NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Interventional Procedures Programme

Specialist Adviser questionnaire

Before completing this questionnaire, please read Conflicts of Interest for Specialist Advisers. Certain conflicts exclude you from offering advice, however, please return the questionnaire to us incomplete for our records.

Please respond in the boxes provided.

Please complete and return to: Deonee.Stanislaus@nice.org.uk

Procedure Name:	**Endoscopic bipolar radiofrequency ablation for treating biliary obstruction caused by cholangiocarcinoma or pancreatic adenocarcinoma**
Name of Specialist Advisor:	Dear Professor Nagy A Habib
Specialist Society:	The Royal College of Surgeons of Edinburgh

1 Do you have adequate knowledge of this procedure to provide advice?

☒ **X** Yes.

☐ No – please return the form/answer no more questions.

1.1 Does the title used above describe the procedure adequately?

☒ **X** Yes.

☐ No. If no, please enter any other titles below.

Comments:

2 Your involvement in the procedure

2.1 Is this procedure relevant to your specialty?

☒ **X** Yes.

☐ Is there any kind of inter-specialty controversy over the procedure?

☐ No. If no, then answer no more questions, but please give any information you can about who is likely to be doing the procedure.

Comments:

The next 2 questions are about whether you carry out the procedure, or refer patients for it. If you are in a specialty that normally carries out the procedure please answer question 2.2.1. If you are in a specialty that normally selects or refers patients for the procedure, please answer question 2.2.2.

2.2.1 If you are in a specialty that does this procedure, please indicate your experience with it:

☐ I have never done this procedure.

☐ I have done this procedure at least once.

☐ I do this procedure regularly.

Comments:

2.2.2 If your specialty is involved in patient selection or referral to another specialty for this procedure, please indicate your experience with it.

☐ I have never taken part in the selection or referral of a patient for this procedure.

☐ I have taken part in patient selection or referred a patient for this procedure at least once.

☐**X** I take part in patient selection or refer patients for this procedure regularly.

Comments:

2.3 Please indicate your research experience relating to this procedure (please choose one or more if relevant):

☐**X** I have done bibliographic research on this procedure.

☐X I have done research on this procedure in laboratory settings (e.g. device-related research).

☐X I have done clinical research on this procedure involving patients or healthy volunteers.

☐ I have had no involvement in research on this procedure.

☐ Other (please comment)

Comments:

3 Status of the procedure

3.1 Which of the following best describes the procedure (choose one):

☐**X** Established practice and no longer new.

☐ A minor variation on an existing procedure, which is unlikely to alter the procedure's safety and efficacy.

☐ Definitely novel and of uncertain safety and efficacy.

☐ The first in a new class of procedure.

Comments:

3.2 What would be the comparator (standard practice) to this procedure?

There are already several radiofrequency (RF) devices in clinical practice for GI diseases. Some of them are for endoscopic use (Barrx™ GI RF product range (Medtronic) and Gold Probe Catheter (Boston Scientific)) and in parallel there are multiple RF devices deployed by interventional radiologists for liver and pancreas tumour ablation, such as the Starburst Probes (AngioDynamics Inc). These RF devices have been used for over a decade and have shown both safety and efficacy.

The difference with the Habib™ EndoHPB is that it is the first device that was designed specifically for use in the common bile duct to ablate bile duct tumours, such as cholangiocarcinoma and tumours of the head of pancreas. Pancreatic tumours are notorious for having the worst survival and represent an unmet medical need. The device has shown safety in over 10,000 cases worldwide and 3 different publications report a 2 or 3 fold survival compared to best medical care. These studies were performed at Massachusetts General Hospital, Boston, USA, Weill Cornell Hospital, New York, USA, The Oriental Biliary Diseases Hospital, Shanghai and Imperial College Healthcare NHS Trust, Hammersmith Hospital, London. Below please find a table which summarises the findings:

Author	Study Type	RF Group	% Survival	p Value
Kahaleh M et al (Dig Dis Sci. 2014 Dec;59(12):3099-10)	Matched with SEER Database data for malignancy and disease stage diagnosis	RF group n=69 Matched = SEER database	Cholangio: Untreated 6.2 months vs RF Treated 17.7 months Pancreatic Cancer: Untreated 5.9 months vs RF treated 14.6 months	p<0.0001 p<0.0001
Westaby et al (Dig Dis Sci. 2015 Nov;60(11):3449-55)	Matched controls	RF group = 23 Matched n=46	RF treated 226 days vs Untreated 123.5 days	p=0.010
Hu B et al (unpublished 2016)Pr	Prospective randomized	RF+Stent n=31 Stent alone n=32	RF + stent 311 days vs Stent alone 172 days	p=0.012

3.3 Please estimate the proportion of doctors in your specialty who are doing this procedure (choose one):

☐ More than 50% of specialists engaged in this area of work.

☐ 10% to 50% of specialists engaged in this area of work.

☐ Fewer than 10% of specialists engaged in this area of work.

☒ Cannot give an estimate.

Comments:

The device is marketed in the UK by a distribution company – APRmedtech.

4 Safety and efficacy

4.1 What is the potential harm of the procedure?

Please list adverse events and major risks (even if uncommon) and, if possible, estimate their incidence, as follows:

1. Adverse events reported in the literature (if possible please cite literature)

Studies have shown the safety of RFA in the management of unresectable malignant bile duct tumours [3,4, 6,7,9,11- 24,26,28] or benign biliary strictures [8], and pancreatic cancer [6,7,17,18] prior to stent placement. Other studies have shown the safety of intraductal RFA using the Habib™ EndoHPB and Habib™ Percutaneous HPB to clear occluded metal stents [5,15].

In the vast majority of these studies [3,6,7,9,11-14,16-19,22-24,26], no serious adverse events, such as bile duct perforation, bleeding, bile leak, aneurysmal dilatation of hepatic artery, thermal injury to the duodenum or pancreas, cholangitis, cholecystitis and pancreatitis, related to RFA procedure occurred. However, in 27 out of the 327 patients (about 8.3%) reported complications from the treatment.

