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:	**Selective internal radiation therapy for unresectable primary intrahepatic cholangiocarcinoma**
Name of Specialist Advisor:	Dr Annelies Maenhout
Specialist Society:	British Nuclear Medicine Society

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.

x I have done this procedure at least once.

☐ I do this procedure regularly.

Comments:

I have been involved in 56 SIRT procedures since 2009, and in 2 cases the primary tumour was a cholangiocarcinoma.

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:

We have been involved in the FOXFIRE trial (treated 2 patients). We have not been involved in any other research trial involving SIRT and in particular not in any research trials including with primary cholangiocarcinoma.

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:

Although it is established practice, it's exact role compared to other hepatic artery based therapies is still unclear.

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

Other hepatic artery based therapies: HAI (hepatic artery infusion), TACE (hepatic artery chemo-embolisation) and DEB-TACE (drug-eluted beads trans-arterial chemo-embolisation).

From my own experience, SIRT treatments are mainly considered later and towards the end stage of the disease, when patients are poor surgical candidates with bilobar masses, intolerant or have become refractory to chemotherapy and also if an unfavourable location for ablation.
SIRT therapy is often the only option left for the patient, and if they are not suitable or able to receive SIRT treatment, they will be offered best supportive care.

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:

Since the CtE programme ceased on 31/03/17, there has been a further reduction in number of sites and number of SIRT procedures per site in general.

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)

   Acute pancreatitis, acute peptic ulceration, radiation pneumonitis and radiation hepatitis. The incidence of those adverse events is very low.

2. Anecdotal adverse events (known from experience)

In the 56 cases we performed in our trust since 2009. Approximately 40% of our patients suffer from only mild symptoms post treatment such as mild transient abdominal pain, nausea and tiredness and in 2 patients there was severe abdominal pain post treatment, which may have been related to an induced gastritis and resolved within days on conservative treatment and 1 case of radiation hepatitis (this patient was part of FOXFIRE trial).

3. Theoretical adverse events

   Exposure to ionising radiation can increase the risk of cancer

4.2 What are the key efficacy outcomes for this procedure?

Progression free survival
Overall survival
Time to progression
Time to progression within liver

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

Only tumours within the liver are targeted and extra hepatic disease is not and may progress

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

Training for the administration of the product is provided by the companies (Sirtex and BTG) and their support is excellent throughout.

Multidisciplinary approach is crucial to deliver this treatment effectively, including discussion of potential patients on MDT (including interventional radiologist, nuclear medicine consultant, surgeon and oncologist).

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

TRIAL:NTC00858429, registered 03/2009

Yttrium Y 90 Glass Microspheres and Capecitabine in Treating Patients With Liver Cholangiocarcinoma or Liver Metastases
M Mulcahy

TRIAL:NCT01798147, registered 02/2013

Selective internal radiotherapy (SIRT) versus transarterial chemoembolization(TACE) for the treatment of intrahepatic cholangiocellular carcinoma (CCC): study protocol for a randomized controlled trial.
Kloeckner R, Ruckes C, Kronfeld K et all

TRIAL: NCT01912053, registered 09/2013

Efficacy Study of Intra-hepatic Administratin of Therasphere in Association With Intravenous Chemotherapy to Treat Cholangiocarcinoam (MispheC)
E Boucher

TRIAL: NCT02167711, registered 06/2014

Selective Internal Radiation Therapy With Yttrium-90 Resin Microspheres Followed by Gemcitabine Plus Cisplatin for Intra-hepatic Cholangiocarcinoma: A Phase II Study
SL Chan, J Koh

TRIAL: NCT02512692, registered 07/2015

90Y Transarterial Radioembolization (TARE) Plus Gemcitabine and Cisplatin in Unresectable Intrahepatic Cholangiocarcinoma
SL Cooper

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).

Yttrium-90 resin microspheres radioembolization (SIRT) of primitive and secondary liver tumors : survival and safety study. V Frusciante, G Catriotta, F Floria et al
Congress : EANM 21-25/10/2017 Poster EP-0863

Effectiveness and safety of transarterial Y-90 radioembolization for unresectable intrahepatic cholangiocarcinoma. G Boni, T Depalo, I Bargellini et al
Congress : EANM 21-25/10/2017 Poster EP-0873

Safety, efficacy and outcome of Y-90-resin-microspheres radioembolization in 73 patients with unresectable intrahepatic cholangiocarcionoma: a single center experience. A Todica, K J Paprottka, F Schöppe et al
Congress : EANM 21-25/10/2017 Poster E-PW052

Quality of life in patients with liver metastases from colorectal cancer treated with first-line selective internal radiotherapy (SIRT): EQ-5D, EORTC QLQ-C30 and LMC21 results from the FOXFIRE prospective randomized study.
Congress: NCRI 07/11/2017

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

Dosimetry: There are different dosimetry models recommended by the 2 approved products often resulting in differences in calculated doses for administration.

