemcitabine combination therapy has UK marketing authorisation for this indication. The prescriber should follow relevant professional guidance, taking full responsibility for the decision. Informed consent should be obtained and documented. See the General Medical Council's Prescribing guidance: prescribing unlicensed medicines for further information.	needed. The footnote now reads: 'Although this use is common in UK clinical practice, at the time of publication (January 2018) many gemcitabine combination therapies did not have a UK marketing authorisation covering the first-line treatment of adults with metastatic pancreatic cancer. The prescriber should follow relevant professional guidance, taking full responsibility for the decision to prescribe. Informed consent should be obtained and documented. See the General Medical Council's Prescribing guidance: prescribing unlicensed medicines for further information.' The committee decided not to provide a comprehensive list of all combinations since there are a number that can be used and the choice depends on clinical judgement and local provision. As highlighted in the comment, erlotinib has a licence for this indication and by adding 'many' to the footnote the inaccuracy has been removed.

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DoH	-	-	-	I wish to confirm that the Department of Health has no substantive comments to make, regarding this consultation	Thank you for your comment.
Intuitive Surgical	All	General	General	In recent weeks, Intuitive Surgical has completed a systematic review of evidence around pancreatectomy – which has been submitted to the FDA. This raises a number of points, which the NICE Clinical Guidelines Committee may wish to consider – as part of developing this Clinical Guideline: Differences and Similarities in Source Documents: There are 4 papers that Intuitive Surgical and NICE both found: 1 that both included (Zhang 2013), 1 that NICE included but Intuitive excluded due to no summary data (Doula 2016), and 2 that were both excluded (Cirocchi 2013 and Correa-Gallego 2014). RCTs: NICE does not include a recently published RCT that Intuitive included that reported positive robotic data (significantly better operative time, EBL, LOS, clinically significant fisula, and wound infection rate) {Chen, S., et al. (2017). "Robot-assisted laparoscopic versus open middle pancreatectomy: short-term results of a randomized controlled trial." Surg Endosc 31(2): 962-971}.	Thank you for your comments. All the citations suggested in the comment have been checked and any unique studies not already included in the guideline have been added. Please see the responses below to the specific concerns raised. Difference and similarities in source documents The randomised controlled trial (RCT) of Chen et al. 2017 concerned the use of middle pancreatectomy in patients with benign resectable or low-grade malignant pancreatic pathology. The committee indicated that middle pancreatectomy would not be used in patients with pancreatic cancer. The study was therefore not included in the review of minimally invasive robotic versus open pancreatectomy.

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				Systematic Reviews: NICE does not include 6x Robotic vs. Open systematic reviews that Intuitive included (Chen 2013 for pancereatectomy and De Rooij 2016, Lei 2014, Pedziwiatr 2017, Peng 2016, Shin 2016 for pancreaticoduodenectomy). (Intuitive also included 5 Robotic vs. Lap systematic reviews that are not relevant for NICE's R vs. O comparison)	The systematic reviews suggested in the comment have been checked. Consequently, the reviews of de Rooij et al. 2016, Lei et al. 2014, Pedziwiatr et al. 2017, Peng et al. 2016 and Shin et al. 2016 have been included in the review of minimally invasive pancreaticoduodenectomy versus open pancreaticoduo-denectomy. As a result, 15 additional studies have been added to this comparison as follows. Four articles (Hakeem et al. 2014; Tee et al. 2015; Wang et al. 2014; Wellner et al. 2014) were added from De Rooij et al. 2016. • One article (Ito et al. 2009) was added from Lei et al. 2014. • Three articles (Boggi et al. 2016; Zhou et al. 2011; Zureikat et al. 2016) were added from Pedziwiatr et al. 2017. • One article (Hammill et al. 2010) was added from Peng et al. 2016. • Six articles (Baker et al. 2016; Chen et al. 2015; Croome et al. 2014; Croome et al. 2015; Dokmak et al. 2015; Song et al. 2015) were added from Shin et al. 2017.

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				Database: NICE chose not to include database papers. Intuitive would wish to emphasise to NICE that database papers are important because of the large n, they can expose differences that otherwise might be to minor to spot. NICE do not include the 4 database papers that Intuitive included (Adam 2015, Konstantinidis 2017, Xourafas 2017, Zureikat 2017). Zureikat 2017 only reported on conversion rates, so it is not relevant for Robotic vs. Open comparisons.	The review by Chen et al. 2013 was excluded as it concerned robotic versus laparoscopic or open pancreatectomy and therefore did not meet the inclusion criteria for the guideline review question. Due to the inclusion of the systematic review of de Rooij et al. 2016, the database study of Abdelgadir Adam et al. 2015 has been included in the review of minimally invasive (laparoscopic or robotic) pancreaticoduodenectomy versus open pancreaticoduodenectomy. The other database studies cited in the comment were excluded (Konstantinidis et al. 2017; Xourafas et al. 2017) as they were published after the final update searches were conducted (April 2017) and were thus not in any of the identified systematic reviews. As pointed out in the comment, Zureikat et al. 2017 database study which examined laparoscopic versus robotic surgery, was not included because the comparison does not meet our inclusion criteria. Pancreatectomy outcomes

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				Pancreatectomy Outcomes: The missing Chen 2017 RCT reported significantly better operative time, EBL, LOS, clinically significant fisula, and wound infection rate for robotics. The missing Chen 2013 systematic review for pancreatectomy reported significantly higher R0 resection rate, lower EBL, and shorter LOS in favor of robotics. NICE missed some of the data available in the Zhang 2013 meta: Significant difference in reoperation rate in favor of robotics RD: -0.12 [-0.2, -0.03], p=0.006 (see Zhang text page 1776) and blood loss (see Zhang table 2). NICE does not mention the significant difference in overall complication rate that NICE themselves reported in table 130 (NICE page 375) in their conclusion section (NICE conclusions section 10.2.6.4 on page 384). Out of the 3x pancreatectomy database papers, NICE did not include (Adam 2015, Konstantinidis 2017, Xourafas 2017), Xourafas 2017 showed fewer transfusions, shorter LOS, and lower postoperative	The RCT of Chen et al. 2017 was not included in the review of minimally invasive robotic pancreatectomy versus open pancreatectomy because the committee indicated that middle pancreatectomy would not be used in people with resectable pancreatic cancer. The review of Chen et al. 2013 was excluded as it concerned robotic versus laparoscopic or open pancreatectomy and therefore did not meet the inclusion criteria for the guideline review question. Regarding Zhang et al. 2013, since 4 of the studies have been excluded (as explained above) there is only one study (Kang et al. 2011) that contributes data to reoperation rate and blood loss, and 3 studies (Kang et al. 2011; Walsh et al. 2011; Waters et al. 2010) that contribute data to complication rate. Consequently, the remaining data show (i) no significant difference in both overall complication rate and reoperation rate, and (ii) a significant difference favouring robotic pancreatectomy on blood loss.

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				complication rates, specifically less bleeding and less delayed gastric emptying.	Due to the inclusion of the systematic review of de Rooij et al. 2016, the database study of Abdelgadir Adam et al. 2015 has been included in the review of minimally invasive (laparoscopic or robotic) pancreaticoduodenectomy versus open pancreaticoduodenectomy. The other database studies cited in the comment were excluded (Konstantinidis et al. 2017; Xourafas et al. 2017) as they were published after the final update searches were conducted (April 2017) and were thus not in any of the identified systematic reviews. As pointed out in the comment, Zureikat et al. 2017 examined laparoscopic versus robotic surgery, was not included because thecomparison does not meet our inclusion criteria. <u>Conclusions that are different for pancreatectomy</u> Regarding length of stay for robotics, as the 4 studies concerning pan-creaticoduodenectomy in Zhang et al. 2013 were excluded from the
				<u>Conclusions that are different for pancreatectomy:</u> Intuitive reported significantly shorter LOS for robotics (Chen 2013, Chen 2017, Xourafas 2017), NICE reported "no clinically important difference"	

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				Intuitive reported significantly lower reoperation rates for robotics from the Zhang 2013 systematic review, NICE reported that this information was not available. Intuitive reported significantly lower EBL for robotics (Chen 2013, Chen 2017) and a lower range of EBL for robotics in Zhang 2013 (no statistics were done), NICE reported that this information was not available. Intuitive reported significantly lower wound infection rates for robotics in Chen 2017, NICE did not report on wound infection rate.	review on robotic pancreatectomy versus open pancreatectomy, there is only one study (Kang et al. 2011) that contributes data to this outcome. As such, this study shows no significant difference in length of stay between robotic and open pancreatectomy. The RCT of Chen et al. 2017 was not included in the review of minimally invasive robotic pancreatectomy versus open pancreatectomy because the committee indicated that middle pancreatectomy would not be used in people with resectable pancreatic cancer. The review by Chen et al. 2013 was excluded as it concerned robotic versus laparoscopic or open pancreatectomy and therefore did not meet the inclusion criteria for the guideline review question. The study by Xourafas et al. 2017 was excluded as it was published after the final update search was conducted (April 2017) and it was not in any of the identified systematic reviews.

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					Regarding reoperation rate and expected blood loss, if the four studies on pancreaticoduodenectomy are excluded, two studies (Kang et al. 2011; Walsh et al. 2011) contribute data to these outcomes. Combining these 2 studies shows that (i) there is no significant difference between robotic and open pancreatectomy on reoperation rate and (ii) there is a significant difference favouring robotic pancreatectomy on blood loss. Both of these outcomes have now been added to the review of robotic and open pancreatectomy. Regarding wound infection rate, this outcome was not considered by the committee because the RCT of Chen et al. 2017 was not included in the pancreatectomy review as explained above. The revised evidence was presented to the committee, who did not consider it to be sufficient to change the original recommendations.

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				Pancreaticoduodenectomy Outcomes: Out of the 5 systematic reviews NICE did not include: Lei 2014 reported significantly shorter LOS for robotics. Pedziwiatr 2017 reported significantly less EBL for robotics. Peng 2016 reported a significantly higher R0 resection rate, shorter LOS, fewer postoperative complication rates, and a lower wound infection rate for robotics. Shin 2016 reported significantly less EBL and shorter LOS for robotics. All other outcomes from these papers and from the de Rooji 2016 review were no significant except for a longer operative time for robotics in Pedziwiatr 2017 and Shin 2016.	Pancreaticoduodenectomy Outcomes As indicated, the reviews of de Rooij et al. 2016, Lei et al. 2014, Pedziwiatr et al. 2017, Peng et al. 2017, and Shin et al. 2017 have been added to the review of robotic pancreaticoduo-denectomy versus open pancreatico-duodenectomy. Consequently, the outcome of length of stay has been added to the review. The updated results in the guideline show the following. (i) There is a significant difference favouring both minimally invasive (robotic or laparoscopic) pancreatico-duodenectomy over open pancreas-ticoduodenectomy on length of stay and blood loss, although there is substantial heterogeneity for both these outcomes. This conclusion is not affected if the type of surgery is taken into account by subgroup analysis. (ii) There is no significant difference between minimally invasive (robotic or laparoscopic) pancreaticoduodenectomy and open pancreaticoduodenectomy on R0 resection rate. There is no heterogeneity in this outcome, hence a subgroup analysis does not change this conclusion.

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				Conclusions that are different for pancreaticoduodenectomy: Intuitive reported a significantly lower overall complication rate for robotics in Peng 2016 and no difference for Lei 2014, Pedziwiatr 2017, and Shin 2016, NICE reported that this information was not available. Intuitive reported a significantly shorter LOS for robotics in 3 (Lei 2014, Peng 2016, Shin 2016) of 4 papers (Pedziwiatr 2017), NICE reported that this information was not available. Intuitive reported a significantly lower wound infection rate for robotics (Peng 2016), NICE did not report on wound infection rate.	Regarding general post-operative complication rate and wound infection rate (as reported in Peng et al. 2016), these outcomes were not considered in this comparison as the committee decided to prioritise the outcomes of pancreatic fistula and delayed gastric emptying. Conclusions that are different for pancreaticoduodenectomy As indicated above, overall complication rate was not considered in this comparison as the committee decided to prioritise the outcomes of pancreatic fistula and delayed gastric emptying. Please note that the outcome of clinically relevant pancreatic fistula (i.e. Grade B-C) has been added to the review. Regarding length of stay, as indicated above, the updated results in the guideline show that there is a significant difference favouring both minimally invasive (robotic or laparoscopic) pancreaticoduodenectomy over open pancreaticoduodenectomy on length of stay,

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				In case it helps, a bibliography of paper missing from NICE documents: Robotic vs. Open pancreatectomy/pancreticoduodenectomy bibliography of papers not included in NICE (n=11) separated by publication type: RCT (1) Chen, S., et al. (2017). "Robot-assisted laparoscopic versus open middle pancreatectomy: short-term results of a randomized controlled trial." Surg Endosc 31(2): 962-971. OBJECTIVE: This first prospective randomized controlled trial was performed to compare short-term outcomes of robot-assisted laparoscopic middle pancreatectomy (RA-MP) with open middle pancreatectomy (OMP). BACKGROUND: RA-MP is a novel minimally invasive surgical technique for benign or borderline tumors in the pancreatic neck or body. Its short-term effectiveness and safety remain unknown, compared to OMP. METHODS: Patients eligible for MP from	although there is substantial heterogeneity for this outcome. As indicated above wound infection rate was not considered in this comparison as the committee decided to prioritise the outcomes of pancreatic fistula and delayed gastric emptying. Please see below for a list of the 19 studies that have been added to the reviews of minimally invasive pancreaticoduodenectomy versus open surgery. 1. Abdelgadir Adam, M. A., et al. (2015). Minimally Invasive Distal Pancreatectomy for Cancer: Short-Term Oncologic Outcomes in 1,733 Patients. World Journal of Surgery 39(10): 2564-2572 2. Baker EH, Ross SW, Seshadri R et al. (2016) Robotic pancreaticoduodenectomy: comparison of complications and cost to the open approach. International Journal of

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				August 2011 to November 2015 were randomized into the RA-MP or OMP group. The primary endpoint was length of hospital stay (LOS). Secondary endpoints were intraoperative parameters, and postoperative and recovery variables. RESULTS: A total of 100 patients were included into the study to analyze primary and secondary endpoints. Demographic characteristics and pathological parameters were similar in both groups. Furthermore, LOS was significantly shorter (15.6 vs. 21.7 days, P = 0.002), median operative time was reduced (160 vs. 193 min, P = 0.002), median blood loss was lower (50 vs. 200 mL, P < 0.001), rate of clinical postoperative pancreatic fistula (POPF) was lower (18 vs. 36.0 %, P = 0.043), nutritional status recovery was better, off-bed return to activity was expedited (3.1 vs. 4.6 days, P < 0.001), and resumption of bowel movement was faster (3.5 vs. 5.0 days, P < 0.001) in the RA-MP group, compared to the OMP group. CONCLUSION: RA-MP was associated with significantly shorter LOS, reduced operative time, blood loss and clinical POPF rate, and expedited postoperative recovery, compared to OMP.	Medical Robotics and Computer Assisted Surgery 12: 554–560 3. Boggi U, Napoli N, Costa F et al. (2016) Robotic-assisted pancreatic resections. World Journal of Surgery 40: 2497–2506 4. Chen S, Chen J-Z, Zhan Q et al. (2015) Robot-assisted laparoscopic versus open pancreaticoduodenectomy: a prospective, matched, mid-term follow-up study. Surgical Endoscopy 29: 3698–3711 5. Croome KP, Farnell MB, Que FG et al. (2014). Total laparoscopic pancreaticoduodenectomy for pancreatic ductal adenocarcinoma: oncologic advantages over open approaches? Annals of Surgery 260(4): 633-640 6. Croome KP, Farnell MB, Que FG et al. (2015) Pancreaticoduodenectomy with major vascular resection: a comparison of laparoscopic versus open approaches. Journal of Gastrointestinal Surgery 19(1): 189–194 7. Delitto D, Luckhurst CM, Black BS et al (2016) Oncologic and perioperative outcomes following selective application of