Iatrogenic thermal injury
RFA may induce iatrogenic thermal injury to adjacent structures, and the iatrogenic thermal injury may lead to perforation of involved or intact bile ducts, or vessel injury. Dolak et al. [4] described a case of partial liver infarction in a 49-year-old patient with Bismuth IV hilar cholangiocarcinoma following an RFA procedure. The authors hypothesised that this event was caused by thermal injury to a segmental branch of a liver artery. The patient was managed conservatively and had a favorable recovery.

Cholangitis
The Dolak study[4], reported five cases of cholangitis following RFA procedures. The risk of cholangitis might be reduced with routine administration of pre- and post-procedural antibiotics [4].

Haemobilia
Tal et al. [21] described three cases of haemobilia that occurred within 4-6 weeks of an RFA procedure. Two patients succumbed to haemorrhagic shock, and the surviving patient was managed with immediate SEMS insertion into the bleeding bile duct. The authors hypothesised that the haemobilia may have been caused by the necrotic effect induced by RFA. As bleeding occurred during stent extraction 4-6 weeks after the RFA procedure in these patients, their conclusion may be challenged. The most likely cause could be mishandling during stent removal. Possible preemptive strategies to avoid biliary bleeding complications include pre-interventional assessment with intraductal ultrasound to exclude large blood vessels in the surrounding tissue. Inserting a SEMS immediately after the RFA procedure may be an effective method for the prevention of late bleeding complications.

Biliary tract perforation
Zhou et al. [28] reported two cases of biliary tract perforation following RFA procedure. In this study, the two cases received overlapping RFA for 2 min at 10 W. Thermal injury induced deep bile duct necrosis and possibly caused the perforations. Furthermore, the dilatation of the bile duct with a balloon catheter (prior to RFA in case 1, and following RFA in case 2) may have aggravated the necrotic effect induced by RFA thermal injury. According to the authors, the insertion of a self-expanding metal stent directly after the RFA procedure appears to be an effective method to treat minor biliary tract perforation. Perforations are mainly related to percutaneous access. To treat these perforations, clinicians should put a stent, leave the drain open so that the bile goes outside the body temporarily (for few days) and give antibiotics so that the perforation heals itself.

When rate of complications of RFA is compared with the rate of serious complications reported for standard ERCP procedures for malignant bile duct obstructions, ERCP procedures (usually to place a stent) have a 39.3% chance of a complication when placing a placing a plastic stent and 11.8% when placing a Self expanding metal stent. For RFA the rate of a serious complication is much lower at 8.3%.

References

1. Barret M, Leblanc S, Vienne A, Rouquette A, Beuvon F, Chaussade S, Prat F. Optimization of the generator settings for endobiliary radiofrequency ablation. *World J Gastrointest Endosc.* 2015 Nov 10;7(16)
2. Daglilar ES,Yoon WJ, Mino-Kenudson M, Brugge WR. Controlled swine bile duct ablation with a bipolar radiofrequency catheter. *Gastrointest Endosc*. 2013 May;77(5):815-9
3. Dolak W, Tribl B, Schwaighofer H, Vogel W, Plieschgnegger W, Seibert F, Hellmich B, Holzapfel A, Wasilewski M, Gschwantler M, Mayer A, Decristoforo B, Dam KZ. Endoscopic radiofrequency ablation for malignant biliary obstruction: results of 43 procedures at 9 Austrian referral centres. *Endoscopy.* 2012;44:A14
4. Dolak W, Schreiber F, Schwaighofer H, Gschwantler M, Plieschnegger W, Ziachehabi A, Mayer A, Kramer L, Kopecky A, Schrutka-Kolbl C, Wolkersdorfer G, Madl C, Berr F, Trauner M, Puspok A. Endoscopic radiofrequency ablation for malignant biliary obstruction: a nationwide retrospective study of 84 consecutive applications. *Surg Endosc.* 2014;28:854-860
5. Duan XH, Wang YL, Han XW, Ren JZ, Li TF, Zhang JH, Zhang K, Chen PF. Intraductal Radiofrequency Ablation Followed by Locoregional Tumor Treatments for Treating Occluded Biliary Stents in Non-Resectable Malignant Biliary Obstruction: A Single-Institution Experience. *PLoS One*. 2015 Aug 5;10(8)
6. Figueroa-Barojas P, Bakhru MR, Habib N, Ellen K, Gaidhane M, Kahaleh M. Safety and efficacy of radiofrequency ablation in the management of unresectable bile duct and pancreatic cancer: A novel palliation technique. *Gastrointestinal Endoscopy*. 2011; 73; 4S AB 127
7. Figueroa-Barojas P, Bakhru M, Habib N, Ellen K, Gaidhane M, Kahaleh M. Safety and efficacy of radiofrequency ablation in the management of unresectable bile duct and pancreatic cancer: a novel palliation technique. *J Oncol.* 2013;2013:910897
8. Hu B, Gao DJ, Wu J, Wang TT, Yang XM, Ye X. Intraductal radiofrequency ablation for refractory benign biliary stricture: Pilot feasibility study. *Dig Endosc.* 2014 Jul;26(4):581-5
9. Hu B, Gao D, Zhang X, Zhang Y. Endobiliary Radiofrequency Ablation Improve Overall Survival of Cholangiocarcinoma: A Multi-Center Randomized Control Study. *Gastrointest Endosc.* 2016 May;83(5 Supp):AB126
10. Itoi T, Isayama H, Sofuni A, Itokawa F, Tamura M, Watanabe Y, Moriyasu F, Kahaleh M, Habib N, Nagao T, Yokoyama T, Kasuya K, Kawakami H. Evaluation of effects of a novel endoscopically applied radiofrequency ablation biliary catheter using an ex-vivo pig liver. *Journal of Hepatobiliary Pancreatology Science.* 2012;19:543-547
11. Kallis Y, Phillips N, Steel A, Kaltsidis H, Vlavianos P, Habib N, Westaby D. Analysis of Endoscopic Radiofrequency Ablation of Biliary Malignant Strictures in Pancreatic Cancer Suggests Potential Survival Benefit. *Dig Dis Sci.* 2015 Nov;60(11):3449-55
12. Laquière A, Boustière C, Leblanc S, Penaranda G, Désilets E, Prat F. Safety and feasibility of endoscopic biliary radiofrequency ablation treatment of extrahepatic cholangiocarcinoma. *Surg Endosc*. 2016 Mar;30(3):1242-8
13. Mizandari M, Pai M, Valek V, Tomas A, Doros A, Quaretti P, Golfieri R, Mosconi C, Guokun A, Kyriakides C, Dickinson R, Nicholls J, Habib N. Percutaneous Intraductal Radiofrequency Ablation is a Safe Option for Malignant Biliary Obstruction: Feasibility and Early Results. *Cardiovasc Intervent Radiol.* 2013;36:814-819