Optimal time for treatment delivery within the patient's overall treatment plan

Currently not being effectively disseminated for NHS patients (apart from research and compassionate use) despite positive contributory value.

5 Audit Criteria
Please suggest a minimum dataset of criteria by which this procedure could be audited.
Patients' demographics, time from diagnosis to SIRT treatment, number of cycles of chemotherapy prior to SIRT treatment, co-morbidities, liver function parameters, any contra-indications to other potential treatments, toxicity, number of patients down-staged with SIRT prior to surgery

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:

Follow-up studies at 3 months with FDG PET-CT and/or cross-sectional imaging using the RECIST criteria and serial tumour markers (CA19.9, CEA, AFP).

Quality-of-life measures: I assume that QALY's would combine the impact of gains in quality of life and in quantity of life, although as far as I am aware, this has not been formally investigated as outcome measure for SIRT procedures in cholangiocarcinoma. There has been a recent abstract presentation on quality-of-life presented at the NCRI on FOXFIRE study patients (see 4.6)

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:

See 4.1

6 Trajectory of the procedure

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

Unlikely to spread at the moment as patients can only receive this treatment if they are self-funded, or as part of research trial or if special request for compassionate use has been accepted by companies providing a complimentary dose.

If the CtE programme would recommence, it would still be unlikely to be more than a niche but nevertheless important modality of treatment given its unique position: the incidence of ICC is 1.67/100000 (USA) and SIRT is only one of the potentially suitable treatments amongst others such as surgery, chemotherapy, ablation and other intrahepatic artery based treatments.

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:

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:

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.

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**

[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).

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**
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.

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:	**Selective internal radiation therapy for unresectable primary intrahepatic cholangiocarcinoma**
Name of Specialist Advisor:	Dr Daniel McGowan
Specialist Society:	British Nuclear Medicine Society

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

☒ Yes.

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

1.1 Does the title used above describe the procedure adequately?

☒ 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?

☒ 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.

☐ 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).

☐ 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):

☒ 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:

The procedure for selective internal radiation therapy (SIRT) is similar whether it is for ICC, mCRC, or HCC patents. Due to trials in the UK such as FOXFIRE and EPOCH there are a number of sites with familiarity of the SIRT procedure.

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

TACE or chemotherapy

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:

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)

Summary in Table 4 of a recent systematic review Al-Adra 2015 (Eur J Surg Oncol), extracts from paper:

"The most common types of morbidity following radioembolization therapy with yttrium-90 microspheres were fatigue (33%), abdominal pain (28%) and nausea (25%)."

"Serious morbidity requiring intervention or long-term sequelae included complications of ulcers (due to bead migration), pleural effusions and ascites. The majority of morbidity was from fever, abdominal pain and nausea. Overall, the complication profile of radioembolization is similar to that of chemoembolization seen in recent systematic reviews of similar disease process"

2. Anecdotal adverse events (known from experience)

3. Theoretical adverse events

Radiation-induced liver disease

4.2 What are the key efficacy outcomes for this procedure?

QoL, PFS, OS, tumour response

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

No

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

Requires a trained multidisciplinary team (including interventional radiologists, nuclear medicine radiologists, oncologists, physicists, radiopharmacy). Training could be provided by visiting existing centres and performing procedures under guidance.

Requires a SPECT/CT system to perform post work up imaging (Tc99m MAA lung shunt). Then a SPECT/CT or PET/CT system to scan the patient after SIRT treatment. The post-SIRT scan can be used to calculate the absorbed dose delivered to the tumour for which appropriate software is needed.

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

SIRCCA

https://www.bsir.org/registries/sirt-registry/

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).

NHS England has recently published its report on the SIRT CtE programme which included ICC https://www.england.nhs.uk/wp-content/uploads/2017/10/selective-internal-radiation-therapy-commissioning-evaluation-report.pdf

EP-0873 Boni et al "Effectiveness and safety of transarterial Y-90 radioembolization for unresectable intrahepatic cholangiocarcinoma" presented at European Association of Nuclear Medicine Annual Meeting 2017 (abstracts https://link.springer.com/content/pdf/10.1007%2Fs00259-017-3822-1.pdf

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

No

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:

PFS, QoL, OS, tumour response (RECIST 1.1)

Delivered dose to tumour (from post-SIRT Y90 imaging). This would allow outcome to be stratified by Y90 absorbed dose to the tumour.