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				Systematic Reveiws (6) Chen, Y., et al. (2013). "A meta-analysis of robotic-assisted pancreatectomy versus laparoscopic and open pancreatectomy." Saudi Med J 34(12): 1229-1236. OBJECTIVE: To perform a meta-analysis of eligible studies from multiple medical centers to assess the safety, feasibility, and efficacy of robotic-assisted pancreatectomy (RP). METHODS: We searched the electronic databases PubMed and EMBASE for studies comparing RP with laparoscopic pancreatectomy (LP) and open pancreatectomy (OP) for patients with pancreatic disease from June 2009 to June 2012. Continuous variables were pooled using the standardized mean difference (SMD) and odds ratio (OR), and dichotomous variables were pooled using the risk difference (RD) method. For all analyses, the 95% confidence interval (CI) was calculated. Three studies comparing RP and LP, and 4 studies comparing RP and OP were suitable	laparoscopic pancreaticoduodenectomy for periampullary malignancies. Journal of Gastrointestinal Surgery 20:1343–1349. 8. Dokmak S, Ftériche FS, Aussilhou B, Bensafta Y, Lévy P, Ruszniewski P, Belghiti J, Sauvanet A (2015) Laparoscopic pancreaticoduodenectomy should not be routine for resection of periampullary tumors. J Am Coll Surg 220(5):831–838 9. Hakeem AR, Verbeke CS, Cairns A (2014) A matched-pair analysis of laparoscopic versus open pancreaticoduodenectomy: oncological outcomes using Leeds Pathology Protocol. Hepatobiliary & Pancreatic Diseases International 13(4): 435-41 10. Hammill C, Cassera M, Swanstrom L et al. (2010) Robotic assistance may provide the technical capability to perform a safe, minimally invasive pancreaticoduodenectomy. HPB 12(S1): 198 11. Ito M, Horiguchi A, Ishihara S et al. (2009) Laparoscopic pancreatic surgery: totally laparoscopic pancreatoduodenectomy and reconstruction. Pancreas 38(8): 1009-1009

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				for meta-analysis. RESULTS: Six published studies met the inclusion criteria. Our results showed that RP can reduce estimated blood loss and duration of hospitalization more than OP. For pancreatic fistula, there were no statistical differences between RP, OP, and LP, and no significant differences in intraoperative conversion rates between RP and LP. Robotic-assisted pancreatectomy may be able to increase microscopic negative margins of resection (R0) and spleen preserving rates. CONCLUSION: Robotic-assisted pancreatectomy was associated with increased R0 resection rates and spleen preserving rates than LP and OP. Moreover, RP can reduce estimated blood loss and duration of hospitalization more than OP. A robotic approach to pancreatectomy may be suited to patients with pancreatic disease. De Rooij, T., et al. (2016). "Minimally Invasive Versus Open Pancreatoduodenectomy: Systematic Review and Meta-analysis of Comparative Cohort and Registry Studies." Annals of Surgery 264(2): 257-267. Objective: This study aimed to appraise and to evaluate the current evidence on minimally	12. Sharpe SM, Talamonti MS, Wang CE et al. (2015) Early national experience with laparoscopic pancreaticoduodenectomy for ductal adenocarcinoma: a comparison of laparoscopic pancreaticoduodenectomy and open pancreaticoduodenectomy from the National Cancer Data Base. Journal of the American College of Surgeons 221(1): 175-84 13. Song KB, Kim SC, Hwang DW et al. (2015) Matched case-control analysis comparing laparoscopic and open pylorus-preserving pancreaticoduodenectomy in patients with periampullary tumors. Annals of Surgery 262(1):146–155 14. Tan CL, Zhang H, Peng B, Li KZ. Outcome and costs of laparoscopic pancreaticoduodenectomy during the initial learning curve vs laparotomy. World Journal of Gastroenterology: WJG. 2015 May 7;21(17): 5311-5319 15. Tee MC, Croome KP, Shubert CR et al. (2015) Laparoscopic pancreatoduodenectomy does not completely mitigate increased perioperative risks in elderly patients. HPB 17(10): 909-18

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				invasive pancreatoduodenectomy (MIPD) versus open pancreatoduodenectomy only in comparative cohort and registry studies. Background: Outcomes after MIPD seem promising, but most data come from single-center, noncomparative series. Methods: Comparative cohort and registry studies on MIPD versus open pancreatoduodenectomy published before August 23, 2015 were identified systematically and meta-analyses were performed. Primary endpoints were mortality and International Study Group on Pancreatic Fistula grade B/C postoperative pancreatic fistula (POPF). Results: After screening 2293 studies, 19 comparative cohort studies (1833 patients) with moderate methodological quality and 2 original registry studies (19,996 patients) were included. For cohort studies, the median annual hospital MIPD volume was 14. Selection bias was present for cancer diagnosis. No differences were found in mortality [odds ratio (OR) = 1.1, 95% confidence interval (CI) = 0.6-1.9] or POPF [(OR) = 1.0, 95% CI = 0.8 to 1.3]. Publication bias was present for POPF. MIPD was associated with prolonged operative times [weighted mean difference (WMD) = 74	16. Tran TB, Dua MM, Worhunsky DJ et al. (2016) The first decade of laparoscopic pancreaticoduodenectomy in the United States: costs and outcomes using the nationwide inpatient sample. Surgical Endoscopy 30(5): 1778-83 17. Wang Y, Bergman S, Piedimonte S et al. (2014) Bridging the gap between open and minimally invasive pancreaticoduodenectomy: the hybrid approach. Canadian Journal of Surgery 57(4): 263-270 18. Wellner UF, Küsters S, Sick O et al. (2014) Hybrid laparoscopic versus open pylorus-preserving pancreatoduodenectomy: retrospective matched case comparison in 80 patients. Langenbeck's Archives of Surgery 399(7): 849-56 19. Zureikat AH, Postlewait LM, Liu Y et al (2016) A multi-institutional comparison of perioperative outcomes of robotic and open pancreaticoduodenectomy. Annals of Surgery 264: 640–649 The committee reviewed and considered the updated evidence for this comparison but

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				minutes, 95% CI = 29-118], but lower intraoperative blood loss (WMD=-385mL, 95% CI=-616 to -154), less delayed gastric emptying (OR = 0.6, 95%=CI 0.5-0.8), and shorter hospital stay (WMD=-3 days, 95% CI=-5 to -2). For registry studies, the median annual hospital MIPD volume was 2.5. Mortality after MIPD was increased in low-volume hospitals (7.5% vs 3.4%; P = 0.003). Conclusions: Outcomes after MIPD seem promising in comparative cohort studies, despite the presence of bias, whereas registry studies report higher mortality in low-volume centers. The introduction of MIPD should be closely monitored and probably done only within structured training programs in high-volume centers. Lei, P., et al. (2014). "Minimally invasive surgical approach compared with open pancreaticoduodenectomy: a systematic review and meta-analysis on the feasibility and safety." Surg Laparosc Endosc Percutan Tech 24(4): 296-305. BACKGROUND:: Laparoscopic and robotic pancreaticoduodenectomy have started utilization tentatively; however, the clinical benefits are still controversial. This study	decided not to change its recommendations. They agreed that they could not make a recommendation related to robotic surgery for the following reasons: (i) This was not the focus of the evidence review (which was minimally invasive compared to open surgery). There is little experience of robotic surgery in this setting in current UK practice. (ii) According to GRADE criteria, even with the additional studies, the evidence was still assessed as being of very low quality. The committee made a research recommendation for randomised controlled trials comparing minimally invasive with open pancreatectomy or pancreaticoduodenectomy to be conducted.

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				aims to evaluate the safety and efficiency of minimally invasive pancreaticoduodenectomy. METHODS:: A systematic literature search was performed through PubMed, EMBASE, and Cochrane Library database without restriction to regions, publication types, or languages. Nine studies that compared laparoscopic/robotic with open pancreaticoduodenectomy were included. Fixed or random-effects models was used to measure the pooled estimates. Sensitivity and subgroup analysis were performed to evaluate the study quality. RESULTS:: Patients who underwent minimally invasive pancreaticoduodenectomy experienced longer operative time (P=0.007), but the estimated blood loss (P=0.007), length of stay, (P=0.02), and wound infection (P=0.04) decreased. Perioperative complications, such as pancreatic fistula, delayed gastric emptying, hemorrhage, bile leakage, reoperation, and mortality, were of no significant differences. Pathologically, lymph node number was similar (P=0.11); meanwhile, margin R0 ratio was higher in minimally invasive approach group (P=0.03). Subgroup analysis manifested robotic	

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				surgery spent comparable surgical time (P=0.16) as laparotomy, with earlier discharge (P=0.04). CONCLUSIONS:: This meta-analysis indicates minimally invasive pancreaticoduodenectomy may be associated with shorter hospital stay, less estimated blood loss, and positive margin rate without compromising surgical safety as open surgery. Surgical duration of robotic method could even be equivalent as laparotomy. Minimally invasive approach can be a reasonable alternative to laparotomy pancreaticoduodenectomy with potential advantages. Nevertheless, future large-volume, well-designed RCTs with extensive follow-up are awaited to confirm and update the findings of this analysis. Pedziwiatr, M., et al. (2017). "Minimally invasive versus open pancreatoduodenectomy-systematic review and meta-analysis." Langenbecks Arch Surg. PURPOSE: The purpose of this systematic review was to compare minimally invasive pancreatoduodenectomy (MIPD) versus open pancreatoduodenectomy (OPD) by using meta-analytical techniques. METHODOLOGY: Medline, Embase, and	

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				Cochrane Library were searched for eligible studies. Data from included studies were extracted for the following outcomes: operative time, overall morbidity, pancreatic fistula, delayed gastric emptying, blood loss, postoperative hemorrhage, yield of harvested lymph nodes, R1 rate, length of hospital stay, and readmissions. Random and fix effect meta-analyses were undertaken. RESULTS: Initial reference search yielded 747 articles. Thorough evaluation resulted in 12 papers, which were analyzed. The total number of patients was 2186 (705 in MIPD group and 1481 in OPD). Although there were no differences in overall morbidity between groups, we noticed reduced blood loss, delayed gastric emptying, and length of hospital stay in favor of MIPD. In contrary, meta-analysis of operative time revealed significant differences in favor of open procedures. Remaining parameters did not differ among groups. CONCLUSION: Our review suggests that although MIPD takes longer, it may be associated with reduced blood loss, shortened LOS, and comparable rate of perioperative complications. Due to heterogeneity of included studies and	

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				differences in baseline characteristics between analyzed groups, the analysis of short-term oncological outcomes does not allow drawing unequivocal conclusions. Peng, L., et al. (2016). "Systematic review and meta-analysis of robotic versus open pancreaticoduodenectomy." Surg Endosc. BACKGROUND: Although robotic pancreaticoduodenectomy (RPD) has been successfully performed since 2003, its advantages over open pancreaticoduodenectomy (OPD) are still uncertain. The aim of this systematic review and meta-analysis was to compare the clinical outcomes of RPD to those of OPD. METHODS: A systematic literature review was performed to identify RPD versus OPD comparative studies published between January 2003 and January 2016. Intraoperative outcomes, post-operative outcomes and oncologic safety were evaluated. Pooled odds ratios (ORs) and weighted mean differences (WMDs) with a 95% confidence interval (95% CI) were calculated using fixed-effect or random-effect models. RESULTS: Nine non-randomized	

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				observational clinical studies involving 680 patients met the inclusion criteria and involved 245 RPDs and 435 OPDs. The overall complication rate was significantly lower in RPD (OR 0.65, 95% CI 0.47-0.91, P = 0.012), as well as the margin positivity rate (OR 0.40, 95% CI 0.20-0.77, P = 0.006), the wound infection rate (OR 0.18, 95% CI 0.06-0.53, P = 0.002) and the length of hospital stay (WMD = -6.00, 95% CI -9.80 to -2.21, P = 0.002). There was no significant difference in the following: the number of lymph nodes harvested; the operation time; the reoperation rate; the incidence of delayed gastric emptying, bile leakage, pancreatic fistula and clinically significant pancreatic fistula; and mortality. The mean conversion rate was 7.3% (range 0-14%). CONCLUSIONS: According to the results of this meta-analysis, RPD is as safe and efficient as OPD and is even favourable in terms of margin-negative resection, overall complication and wound infection rates and length of hospital stay. Given that there have not yet been any high-quality randomized controlled trials (RCTs), the evidence is still limited. Additional prospective, multi-centre RCTs are needed to	

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				further define the role of the robotic technique in PD. Shin, S. H., et al. (2016). "Totally laparoscopic or robot-assisted pancreaticoduodenectomy versus open surgery for periampullary neoplasms: separate systematic reviews and meta-analyses." Surg Endosc. OBJECTIVE: To compare perioperative and oncologic outcomes of pure (totally) laparoscopic pancreaticoduodenectomy (TLPD) or robot-assisted pancreaticoduodenectomy (RAPD) with those of conventional open pancreaticoduodenectomy (OPD). METHODS: A systematic literature search was performed using PubMed, EMBASE, and Cochrane library databases. Studies comparing TLPD with OPD and RAPD with OPD were included; only original studies reporting more than 10 cases for each technique were included. Studies were combined using a random-effects model to report heterogeneous data, or a fixed-effects model was applied. RESULTS: TLPD involved longer operative time (weighted mean difference [WMD]: 116.85 min; 95%	

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				confidence interval [CI] 54.53-179.17) and significantly shorter postoperative hospital stay (WMD: -3.68 days; 95% CI -4.65 to -2.71). Overall morbidity and postoperative pancreatic fistula were not significantly different between TLPD and OPD. RAPD was associated with a longer operative time, less intraoperative blood loss, and shorter hospital stay. Oncologic outcomes were not significantly different among the procedure types. CONCLUSIONS: Compared to OPD, TLPD and RAPD were feasible and oncologically safe procedures. However, there are no prospective studies, and the majority of the studies on TLPD and RAPD have remained in the early training phase. In addition to randomized controlled trials or prospective studies, new data from the late training phase of learning experiences should also be analyzed. Database papers (4) Adam, M. A., et al. (2015). "Minimally Invasive Distal Pancreatectomy for Cancer: Short-Term Oncologic	

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				Outcomes in 1,733 Patients." World J Surg 39(10): 2564-2572. Background: Data from high-volume institutions suggest that minimally invasive distal pancreatectomy (MIDP) provides favorable perioperative outcomes and adequate oncologic resection for pancreatic cancer; however, these outcomes may not be generalizable. This study examines patterns of use and short-term outcomes from MIDP (laparoscopic or robotic) versus open distal pancreatectomy (ODP) for pancreatic adenocarcinoma in the United States. Methods: Adult patients undergoing distal pancreatectomy were identified from the National Cancer Database, 2010–2011. Multivariable modeling was applied to compare short-term outcomes from MIDP versus ODP for pancreatic adenocarcinoma. Results: 1733 patients met inclusion criteria: 535 (31 %) had MIDP and 1198 (69 %) ODP. Use of MIDP increased 43 % between 2010 and 2011; the conversion rate from MIDP to ODP was 23 %. MIDP cases were performed at 215 hospitals, with 85 % of hospitals performing <10 cases overall. After adjustment, pancreatic adenocarcinoma	

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				patients undergoing MIDP versus ODP had a similar likelihood of complete resection (OR 1.48, p = 0.10), number of lymph nodes removed (RR 1.01, p = 0.91), and 30-day readmission rate (OR 1.02, p = 0.96); however, length of stay was shorter (RR 0.84, p < 0.01). Conclusions: Use of MIDP for cancer is increasing, with most centers performing a low volume of these procedures. Use of MIDP for body and tail pancreatic adenocarcinoma appears to have short-term outcomes that are similar to those of open procedures with the benefit of a shorter hospital stay. Larger studies with longer follow-up are needed. © 2015 Société Internationale de Chirurgie Konstantinidis, I. T., et al. (2017). "Minimally invasive distal pancreatectomy: greatest benefit for the frail." Surg Endosc. Objective: The benefits of minimally invasive distal pancreatectomy (MIDP) over open surgery continue to be investigated. Frailty is a known predictor of postoperative outcome. We hypothesized that the benefit of minimally invasive distal pancreatectomy is the greatest for the frailest of patients. Methods: Data	