14. Monga A, Gupta R, Ramchandi M, Rao GV, Santosh D, Reddy DN. Endoscopic radiofrequency ablation of cholangiocarcinoma: a new palliative treatment modality (with videos). *Gastrointestinal Endoscopy.* 2011;74:935-7
15. Pai M, Valek V, Tomas A, Doros A, Quaretti P, Golfieri R, Mosconi C, Habib N. Percutaneous Intraductal Radiofrequency Ablation for Clearance of Occluded Metal Stent in Malignant Biliary Obstruction: Feasibility and Early Results. *Cardiovasc Intervent Radiol.* 2014 Feb;37(1):235-40
16. Rustagi T, Jamidar PA. Intraductal Radiofrequency Ablation for Management of Malignant Biliary Obstruction. *Dig Dis Sci.* 2014 ;59(11):2635-41
17. Sharaiha RZ, Natov N, Glockenberg KS, Widmer J, Gaidhane M, Kahaleh M. Comparison of Metal Stenting with Radiofrequency Ablation Versus Stenting Alone for Treating Malignant Biliary Strictures: Is There an Added Benefit? *Dig Dis Sci.* 2014 Dec;59(12):3099-102
18. Sharaiha RZ, Sethi A, Weaver KR, Gonda TA, Shah RJ, Fukami N, Kedia P, Kumta NA, Clavo CM, Saunders MD, Cerecedo-Rodriguez J, Barojas PF, Widmer JL, Gaidhane M, Brugge WR, Kahaleh M. Impact of Radiofrequency Ablation on Malignant Biliary Strictures: Results of a Collaborative Registry. *Dig Dis Sci.* 2015 60(7)2164-9
19. Steel AW, Postgate AJ, Khorsandi S, Nicholls J, Jiao L, Vlavianos P, Habib N, Westaby D. Endoscopically applied radiofrequency ablation appears to be safe in the treatment of malignant biliary obstruction. *Gastrointestinal Endoscopy.* 2011;73:149-53.
20. Strand DS, Cosgrove ND, Patrie JT, Cox DG, Bauer TW, Adams RB, Mann JA, Sauer BG, Shami VM, Wanng AY. ERCP-directed radiofrequency ablation and photodynamic therapy are associated with comparable survival in the treatment of unresectable cholangiocarcinoma. *Gastrointest Endosc.* 2014 Nov;80(5):794-804
21. Tal AO, Vermehren J, Friedrich-Rust M, Bojunga J, Sarrazin C, Zeuzem S, Trojan J, Albert JG. Intraductal endoscopic radiofrequency ablation for the treatment of hilar non-resectable malignant bile duct obstruction. *World Journal of Gastrointestinal Endoscopy.* 2014;6:13-19
22. Wang F, Li Q, Zhang X, Jiang G, Ge X, Yu H, Nie J, Ji G, Miao L. Endoscopic Radiofrequency Ablation for Malignant Biliary Strictures. *Exp Ther Med.* 2016; 11: 2484-2488
23. Wang J, Zhao L, Zhou C, Gao K, Huang Q, Wei B, Gao J. Percutaneous Intraductal Radiofrequency Ablation Combined with Biliary Stent Placement for Nonresectable Malignant Biliary Obstruction Improves Stent Patency but not Survival. *Medicine*. 2016; 95 (15): e3329
24. Wang Y, Cui W, Fan W, Zhang Y, Yao W, Huang K, Li J. Percutaneous Intraductal Radiofrequency Ablation in the Management of Unresectable Bismuth Types III and IV Hilar Cholangiocarcinoma. *Oncotarget*. 2016 Jun 17. doi: 10.18632/oncotarget.10116. [Epub ahead of print]
25. Weigt J, Kandulski A, Malfertheiner P. Endoscopic intraductal radiofrequency ablation of remnant intrapapillary mucinous neoplasm with acute hemorrhage after incomplete surgical resection. *Endoscopy.* 2014; 46 Suppl 1: E489-90
26. Wu TT, Li HC, Li WM, Ao GK, Lin H, Zheng F, Song JY. Percutaneous Intraluminal Radiofrequency Ablation for Malignant Extrahepatic Biliary Obstruction: A Safe and Feasible Method. *Dig Dis Sci.* 2015 Jul;60(7):2158-63

27. Zacharoulis D, Lazoura O, Sioka E, Potamianos S, Tzovaras G, Nicholls J, Koukoulis G, Habib N. Habib EndoHPB: a novel endobiliary radiofrequency ablation device. An experimental study. *J Invest Surg.* 2013 Feb;26(1):6-10

28. Zhou C, Wei B, Gao K, Zhai R. Biliary Tract Perforation Following Percutaneous Endobiliary Radiofrequency Ablation: A report of two cases. *Oncology Letters*. 2016; 11: 3813-3816
29. Perdue DG, et al. Plastic versus self-expanding metallic stents for malignant hilar biliary obstruction: a prospective multicentre observational cohort study. J Clin Gastroenterol 2008:42:1040-1046

2. Anecdotal adverse events (known from experience)

3. Theoretical adverse events

   Perforation of stomach wall, perforation of the bile duct, aneurysmal dilatation of the hepatic artery, necrotic infection, abscess, damage to neighbouring tissue.