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?

Relatively slowly due to the initial training required to set up the multidisciplinary group. However, hospitals who have taken part in clinical trials (such as FOXFIRE or EPOCH) will already be trained.

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

☐ 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.

☒ Minor.

Comments:

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?

A forthcoming EU directive (2013/59 Euratom) mandates that treatments should be planned according to the radiation doses delivered to individual patients and that the verification of the radiation dose delivered should take place. This will come into force in Feb 2018. At this point centres will need to have appropaite software and undertake post-SIRT imaging in order to calculate this for SIRT treatments.

Recently the European Association of Nuclear Medicine Internal Dosimetry Task Force produced a report on Treatment Planning for Molecular Radiotherapy: Potential and Prospects (http://www.eanm.org/content-eanm/uploads/documents/EANM_2017_iDTF-Report_online.pdf). An extract from the text regarding Y90 SIRT listing areas that should be investigated:

"Standardisation of PET and SPECT imaging, particularly for bremsstrahlung, is needed as is standardisation of dosimetry procedures to facilitate direct comparisons of results obtained from different centres. The promising indications of absorbed dose effect relationships imply that a multicentre study would produce the evidence for personalised treatments. A potential for treatment planning would be to focus on delivering the maximum tolerable dose to healthy tissue

8 Data protection and conflicts of interest

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

8.1 Data Protection

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☑ 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** ☒ **NO**
Fee-paid work – any work commissioned by the healthcare industry **–**	☐ **YES**

[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).

this includes income earned in the course of private practice	☒ **NO**
Shareholdings – any shareholding, or other beneficial interest, in shares of the healthcare industry	☐ **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** ☒ **NO**
Investments – any funds that include investments in the healthcare industry	☐ **YES** ☒ **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** ☒ **NO**
Do you have a **non-personal** interest? The main examples are as follows:	
Fellowships endowed by the healthcare industry	☐ **YES** ☒ **NO**
Support by the healthcare industry or NICE that benefits his/her position or department, eg grants, sponsorship of posts	☐ **YES** ☒ **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.

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:	**Selective internal radiation therapy for unresectable primary intrahepatic cholangiocarcinoma**
Name of Specialist Advisor:	Dr Daniel McGowan
Specialist Society:	British Nuclear Medicine Society

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

☒ Yes.

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

1.1 Does the title used above describe the procedure adequately?

☒ 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?

☒ 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.

☐ 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).

☐ 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):

☒ 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:

The procedure for selective internal radiation therapy (SIRT) is similar whether it is for ICC, mCRC, or HCC patents. Due to trials in the UK such as FOXFIRE and EPOCH there are a number of sites with familiarity of the SIRT procedure.

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

TACE or chemotherapy

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:

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)

Summary in Table 4 of a recent systematic review Al-Adra 2015 (Eur J Surg Oncol), extracts from paper:

"The most common types of morbidity following radioembolization therapy with yttrium-90 microspheres were fatigue (33%), abdominal pain (28%) and nausea (25%)."

"Serious morbidity requiring intervention or long-term sequelae included complications of ulcers (due to bead migration), pleural effusions and ascites. The majority of morbidity was from fever, abdominal pain and nausea. Overall, the complication profile of radioembolization is similar to that of chemoembolization seen in recent systematic reviews of similar disease process"

2. Anecdotal adverse events (known from experience)

3. Theoretical adverse events

Radiation-induced liver disease

4.2 What are the key efficacy outcomes for this procedure?

QoL, PFS, OS, tumour response

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

No

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

Requires a trained multidisciplinary team (including interventional radiologists, nuclear medicine radiologists, oncologists, physicists, radiopharmacy). Training could be provided by visiting existing centres and performing procedures under guidance.

Requires a SPECT/CT system to perform post work up imaging (Tc99m MAA lung shunt). Then a SPECT/CT or PET/CT system to scan the patient after SIRT treatment. The post-SIRT scan can be used to calculate the absorbed dose delivered to the tumour for which appropriate software is needed.

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

SIRCCA

https://www.bsir.org/registries/sirt-registry/

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).