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				from the pancreas-targeted National Surgical Quality Improvement Program (NSQIP) database for 2014 were reviewed. A modified frailty index (mFI) with 11 preoperative variables previously validated for use in NSQIP was used to determine the correlation between frailty and postoperative outcomes, including Clavien grade IV complications. Patients were classified into non-frail (mFI = 0) or frail (mIF > 0), in which they were subclassified into mildly frail (mFI 1 or 2) or severely frail (mFI = 3). Results: A total of 1,038 distal pancreatectomies (DP) were included in the analysis, of which 387 were minimally invasive (MIDP: laparoscopic: 285, robotic: 102), 558 open DP (ODP), and 93 MIDP converted to open (MIDPcODP: laparoscopic: 80, robotic: 13). More than 90% of patients had an mFI of 0 or 1 (mFI 0 = 473 (45.6%), 1 = 466 (44.9%), 2 = 94 (9.1%), and 3 = 5 (0.5%), respectively). Overall, 4.6% of patients experienced Clavien grade IV complications and 1.1% a mortality. Non-frail patients experienced a similar rate of grade IV Clavien complications with MIDP vs. ODP vs. MIDPcOP (2.3 vs. 2.3 vs. 4.9%; p = 0.6), whereas frail patients (mFI > 0) had a lower	

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				rate of complications with MIDP (2.4 vs. 8.3 vs. 11.5; p = 0.007). Worsening frailty correlated with an increase in complications (non-frail: 2.5%; mildly frail: 6.3%; severely frail: 20%; p = 0.005). Conclusion: MIDP is associated with a lower risk of Clavien grade IV complications compared to ODP for frail patients, especially for benign disease. Thus, minimally invasive approach may mitigate risk in frail patients. © 2017 Springer Science+Business Media New York Xourafas, D., et al. (2017). "Comparison of Perioperative Outcomes between Open, Laparoscopic, and Robotic Distal Pancreatectomy: an Analysis of 1815 Patients from the ACS-NSQIP Procedure-Targeted Pancreatectomy Database." J Gastrointest Surg. BACKGROUND: Robotic surgery is gaining acceptance for distal pancreatectomy (DP). Nevertheless, no multi-institutional data exist to demonstrate the ideal clinical circumstances for use and the efficacy of the robot compared to the open or laparoscopic techniques, in terms of perioperative outcomes. METHODS: The 2014 ACS-NSQIP procedure-targeted pancreatectomy	

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				data for patients undergoing DP were analyzed. Demographics and clinicopathological and perioperative variables were compared between the three approaches. Univariate and multivariable analyses were used to evaluate outcomes. RESULTS: One thousand eight hundred fifteen DPs comprised 921 open distal pancreatectomies (ODPs), 694 laparoscopic distal pancreatectomies (LDPs), and 200 robotic distal pancreatectomies (RDPs). The three groups were comparable with respect to demographics, ASA score, relevant comorbidities, and malignant histology subtype. Compared to the ODP group, patients undergoing RDP had lower T-stages of disease (P = 0.0192), longer operations (P = 0.0030), shorter hospital stays (P < 0.0001), and lower postoperative 30-day morbidity (P = 0.0476). Compared to the LDP group, RDPs were longer operations (P < 0.0001) but required fewer concomitant vascular resections (P = 0.0487) and conversions to open surgery (P = 0.0068). On multivariable analysis, neoadjuvant therapy (P = 0.0236), malignant histology (P = 0.0124), pancreatic reconstruction (P =	

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				0.0006), and vascular resection (P = 0.0008) were the strongest predictors of performing an ODP. CONCLUSIONS: The open, laparoscopic, and robotic approaches to distal pancreatectomy offer particular advantages for well-selected patients and specific clinicopathological contexts; therefore, clearly demonstrating the most suitable use and superiority of one technique over another remains challenging. Zureikat, A. H., et al. (2017). "Minimally invasive hepatopancreatobiliary surgery in North America: an ACS-NSQIP analysis of predictors of conversion for laparoscopic and robotic pancreatectomy and hepatectomy." HPB (Oxford). Background: Procedural conversion rates represent an important aspect of the feasibility of minimally invasive surgical (MIS) approaches. This study aimed to outline the rates and predictors of procedural completion/conversion for MIS hepatectomy and pancreatectomy. Methods: All 2014 ACS-NSQIP laparoscopic and robotic hepatectomy and pancreatectomy procedures were identified and grouped into pure, open assist, or unplanned conversion to	

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				open. Risk adjusted multinomial logistic regression models were generated with completion (Pure) set as the primary outcome. Results: 1667 (laparoscopic = 1360, robotic = 307) resections were captured. After risk adjustment, robotic DP was associated with similar open assist (relative risk ratio -1.9%, P = 0.602), but lower unplanned conversion (-8.2%, P = 0.004) and open assist + unplanned conversion (-10.1%, P = 0.015) compared to laparoscopic DP; while robotic PD was associated with lower open assist (-22.2%, P < 0.001), unplanned conversions (-15%, P = 0.006) and open assist + unplanned conversions (-37.2, P < 0.001) compared to laparoscopic PD. The robotic and laparoscopic approaches to hepatectomy were not associated with differences in pure MIS completion rates (P = NS) after risk adjustment. Conclusions: The robotic approach to pancreatectomy was associated with higher rates of pure MIS completion compared to laparoscopy, whereas no difference in MIS completion rates was noted for robotic versus laparoscopic hepatectomy.	

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Intuitive Surgical	All	General	General	In case it helps, a bibliography of evidence on robotic pancreatectomy created by Intuitive Surgical: Robotic Pancreatectomy/ Pancreaticoduodenectomy (2010-May 31st, 2017): Include(17) Adam, M. A., et al. (2015). "Minimally Invasive Distal Pancreatectomy for Cancer: Short-Term Oncologic Outcomes in 1,733 Patients." World J Surg 39(10): 2564-2572. Background: Data from high-volume institutions suggest that minimally invasive distal pancreatectomy (MIDP) provides favorable perioperative outcomes and adequate oncologic resection for pancreatic cancer; however, these outcomes may not be generalizable. This study examines patterns of use and short-term outcomes from MIDP (laparoscopic or robotic) versus open distal pancreatectomy (ODP) for pancreatic adenocarcinoma in the United States. Methods: Adult patients undergoing distal	Thank you for your comment and for providing these references. The reasons for either including or excluding them from the relevant reviews are as follows. Adam, M. A., et al. (2015). "Minimally Invasive Distal Pancreatectomy for Cancer: Short-Term Oncologic Outcomes in 1,733 Patients." World J Surg 39(10): 2564-2572. *This study was excluded as only meta-analyses and randomised controlled trials (RCTs) were included in the review of minimally invasive versus open pancreaticoduodenectomy.*

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				pancreatectomy were identified from the National Cancer Database, 2010–2011. Multivariable modeling was applied to compare short-term outcomes from MIDP versus ODP for pancreatic adenocarcinoma. Results: 1733 patients met inclusion criteria: 535 (31 %) had MIDP and 1198 (69 %) ODP. Use of MIDP increased 43 % between 2010 and 2011; the conversion rate from MIDP to ODP was 23 %. MIDP cases were performed at 215 hospitals, with 85 % of hospitals performing <10 cases overall. After adjustment, pancreatic adenocarcinoma patients undergoing MIDP versus ODP had a similar likelihood of complete resection (OR 1.48, p = 0.10), number of lymph nodes removed (RR 1.01, p = 0.91), and 30-day readmission rate (OR 1.02, p = 0.96); however, length of stay was shorter (RR 0.84, p < 0.01). Conclusions: Use of MIDP for cancer is increasing, with most centers performing a low volume of these procedures. Use of MIDP for body and tail pancreatic adenocarcinoma appears to have short-term outcomes that are similar to those of open procedures with the benefit of a shorter hospital stay. Larger studies with	

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				longer follow-up are needed. © 2015 Société Internationale de Chirurgie Chen, S., et al. (2017). "Robot-assisted laparoscopic versus open middle pancreatectomy: short-term results of a randomized controlled trial." Surg Endosc 31(2): 962-971. OBJECTIVE: This first prospective randomized controlled trial was performed to compare short-term outcomes of robot-assisted laparoscopic middle pancreatectomy (RA-MP) with open middle pancreatectomy (OMP). BACKGROUND: RA-MP is a novel minimally invasive surgical technique for benign or borderline tumors in the pancreatic neck or body. Its short-term effectiveness and safety remain unknown, compared to OMP. METHODS: Patients eligible for MP from August 2011 to November 2015 were randomized into the RA-MP or OMP group. The primary endpoint was length of hospital stay (LOS). Secondary endpoints were intraoperative parameters, and postoperative and recovery variables. RESULTS: A total of 100 patients were included into the study to analyze primary and secondary endpoints. Demographic characteristics and pathological	 Chen, S., et al. (2017). "Robot-assisted laparoscopic versus open middle pancreatectomy: short-term results of a randomized controlled trial." Surg Endosc 31(2): 962-971. *This study was not included in the review of robotic versus open pancreatectomy as it concerned middle pancreatectomy, which would not be used in patients with resectable pancreatic cancer.*

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				parameters were similar in both groups. Furthermore, LOS was significantly shorter (15.6 vs. 21.7 days, P = 0.002), median operative time was reduced (160 vs. 193 min, P = 0.002), median blood loss was lower (50 vs. 200 mL, P < 0.001), rate of clinical postoperative pancreatic fistula (POPF) was lower (18 vs. 36.0 %, P = 0.043), nutritional status recovery was better, off-bed return to activity was expedited (3.1 vs. 4.6 days, P < 0.001), and resumption of bowel movement was faster (3.5 vs. 5.0 days, P < 0.001) in the RA-MP group, compared to the OMP group. CONCLUSION: RA-MP was associated with significantly shorter LOS, reduced operative time, blood loss and clinical POPF rate, and expedited postoperative recovery, compared to OMP. Chen, Y., et al. (2013). "A meta-analysis of robotic-assisted pancreatectomy versus laparoscopic and open pancreatectomy." Saudi Med J 34(12): 1229-1236. OBJECTIVE: To perform a meta-analysis of eligible studies from multiple medical centers to assess the safety, feasibility, and efficacy of robotic-assisted pancreatectomy (RP).	Chen, Y., et al. (2013). "A meta-analysis of robotic-assisted pancreatectomy versus laparoscopic and open pancreatectomy." Saudi Med J 34(12): 1229-1236. *This review was excluded as it does not meet the inclusion criteria (it examines robotic versus laparoscopic or open pancreatectomy).*

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				METHODS: We searched the electronic databases PubMed and EMBASE for studies comparing RP with laparoscopic pancreatectomy (LP) and open pancreatectomy (OP) for patients with pancreatic disease from June 2009 to June 2012. Continuous variables were pooled using the standardized mean difference (SMD) and odds ratio (OR), and dichotomous variables were pooled using the risk difference (RD) method. For all analyses, the 95% confidence interval (CI) was calculated. Three studies comparing RP and LP, and 4 studies comparing RP and OP were suitable for meta-analysis. RESULTS: Six published studies met the inclusion criteria. Our results showed that RP can reduce estimated blood loss and duration of hospitalization more than OP. For pancreatic fistula, there were no statistical differences between RP, OP, and LP, and no significant differences in intraoperative conversion rates between RP and LP. Robotic-assisted pancreatectomy may be able to increase microscopic negative margins of resection (R0) and spleen preserving rates. CONCLUSION: Robotic-assisted pancreatectomy was associated with	

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				increased R0 resection rates and spleen preserving rates than LP and OP. Moreover, RP can reduce estimated blood loss and duration of hospitalization more than OP. A robotic approach to pancreatectomy may be suited to patients with pancreatic disease. De Rooij, T., et al. (2016). "Minimally Invasive Versus Open Pancreatoduodenectomy: Systematic Review and Meta-analysis of Comparative Cohort and Registry Studies." Annals of Surgery 264(2): 257-267. Objective: This study aimed to appraise and to evaluate the current evidence on minimally invasive pancreatoduodenectomy (MIPD) versus open pancreatoduodenectomy only in comparative cohort and registry studies. Background: Outcomes after MIPD seem promising, but most data come from single-center, noncomparative series. Methods: Comparative cohort and registry studies on MIPD versus open pancreatoduodenectomy published before August 23, 2015 were identified systematically and meta-analyses were performed. Primary endpoints were mortality and International Study Group on Pancreatic Fistula grade B/C postoperative	 de Rooij T, Lu MZ, Steen MW et al. (2016) Minimally invasive versus open pancreatoduodenectomy: systematic review and meta-analysis of comparative cohort and registry studies. Annals of Surgery 264(2): 257-67. *This review has been included in the updated minimally invasive versus open pancreatico-duodenectomy review.*

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				pancreatic fistula (POPF). Results: After screening 2293 studies, 19 comparative cohort studies (1833 patients) with moderate methodological quality and 2 original registry studies (19,996 patients) were included. For cohort studies, the median annual hospital MIPD volume was 14. Selection bias was present for cancer diagnosis. No differences were found in mortality [odds ratio (OR) = 1.1, 95% confidence interval (CI) = 0.6-1.9] or POPF [(OR) = 1.0, 95% CI = 0.8 to 1.3]. Publication bias was present for POPF. MIPD was associated with prolonged operative times [weighted mean difference (WMD) = 74 minutes, 95% CI = 29-118], but lower intraoperative blood loss (WMD=-385mL, 95% CI=-616 to -154), less delayed gastric emptying (OR = 0.6, 95%=CI 0.5-0.8), and shorter hospital stay (WMD=-3 days, 95% CI=-5 to -2). For registry studies, the median annual hospital MIPD volume was 2.5. Mortality after MIPD was increased in low-volume hospitals (7.5% vs 3.4%; P = 0.003). Conclusions: Outcomes after MIPD seem promising in comparative cohort studies, despite the presence of bias, whereas registry studies report higher mortality in low-	

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				volume centers. The introduction of MIPD should be closely monitored and probably done only within structured training programs in high-volume centers. Gavriilidis, P., et al. (2016). "Robotic versus laparoscopic distal pancreatectomy – The first meta-analysis." HPB 18(7): 567-574. Background Minimally invasive pancreaticoduodenectomy is considered hazardous for the majority of authors and minimally distal pancreatectomy is still a debated topic. The aim of this study was to compare robotic distal pancreatectomy (RDP) versus laparoscopic distal pancreatectomy (LDP) using meta-analysis. Method EMBASE, Medline and PubMed were searched systematically to identify full-text articles comparing robotic and laparoscopic distal pancreatectomies. The meta-analysis was performed by using Review Manager 5.3. Results Nine studies fulfilled the inclusion criteria and included 637 patients (246 robotic and 391 laparoscopic). RDP had a shorter hospital length of stay by 1 day (P = 0.01). On the other hand, LDP had shorter operative time by 30 min, although	 Gavriilidis, P., et al. (2016). "Robotic versus laparoscopic distal pancreatectomy – The first meta-analysis." HPB 18(7): 567-574. *This study was excluded as it does not meet the inclusion criteria (it compares robotic vs total laparoscopy).*

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				this was statistically nonsignificant (P = 0.12). RDP showed a significantly increased readmission rate (P = 0.04). There was no difference in the conversion rate, incidence of postoperative pancreatic fistula, International Study Group of Pancreatic Fistula grade B–C rate, major morbidity, spleen preservation rate and perioperative mortality. All surgical specimens of RDP reported R0 negative margins, whereas 7 specimens in the LDP group had affected margins. Conclusions In terms of feasibility, safety and oncological adequacy, there is no essential difference between the two techniques so far. The 30 min longer operative time of the RDP is due to the docking and undocking of the robot. The shorter length of stay by 1 day should be judged in combination with the increased 90-day readmission rate. © 2016 International Hepato-Pancreato-Biliary Association Inc. Huang, B., et al. (2016). "Systematic review and meta-analysis of robotic versus laparoscopic distal pancreatectomy for benign and malignant pancreatic lesions." Surg Endosc 30(9): 4078-4085.	 Huang, B., et al. (2016). "Systematic review and meta-analysis of robotic versus laparoscopic distal pancreatectomy for benign and malignant pancreatic lesions." Surg Endosc 30(9): 4078-4085. *This review was excluded as it does not*