4.2 What are the key efficacy outcomes for this procedure?

Length of time stent remains patent
Survival compared with Best Medical Care

4.3 Are there uncertainties or concerns about the *efficacy* of this procedure? If so, what are they?

There has been no randomised controlled trial reported. An RCT is underway in China:
https://clinicaltrials.gov/ct2/show/NCT01844245

4.4 What training and facilities are needed to do this procedure safely?

The procedure should be performed in the same setting as for standard ERCP procedures using local standard practice and can therefore be utilized in both tertiary and secondary hospitals.

In the UK, the device is marketed via a medical device distribution company (APR Medtech, Thame, UK. www.aprmedtech.com) who will provide support and training.

4.5 Are there any major trials or registries of this procedure currently in progress? If so, please list.

Dr Michel Kahaleh: Radio Frequency Ablation in the Management of Pancreato-Biliary Disorders: A Multicentre Registry (RFA Registry)

https://clinicaltrials.gov/ct2/show/NCT01439698

Publication:

Sharaiha RZ[1], Sethi A, Weaver KR, Gonda TA, Shah RJ, Fukami N, Kedia P, Kumta NA, Clavo CM, Saunders MD, Cerecedo-Rodriguez J, Barojas PF, Widmer JL, Gaidhane M, Brugge WR, Kahaleh M. Impact of Radiofrequency Ablation on Malignant Biliary Strictures: Results of a Collaborative Registry. Dig Dis Sci. 2015 Jul;60(7):2164-9. doi: 10.1007/s10620-015-3558-3. Epub 2015 Feb 21.

https://www.ncbi.nlm.nih.gov/pubmed/25701319

4.6 Are you aware of any abstracts that have been *recently* presented/ published on this procedure that may not be listed in a standard literature search, for example PUBMED? (This can include your own work). If yes, please list.
Please note that NICE will do a literature search: we are only asking you for any very recent or potentially obscure abstracts and papers. Please do not feel the need to supply a comprehensive reference list (but you may list any that you think are particularly important if you wish).

No

4.7 Is there controversy, or important uncertainty, about any aspect of the way in which this procedure is currently being done or disseminated?

Not that I am aware of.

5 Audit Criteria

Please suggest a minimum dataset of criteria by which this procedure could be audited.

5.1 Outcome measures of benefit (including commonly used clinical outcomes, both short and long - term; and quality-of-life measures). Please suggest the most appropriate method of measurement for each:

5.2 Adverse outcomes (including potential early and late complications). Please state timescales for measurement e.g. bleeding complications up to 1 month post-procedure:

6 Trajectory of the procedure

6.1 In your opinion, how quickly do you think use of this procedure will spread?

6.2 This procedure, if safe and efficacious, is likely to be carried out in (choose one):

☒ **X** Most or all district general hospitals.

☐ A minority of hospitals, but at least 10 in the UK.

☐ Fewer than 10 specialist centres in the UK.

☐ Cannot predict at present.

Comments:

6.3 The potential impact of this procedure on the NHS, in terms of numbers of patients eligible for treatment and use of resources, is:

☐ Major.

☐ Moderate.

☒ **X** Minor.

Comments:
The patients receiving this procedure would be having a standard ERCP and stent placement. The procedure adds about 5-10 minutes to the ERCP.

7 Other information

7.1 Is there any other information about this procedure that might assist NICE in assessing the possible need to investigate its use?

8 Data protection and conflicts of interest

8. Data protection, freedom of information and conflicts of interest

8.1 Data Protection

The information you submit on this form will be retained and used by the NICE and its advisers for the purpose of developing its guidance and may be passed to other approved third parties. Your name and specialist society will be published in NICE publications and on the NICE website. The specialist advice questionnaire will be published in accordance with our guidance development processes and a copy will be sent to the nominating Specialist Society. Please avoid identifying any individual in your comments.

☑ I have read and understood this statement and accept that personal information sent to us will be retained and used for the purposes and in the manner specified above and in accordance with the Data Protection Act 1998.

8.2 Declarations of interest by Specialist Advisers advising the NICE Interventional Procedures Advisory Committee

Nothing in your submission shall restrict any disclosure of information by NICE that is required by law (including in particular, but without limitation, the Freedom of Information Act 2000).

Please submit a conflicts of interest declaration form listing any potential conflicts of interest including any involvement you may have in disputes or complaints relating to this procedure.

Please use the "Conflicts of Interest for Specialist Advisers" policy as a guide when declaring any conflicts of interest. Specialist Advisers should seek advice if needed from the Associate Director – Interventional Procedures.

Do you or a member of your family[1] have a **personal pecuniary** interest? The main examples are as follows:

Consultancies or directorships attracting regular or occasional payments in cash or kind	☐	**YES**
	X	**NO**
Fee-paid work – any work commissioned by the healthcare industry **– this includes income earned in the course of private practice**	**X**	**YES**
	☐	**NO**
Shareholdings – any shareholding, or other beneficial interest, in shares of the healthcare industry	**X**	**YES**
	☐	**NO**
Expenses and hospitality – any expenses provided by a healthcare industry company beyond those reasonably required for accommodation, meals and travel to attend meetings and conferences	☐	**YES**
	X	**NO**
Investments – any funds that include investments in the healthcare industry	☐	**YES**
	X	**NO**
Do you have a **personal non-pecuniary** interest – for example have you made a public statement about the topic or do you hold an office in a professional organisation or advocacy group with a direct interest in the topic?	**X**	**YES**
	☐	**NO**

Do you have a **non-personal** interest? The main examples are as follows:

Fellowships endowed by the healthcare industry	☐	**YES**
	X	**NO**

[1] 'Family members' refers to a spouse or partner living in the same residence as the member or employee, children for whom the member or employee is legally responsible, and adults for whom the member or employee is legally responsible (for example, an adult whose full power of attorney is held by the individual).