NHS England has recently published its report on the SIRT CtE programme which included ICC https://www.england.nhs.uk/wp-content/uploads/2017/10/selective-internal-radiation-therapy-commissioning-evaluation-report.pdf

EP-0873 Boni et al "Effectiveness and safety of transarterial Y-90 radioembolization for unresectable intrahepatic cholangiocarcinoma" presented at European Association of Nuclear Medicine Annual Meeting 2017 (abstracts https://link.springer.com/content/pdf/10.1007%2Fs00259-017-3822-1.pdf

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

No

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:

PFS, QoL, OS, tumour response (RECIST 1.1)

Delivered dose to tumour (from post-SIRT Y90 imaging). This would allow outcome to be stratified by Y90 absorbed dose to the tumour.

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?

Relatively slowly due to the initial training required to set up the multidisciplinary group. However, hospitals who have taken part in clinical trials (such as FOXFIRE or EPOCH) will already be trained.

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

☐ 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.

☒ Minor.

Comments:

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?

A forthcoming EU directive (2013/59 Euratom) mandates that treatments should be planned according to the radiation doses delivered to individual patients and that the verification of the radiation dose delivered should take place. This will come into force in Feb 2018. At this point centres will need to have appropaite software and undertake post-SIRT imaging in order to calculate this for SIRT treatments.

Recently the European Association of Nuclear Medicine Internal Dosimetry Task Force produced a report on Treatment Planning for Molecular Radiotherapy: Potential and Prospects (http://www.eanm.org/content-eanm/uploads/documents/EANM_2017_iDTF-Report_online.pdf). An extract from the text regarding Y90 SIRT listing areas that should be investigated:

"Standardisation of PET and SPECT imaging, particularly for bremsstrahlung, is needed as is standardisation of dosimetry procedures to facilitate direct comparisons of results obtained from different centres. The promising indications of absorbed dose effect relationships imply that a multicentre study would produce the evidence for personalised treatments. A potential for treatment planning would be to focus on delivering the maximum tolerable dose to healthy tissue

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** ☒ **NO**
Fee-paid work – any work commissioned by the healthcare industry **–**	☐ **YES**

[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).

this includes income earned in the course of private practice	☒	**NO**
Shareholdings – any shareholding, or other beneficial interest, in shares of the healthcare industry	☐ ☒	**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** **NO**
Investments – any funds that include investments in the healthcare industry	☐ ☒	**YES** **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** **NO**
Do you have a **non-personal** interest? The main examples are as follows:		
Fellowships endowed by the healthcare industry	☐ ☒	**YES** **NO**
Support by the healthcare industry or NICE that benefits his/her position or department, eg grants, sponsorship of posts	☐ ☒	**YES** **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

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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.

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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.

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:	**Selective internal radiation therapy for unresectable primary intrahepatic cholangiocarcinoma**
Name of Specialist Advisor:	Glenn Flux
Specialist Society:	**British Nuclear Medicine Society**

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?

X 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:

X 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.

X 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):

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).

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

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

X Other (please comment)

Comments:

I have conducted research into the imaging and dosimetry for this product and am currently supervising a PhD student working in this area.

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:

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

My expertise is not clinical. Sorafenib is a comparator.

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)

Over-irradiation of the normal liver or shunting to the lung which in some cases has been fatal. Radiation related outcomes are summarised in the review article:

Cremonesi M, Chiesa C, Strigari L et al. Radioembolization of hepatic lesions from a radiobiology and dosimetric perspective Front Oncol. 2014 19;4:210. doi: 10.3389/fonc.2014.00210.

2. Anecdotal adverse events (known from experience)

3. Theoretical adverse events

4.2 What are the key efficacy outcomes for this procedure?

A decrease in tumour volume or eradication, as a function of the absorbed doses delivered.

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

Efficacy is dependent on the absorbed doses delivered to tumours. Threshold absorbed doses required for effective treatment have been identified although not yet confirmed in a multicentre trial.

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

Close involvement of physics is essential. A medical physics expert should be trained in quantitative imaging with radionuclides, including bremsstrahlung and PET/CT imaging, and internal dosimetry.

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

In addition to clinical trials to evaluate the efficacy OF SIRT, BTG are currently performing a dosimetry trial (TARGET) to determine the role of dosimetry in personalising treatments.

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).

A large number of abstracts were presented at the European Association of Nuclear Medicine annual congress 2017 that demonstrated the importance of nuclear medicine and dosimetry as an integral aspect relating to treatment efficacy and toxicity (https://link.springer.com/content/pdf/10.1007%2Fs00259-017-3822-1.pdf). There are many ongoing research projects in this area.