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				BACKGROUND AND OBJECTIVE: The number of published series on minimally invasive distal pancreatectomy has significantly increased. Robotic systems can overcome some limitations of laparoscopy. This study aimed to compare two techniques in distal pancreatectomy. METHODS: Multiple electronic databases were systematically searched to identify studies (up to July 2015) that compared perioperative outcomes between robotic distal pancreatectomy (RDP) and laparoscopic distal pancreatectomy (LDP). Relative risks with 95 % confidence intervals (CIs) were estimated. RESULTS: Nine studies were enrolled in this review. Four studies reported on operative time, indicating no difference between the RDP and LDP groups (WMD = 21.55, 95 % CI -65.28-108.37, P = 0.63). No significant difference between the two groups was indicated with respect to the number of patients who converted to open (OR 0.35, 95 % CI 0.11-1.13, P = 0.08), spleen preservation rate (OR 2.37, 95 % CI 0.50-11.30, P = 0.28), and transfusion rate (OR 1.30, 95 % CI 0.54-3.13, P = 0.56). In addition, no difference was indicated in the	*meet the inclusion criteria (it examines robotic versus laparoscopic pancreatectomy).*

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				incidence of pancreatic fistulas (OR 1.05, 95 % CI 0.67-1.65, P = 0.83) and length of hospital stay between the two groups (WMD = -0.61, 95 % CI -1.40-0.19, P = 0.13). CONCLUSIONS: RDP seems to be a safe and effective alternative to LDP. Large randomized controlled trials are needed to verify the results of this meta-analysis. Konstantinidis, I. T., et al. (2017). "Minimally invasive distal pancreatectomy: greatest benefit for the frail." Surg Endosc. Objective: The benefits of minimally invasive distal pancreatectomy (MIDP) over open surgery continue to be investigated. Frailty is a known predictor of postoperative outcome. We hypothesized that the benefit of minimally invasive distal pancreatectomy is the greatest for the frailest of patients. Methods: Data from the pancreas-targeted National Surgical Quality Improvement Program (NSQIP) database for 2014 were reviewed. A modified frailty index (mFI) with 11 preoperative variables previously validated for use in NSQIP was used to determine the correlation between frailty and postoperative outcomes, including Clavien grade IV complications.	Konstantinidis, I. T., et al. (2017). "Minimally invasive distal pancreatectomy: greatest benefit for the frail." Surg Endoscopy. *This study was excluded as only RCTs and studies included in identified systematic reviews were included in the guideline review of minimally invasive versus open pancreatectomy.*

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				Patients were classified into non-frail (mFI = 0) or frail (mIF > 0), in which they were subclassified into mildly frail (mFI 1 or 2) or severely frail (mFI = 3). Results: A total of 1,038 distal pancreatectomies (DP) were included in the analysis, of which 387 were minimally invasive (MIDP: laparoscopic: 285, robotic: 102), 558 open DP (ODP), and 93 MIDP converted to open (MIDPcODP: laparoscopic: 80, robotic: 13). More than 90% of patients had an mFI of 0 or 1 (mFI 0 = 473 (45.6%), 1 = 466 (44.9%), 2 = 94 (9.1%), and 3 = 5 (0.5%), respectively). Overall, 4.6% of patients experienced Clavien grade IV complications and 1.1% a mortality. Non-frail patients experienced a similar rate of grade IV Clavien complications with MIDP vs. ODP vs. MIDPcOP (2.3 vs. 2.3 vs. 4.9%; p = 0.6), whereas frail patients (mFI > 0) had a lower rate of complications with MIDP (2.4 vs. 8.3 vs. 11.5; p = 0.007). Worsening frailty correlated with an increase in complications (non-frail: 2.5%; mildly frail: 6.3%; severely frail: 20%; p = 0.005). Conclusion: MIDP is associated with a lower risk of Clavien grade IV complications compared to ODP for frail patients, especially for benign disease. Thus,	

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				minimally invasive approach may mitigate risk in frail patients. © 2017 Springer Science+Business Media New York Lei, P., et al. (2014). "Minimally invasive surgical approach compared with open pancreaticoduodenectomy: a systematic review and meta-analysis on the feasibility and safety." Surg Laparosc Endosc Percutan Tech 24(4): 296-305. BACKGROUND:: Laparoscopic and robotic pancreaticoduodenectomy have started utilization tentatively; however, the clinical benefits are still controversial. This study aims to evaluate the safety and efficiency of minimally invasive pancreaticoduodenectomy. METHODS:: A systematic literature search was performed through PubMed, EMBASE, and Cochrane Library database without restriction to regions, publication types, or languages. Nine studies that compared laparoscopic/robotic with open pancreaticoduodenectomy were included. Fixed or random-effects models was used to measure the pooled estimates. Sensitivity and subgroup analysis were performed to evaluate the study quality. RESULTS:: Patients who underwent	Lei, P., et al. (2014). "Minimally invasive surgical approach compared with open pancreaticoduodenectomy: a systematic review and meta-analysis on the feasibility and safety." Surg Laparosc Endosc Percutan Tech 24(4): 296-305. *This review has been included in the updated review of minimally invasive versus open pancreaticoduodenectomy.*

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				minimally invasive pancreaticoduodenectomy experienced longer operative time (P=0.007), but the estimated blood loss (P=0.007), length of stay, (P=0.02), and wound infection (P=0.04) decreased. Perioperative complications, such as pancreatic fistula, delayed gastric emptying, hemorrhage, bile leakage, reoperation, and mortality, were of no significant differences. Pathologically, lymph node number was similar (P=0.11); meanwhile, margin R0 ratio was higher in minimally invasive approach group (P=0.03). Subgroup analysis manifested robotic surgery spent comparable surgical time (P=0.16) as laparotomy, with earlier discharge (P=0.04). CONCLUSIONS:: This meta-analysis indicates minimally invasive pancreaticoduodenectomy may be associated with shorter hospital stay, less estimated blood loss, and positive margin rate without compromising surgical safety as open surgery. Surgical duration of robotic method could even be equivalent as laparotomy. Minimally invasive approach can be a reasonable alternative to laparotomy pancreaticoduodenectomy with potential advantages. Nevertheless, future large-	

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				volume, well-designed RCTs with extensive follow-up are awaited to confirm and update the findings of this analysis. Orti-Rodríguez, R. J. (2012). "Is Robotic pancreatic surgery expected access by the minimal access pancreatic surgeons?" World Journal of Laparoscopic Surgery 5(1): 49-53. Objectives: Many surgeons have demonstrated the feasibility of laparoscopic pancreatoduodenectomies (PD), but benefits comparable to or even more prominent than those of an open procedure has not been clinically proven. Robotic surgery has improved some aspects of the laparoscopic approach. We compare both types of approach for PD. Methods: The literature was systematically reviewed to find all the PD procedures totally performed by a laparoscopic or by a robotic approach. Results: Between 1996 and 2012, 192 patients underwent a total laparoscopic PD and 109 a total robotic PD. The mean operating room time and mean estimated blood loss was 388.8 minutes and 178.7 ml for LG and 397.4 minutes and 319.06 ml for RG. Morbidity was found in 18 cases of RG	Orti-Rodríguez, R. J. (2012). "Is Robotic pancreatic surgery expected access by the minimal access pancreatic surgeons?" World Journal of Laparoscopic Surgery 5(1): 49-53. *This review was excluded as it does not meet the inclusion criteria (it examines robotic versus laparoscopic pancreaticoduodenectomy).*

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				and in 69 of LG. Mortality and conversion rates were similars in both arms. Conclusion: This review can not find clear difference between both groups in spite of the short literature available. Pedziwiatr, M., et al. (2017). "Minimally invasive versus open pancreatoduodenectomy-systematic review and meta-analysis." Langenbecks Arch Surg. PURPOSE: The purpose of this systematic review was to compare minimally invasive pancreatoduodenectomy (MIPD) versus open pancreatoduodenectomy (OPD) by using meta-analytical techniques. METHODOLOGY: Medline, Embase, and Cochrane Library were searched for eligible studies. Data from included studies were extracted for the following outcomes: operative time, overall morbidity, pancreatic fistula, delayed gastric emptying, blood loss, postoperative hemorrhage, yield of harvested lymph nodes, R1 rate, length of hospital stay, and readmissions. Random and fix effect meta-analyses were undertaken. RESULTS: Initial reference search yielded 747 articles. Thorough evaluation resulted in 12 papers, which were analyzed. The total number of	Pędziwiatr M, Małczak P, Pisarska M et al. (2017) Minimally invasive versus open pancreatoduodenectomy—systematic review and meta-analysis. Langenbeck's Archives of Surgery 402(5): 841-851. *This review has been included in the updated review of minimally invasive versus open pancreaticoduodenectomy.*

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				patients was 2186 (705 in MIPD group and 1481 in OPD). Although there were no differences in overall morbidity between groups, we noticed reduced blood loss, delayed gastric emptying, and length of hospital stay in favor of MIPD. In contrary, meta-analysis of operative time revealed significant differences in favor of open procedures. Remaining parameters did not differ among groups. CONCLUSION: Our review suggests that although MIPD takes longer, it may be associated with reduced blood loss, shortened LOS, and comparable rate of perioperative complications. Due to heterogeneity of included studies and differences in baseline characteristics between analyzed groups, the analysis of short-term oncological outcomes does not allow drawing unequivocal conclusions. Peng, L., et al. (2016). "Systematic review and meta-analysis of robotic versus open pancreaticoduodenectomy." Surg Endosc. BACKGROUND: Although robotic pancreaticoduodenectomy (RPD) has been successfully performed since 2003, its advantages over open	 Peng, L., et al. (2016). "Systematic review and meta-analysis of robotic versus open pancreaticoduodenectomy." Surg Endosc. *This review has been included in the updated review of minimally invasive versus open pancreaticoduodenectomy.*

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				pancreaticoduodenectomy (OPD) are still uncertain. The aim of this systematic review and meta-analysis was to compare the clinical outcomes of RPD to those of OPD. METHODS: A systematic literature review was performed to identify RPD versus OPD comparative studies published between January 2003 and January 2016. Intraoperative outcomes, post-operative outcomes and oncologic safety were evaluated. Pooled odds ratios (ORs) and weighted mean differences (WMDs) with a 95% confidence interval (95% CI) were calculated using fixed-effect or random-effect models. RESULTS: Nine non-randomized observational clinical studies involving 680 patients met the inclusion criteria and involved 245 RPDs and 435 OPDs. The overall complication rate was significantly lower in RPD (OR 0.65, 95% CI 0.47-0.91, P = 0.012), as well as the margin positivity rate (OR 0.40, 95% CI 0.20-0.77, P = 0.006), the wound infection rate (OR 0.18, 95% CI 0.06-0.53, P = 0.002) and the length of hospital stay (WMD = -6.00, 95% CI -9.80 to -2.21, P = 0.002). There was no significant difference in the following: the number of lymph nodes	

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				harvested; the operation time; the reoperation rate; the incidence of delayed gastric emptying, bile leakage, pancreatic fistula and clinically significant pancreatic fistula; and mortality. The mean conversion rate was 7.3% (range 0-14%). CONCLUSIONS: According to the results of this meta-analysis, RPD is as safe and efficient as OPD and is even favourable in terms of margin-negative resection, overall complication and wound infection rates and length of hospital stay. Given that there have not yet been any high-quality randomized controlled trials (RCTs), the evidence is still limited. Additional prospective, multi-centre RCTs are needed to further define the role of the robotic technique in PD. Shin, S. H., et al. (2016). "Totally laparoscopic or robot-assisted pancreaticoduodenectomy versus open surgery for periampullary neoplasms: separate systematic reviews and meta-analyses." Surg Endosc. OBJECTIVE: To compare perioperative and oncologic outcomes of pure (totally) laparoscopic pancreaticoduodenectomy (TLPD) or robot-assisted	 Shin SH, Kim YJ, Song KB et al. (2017) Totally laparoscopic or robot-assisted pancreaticoduodenectomy versus open surgery for periampullary neoplasms: separate systematic reviews and meta-analyses. Surgical Endoscopy 31(9): 3459-3474. *This review has been included in the minimally invasive versus open pancreaticoduodenectomy review.*

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				pancreaticoduodenectomy (RAPD) with those of conventional open pancreaticoduodenectomy (OPD). METHODS: A systematic literature search was performed using PubMed, EMBASE, and Cochrane library databases. Studies comparing TLPD with OPD and RAPD with OPD were included; only original studies reporting more than 10 cases for each technique were included. Studies were combined using a random-effects model to report heterogeneous data, or a fixed-effects model was applied. RESULTS: TLPD involved longer operative time (weighted mean difference [WMD]: 116.85 min; 95% confidence interval [CI] 54.53-179.17) and significantly shorter postoperative hospital stay (WMD: -3.68 days; 95% CI -4.65 to -2.71). Overall morbidity and postoperative pancreatic fistula were not significantly different between TLPD and OPD. RAPD was associated with a longer operative time, less intraoperative blood loss, and shorter hospital stay. Oncologic outcomes were not significantly different among the procedure types. CONCLUSIONS: Compared to OPD, TLPD and RAPD were feasible and	

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				oncologically safe procedures. However, there are no prospective studies, and the majority of the studies on TLPD and RAPD have remained in the early training phase. In addition to randomized controlled trials or prospective studies, new data from the late training phase of learning experiences should also be analyzed. Wright, G. P. and A. H. Zureikat (2016). "Development of Minimally Invasive Pancreatic Surgery: an Evidence-Based Systematic Review of Laparoscopic Versus Robotic Approaches." J Gastrointest Surg 20(9): 1658-1665. INTRODUCTION: Laparoscopic and robotic surgery of the pancreas has only recently emerged as viable treatment options for benign and malignant disease. This review seeks to evaluate the current body of evidence on these approaches to pancreaticoduodenectomy and distal pancreatectomy. METHODS: A systematic review of large published series was performed utilizing the PubMed search engine. RESULTS: Based on these reports, both the laparoscopic and robotic techniques for these complex procedures appear to be	 Wright, G. P. and A. H. Zureikat (2016). "Development of Minimally Invasive Pancreatic Surgery: an Evidence-Based Systematic Review of Laparoscopic Versus Robotic Approaches." J Gastrointest Surg 20(9): 1658-1665. *This review was excluded as it does not meet the inclusion criteria (it examines robotic versus laparoscopic pancreatectomy).*

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				safe and effective, if performed by high volume experienced pancreatic surgeons. The advantages of each approach are highlighted, emphasizing the data available on the learning curve and potential dissemination. CONCLUSIONS: Both minimally invasive approaches to pancreatic resection are safe and feasible. Xourafas, D., et al. (2017). "Comparison of Perioperative Outcomes between Open, Laparoscopic, and Robotic Distal Pancreatectomy: an Analysis of 1815 Patients from the ACS-NSQIP Procedure-Targeted Pancreatectomy Database." J Gastrointest Surg. BACKGROUND: Robotic surgery is gaining acceptance for distal pancreatectomy (DP). Nevertheless, no multi-institutional data exist to demonstrate the ideal clinical circumstances for use and the efficacy of the robot compared to the open or laparoscopic techniques, in terms of perioperative outcomes. METHODS: The 2014 ACS-NSQIP procedure-targeted pancreatectomy data for patients undergoing DP were analyzed. Demographics and clinicopathological and perioperative	Xourafas, D., et al. (2017). "Comparison of Perioperative Outcomes between Open, Laparoscopic, and Robotic Distal Pancreatectomy: an Analysis of 1815 Patients from the ACS-NSQIP Procedure-Targeted Pancreatectomy Database." J Gastrointest Surg. *This study was excluded as only RCTs and systematic reviews were included in the guideline review of minimally invasive versus open pancreatectomy.*