Support by the healthcare industry or NICE that benefits his/her position or department, eg grants, sponsorship of posts

☐ **YES**

X NO

If you have answered YES to any of the above statements, please describe the nature of the conflict(s) below.

Comments:
I am the inventor of the EndoHPB device. The device is currently marketed via a spin out company from Imperial College London, EMcision Limited. I am a director and shareholder in the company. I have given presentations and I am a co-author on publications relating to the device.

I perform a small number of private or insurance paid surgeries at the private wing of the Hammersmith Hospital.

Thank you very much for your help.

Dr Tom Clutton-Brock, Interventional Procedures Advisory Committee Chair

Professor Carole Longson, Director, Centre for Health Technology Evaluation.

Jan 2016

Conflicts of Interest for Specialist Advisers

1 Declarations of interest by Specialist Advisers advising the NICE Interventional Procedures Advisory Committee

1.1 Any conflicts of interest set out below should be declared on the questionnaire the Specialist Adviser completes for the procedure.

1.2 Specialist Advisers should seek advice if required from the Associate Director – Interventional Procedures.

2 Personal pecuniary interests

2.1 A personal pecuniary interest involves a current personal payment to a Specialist Adviser, which may either relate to the manufacturer or owner of a product or service being evaluated, in which case it is regarded as **'specific'** or to the industry or sector from which the product or service comes, in which case it is regarded as **'non-specific'**. The main examples are as follows.

2.1.1 **Consultancies** – any consultancy, directorship, position in or work for the healthcare industry that attracts regular or occasional payments in cash or kind (this includes both those which have been undertaken in the 12 months preceding the point at which the declaration is made and which are planned but have not taken place).

2.1.2 **Fee-paid work** – any work commissioned by the healthcare industry for which the member is paid in cash or in kind (this includes both those which have been undertaken in the 12 months preceding the point at which the declaration is made and which are planned but have not taken place).

2.1.3 **Shareholdings** – any shareholding, or other beneficial interest, in shares of the healthcare industry that are either held by the individual or for which the individual has legal responsibility (for example, children, or relatives whose full Power of Attorney is held by the individual). This does not include shareholdings through unit trusts, pensions funds, or other similar arrangements where the member has no influence on financial management.

2.1.4 **Expenses and hospitality** – any expenses provided by a healthcare industry company beyond that reasonably required for accommodation, meals and travel to attend meetings and conferences (this includes both those which have been undertaken in the 12 months preceding the point at which the declaration is made and which are planned but have not taken place.

2.1.5 **Investments** – any funds which include investments in the healthcare industry that are held in a portfolio over which individuals have the ability to instruct the fund manager as to the composition of the fund.

2.2 No personal interest exists in the case of:

2.2.1 assets over which individuals have no financial control (for example, wide portfolio unit trusts and occupational pension funds) and where the fund manager has full discretion as to its composition (for example, the Universities Superannuation Scheme)

2.2.2 accrued pension rights from earlier employment in the healthcare industry.

3 **Personal family interest**

3.1 This relates to the personal interests of a family member and involves a **current payment** to the family member of the Specialist Adviser. The interest may relate to the manufacturer or owner of a product or service being evaluated, in which case it is regarded as '**specific**', or to the industry or sector from which the product or service comes, in which case it is regarded as '**non-specific**'. The main examples include the following.

3.1.1 Any consultancy, directorship, position in or work for a healthcare industry that attracts regular or occasional payments in cash or in kind.

3.1.2 Any fee-paid work commissioned by a healthcare industry for which the member is paid in cash or in kind.

3.1.3 Any shareholdings, or other beneficial interests, in a healthcare industry which are either held by the family member or for which an individual covered by this Code has legal responsibility (for example, children, or adults whose full Power of Attorney is held by the individual).

3.1.4 Expenses and hospitality provided by a healthcare industry company (except where they are provided to a general class of people such as attendees at an open conference)

3.1.5 Funds which include investments in the healthcare industry that are held in a portfolio over which individuals have the ability to instruct the fund manager as to the composition of the fund.

3.2 No personal family interest exists in the case of:

3.2.1 assets over which individuals have no financial control (for example, wide portfolio unit trusts and occupational pension funds) and where the fund manager has full discretion as to its composition (for example, the Universities Superannuation Scheme)

3.2.2 accrued pension rights from earlier employment in the healthcare industry.

4 **Personal non-pecuniary interests**

These might include, but are not limited to:

4.1 a clear opinion, reached as the conclusion of a research project, about the clinical and/or cost effectiveness of an intervention under review

4.2 a public statement in which an individual covered by this Code has expressed a clear opinion about the matter under consideration, which could reasonably be interpreted as prejudicial to an objective interpretation of the evidence

4.3 holding office in a professional organisation or advocacy group with a direct interest in the matter under consideration

4.4 other reputational risks in relation to an intervention under review.

5 Non-personal interests

5.1 A non-personal interest involves payment that benefits a department or organisation for which a Specialist Advisor is responsible, but that is not received by the Specialist Advisor personally. This may either relate to the product or service being evaluated, in which case it is regarded as **'specific,'** or to the manufacturer or owner of the product or service, but is unrelated to the matter under consideration, in which case it is regarded as **'non-specific'**. The main examples are as follows.

5.1.1 **Fellowships** – the holding of a fellowship endowed by the healthcare industry.

5.1.2 **Support by the healthcare industry or NICE** – any payment, or other support by the healthcare industry or by NICE that does not convey any pecuniary or material benefit to a member personally but that does benefit his/her position or department. For example:

- a grant from a company for the running of a unit or department for which a Specialist Advisor is responsible
- a grant, fellowship or other payment to sponsor a post or member of staff in the unit for which a Specialist Adviser is responsible. This does not include financial assistance for students
- the commissioning of research or other work by, or advice from, staff who work in a unit for which the specialist advisor is responsible
- one or more contracts with, or grants from, NICE.