Abstracts included results showing correlation of tumour response with the absorbed doses delivered and optimised imaging for the visualisation and quantification of nuclear medicine images.

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

The basis for administration varies. It is currently primarily based on body surface area or whole liver dosimetry. There are stroing argument that it should be based on personalised dosimetry.

5 Audit Criteria

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

No comment

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:

Metabolic as well as anatomical changes in lesions

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:

Lung toxicity and normal liver decompensation

6 Trajectory of the procedure

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

A doubling rate is difficult to predict, although there is an increase in the use of radiotherapeutics.

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:

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.

X Moderate.

☐ Minor.

Comments:

A necessarily relative measure, so hard to judge.

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?

There are 2 major products at present, but at least one more in development. The treatment offers a different treatment option and makes use of theragnostics. As such, its use will continue to develop. It isn't a simple question of whether the treatment works or not, but a question of what level of treatment would work to what degree for which patient and should be evaluated as such. The potential for personalised treatments, based on imaging and internal dosimetry, is not available to 'cold therapeutics'.

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**	☐	**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	X	**YES**
	☐	**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

X **YES**

☐ **NO**

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

Comments:
I have received research funding (~ £25,000) from Sirtex for the development of patient specific phantoms. I have received ~£3000 from BTG for chairing meetings and providing advice concerning dosimetry. I have received travel and accommodation costs from both.

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.

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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.

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:	**Selective internal radiation therapy for unresectable primary intrahepatic cholangiocarcinoma**
Name of Specialist Advisor:	Mr Hassan Malik
Specialist Society:	British Association of Surgical Oncology

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

☒ Yes.

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

1.1 Does the title used above describe the procedure adequately?

☒ 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?

☒ 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:

Not currently funded, SIRCCA RCT will investigate radio-embolisation for IHC in first line setting

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.

☒ 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).

☐ 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):

☐ 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:

Procedure is established for management for a number of liver malignancies – primary and metastatic in various lines of treatment. Re IHC, it is not currently standard of care so although the procedure is established this TA would be a minor variation in terms of patient inclusion criteria. With regards to safety, the management of biliary obstruction secondary to the IHC has to be considered in the context of SIRT, as well as the potential radio-sensitising effect of the Cis/Gem chemotherapy which is currently standard of care in this setting.

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

Cisplatin/Gemcitabine chemotherapy

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:

No hepatobiliary surgeons are undertaking radio-embolization in the UK as far as I am aware.

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)

Short term: Pulmonary toxicity, pancreatitis, gastritis, lethargy, death,

Long term: liver fibriosis, development of portal hypertension

2. Anecdotal adverse events (known from experience)

3. Theoretical adverse events

4.2 What are the key efficacy outcomes for this procedure?

Overall survival, PFS, PROMS/QOL

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

Uncertainty of benefit above and beyond systemic chemotherapy

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

The criteria to manage radio-embolic products is stringent and only a limited number of UK centres are licenced to use this treatment. An interventional radiologists undertaking these procedures will be able to advise on the industry standards that they use.

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

Yes – SIRCCA trial

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).

Radioembolization for Unresectable Intrahepatic Cholangiocarcinoma: Review of Safety, Response Evaluation Criteria in Solid Tumors 1.1 Imaging Response and Survival. Swinburne NC, Biederman DM, Besa C, Tabori NE, Fischman AM, Patel RS, Nowakowski FS, Gunasekaran G, Schwartz ME, Lookstein RA, Kim E. Cancer Biother Radiopharm. 2017 Jun;32(5):161-168. doi: 10.1089/cbr.2017.2189. Epub 2017 Jun 9.

Improving patient selection for selective internal radiation therapy of intra-hepatic cholangiocarcinoma: A meta-regression study. Cucchetti A, Cappelli A, Mosconi C, Zhong JH, Cescon M, Pinna AD, Golfieri R. Liver Int. 2017 Jul;37(7):1056-1064. doi: 10.1111/liv.13382. Epub 2017 Mar 2.

Comparison of Choi criteria and Response Evaluation Criteria in Solid Tumors (RECIST) for intrahepatic cholangiocarcinoma treated with glass-microspheres Yttrium-90 selective internal radiation therapy (SIRT). Beuzit L, Edeline J, Brun V, Ronot M, Guillygomarc'h A, Boudjema K, Gandon Y, Garin E, Rolland Y. Eur J Radiol. 2016 Aug;85(8):1445-52. doi: 10.1016/j.ejrad.2016.05.020. Epub 2016 Jun 2.