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				variables were compared between the three approaches. Univariate and multivariable analyses were used to evaluate outcomes. RESULTS: One thousand eight hundred fifteen DPs comprised 921 open distal pancreatectomies (ODPs), 694 laparoscopic distal pancreatectomies (LDPs), and 200 robotic distal pancreatectomies (RDPs). The three groups were comparable with respect to demographics, ASA score, relevant comorbidities, and malignant histology subtype. Compared to the ODP group, patients undergoing RDP had lower T-stages of disease (P = 0.0192), longer operations (P = 0.0030), shorter hospital stays (P < 0.0001), and lower postoperative 30-day morbidity (P = 0.0476). Compared to the LDP group, RDPs were longer operations (P < 0.0001) but required fewer concomitant vascular resections (P = 0.0487) and conversions to open surgery (P = 0.0068). On multivariable analysis, neoadjuvant therapy (P = 0.0236), malignant histology (P = 0.0124), pancreatic reconstruction (P = 0.0006), and vascular resection (P = 0.0008) were the strongest predictors of performing an ODP. CONCLUSIONS: The open,	

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				laparoscopic, and robotic approaches to distal pancreatectomy offer particular advantages for well-selected patients and specific clinicopathological contexts; therefore, clearly demonstrating the most suitable use and superiority of one technique over another remains challenging. Zhang, J., et al. (2013). "Robotic versus open pancreatectomy: a systematic review and meta-analysis." Ann Surg Oncol 20(6): 1774-1780. BACKGROUND: Robotic surgery is gaining momentum with advantages for minimally invasive management of pancreatic diseases. The objective of this meta-analysis is to compare the clinical and oncologic safety and efficacy of robotic versus open pancreatectomy. METHODS: A systematic review of the literature was performed to identify studies comparing robotic pancreatectomy and open pancreatectomy. Postoperative outcomes, intraoperative outcomes, and oncologic safety were evaluated. Meta-analysis was performed using a random-effect model. RESULTS: Seven studies matched the selection criteria, including 137 (40 %) cases of robotic	 Zhang, J., et al. (2013). "Robotic versus open pancreatectomy: a systematic review and meta-analysis." Ann Surg Oncol 20(6): 1774-1780. *This systematic review and meta-analysis was included in the guideline.*

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				pancreatectomy and 203 (60 %) cases of open pancreatectomy. None of the included studies were randomized. Overall complication rate was significantly lower in robotic group [risk difference (RD) = -0.12, 95 % confidence interval (CI) -0.22 to -0.01, P = 0.03], as well as reoperation rate (RD = -0.12; CI -0.2 to -0.03, P = 0.006) and margin positivity (RD = -0.18; 95 % CI -0.3 to -0.06, P = 0.003). There was no significant difference in postoperative pancreatic fistula (POPF) incidence and mortality. The median (range) conversion rate was 10 % (0-12 %). CONCLUSIONS: The results of this meta-analysis suggest that robotic pancreatectomy is as safe and efficient as, if not superior to, open surgery for patients with benign or malignant pancreatic diseases. However, the evidence is limited and more randomized controlled trials are needed to further clearly define this role. Zhou, J. Y., et al. (2016). "Robotic versus Laparoscopic Distal Pancreatectomy: A Meta-Analysis of Short-Term Outcomes." PLoS One 11(3): e0151189.	 Zhou, J. Y., et al. (2016). "Robotic versus Laparoscopic Distal Pancreatectomy: A Meta-Analysis of Short-Term Outcomes." PLoS One 11(3): e0151189. *This review was excluded as it*

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				AIM: To compare the safety and efficacy of robotic-assisted distal pancreatectomy (RADP) and laparoscopic distal pancreatectomy (LDP). METHODS: A literature search of PubMed, EMBASE, and the Cochrane Library database up to June 30, 2015 was performed. The following key words were used: pancreas, distal pancreatectomy, pancreatic, laparoscopic, laparoscopy, robotic, and robotic-assisted. Fixed and random effects models were applied. Study quality was assessed using the Newcastle-Ottawa Scale. RESULTS: Seven non-randomized controlled trials involving 568 patients met the inclusion criteria. Compared with LDP, RADP was associated with longer operating time, lower estimated blood loss, a higher spleen-preservation rate, and shorter hospital stay. There was no significant difference in transfusion, conversion to open surgery, R0 resection rate, lymph nodes harvested, overall complications, severe complications, pancreatic fistula, severe pancreatic fistula, ICU stay, total cost, and 30-day mortality between the two groups. CONCLUSION: RADP is a safe and feasible alternative to	*does not meet the inclusion criteria (it examines robotic versus laparoscopic pancreatectomy).*

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				LDP with regard to short-term outcomes. Further studies on the long-term outcomes of these surgical techniques are required. CORE TIP: To date, there is no consensus on whether laparoscopic or robotic-assisted distal pancreatectomy is more beneficial to the patient. This is the first meta-analysis to compare laparoscopic and robotic-assisted distal pancreatectomy. We found that robotic-assisted distal pancreatectomy was associated with longer operating time, lower estimated blood loss, a higher spleen-preservation rate, and shorter hospital stay. There was no significant difference in transfusion, conversion to open surgery, overall complications, severe complications, pancreatic fistula, severe pancreatic fistula, ICU stay, total cost, and 30-day mortality between the two groups. Zureikat, A. H., et al. (2017). "Minimally invasive hepatopancreatobiliary surgery in North America: an ACS-NSQIP analysis of predictors of conversion for laparoscopic and robotic pancreatectomy and hepatectomy." HPB (Oxford). Background: Procedural conversion rates represent an important aspect of the	 Zureikat, A. H., et al. (2017). "Minimally invasive hepatopancreatobiliary surgery in North America: an ACS-NSQIP analysis of predictors of conversion for laparoscopic and robotic pancreatectomy and hepatectomy." HPB (Oxford). *This review was excluded as it does*

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				feasibility of minimally invasive surgical (MIS) approaches. This study aimed to outline the rates and predictors of procedural completion/conversion for MIS hepatectomy and pancreatectomy. Methods: All 2014 ACS-NSQIP laparoscopic and robotic hepatectomy and pancreatectomy procedures were identified and grouped into pure, open assist, or unplanned conversion to open. Risk adjusted multinomial logistic regression models were generated with completion (Pure) set as the primary outcome. Results: 1667 (laparoscopic = 1360, robotic = 307) resections were captured. After risk adjustment, robotic DP was associated with similar open assist (relative risk ratio -1.9%, P = 0.602), but lower unplanned conversion (-8.2%, P = 0.004) and open assist + unplanned conversion (-10.1%, P = 0.015) compared to laparoscopic DP; while robotic PD was associated with lower open assist (-22.2%, P < 0.001), unplanned conversions (-15%, P = 0.006) and open assist + unplanned conversions (-37.2, P < 0.001) compared to laparoscopic PD. The robotic and laparoscopic approaches to hepatectomy	*not meet the inclusion criteria (it examines robotic versus laparoscopic pancreatectomy).*

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				were not associated with differences in pure MIS completion rates (P = NS) after risk adjustment. Conclusions: The robotic approach to pancreatectomy was associated with higher rates of pure MIS completion compared to laparoscopy, whereas no difference in MIS completion rates was noted for robotic versus laparoscopic hepatectomy. © 2017 International Hepato-Pancreato-Biliary Association Inc.	
Intuitive Surgical	All	General	General	In case it helps, Intuitive's Literature Review Methods for Systematic Review (FDA submission): Literature Review Methods (Pancreatectomy) MONTHLY LITERATURE SEARCH STRATEGY AND ROBOTIC LIBRARY Monthly searches were run using PubMed and Scopus databases pursuant to Intuitive Surgical Work Instruction #1008450. The specific searches were conducted as described below. PubMed: (robotic[All Fields] OR robot assist[All Fields] OR robotically assisted[All Fields] OR robot-assist[All Fields] OR da vinci[All Fields] OR	Thank you for providing information about the search strategy and inclusion/exclusion criteria used to identify studies related to robotic pancreatectomy. As described in responses to other comments, the focus of the evidence review was on minimally invasive versus open pancreaticoduodenectomy, and minimally invasive robotic versus open pancreatectomy rather than comparing different modes of minimally invasive surgery (i.e. laparoscopic versus robotic). The committee decided to focus on these comparisons because there is insufficient experience with robotic surgery in this setting in current UK practice. Our search

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				"davinci"[All Fields] OR intuitive surgical[All Fields] OR ("robotic"[All Fields] AND "surgery"[all fields]) Scopus: "TITLE-ABS-KEY(da*vinci) OR (robotic surgery) OR ("intuitive surgical") OR (robotic assist*) OR (robot*surgery) OR (robotic-assist*) All citations returned from the above searches were exported into an EndNote library, duplications were removed and titles and abstracts were reviewed by Intuitive Surgical Clinical Affairs personnel knowledgeable in robotic literature for inclusion to the library. The inclusion criterion was met if the publication was related to *da Vinci*-assisted robotic surgery. This search process is repeated on a monthly basis with selected citations imported into the EndNote robotic library.	terms therefore related to the surgery types themselves, i.e. pancreaticoduodenectomy, pancreatectomy, Whipple etc. rather than the details of the robotic or laparoscopic procedures. From the retrieved references, cited in other comments from the stakeholder, it appears as if the population searched for was wider than the guideline searches (i.e. some of the references cited in the comments are not directly related to people with pancreatic cancer). Please see guideline Appendix C for the relevant review protocol and Appendix D for the corresponding search strategy.

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				SELECTION PROCESS FOR LITERATURE SEARCH CONDUCTED FOR ROBOTIC-ASSISTED PANCREATECTOMY. This search of the library was conducted on June 12th, 2017. The library was searched for literature published between January 1, 2010 and May 31st, 2017 for the following criteria: Inclusion criteria: 1. Robotic-assisted pancreatectomy/ pancreaticoduodenectomy procedure 2. Publication between January 1, 2010 and May 31st, 2017 3. Level of Evidence (≤ 2a) 4. Study is a RCT, Meta-Analysis / Systematic Review, or independent database study reporting on Robotic and Lap and/or Open surgery Exclusion criteria (applied in order listed): 1. Not in English 2. Paper reports on a pediatric population 3. Publication is an HTA that was not published in a peer reviewed journal	

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				4. Alternate technique/approach (e.g. single-port, hand-assist, etc.) 5. No stratified analysis by study arm (e.g. combines results from robotic, laparoscopic and/or open cohorts) 6. Pancreatectomy data mixed with other procedures (e.g. data from multiple surgical procedures combined) 7. Original research study does not provide quantitative results or a review paper does not provide meta/summary analysis for at least one of the findings relative to the outcomes of interest (i.e, operative time, conversions, estimated blood loss and/or transfusions, complications, length of hospital stay, mortality) 8. Original research publication includes redundant patient population and similar conclusions	

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				9. Study is a review paper that only includes redundant publications and similar conclusions Robotic-Assisted Pancreatectomy Flowchart (search dates January 1st, 2010 through April 30th, 2017)	
Intuitive Surgical	Full	379 384 389 391	10.2.6.1 (starting line 8) 10.2.6.4 (starting line 7) 10.2.8 (starting line 9) 10.2.9 (starting line 41)	The entirety of the evidence for a lack of differences between surgical approaches rests on two systematic reviews, one for pancreaticodudonectomy (Doula 2016, where the assessors of the evidence chose to mix robotic and lap data that were reported separately) and one for pancreatectomy (Zhang 2013). It is not clear why they chose to analyze the primary papers from these reviews separately, since the Zhang paper includes 4 primary papers that report on pancreaticoduodenectomy, 1 on distal, 1 on neck/body, and 1 on neck/pancreaticoduodenectomy. The other 9 papers cited in the resectable cancer section did not have to do with surgical approach and did not include robotic cases. NICE included RCTs and systematic reviews only (no database papers) and did not compare robotic assisted surgery and lap	Thank you for your comment. The focus of the evidence review was on minimally invasive versus open pancreaticoduodenectomy, and minimally invasive robotic versus open pancreatectomy rather than comparing different modes of minimally invasive surgery (i.e. laparoscopic versus robotic). The committee decided to focus on these comparisons because there is insufficient experience with robotic surgery in this setting in current UK practice. We have assessed the references that you provided and the evidence has been updated in light of the citations kindly provided in the comment. Regarding the review of minimally invasive (laparoscopic or robotic) pancreaticoduodenectomy versus open pancreaticoduodenectomy, 19 studies from 5

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					systematic reviews have been added. For outcomes in which there was substantial heterogeneity (i.e. where I^2>50%), a random effects analysis has been used and a subgroup analysis by type of surgery (i.e. laparoscopic or robotic) conducted. As pointed out in the comment, the studies that comprise the meta-analysis of Zhang et al. 2013 include 4 studies on robotic versus open pancreaticoduodenectomy. These studies (Buchs et al. 2011; Chalikonda et al. 2012; Hammill et al. 2010; Zhou et al. 2011) have been removed from the evidence for this comparison as they have been included in the minimally invasive versus open pancreaticoduoden-ectomy review. Due to the inclusion of the systematic review of de Rooij et al. 2016, 3 database papers have now been included in the review of minimally invasive (laparoscopic or robotic) pancreaticoduodenectomy versus open pancreaticoduodenectomy. The committee reviewed and considered the updated evidence but decided not to change its

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					recommendations on the basis of this. They agreed that they could not make a recommendation related to robotic surgery for the following reasons. (i) This was not the focus of the evidence review (which was minimally invasive compared to open surgery). There is little experience of robotic surgery in this setting in current UK practice. (ii) According to GRADE criteria, even with the additional studies, the evidence was still assessed as being of very low quality. The committee made a research recommendation for randomised controlled trials comparing minimally invasive with open pancreatectomy/pancreaticoduodenectomy to be conducted.
Intuitive Surgical	Appendix D	5		There is a typo in the header for the resectable pancreatic cancer section. It reads: "Management of resectable and unrespectable pancreatic cancer	Thank you for your comment. We have amended this accordingly.
Intuitive Surgical	Appendix D	56		There is a typo in the header for the resectable pancreatic cancer section. It reads: "Management of resectable and unrespectable pancreatic cancer	Thank you for your comment. We have amended this accordingly.
Nutrition Interest Group of the	Short	5	10	Would it be possible to include a definition of the composition of a multidisciplinary team? There are multidisciplinary teams that do not include the full	Thank you for your comment. The guideline review question focused on whether referral to a specialist multidisciplinary team would improve

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Pancreatic Society (NIGPS)				complement of clinical nurse specialists or dietitians, and lack of access to psychology, which may be improved with a statement defining the multidisciplinary team. Whilst it is widely recognised that there needs to be improved funding for these disciplines, ubt without inclusion of dietitians in the IOG documentation	management and outcome. The composition of a multidisciplinary team was not part of this question and therefore we have not reviewed the evidence base on it and are unable to make any recommendations. The committee did not prioritise multidisciplinary team composition as a separate review question because specialist pancreatic multidisciplinary teams already exist.
Nutrition Interest Group of the Pancreatic Society (NIGPS)	Short	7	4	We welcome this recommendation, this will improve nutritional status and quality of life in many patients.	Thank you for your comment in support of the guideline.
Nutrition Interest Group of the Pancreatic Society (NIGPS)	Short	7	6	The statement on fish oils appears strong given the lack of evidence. Some believe there is still potential for these products, given that many trials were analysed on 'an intention to treat' basis, which, given there is a dose requirement, and data should be analysed in those who achieved the required dose. In addition, there was very little use of pancreatic enzyme replacement therapy in these patient cohorts, so a lipid based supplement may not be well absorbed until exocrine insufficiency is corrected. Perhaps inclusion of this in the second research recommendation could be considered?	Thank you for your comment. The committee reviewed the evidence for fish oils as a nutritional intervention. It was found not to reduce weight loss. The quality of the evidence base was moderate which means that even though there was some uncertainty, it is a relatively robust finding. The committee therefore agreed to make a strong recommendation against the specific use of fish oils for managing weight loss in people with unresectable pancreatic cancer. They discussed the stakeholder comment but concluded that the recommendation should remain as it is. Given

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					that some research had already been identified which did not find this to be effective the committee decided not to prioritise this for further research.
Nutrition Interest Group of the Pancreatic Society (NIGPS)	Short	7	1	Patient feedback and clinical experience has highlighted that access to dietetics is varied across England and Wales, and often patients are seen outside of specialist centres. HPB dietetics has recently emerged as a sub specialty of dietetics. Future studies evaluating individualised nutritional counselling should include the experience/ education level of the dietitian providing advice so that distinction can made between specialist and non specialist advice. While there is increasing interest in treatment strategies for malnutrition in pancreatic cancer patients, focus should also be directed to the aetiology which is not fully understood.	Thank you for your comment. The committee recognised that further research in this area is needed and therefore made a research recommendation about the effectiveness of nutritional interventions (including pancreatic enzyme replacement, types of feed, route of administration, timing). The committee decided that unless the effectiveness of such interventions were established they could not add dietetic advice as an intervention in the research recommendation because the content of such advice would be too uncertain. However, the committee agreed that such research would help to improve nutritional support to people with pancreatic cancer. If, or when, the effectiveness is established it will have an impact on access to such services. The committee agreed that a better understanding of the aetiology of malnutrition may improve treatment strategies, but this was outside the scope of this guideline.
Nutrition Interest Group of the	Short	9	10	We are delighted to see this. This will require additional staffing for clinical nurse specialists and dietitians. A definition of what this specialist input	Thank you for your comment. The committee agreed that additional open access to specialist services should be available to provide

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Pancreatic Society (NIGPS)				should include would be helpful to support this desperately needed service.	information and support (in line with advice from NHS England's enhanced recovery programmes). However, there was not enough evidence to state what the ongoing specialist assessment and care should consist of. Due to this lack of evidence the committee was unable to make recommendations about what assessments should be done and frequency of follow-up. The committee discussed that tests and follow-up frequency would vary depending on too many factors (e.g. complexity of surgery, types of symptoms, and the patient's age) and wanted to leave this to clinical judgement. This is described in Section 10.4.8 of the full guideline and its subsections. After further discussion, the committee agreed that no definition could be provided.
Nutrition Interest Group of the Pancreatic Society (NIGPS)	Short	14	18	More emphasis needs to be placed on accurate body composition methods. The majority of patients presenting with pancreatic cancer have (or had!) an elevated BMI. While weight stabilisation may still be beneficial in those with extensive weight loss, increasing fat mass (particularly intra-muscular fat) may impair muscle function and contractility further in sarcopenic patients. Lean tissue measurement, rather than BMI, should be considered as an outcome measurement in studies evaluating	Thank you for your comment. We have now added 'lean tissue mass' to the list of outcomes for this research recommendation.