5.2 Specialist Advisers are under no obligation to seek out knowledge of work done for, or on behalf of, the healthcare industry within departments for which they are responsible if they would not normally expect to be informed.

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Specialist Adviser questionnaire

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Please respond in the boxes provided.

Please complete and return to: Deonee.Stanislaus@nice.org.uk

Procedure Name:	**Endoscopic bipolar radiofrequency ablation for treating biliary obstruction caused by cholangiocarcinoma or pancreatic adenocarcinoma**
Name of Specialist Advisor:	Dr Yiannis Kallis
Specialist Society:	British Society of Gastroenterology (BSG)

1 Do you have adequate knowledge of this procedure to provide advice?

X Yes.

☐ No – please return the form/answer no more questions.

1.1 Does the title used above describe the procedure adequately?

X Yes.

☐ No. If no, please enter any other titles below.

Comments:

2 Your involvement in the procedure

2.1 Is this procedure relevant to your specialty?

X Yes.

☐ Is there any kind of inter-specialty controversy over the procedure?
No

☐ No. If no, then answer no more questions, but please give any information you can about who is likely to be doing the procedure.

Comments:

The next 2 questions are about whether you carry out the procedure, or refer patients for it. If you are in a specialty that normally carries out the procedure please answer question 2.2.1. If you are in a specialty that normally selects or refers patients for the procedure, please answer question 2.2.2.

2.2.1 If you are in a specialty that does this procedure, please indicate your experience with it:

☐ I have never done this procedure.

X I have done this procedure at least once.

☐ I do this procedure regularly.

Comments:

2.2.2 If your specialty is involved in patient selection or referral to another specialty for this procedure, please indicate your experience with it.

☐ I have never taken part in the selection or referral of a patient for this procedure.

☐ I have taken part in patient selection or referred a patient for this procedure at least once.

☐ I take part in patient selection or refer patients for this procedure regularly.

Comments:

2.3 Please indicate your research experience relating to this procedure (please choose one or more if relevant):

☐ I have done bibliographic research on this procedure.

☐ I have done research on this procedure in laboratory settings (e.g. device-related research).

X I have done clinical research on this procedure involving patients or healthy volunteers.

☐ I have had no involvement in research on this procedure.

☐ Other (please comment)

Comments:

I have published a retrospective case-control analysis of this procedure in biliary obstruction from pancreatic carcinoma (PCA) and in biliary metal stent occlusion in patients with pancreatic carcinoma and cholangiocarcinoma (CCA). (Dig Dis Sci. 2015 Nov;60(11):3449-55). I have also conducted a retrospective analysis if biliary RFA in the management of metal stent occlusion due to tumour ingrowth (unpublished data).

3 Status of the procedure

3.1 Which of the following best describes the procedure (choose one):

☐ Established practice and no longer new.

☐ A minor variation on an existing procedure, which is unlikely to alter the procedure's safety and efficacy.

X☐ Definitely novel and of uncertain safety and efficacy.

☐ The first in a new class of procedure.

Comments:

There have been numerous retrospective case-control analyses and case series published over the last 6 years, but as yet no data from large prospective randomised controlled trials.

3.2 What would be the comparator (standard practice) to this procedure?

This would depend on the clinical indication

i) malignant biliary obstruction secondary to PCA or CCA: comparator would be biliary metal/plastic stenting alone or photodynamic therapy (PDT) with stenting
ii) metal stent occlusion secondary to tumour ingrowth: comparator would be re-stenting alone

3.3 Please estimate the proportion of doctors in your specialty who are doing this procedure (choose one):

☐ More than 50% of specialists engaged in this area of work.

☐ 10% to 50% of specialists engaged in this area of work.

x Fewer than 10% of specialists engaged in this area of work.

☐ Cannot give an estimate.

Comments:

4 Safety and efficacy

4.1 What is the potential harm of the procedure?

Please list adverse events and major risks (even if uncommon) and, if possible, estimate their incidence, as follows:

1. Adverse events reported in the literature (if possible please cite literature)

Cholangitis or cholecystitis (5-10%)

Pancreatitis (< 5%)

Haemobilia (< 5%)

Hepatic artery pseudoaneurysm (< 2%)

Hepatic infarction (< 2%)

Bile duct perforation/bile leak (< 2%)

Portal vein thrombosis (< 2%)

2. Anecdotal adverse events (known from experience)

Abscess formation

3. Theoretical adverse events

No others

4.2 What are the key efficacy outcomes for this procedure?

Stent patency rates

Overall survival rates

Intervention free survival rate

Cholangitis related stent dysfunction

Quality of life measures

4.3 Are there uncertainties or concerns about the *efficacy* of this procedure? If so, what are they?

There is now considerable data showing good technical feasibility and acceptable safety rates in both PCA and CCA in studies with sample sizes between 10-65 patients. Retrospective matched case-control studies suggest superior efficacy vs.

biliary stenting alone (above outcome measures 4.2) but this has not yet been tested in RCTs.

4.4 What training and facilities are needed to do this procedure safely?

Bipolar RF energy source and endobiliary RFA catheter.
Otherwise standard ERCP equipment, facility and endoscopy nursing staff/fluoroscopy support. It would be recommended that endobiliary RF operators (ERCP endoscopists) gain familiarity with how the probe is deployed and with the use of the RF generator and settings, but otherwise endoscopic RFA would be a relatively straightforward procedure for an experienced ERCP endoscopist.

4.5 Are there any major trials or registries of this procedure currently in progress? If so, please list.

EndoHPB RCT was registered in Weill Cornell, New York, 2014, but the status of this trial in unknown to me.
Two UK based phase 2 RCT of the EndoHPB RFA probe in PCA and CCA respectively are have been at a planning stage for sometime. I am not aware that recruitment is yet underway.
There was a US based registry of endobiliary RFA procedures, data from which was published in 2015
(Dig Dis Sci. **2015** Jul;60(7):2164-9)

4.6 Are you aware of any abstracts that have been *recently* presented/ published on this procedure that may not be listed in a standard literature search, for example PUBMED? (This can include your own work). If yes, please list.
Please note that NICE will do a literature search: we are only asking you for any very recent or potentially obscure abstracts and papers. Please do not feel the need to supply a comprehensive reference list (but you may list any that you think are particularly important if you wish).

No

4.7 Is there controversy, or important uncertainty, about any aspect of the way in which this procedure is currently being done or disseminated?

There is little controversy with respect to the technical aspects of how this modality is delivered or the patient types and disease conditions that would be suitable for this therapy. Some doubt remains as to true efficacy in the absence of RCT data.

5 Audit Criteria
Please suggest a minimum dataset of criteria by which this procedure could be audited.

5.1 Outcome measures of benefit (including commonly used clinical outcomes, both short and long - term; and quality-of-life measures). Please suggest the most appropriate method of measurement for each:

30day, 6 month survival and overall survival rates

30day, 6 month and overall stent patency rates
(as assessed by radiological evidence of stent occlusion and recurrence of jaundice)

Stent occlusion related cholangitis rate
(as measured by evidence of biliary infection in the context of stent occlusion)

Stent intervention free survival rate
(as measured by survival rate in absence of evidence of stent occlusion)

Time to resolution of jaundice (as measured by serum bilirubin < 50mcmol/L)

5.2 Adverse outcomes (including potential early and late complications). Please state timescales for measurement e.g. bleeding complications up to 1 month post-procedure:

30d mortality

30d infection rate – cholangitis, cholecystitis, liver abscess

30d bile leak/perforation rate

7 day pancreatitis and bleeding rate

6 Trajectory of the procedure

6.1 In your opinion, how quickly do you think use of this procedure will spread?

I would estimate year-on-year uptake of this procedure across the endoscopy units in the country to increase by a maximum of 5-10% and be limited to high volume advanced HPB endoscopy centres initially.

6.2 This procedure, if safe and efficacious, is likely to be carried out in (choose one):

☐ Most or all district general hospitals.

x A minority of hospitals, but at least 10 in the UK.

☐ Fewer than 10 specialist centres in the UK.

☐ Cannot predict at present.

Comments:

I would expect the bulk of this endoscopic work to be delivered in ERCP endoscopy units associated with regional HPB cancer centres.

6.3 The potential impact of this procedure on the NHS, in terms of numbers of patients eligible for treatment and use of resources, is:

☐ Major.

☐ Moderate.

x Minor.

Comments:
I would anticipate that this procedure is limited to HPB cancer centres. In the absence of RCT data, I would predict that endobiliary RFA would not become standard of care in the first line management of malignant bile duct obstruction due to PCA or CCA. In this setting, I do not expect more than 100-200 procedures a year in the UK. This may increase several-fold with positive RCT data. This projected number would also include the application of endobiliary RFA for the management of stent occlusion due to tumour ingrowth, an area that again currently lacks good data for efficacy.
The capital costs for delivering endobiliary RFA are limited. Erbe VIO, and other similar machines already available in endoscopy units, could be used as RF energy sources. The only additional cost would thus be the single-use RFA catheter itself.

7 Other information

7.1 Is there any other information about this procedure that might assist NICE in assessing the possible need to investigate its use?

Until recently, most of the published data on endobiliary RFA pertained to one make of catheter, the Habib EndoHPB catheter. There are now other similar RFA catheters that have come to market, such as the ELRA system (StarMed).

8 Data protection and conflicts of interest

8. Data protection, freedom of information and conflicts of interest

8.1 Data Protection

The information you submit on this form will be retained and used by the NICE and its advisers for the purpose of developing its guidance and may be passed to other approved third parties. Your name and specialist society will be published in NICE publications and on the NICE website. The specialist advice questionnaire will be published in accordance with our guidance development processes and a copy will be sent to the nominating Specialist Society. Please avoid identifying any individual in your comments.

x I have read and understood this statement and accept that personal information sent to us will be retained and used for the purposes and in the manner specified above and in accordance with the Data Protection Act 1998.

8.2 Declarations of interest by Specialist Advisers advising the NICE Interventional Procedures Advisory Committee

Nothing in your submission shall restrict any disclosure of information by NICE that is required by law (including in particular, but without limitation, the Freedom of Information Act 2000).

Please submit a conflicts of interest declaration form listing any potential conflicts of interest including any involvement you may have in disputes or complaints relating to this procedure.

Please use the "Conflicts of Interest for Specialist Advisers" policy as a guide when declaring any conflicts of interest. Specialist Advisers should seek advice if needed from the Associate Director – Interventional Procedures.

Do you or a member of your family[1] have a **personal pecuniary** interest? The main examples are as follows:

Consultancies or directorships attracting regular or occasional payments in cash or kind	☐	**YES**
	x	**NO**
Fee-paid work – any work commissioned by the healthcare industry **– this includes income earned in the course of private practice**	☐	**YES**
	x	**NO**
Shareholdings – any shareholding, or other beneficial interest, in shares of the healthcare industry	☐	**YES**
	x	**NO**
Expenses and hospitality – any expenses provided by a healthcare industry company beyond those reasonably required for accommodation, meals and travel to attend meetings and conferences	☐	**YES**
	x	**NO**
Investments – any funds that include investments in the healthcare industry	☐	**YES**
	x	**NO**
Do you have a **personal non-pecuniary** interest – for example have you made a public statement about the topic or do you hold an office in a professional organisation or advocacy group with a direct interest in the topic?	☐	**YES**
	x	**NO**

Do you have a **non-personal** interest? The main examples are as follows:

Fellowships endowed by the healthcare industry	☐	**YES**
	x	**NO**

[1] 'Family members' refers to a spouse or partner living in the same residence as the member or employee, children for whom the member or employee is legally responsible, and adults for whom the member or employee is legally responsible (for example, an adult whose full power of attorney is held by the individual).