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				nutritional intervention in patients with pancreatic cancer.	
Pancreatic Cancer UK, Pancreatic Cancer Action and the Pancreatic Cancer Research Fund	N/A	N/A	N/A	All of the following comments are informed by survey responses from pancreatic cancer patients, carers, medical professionals and researchers, all of whom were consulted by Pancreatic Cancer UK between 21 August and 11 September 2017. Pancreatic Cancer Action and the Pancreatic Cancer Research Fund support this consultation response, which has been prepared by Pancreatic Cancer UK.	Thank you for your comment. Responses to the specific issues raised are provided below.
Pancreatic Cancer UK, Pancreatic Cancer Action and the Pancreatic Cancer Research Fund	Full	55	21-22	Question 1: One concern raised in response to our survey was that recommendation 2 would be challenging to implement for patients who are not fit enough for an endoscopic ultrasound (EUS). Question 3: Those who raised this concern suggested endoscopic retrograde cholangiopancreatography (ERCP) should be offered instead in such circumstances.	Thank you for your comment. Based on their knowledge and experience the committee agreed that endoscopic retrograde cholangiopancreatography (ERCP) is associated with higher morbidity and mortality than endoscopic ultrasound (EUS). Therefore it would not be a suitable option for patients who were not fit enough for EUS. However, for these people, a PET/CT scan would be another non-invasive option which the committee has now recommended.
Pancreatic Cancer UK, Pancreatic	Full	72	35-38	Pancreatic Cancer UK's specialist nurses who work on its support line felt recommendations 4 and 5 are particularly welcome and could help ensure more	Thank you for your comment. In relation to the concern raised about availability of endoscopic ultrasound (EUS), the committee agreed that

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Cancer Action and the Pancreatic Cancer Research Fund				people are diagnosed at an earlier stage with greater prospect of life-saving treatment, given that jaundice is found to be a late symptom resulting from occlusion of the common bile duct (OCD). Question 1: One concern raised in response to our survey of health professionals was that relevant staff may not necessarily know where endoscopic ultrasound (EUS) should take place. Question 3: One suggestion received in our survey was that the guidelines should specify that EUS should include the full chest, abdomen and thorax.	people with pancreatic cancer would have access to pancreatic cancer centres and all of these would already have access to EUS. The committee believed that the relevant staff would know where this would take place. EUS of the pancreas is a procedure that involves endoscopic scanning of the pancreas and does not involve the abdomen, chest or thorax. The committee therefore did not specify this in its recommendation.
Pancreatic Cancer UK, Pancreatic Cancer Action and the Pancreatic Cancer Research Fund	Full	113	23-35	Question 1: Recommendations 6-10 were seen to be providing needed guidance by Pancreatic Cancer UK's specialist nurses and other responding health professionals, but some felt the recommendations could be even more positively impactful on practice if they included guidance on a surveillance programme. A medical professional also felt the recommendations lacked guidance on a preferred approach for non-high risk cysts. Question 3: For recommendations 6-10, consider giving direction on surveillance programmes.	Thank you for your comment. The committee focused on the most effective diagnostic pathway to identify pancreatic cysts at high risk of being malignant. Given the wide variety of pancreatic cystic lesions and the fact that pancreatic cysts are relatively commonplace the committee believed that a focus on high-risk cysts was the main priority for clinical practice. A surveillance programme related to all pancreatic cysts (including low-risk cysts) was therefore not covered. Please see Section 5.3.8 of the full guideline and its subsections which elucidate the decision-making process of the committee

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					regarding recommendations related to pancreatic cysts.
Pancreatic Cancer UK, Pancreatic Cancer Action and the Pancreatic Cancer Research Fund	Full	131	36-38	Question 1: Europac currently offers screening for people with two or more first-degree relatives with pancreatic cancer, rather than the three such relatives specified in the draft recommendation. Therefore, we are concerned that recommendation 13 could impact negatively on the number of people who are screened for pancreatic cancer and manage to catch the disease at a stage when their life can still be saved. Question 3: We encourage NICE to consider revising recommendation 13, in light of Europac's practice, to say '2 or more' rather than '3 or more'.	Thank you for your comment. The committee discussed this and revised its recommendation to '2 or more first-degree relatives' based on the EUROPAC inclusion criteria as well as the statement of the 'International Cancer of the Pancreas Screening (CAPS) Consortium' (Canto et al. 2012). We have also updated the related 'evidence to recommendations' section of the full guideline (Section 5.4.8) to reflect this change.
Pancreatic Cancer UK, Pancreatic Cancer Action and the Pancreatic Cancer Research Fund	Full	131 / 132	31-40 / 1-4 respectively	Question 1: In our survey, we were told by some that recommendations 12-15 risked a negative impact, as the recommendations lacked any specification of the need to consider the sensitivity, specificity and risks to the individual patient for the different surveillance measures recommended. Pancreatic Cancer UK's Patient Charter, written in light of the charity's experience supporting countless people with the disease, argues that patients must have their treatment options sensitively and clearly communicated to them as part of a minimum standard of care.	Thank you for your comment. The committee agreed that the evidence on the diagnostic yield of CT, MRI and endoscopic ultrasound (EUS) for surveillance in people with an inherited high risk of pancreatic cancer had shown they were all accurate at identifying early tumours. However, from the available evidence the committee could not identify which of these investigations was the most effective. The Committee also noted that repeated CT scanning would expose people to harms associated with radiation and therefore did not want to recommend this as an option for

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				Question 3: Add greater detail of the considerations that should be made before a patient is considered for / offered a particular surveillance option. Give guidance to health professionals on how to consider the pros and cons of options for each type of patient, and link to advice on how to communicate these options in a sensitive and clear manner, as per the suggestions in comment 8 below taken from Pancreatic Cancer UK's Patient Charter.	people without hereditary pancreatitis in whom a larger percentage of people would have a relatively smaller risk. However, the committee agreed that a pancreatic protocol CT scan for pancreatic cancer surveillance should be considered for people with hereditary pancreatitis and a PRSS1 mutation who would be at higher risk of developing pancreatic cancer. The committee also agreed that sensitive communication, information provision (including conversations about the pros and cons of any investigation or treatment that are tailored to individual needs) and support are principles of good standards of practice in the NHS. These principles are covered in the NICE guideline 'Patient experience in adult NHS services' CG138 (2012) to which the pancreatic cancer guideline cross-refers in Section 8.1.7 of the full guideline (in the chapter on support needs).
Pancreatic Cancer UK, Pancreatic Cancer Action and the Pancreatic	Full	186 / 187	35-42 / 1-5 respectively	In case it is useful to note, our survey respondents unanimously agreed that recommendations 19 and 20 were correct and would have a positive impact. For example, a health professional who responded said: "It is very beneficial to assess the patient from a holistic point of view to ensure comprehensive care (is) given." A patient who responded to our survey	Thank you for your comment. The committee noted that the two studies supported the conclusions in the guideline. The studies were not included in the guideline because of their study design or population. • Lee et al. (2012) summarises abstracts presented at the ASCO Gastrointestinal

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Cancer Research Fund				also pointed out that the benefits of these recommendations would extend beyond those with the disease: "I and numerous other pancreatic cancer patients suffer from most of these symptoms with little or no support. They will be beneficial for me as a patient and also for partners as my wife has also struggled with the shock of initial diagnosis and ongoing problems." In addition to the evidence considered by the Committee, the case for recommendations 19 and 20 is bolstered by the following two studies: (i) Lee, V., Cheng, H., and Saif, MW, 2012. 'Quality of life in patients with pancreatic cancer', Journal of the Pancreas (JOP) 13 (2), 182-4. (ii) Jennifer S. Temel, M.D., Joseph A. Greer, Ph.D., Alona Muzikansky, M.A., Emily R. Gallagher, R.N., Sonal Admane, M.B., B.S., M.P.H., Vicki A. Jackson, M.D., M.P.H., Constance M. Dahlin, A.P.N., Craig D. Blinderman, M.D., Juliet Jacobsen, M.D., William F. Pirl, M.D., M.P.H., J. Andrew Billings, M.D., and Thomas J. Lynch, M.D., 2010. 'Early palliative care for patients with metastatic	Cancers Symposium which means that it did not match study design criteria. • Temel et al. (2012) relates to palliative care of cancer patients (i.e. any cancer type) which means that it did not meet the population criteria of the protocol.

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				non-small-cell lung cancer', The New England Journal of Medicine, 19 August; Whilst the second study is for a different tumour type, there are similarities, such as poor short-term prognoses, which may make it of sufficient interest to the Committee. The study found that patients who received early palliative care went on to receive less aggressive care at the end of life and experienced longer survival. A nurse for Pancreatic Cancer UK's support line said that, "Anecdotally on the support service I would say most of these points in recommendation 19 are not addressed adequately…If implemented, patients will feel more supported, holistic care will be put into place, and they will be able to treat the whole person, not just the physical aspect." Question 1: In order to refer patients to the most appropriate care, evaluate the impact of these recommended measures and log variation in delivery, some survey respondents expressed an interest in improving Quality of Life measures for pancreatic cancer patients. NICE may wish to	The committee discussed the stakeholder comment that results from the study by Temel et al. (2012) could be generalised to people with pancreatic cancer. However, the population was too wide to extrapolate to the specific needs of people with pancreatic cancer. The committee therefore did not include this evidence in their deliberations for the recommendations. The committee agreed with the stakeholder that there are considerable unmet support needs and the aim of the recommendations in this section is to raise awareness about the psychological impact.

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				consider adding this to recommendations 19 and 20 in order to ensure appropriate referral, inform improvements and increase impact in the longer term. One key challenge raised by survey respondents, again, was resources. For example, a nurse for Pancreatic Cancer UK's support line said: "One of the frequent comments we hear, and more frequently of late, is that patients/carers cannot reach keyworker/secretary/CNS in local team, either unable to reach or calls not returned in time, thus why they use this support line service." A health professional also said to us that: "Apart from having an HPB/ Pancreatic Cancer Specialist Nurse I believe stronger links to Community Specialist Palliative care is absolutely vital in the treatment of these potential symptoms." Question 3: To ensure that patients have access to psychological support when local CNS / key worker or other relevant NHS resources are lacking, we advise that recommendations 19 and 20 specify that health professionals must offer information about	The committee agree that improving quality of life is the aim of this guideline and that this may include the development of measures for people with pancreatic cancer. However, the committee decided that this could not be added to recommendations 19 and 20 because improving quality of life is an overall aim rather than only related to these 2 recommendations. In relation to resources, the committee agreed that the guideline would streamline diagnosis and staging and therefore contribute to a more targeted use of resources. The committee also agreed with the comment related to stronger links to community specialist palliative care. However, making recommendations related to this was outside the scope of this guideline and falls more into the remit of End of life care for adults in the last year of life: service delivery which is currently in development.

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				non-NHS information and support services, in addition to NHS services, such as those provided by Pancreatic Cancer UK and Pancreatic Cancer Action. A patient who responded to our survey also suggested: "There should be much greater emphasis on early and intensive nutritional support as it helps the patient cope better with subsequent treatment." Whilst recommendation 19 acknowledges this, better implementation may be achieved by more greatly emphasising the need to offer nutritional/dietary support from the very beginning of the care pathway.	In relation to information provision the committee decided that it was not possible to specify the source of support that should be made available. The committee agreed that information needed to be provided to all people with pancreatic cancer. However, the committee was aware, based on the evidence and their experience that people have individualised requirements and that information and support needs to be tailored accordingly. The committee was aware that when the guideline is published a selection of sources for support will be signposted via a link entitled 'Information for the public' in the web version of the guideline. The committee discussed the nutritional needs of people with pancreatic cancer in Section 8.3 of the full guideline and the committee felt that there was little evidence for specific nutritional interventions. They therefore made a research recommendation related to this. However, they recognised the importance of good nutritional support and have therefore cross-referred to the NICE guideline on Nutritional support in adults CG32 (2017).

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Pancreatic Cancer UK, Pancreatic Cancer Action and the Pancreatic Cancer Research Fund	Full	137	18-20	Question 1: Whilst the draft guidelines rightly observe a lack of published evidence to inform recommendation 16, the NICE Committee may wish to note that Pancreatic Cancer UK recently presented research at a Public Health England (PHE) conference prepared by the London School of Hygiene and Tropic Medicine which suggests considerable variation in pancreatic cancer outcomes across Hepato-Pancreatic Biliary (HPB) units. Pancreatic Cancer UK is more than willing to share these findings with NICE. Combined with our charities' knowledge and experience, we believe that recommendation 16 could reduce this variation but we believe it would have a more positive impact on practice if the recommendation specified that: (i) the multi-disciplinary team (MDT) should refer the patient to a named Clinical Nurse Specialist (CNS) or key worker, (ii) the diagnosis should be given in a face-to-face manner in a quiet, private room (iii) the patient should be given the option of having a family member or friend with them for the meeting (iv) high-quality, understandable information should be provided which covers a description of the cancer, the patient's	Thank you for your comment. The committee agreed that this recommendation will reduce variation in practice because this guidance is intended for general application throughout the country. The review question, on which the recommendation was based, looked at whether or not people's outcomes were improved if they were reviewed by a specialist pancreatic multidisciplinary team (MDT). It did not look for evidence on who should be in the MDT, or how the MDT should communicate with patients. These issues could not, therefore, be addressed in the recommendations. On reflection the committee believed that the additional points highlighted in the comment in relation to this recommendation are not specific to pancreatic cancer care, but are principles of good standards of practice in the NHS. These principles are covered in the NICE guideline 'Patient experience in adult NHS services' CG138 (2012) to which the pancreatic cancer guideline recommendations cross-refer (see Section 8.1.7 of the full guideline; this is in the chapter on support needs).