Support by the healthcare industry or NICE that benefits his/her position or department, eg grants, sponsorship of posts

☐ **YES**

x NO

If you have answered YES to any of the above statements, please describe the nature of the conflict(s) below.

Comments:

Thank you very much for your help.

Dr Tom Clutton-Brock, Interventional Procedures Advisory Committee Chair

Professor Carole Longson, Director, Centre for Health Technology Evaluation.

Jan 2016

Conflicts of Interest for Specialist Advisers

1 Declarations of interest by Specialist Advisers advising the NICE Interventional Procedures Advisory Committee

1.1 Any conflicts of interest set out below should be declared on the questionnaire the Specialist Adviser completes for the procedure.

1.2 Specialist Advisers should seek advice if required from the Associate Director – Interventional Procedures.

2 Personal pecuniary interests

2.1 A personal pecuniary interest involves a current personal payment to a Specialist Adviser, which may either relate to the manufacturer or owner of a product or service being evaluated, in which case it is regarded as **'specific'** or to the industry or sector from which the product or service comes, in which case it is regarded as **'non-specific'**. The main examples are as follows.

2.1.1 **Consultancies** – any consultancy, directorship, position in or work for the healthcare industry that attracts regular or occasional payments in cash or kind (this includes both those which have been undertaken in the 12 months preceding the point at which the declaration is made and which are planned but have not taken place).

2.1.2 **Fee-paid work** – any work commissioned by the healthcare industry for which the member is paid in cash or in kind (this includes both those which have been undertaken in the 12 months preceding the point at which the declaration is made and which are planned but have not taken place).

2.1.3 **Shareholdings** – any shareholding, or other beneficial interest, in shares of the healthcare industry that are either held by the individual or for which the individual has legal responsibility (for example, children, or relatives whose full Power of Attorney is held by the individual). This does not include shareholdings through unit trusts, pensions funds, or other similar arrangements where the member has no influence on financial management.

2.1.4 **Expenses and hospitality** – any expenses provided by a healthcare industry company beyond that reasonably required for accommodation, meals and travel to attend meetings and conferences (this includes both those which have been undertaken in the 12 months preceding the point at which the declaration is made and which are planned but have not taken place.

2.1.5 **Investments** – any funds which include investments in the healthcare industry that are held in a portfolio over which individuals have the ability to instruct the fund manager as to the composition of the fund.

2.2 No personal interest exists in the case of:

2.2.1 assets over which individuals have no financial control (for example, wide portfolio unit trusts and occupational pension funds) and where the fund manager has full discretion as to its composition (for example, the Universities Superannuation Scheme)

2.2.2 accrued pension rights from earlier employment in the healthcare industry.

3 **Personal family interest**

3.1 This relates to the personal interests of a family member and involves a **current payment** to the family member of the Specialist Adviser. The interest may relate to the manufacturer or owner of a product or service being evaluated, in which case it is regarded as '**specific**', or to the industry or sector from which the product or service comes, in which case it is regarded as '**non-specific**'. The main examples include the following.

3.1.1 Any consultancy, directorship, position in or work for a healthcare industry that attracts regular or occasional payments in cash or in kind.

3.1.2 Any fee-paid work commissioned by a healthcare industry for which the member is paid in cash or in kind.

3.1.3 Any shareholdings, or other beneficial interests, in a healthcare industry which are either held by the family member or for which an individual covered by this Code has legal responsibility (for example, children, or adults whose full Power of Attorney is held by the individual).

3.1.4 Expenses and hospitality provided by a healthcare industry company (except where they are provided to a general class of people such as attendees at an open conference)

3.1.5 Funds which include investments in the healthcare industry that are held in a portfolio over which individuals have the ability to instruct the fund manager as to the composition of the fund.

3.2 No personal family interest exists in the case of:

3.2.1 assets over which individuals have no financial control (for example, wide portfolio unit trusts and occupational pension funds) and where the fund manager has full discretion as to its composition (for example, the Universities Superannuation Scheme)

3.2.2 accrued pension rights from earlier employment in the healthcare industry.

4 **Personal non-pecuniary interests**

These might include, but are not limited to:

4.1 a clear opinion, reached as the conclusion of a research project, about the clinical and/or cost effectiveness of an intervention under review

4.2 a public statement in which an individual covered by this Code has expressed a clear opinion about the matter under consideration, which could reasonably be interpreted as prejudicial to an objective interpretation of the evidence

4.3 holding office in a professional organisation or advocacy group with a direct interest in the matter under consideration

4.4 other reputational risks in relation to an intervention under review.

5 Non-personal interests

5.1 A non-personal interest involves payment that benefits a department or organisation for which a Specialist Advisor is responsible, but that is not received by the Specialist Advisor personally. This may either relate to the product or service being evaluated, in which case it is regarded as **'specific,'** or to the manufacturer or owner of the product or service, but is unrelated to the matter under consideration, in which case it is regarded as **'non-specific'**. The main examples are as follows.

5.1.1 **Fellowships** – the holding of a fellowship endowed by the healthcare industry.

5.1.2 **Support by the healthcare industry or NICE** – any payment, or other support by the healthcare industry or by NICE that does not convey any pecuniary or material benefit to a member personally but that does benefit his/her position or department. For example:

- a grant from a company for the running of a unit or department for which a Specialist Advisor is responsible
- a grant, fellowship or other payment to sponsor a post or member of staff in the unit for which a Specialist Adviser is responsible. This does not include financial assistance for students
- the commissioning of research or other work by, or advice from, staff who work in a unit for which the specialist advisor is responsible
- one or more contracts with, or grants from, NICE.

5.2 Specialist Advisers are under no obligation to seek out knowledge of work done for, or on behalf of, the healthcare industry within departments for which they are responsible if they would not normally expect to be informed.