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				treatment options (including details of opportunities to assist research / clinical trials), the side effects of treatment and how to manage them, details of how pancreatic cancer can affect diet and nutrition along with options to manage this, contact details for the CNS / key worker, and information about other support available. (v) patients should be informed of their right to receive a second opinion, with the understanding that delays can lead to a reduction in treatment options. These recommendations are set out in Pancreatic Cancer UK's Patient Charter and endorsed by the Association of Upper Gastrointestinal Surgeons of Great Britain and Northern Ireland (AUGIS), the Pancreatic Society of Great Britain and Northern Ireland, and the Great Britain and Ireland Hepato Pancreato Biliary Association (GBIHPBA). In our survey, health professionals told us that a key challenge with recommendation 16 will be to ensure sufficient resource for good communication between the patient, MDT and other specialists. To quote one respondent: "(We) need to have good coordination	

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				with local & specialist sites so patients don't get 'lost' in the system and so that patients receive the best communication. We have had situations where patients feel as if they are being referred backwards and forwards and no one knows who has said what to the patient." Question 3: If recommendation 16 is expanded to include the five recommendations given here in answer to question 1, health professionals should all be introduced to a CNS / key worker who can work to ensure clearer, more effective communication. In addition, extra resource will help users to overcome this challenge. To quote one health professional survey respondent: "Owing to ever increasing numbers of patients and increasingly limited resources and time I do feel this will be challenging to implement." Another respondent suggested that the recommendations should specify which resources should be in place, in order to reduce variation between MDTs: "A guide/ list of which healthcare professionals should be included (for) a specialist pancreatic MDT. Personally I feel this should include specialist Radiologists, Pathologists, Surgeons, Oncologists, Palliative care, CNS, Dietitian and an administrator/ co-ordinator. My	

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				experience is that nationally the provision of a specialist team varies considerably."	
Pancreatic Cancer UK, Pancreatic Cancer Action and the Pancreatic Cancer Research Fund	Full	169	29-31	In case it is useful to note, our survey respondents unanimously agreed that recommendation 17 was correct and would have a positive impact. Respondents felt recommendation 17 would help with assessing distant metastases and inform decisions about operability and other treatments, including clinical trials.	Thank you for your comment in support of the guideline.
Pancreatic Cancer UK, Pancreatic Cancer Action and the Pancreatic Cancer Research Fund	Full	169	32-41	Question 1: Recommendation 18 could have a more positive impact if it was reworded to say 'offer' rather than 'consider'. We suggest this change because of a study not considered by the Committee (Somer, I., and Bipat, S., 2017, Contrast-enhanced CT in determining resectability in patients with pancreatic carcinoma: a meta-analysis of the positive predictive values of CT', European Radiology 27(8), 3408-3435.). This meta-analysis found that 19% of pancreatic patients underwent surgical exploration, only then not to be resected due to the discovery of liver metastases, peritoneal metastases, or lymph node metastases. Keeping the recommendation wording of 'consider' would give a higher likelihood of unsuccessful surgery, which would be more	Thank you for your comment. The use of the term 'consider' reflects the strength of the evidence base upon which the recommendation was made, in line with NICE methodology. The quality of evidence in this area was not strong enough to make this an 'offer' recommendation. The meta-analysis conducted by Somers & Bipat 2017 was excluded because the majority of the included articles were retrospective studies (which the review protocol had specified were to be included only if there were no prospective studies). The two prospective

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				challenging for patients and health professionals accordingly. Whether the recommendation is worded as 'consider' or 'offer', health professionals who responded to our survey advised that decisions to stage should be balanced against the risks of delaying treatment. For example, one respondent said: "If all these options are recommended the patient would be having a lot of investigations that may not be needed. MRI liver is very over booked and long waiting lists." Question 2: Health professionals advised us that greater resources will be required, e.g. for EUS and PET-CT, to implement recommendation 18. Question 3: The above research by Somer and Bipat suggests that the chances of unsuccessful surgery can be reduced by rewording recommendation 18 from 'consider' to 'offer'. However, this should be conditional on the ready availability of the resources urgently required. Inefficient staging should also be avoided. For example, the Committee could reconsider whether a PET-CT could actually make a laparoscopy with laparoscopic ultrasound unnecessary.	studies that were in the meta-analysis were included in the review. The committee intentionally worded this recommendation using 'consider' for two reasons: (i) the evidence was not strong enough to word this as 'offer'; (ii) 'consider' implies that the healthcare professional would tailor the choice to the individual's needs (e.g. whether they are fit enough for a procedure). The committee also used the additional wording of 'if the test results will change the clinical management the person receives' related to these diagnostic tests which means that this would apply to a smaller proportion of people (where there are doubts about the management pathway). Based on further evidence the committee have also now added a recommendation on PET/CT scans which as the stakeholder points out make a laparoscopy with laparoscopic ultrasound unnecessary and therefore also lead to a reduction in costs.

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Pancreatic Cancer UK, Pancreatic Cancer Action and the Pancreatic Cancer Research Fund	Full	218	2-7	Question 1: In one respect, we hope that recommendations 21 and 22 will have a positive impact by encouraging health professionals to consider patients' pain management needs and address them sooner. Pancreatic Cancer UK's support line specialist nurses commented that pain management is often thought about and implemented too late. Nevertheless, by prohibiting other pain management treatments for particular patients, the recommendations also risk a negative impact on patient choice, health and wellbeing. To quote a Pancreatic Cancer UK patient representative's reaction to recommendations 21 and 22: "I know of other patients with severe pain and discomfort and I think they would disagree with this and think they should be given the choice of all pain relief options." Question 2: Respondents to our survey were generally enthusiastic about the inclusion of coeliac plexus block in the guidelines, and we favour its inclusion in recommendation 21. To ensure access to coeliac plexus block, some health professionals advised us that investment may be required.	Thank you for your comment. The committee looked for evidence for the effectiveness of a number of interventions for pain control, such as sympathectomy (splanchnicectomy) and neurolytic techniques (nerve block/ablation, coeliac plexus block/ablation, coeliac ganglion block/ablation, and superior hypogastric block/ablation). However, they did not make clinical practice recommendations for several of the comparisons of interest as they considered the quality of the evidence to be insufficient to allow them to adequately evaluate the benefits and harms for people. The committee discussed, based on their experience, that current practice for pain management in people with pancreatic cancer is pharmaceutical management with analgesics. If these analgesics do not adequately control the pain or the person has difficulties with side effects of the analgesia then neurolytic coeliac plexus block may be considered. This decision was also based on health economic considerations because the number of people receiving this would not be very large, the procedure is already available and it may reduce the

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				Question 3: We encourage the NICE Committee to carefully consider the negative impact on patient experience, and potentially its other critical outcome measures for these recommendations, of ruling out access to particular forms of pain management. For example, for a patient who is still in pain after being treated with the treatments in recommendation 21, being denied the right to try thoracic splanchnicectomy could add immense frustration and avoidable pain to the rest of their life.	requirement for pharmaceutical analgesia which would also be cost saving. The committee considered whether thoracic splanchnicectomy was effective, but no evidence for the effectiveness of this procedure was identified. Given that it is an invasive technique requiring general anaesthetic and that it is not currently in widespread use in the UK, the committee believed that the procedure has a risk of being harmful without evidence of being effective and therefore recommended that it should not be used. These factors and other issues that were considered when making the recommendations are described in the full guideline in Section 8.2.8 and its subsections.
Pancreatic Cancer UK, Pancreatic Cancer Action and the Pancreatic Cancer	Full	255	1-10	Comments from Pancreatic Cancer UK's specialist nurses sum up the positive impact recommendations 23-26 will have: "Overall, these recommendations will benefit care of patients and improve quality of life. In resected patients, early enteral nutrition will be less invasive, again giving better quality of life." "Exocrine insufficiency will be picked up and treated earlier and this leads to healthier patients nutritionally, better recovery from surgery, better	Thank you for your comment. Based on the evidence, the committee was confident that recommending pancreatic enzyme replacement therapy (PERT) would improve the nutritional status for people with unresectable pancreatic cancer. The evidence also showed that there were fewer post-operative complications with enteral nutrition compared with parenteral nutrition following pancreatoduodenectomy and

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Research Fund				tolerance to treatments and so on..." Patients who responded to our survey agreed. For example, in relation to recommendation 26, a pancreatic cancer survivor said: "Eating food before and after the operation is almost impossible so all ways of improving this will be beneficial." Question 1: The main challenges identified that could put this positive impact at risk were firstly timing, and secondly expertise. On timing, for example, a Pancreatic Cancer UK specialist nurse said: "Because clinicians often don't implement use of PERT (pancreatic enzyme replacement therapy) until symptoms of PEI (pancreatic exocrine insufficiency) appear - we know these are late signs and a person can be malabsorbing for a long time." Several health professionals also said that the expertise of a dietician would be needed to ensure that the recommendations are effectively followed. For example, commenting on recommendation 24, a health professional advised: "Where required, appropriate doses and effective counselling is vital, as prescribing this at an insufficient/ ineffective dose and failing to counsel patients appropriately on how	no clinically important difference in overall survival. The committee therefore agreed with the stakeholder's survey respondents that these recommendations overall would benefit people with pancreatic cancer. The committee agreed that the implementation of the guideline would eventually lead to more efficient use of time and also improve staff's skill sets in this area. Time spent on providing better nutritional care would be offset by preventing conditions such as cachexia or sarcopenia. Based on the evidence the committee recommended enteric coated pancreatin treatment to manage weight loss in people with unresectable pancreatic cancer as this was the type of PERT used in the trials. The committee also made a weaker recommendation for the use of PERT to manage weight loss in people with resectable pancreatic cancer.

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				to take it makes the treatment futile." A comment from a pancreatic cancer survivor showed that effective counselling is also key to ensuring that patients understand, look out for and respond correctly to problems when they arise to minimise suffering: "(Note) the importance of having a good Dietician to explain the type of problems that can happen after a Whipple procedure. Also, how to take Creon e.g. correct dosage, what foods to avoid and the importance of nutrients and vitamins which are lost when a sufferer experiences malabsorption." On Pancreatic Cancer UK's support line, the charity's specialist nurses frequently hear from patients who are not taking PERT correctly and have not been given the right information to do so. They continue to experience distressing symptoms and malabsorption, sometimes for several years. Whilst recommendation 24 is welcome, we are concerned that it does not go far enough to minimise the chance of similar such cases arising in the future by opting for the phrasing 'consider' instead of 'offer'. Question 3: As the above evidence from Pancreatic Cancer UK's support line specialist nurses, health professional and patient contacts all shows, recommendations 23-26 could have a greater	The committee agreed that these recommendations would reduce variation in practice because this guidance is intended for general application throughout the country. It will therefore improve both timing and expertise and availability related to this treatment.

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				positive impact if they specified more clearly how soon they should be followed in the treatment pathway and by whom (i.e. at an early stage by a specialist dietician). To ensure that the recommendations are correctly followed and patient experience is improved, they should also specify that related advice and support must be given to the patient by the specialist dietician. Given the importance of effective counselling by a specialist dietician, we feel strongly that early stage referral to them should be specified in recommendations 23-26. Specific to recommendation 24, we also feel that 'offer' would be more appropriate than 'consider', provided that the patient is referred to a specialist dietician who can best assess and advise the patient's dietary needs.	The review related to nutritional interventions rather than the composition of the multidisciplinary team providing these interventions or the timing of such interventions. The committee could therefore not comment on these issues. In relation to the wording of 'consider' rather than 'offer', the use of the term 'consider' reflects the strength of the evidence base upon which the recommendation was made, in line with NICE methodology. There was no evidence for the use of PERT for the management of weight loss in people with resectable cancer and therefore the committee decided to make a weaker recommendation in favour of PERT.
Pancreatic Cancer UK, Pancreatic Cancer Action and the Pancreatic Cancer	Full	312 / 313	42-43 / 1-13 respectively	We warmly welcome recommendation 27. Too often, Pancreatic Cancer UK's support line hears from people whose surgery has been unnecessarily delayed, impacting on their prognosis, psychological wellbeing and quality of life. We hope that recommendation 27 will send an unambiguous message that the only life-saving treatment for	Thank you for your comment and support for the recommendations. Based on the evidence and their expertise the committee agreed that recommendations 27 to 31 would improve patient care. These recommendations were also based on a health economic model which assessed these surgical techniques and procedures to be cost-effective. The committee

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Research Fund				pancreatic cancer should be given where appropriate without delay. We also feel that recommendations 28-31 will encourage more efficient practice that is easier for patients to recover from, hopefully reducing surgery waiting times and increasing eligibility for life-saving surgery respectively in the future. To give some specific examples, Pancreatic Cancer UK's expert nurses and several other health professionals commented that: - Recommendation 28 will reduce the need for separate future procedures - Recommendation 30 will discourage use of plastic stents, which are often more troublesome (e.g. providing inferior drainage) and unsuitable for later stages of treatment - Recommendation 31, like with recommendation 30, will encourage endoscopic procedures which are also less traumatic and potentially easier to arrange than surgery. An overall reduction in surgery waiting times for pancreatic cancer could lead to a significant improvement in surgical success rates, as well as	therefore could make strong recommendations based on the clinical and health economic evidence. The study by Roberts et al. (2017) was not included in the guideline review because it did not meet the protocol criteria because it focused on the timing rather than the effectiveness of the intervention

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				cost efficiencies, judging by the early evidence from the fast-track surgery pilot underway at University Hospitals Birmingham NHS Foundation Trust. Question 2: Several health professionals responding to our survey said that availability of surgery before stenting remains a challenge. Whilst efforts to address this may incur a cost, it should also be noted that evidence from the fast-track surgery pilot suggests the NHS can save £3,200 per patient by reducing the average time to surgery from two months to just over two weeks. We encourage the NICE Committee to review the published results of the pilot: Roberts, K.J. et al., 2017. 'A reduced time to surgery within a 'fast track' pathway for periampullary malignancy is associated with an increased rate of pancreatoduodenectomy.' HPB: The official journal of the International Hepato-Pancreato-Biliary Association, 19(8), 713-720. Further such evidence may be provided by Derek O'Reilly in relation to his distinguished work developing and piloting the Manchester Cancer Jaundice Pathway. Question 3: With stenting recommendations, such as recommendation 29, unless clear criteria are offered, it may be unclear to some professionals whether a	 Based on the evidence, the committee agreed that endoscopic stenting was associated with improvements in quality of life compared to

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				patient should be stented or not. A solution would be to advise that decision-making on stenting should involve discussion with a specialist MDT (multi-disciplinary team) first.	surgical bypass. The committee, therefore, made a strong recommendation for endoscopic stenting in people with unresectable pancreatic cancer as stent placement would avoid a major operation in someone who was likely to be quite poorly. Based on their knowledge and experience the committee also agreed to recommend that surgical biliary bypass should be considered for people whose pancreatic cancer was deemed unresectable during an attempted resection. This would mean the person would not need to have a potential additional procedure in future to insert a stent (the reasons why the committee made these recommendations are provided in Section 9.1.8.3 of the full guideline). The committee also agree that a multidisciplinary team should decide what care is needed, and involve the person with suspected or confirmed pancreatic cancer in the decision (see the recommendation in Section 6.7 of the full guideline).
Pancreatic Cancer UK, Pancreatic Cancer Action and the	Full	339	2-7	Overall, we would expect recommendations 32-34 to bring improvements to symptom control, bringing relief from vomiting, for example. Drawing upon views shared by survey respondents, we would expect:	Thank you for your comment. The committee agreed that these recommendations would improve symptom control for people with

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Pancreatic Cancer Research Fund				- Recommendation 32 to reduce complications from the tumour at a later stage and reduce the need for further invasive interventional procedures - Recommendation 33 to ease unpleasant symptoms, such as vomiting. A health professional remarked that, in their experience this can hugely affect a patient's quality of life and even extend length of life if an obstruction is impairing nutritional intake - Recommendation 34 to delay or even completely avoid the need for a duodenal stent, which can become blocked, require multiple hospital admissions and need further procedures which can be unpleasant for the patient. Question 1: A challenge for recommendation 34 in particular could be that the patient may, when feeling unwell and/or facing a short prognosis, wish to opt for a stent. To quote a health professional who responded to our survey: "Asking a patient to undergo a far more invasive operation if said patient is very unwell and/or has a short prognosis seems cruel and unnecessary. In this circumstance a stent seems much kinder." A health professional also pointed out a significant disadvantage of	pancreatic cancer and therefore increase their quality of life. The committee intentionally made recommendation 34 a weak recommendation because they recognised the potential risk of complications associated with surgery or stent insertion. However, the committee considered that the potential benefits of the procedure, based on the evidence assessed, would outweigh these risks. The committee agreed that it was very important that the person with pancreatic cancer should be involved in decision making and that information on benefits and risks should be conveyed and discussed. Such principles of care are covered in the NICE guideline 'Patient experience in adult NHS services' CG138 (2012) to which the guideline recommendations cross-refer in Section 8.1.7 of the full guideline (in the chapter on support needs). With regard to questions 1 and 3, gastrojejunostomy is a surgical procedure in which the stomach is joined to the jejunum. Therefore this is not relevant in this guideline.

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				gastrojejunostomy further down the line, raising the challenge of: "Informing the relative when to stop feeding through the gastrojejunostomy when the patient is at the end of their life." Question 3: In light of the challenges described immediately above, it seems wise for recommendation 34 to continue to be worded only as 'consider'. It is also important, as ever, that patients are informed of the advantages and disadvantages of treatment options, including the particular challenges of gastrojejunostomy mentioned above towards end-of-life.	
Pancreatic Cancer UK, Pancreatic Cancer Action and the Pancreatic Cancer Research Fund	Full	361	20-21	We urge the NICE Committee to revise recommendation 35 in light of the findings presented in the following paper: 'The role of induction chemotherapy and chemoradiotherapy in localised pancreatic cancer: initial experience in Scotland'; Journal of Gastrointestinal Oncology; Grose, Derek et al.; 2017:8(4): 683-695. The NICE Committee will see that this paper is the latest to suggest that neo-adjuvant therapy can increase the chance of resectability in patients with borderline/non-resectable tumours. Considering this	Thank you for your comment. As noted in Section 10.1.8 (evidence to recommendations) in the full guideline, although the committee was aware that the use of neoadjuvant treatment is common, it did not consider the current evidence base (which consisted predominantly of single-arm cohort studies) to merit a positive recommendation to consider or offer neoadjuvant treatment. The committee evaluated the results of the study by Grose et al. 2017, a retrospective review of a prospective database, but did not consider the results to be sufficient to amend its

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				alongside the fact that 80 per cent of pancreatic cancer patients are diagnosed at an advanced stage, it is clear that neo-adjuvant therapy currently has a key role to play in improving the appallingly low survival rates for people affected by the disease. The NICE Committee will also see in the above paper that neo-adjuvant therapy can reduce the chance of cancerous cells remaining post-surgery, therefore reducing the possibility of relapse. If permitted by the Committee, neo-adjuvant therapy could play a significant role in increasing the unacceptably low long-term survival rates for pancreatic cancer, with just seven per cent of UK patients living beyond five years after diagnosis. Question1: It will be understandably challenging for health professionals to implement recommendation 35's proposed restriction on a relatively well-resourced, well-evidenced treatment. According to	recommendations that neoadjuvant treatment should, for the time being, only be used as part of a clinical trial in people with resectable or borderline resectable pancreatic cancer. Although the study showed that neoadjuvant therapy was favoured on R0 and R1 resection rates compared to surgery alone, there was no statistically significant difference on these outcomes between the two arms. Similarly, whilst the post-operative tumour, node and metastasis (TNM) classifications of the 34 patients who had surgery favoured neoadjuvant treatment compared to surgery only, there was also no statistically significant difference. Since the study by Grose et al. 2017 was not randomised, any observed differences may be the result of the fact that patients were considered for chemoradiotherapy only if they demonstrated stable disease or better on CT, with the remaining patients proceeding to surgery. Regarding the issue raised in the comment about the impact of the recommendation: the committee recognises that neoadjuvant

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				the evidence, recommendation 35 would have a significant negative impact on the prognoses of people with unresectable, but potentially downgradable pancreatic cancer. We would also expect the denial of potentially life-saving treatment to also a huge emotional toll on the patient and their loved ones. Question 3: In light of the paper by Grose et al., we feel that it is appropriate for health professionals to be able to consider neoadjuvant therapy for people with unresectable pancreatic cancer if the tumour could be downgraded and become resectable as a result. Recommendation 35 should be edited accordingly. Like all such treatments, we would expect health professionals to provide high quality, fully understandable information to the patient about the risks and benefits of the different treatment options available to them.	treatment is relatively common and that people with pancreatic cancer experience substantial physical and emotional suffering. However, the studies included in the evidence generally used samples that were composed of people deemed to have resectable or borderline resectable tumours. Whilst the study by Grose et al. 2017 provided data for patients with unresectable but potentially downgradable pancreatic cancer, only 16% (3 of 19 patients) could in fact have their pancreatic cancer downstaged. The committee did not consider this evidence sufficient to recommend its use as standard practice. Please see Chapters 7 and 11 of the full guideline for the committee's recommendations regarding, respectively, staging and the treatment of unresectable (i.e. locally advanced and metastatic) pancreatic cancer). Given the low quality of the evidence, the committee did not consider it to be sufficient to

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					merit a recommendation to consider or offer neoadjuvant treatment.
Pancreatic Cancer UK, Pancreatic Cancer Action and the Pancreatic Cancer Research Fund	Full / Short	All	All	In comment 14, we gave examples of initiatives by Mr Keith Roberts and Mr Derek O'Reilly which have shown the benefits of accelerating treatment pathways. In light of this evidence, we are concerned that the draft guidelines do not emphasise the critical importance of speed in treating pancreatic cancer once diagnosed. In our survey of Pancreatic Cancer UK's specialist nurses and health professional contacts, speed was a common concern that came up. For example: - "There needs to be a process for rapid decision making with Specialist MDT prior to intervention:" Health professional. - "It's the speed of which they happen which is more relevant:" Pancreatic Cancer UK specialist nurse - "It can be more about timescales of these investigations - with long gaps between each one and results and out-patient appointments - it needs to be tightened up here so that pancreatic cancer patients are not waiting months to start treatment:" Pancreatic Cancer UK specialist nurse	Thank you for your comment. The committee has now acknowledged in the general introduction to the full guideline and the context section of the short version that there are often delays in access to diagnosis and treatment (as highlighted in the NHS England Five Year Forward View). The committee believes that the guideline will help people to receive more timely diagnosis and treatment. The committee made a strong recommendation in terms of fast-tracking to surgical resection which the committee believes will improve outcomes. However, specifying timeframes for interventions was not part of the scope of this guideline. The committee supports upgrading patients with suspected pancreatic cancer onto the 62-day pathway target set by the Department of Health.

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				- "Getting patients to specialist centres needs to be speeded up:" Health professional We urge the NICE Committee to address this concern by using the guidelines to give health professionals greater encouragement to accelerate patients' treatment whenever effective. As leaders in their fields, we also encourage the NICE Committee members to individually and collectively work in a proactive fashion to ensure that the final guidelines are followed. Subject to the suggested improvements in this consultation response being accepted, we are excited by the guidelines' potential, if followed, to ensure more consistent, higher quality treatment that will improve patient information, choice, experience and outcomes.	
Pancreatic Cancer UK, Pancreatic Cancer Action and the Pancreatic Cancer	Short	3-5	3-20, 1-27, 1-8 respectively	Question 2: As a whole, we feel that the NICE Committee's recommendations will have a positive impact on the speed of diagnosis, increasing professionals' ability to extend or ideally save lives. In addition to the specific suggested improvements already detailed, several health professionals who responded to our survey also pointed out that, for the diagnosis recommendations to be successfully	Thank you for your comment. The committee agreed that the diagnostic tests described in the recommendations are already available in specialist centres and are already utilised as part of current practice. Therefore there is unlikely to be a significant requirement for increases in capacity and more effective use of these resources, in line with the

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Research Fund				implemented, the capacity of specialist centres will need to increase, particularly for radiology, endoscopy and imaging. Question 3: Regarding the cost implications of the diagnosis recommendations, it would be helpful to include advice on what action medical professionals should take to ensure swift diagnosis when the nearest specialist centres do not have sufficient capacity (e.g. refer to the next nearest centre with capacity, rather than wait for availability).	recommendations made by this guideline, may actually lead to cost savings by refining the diagnostic pathway. What to do to ensure speed of access to diagnostic tests in specialist centres when there is limited capacity was outside the scope of the guideline. Hence the committee could not make recommendations about which actions to take in these circumstances.
Pancreatic Cancer UK, Pancreatic Cancer Action and the Pancreatic Cancer Research Fund	Short	9 / 10	15-21 / 1-17 respectively	We welcome recommendations 1.9.1 – 1.9.9, which we hope will ensure that these effective standard practices are more consistently followed. Pancreatic Cancer UK's specialist nurses fed back that they encounter variation in the quality of care for people with unresectable pancreatic cancer, but feel that these recommendations will standardise chemotherapy treatment plans for patients across England. In their experience, they felt that each of the recommendations in this section could lead to a potential of survival benefit Question 1: For 1.9.5: Pancreatic Cancer UK's specialist nurses suggested there could be a role for Gem-Abraxane, assuming this recommendation would be applied to individuals with metastatic	Thank you for your comment. The NICE Technology Appraisal guidance on 'Paclitaxel as albumin-bound nanoparticles with gemcitabine for untreated metastatic pancreatic cancer' TA476 (2017) was published after the pancreatic cancer guideline went out for consultation. We have now added a cross-reference to TA476 in recommendation 1.9.5.

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				pancreatic cancer. Potential confusion could be caused if the NICE Committee's guidelines are not consistent with NICE's recent recommendations regarding Abraxane. Question 3: The recommendations should be appropriately updated to utilise the availability of Gem-Abraxane on the NHS in England for patients who do not meet Folfirinox criteria.	
RCN	-	-	-	The RCN has no comments to inform on the Pancreatic cancer: diagnosis and management in adults draft guidance consultation at this time	Thank you for your comment.
Royal College of General Practitioners	Full	Pages 45 to 134		The potential to improve earlier diagnosis in Primary care is not fully explored in this guideline. The possible presentations considered are limited to 5.1 Jaundice, 5.2 Without Jaundice but with a pancreatitic abnormality and 5.3 Pancreatitic cysts Epigastric Pain: occurs in approximately 70% of cases Jaundice: occurs in approximately 50% of cases Unexplained weight loss Occurs in 10-30% of cases Other common symptoms include nausea, anorexia, malaise and vomiting but these are usually late symptoms	Thank you for your comment. The groups that this guideline covers are adults referred to secondary care with suspected pancreatic cancer and adults with newly diagnosed or recurrent pancreatic ductal adenocarcinoma. Symptoms and signs leading to improved and earlier recognition and referral of people with suspected pancreatic cancer is outside the scope of this guideline. For recommendations related to this please see the NICE guideline on 'Suspected cancer: recognition and referral' NG12 (2017).

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				However this does not include atypical presentations in primary care such 1. New onset type 2 diabetes mellitus: New-onset type 2 diabetes in an underweight or normal weight patient, not associated with weight gain 2. Resistant dyspepsia/persistent epigastric pain: Patients may also describe their abdominal pain radiating to the back and/or back pain that is relieved on leaning forward. 3. IBS like symptoms in those >45 years: IBS is very rare as a new onset symptom at this age and should ring alarm bells so it is essential to think of and exclude pancreatic carcinoma as a cause for bloatedness and flatulence. 4. Altered bowel movements: A patient may notice increased bowel movement frequency and pale, offensive smelling stools that don't flush away easily. 5. Venous Thromboembolism: A Deep Vein Thrombosis (DVT) may be a manifestation of an underlying malignancy. If a	

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				patient presents with no obvious risk factors it is worth considering an abdominal malignancy such as pancreatic cancer. 6.Peristent thrombocystosis or viscosity The use of QRISK cancer also does not appeared to be covered which uses the Positive Predictive Values (PPVs) of paired symptoms The guideline does not appear to cover pancreatic cancer screening in individuals with family history of pancreatic cancer	
Royal College of Physicians	General			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 for Gastroenterology (BSG).	Thank you for your comment. We have responded to the comments submitted by the British Society of Gastroenterology (BSG).
Shire	Short	General	General	Surgery – this surgery is extremely difficult to undergo and to perform. Managing patient and carer expectations is key and consideration should be given to limiting pancreatic cancer surgery to proven centres of excellence only.	Thank you for your comment. In the scope of this guideline all review questions related to surgery addressed the clinical and cost effectiveness of surgical procedures. The settings (centres of excellence) and level of expertise needed to conduct these procedures were outside the scope of this guideline.

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					In relation to managing expectations, recommendation 1.2.1 states that a specialist pancreatic cancer multidisciplinary team should decide what care is needed and involve the person with suspected or confirmed pancreatic cancer in the decision. The committee agreed that involving the person with suspected or confirmed pancreatic cancer would include discussions about the benefits and harms of surgery (e.g. that it is difficult to undergo and is a complex procedure to perform).
Shire	Short	3	General	Diagnosis - Upper abdominal pain symptoms are not mentioned, nor steatorrhea. There is a general point to made here about the symptoms identified not being encompassing enough for pancreatic cancer. Please make reference to the ACE MCD pilots? (See link here). There are also pilots for vague symptoms, which could also fall under the 'research' buckets.	Thank you for your comment. Symptoms and signs leading to the recognition and referral of people with suspected pancreatic cancer is outside the scope of this guideline. For recommendations related to this please see the NICE guideline on 'Suspected cancer: recognition and referral' NG12 (2017).
Shire	short	10	General	Nab-paclitaxel plus gemcitabine has been recommended by NICE for people with metastatic pancreatic cancer – only if other combination chemotherapies are not suitable, and they would otherwise have gemcitabine monotherapy – and should therefore be incorporated into this section. Technology appraisal guidance [TA476]	Thank you for your comment. The NICE Technology Appraisal guidance 'Paclitaxel as albumin-bound nanoparticles with gemcitabine for untreated metastatic pancreatic cancer' TA476 (2017) was published after the pancreatic cancer guideline went out for

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				Add in a statement to the effect that treatment in a clinical trial should be offered wherever possible.	consultation. We have now added a cross-reference to TA476 in recommendation 1.9.5.
Shire	short	10	10	It is recognised that oxaliplatin is unlicensed in this treatment. What is not widely known is that the evidence base of oxaliplatin based therapies in this area of treatment has conflicting data. Reference to be made for Conko-003 trial (*Oettle H, et al. J Clin Oncol 2014;32:2423)* and Pancreox trial (Gill S et al. *Journal of Clinical Oncology* 34, no. 32 November 2016, 3914-3920.) for a full informed choice to be made. We are concerned that this recommendation may imply that there is no conflicting data.	Thank you for your comment. The rationale for these recommendations is provided in Section 11.2.8 of the full guideline and its subsections. The evidence showed that oxaliplatin-based chemotherapy improved progression-free survival. The inconsistency that is referred to in the comment was also highlighted in the discussion of this evidence (see Section 11.2.8.3). It is therefore a weak recommendation to indicate that healthcare professionals could use this intervention, but that its use would be subject to clinical judgement. After further discussion the committee agreed that no change to the document is needed.
Shire	short	10	13	To add a comment: "3rd line treatment options should be explored for eligible patients." To add a footnote in this section: "There are other licensed, but as yet, not reimbursed treatment options which can be explored." Reference: https://www.gov.uk/government/uploads/system/uploads/attachment_data/file/404423/patients-add-priv-care.pdf	Thank you for your comment. Making recommendations for people paying for private additional care is outside the remit of NICE as a whole.
Shire	Short	13	General	Early diagnosis – this area is pivotal and as such we would suggest listing a research requirement	Thank you for your comment. The groups that this guideline covers are adults referred to secondary care with suspected pancreatic

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				here. (Guidance even states on p. 13 "Because of late diagnosis, only approximately 8% of people with pancreatic cancer are eligible for potentially curative surgery) One suggestion for further research and raising awareness is the link between newly-onset diabetes not associated with weight gain and is a clear 'red flag' for GPs to act on when finding it in patients.	cancer and adults with newly diagnosed or recurrent pancreatic ductal adenocarcinoma. Symptoms and signs leading to improved and earlier recognition and referral of people with suspected pancreatic cancer is outside the scope of this guideline. For recommendations related to this please see the NICE guideline on 'Suspected cancer: recognition and referral' NG12 (2017).

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