Glass Microspheres 90Y Selective Internal Radiation Therapy and Chemotherapy as First-Line Treatment of Intrahepatic Cholangiocarcinoma. Edeline J, Du FL, Rayar M, Rolland Y, Beuzit L, Boudjema K, Rohou T, Latournerie M, Campillo-Gimenez B, Garin E, Boucher E. Clin Nucl Med. 2015 Nov;40(11):851-5. doi: 10.1097/RLU.0000000000000904

Selective internal radiotherapy (SIRT) versus transarterial chemoembolization (TACE) for the treatment of intrahepatic cholangiocellular carcinoma (CCC): study protocol for a randomized controlled trial. Kloeckner R, Ruckes C, Kronfeld K, Wörns MA, Weinmann A, Galle PR, Lang H, Otto G, Eichhorn W, Schreckenberger M, Dueber C, Pitton MB. Trials. 2014 Aug 6;15:311. doi: 10.1186/1745-6215-15-311

Radioembolization of liver tumors with yttrium-90 microspheres. Ahmadzadehfar H, Biersack HJ, Ezziddin S. Semin Nucl Med. 2010 Mar;40(2):105-21. doi: 10.1053/j.semnuclmed.2009.11.001. Review

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

I'm not aware of this treatment being available in this proposed setting in the NHS

5 Audit Criteria

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

Total numbers screened, total numbers treated, baseline liver function tests, treatment related complications, PFS, OS, QOL

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:

EORTC QLQ-C30

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:

Due to the deleterious effect of radiotherapy in the liver, late complications including development of liver cirrhosis and portal hypertension can occur several years after the procedure. Thus adverse outcomes need to reported up to at least 5 years after the procedure.

6 Trajectory of the procedure

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

Quickly if funded as beyond chemotherapy there are limited alternative options in this patient setting.

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

☐ 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.

■ Minor.

Comments:
Chioonagiocarcinoma is a relatively rare tumour with approximately 2500 deaths per year. The IHC variant only occurs in about 25% of cases, of whom a proportion will be eligible for this treatment. Thus the impact in terms of patient numbers will be limited.

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

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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**

■ **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).

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Shareholdings – any shareholding, or other beneficial interest, in shares of the healthcare industry	☐ **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** ■ **NO**
Investments – any funds that include investments in the healthcare industry	☐ **YES** ■ **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** ■ **NO**

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

Fellowships endowed by the healthcare industry	☐ **YES** ■ **NO**
Support by the healthcare industry or NICE that benefits his/her position or department, eg grants, sponsorship of posts	☐ **YES** ■ **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

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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

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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.

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:	**Selective internal radiation therapy for unresectable primary intrahepatic cholangiocarcinoma**
Name of Specialist Advisor:	Dr Nadeem Shaida
Specialist Society:	British Nuclear Medicine Society

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

☒ Yes.

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

1.1 Does the title used above describe the procedure adequately?

☒ 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?

☒ 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:

Procedure performed by Interventional Radiologists – Nuclear Medicine physicians heavily involved in planning and dosing the treatment. In some centres the nuclear medicine physician will also inject the spheres.

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:

I have performed this procedure many times for other indications (eg. Colorectal metastases or hepatocellular carcinoma). I have perfomed it for this indication a few times (approx. 5)

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).

☐ 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 treated patients who have been enrolled in clinical trials. In addition I have treated patients who were part of the CtE process whilst that was ongoing.

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.

☒ Definitely novel and of uncertain safety and efficacy.

☐ The first in a new class of procedure.

Comments:

Data is building on other types of liver tumour (mets/HCC). For cholangiocarcinoma there is less data available – what there is suggests that overall survival is of the order of around 12-15months (although huge heterogeneity due to other features of the tumour – multifocal etc.) but what is also interesting is that some tumours can be downstaged to make resection feasible.

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

Chemotherapy

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:

Because of the challenging dosing etc., a mature set up with nuclear medicine and Interventional Radiology is required. This means only large centres in the UK are performing this and within most of those centres there will likely be only 1 or 2 IRs involved.

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)

Radiation Induced Liver Damage (RILD)

Radiation gastritis or bowel injury

Radiation pneumonitis

Cholecystitis

Fatigue, nausea

2. Anecdotal adverse events (known from experience)

Non-target embolisation causing non radiation induced pain

Cachexia

3. Theoretical adverse events

n/a

4.2 What are the key efficacy outcomes for this procedure?

Overall survival, local progression free survival, downstaging to resectability

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

Yes – there is heterogeneity in results depending on size multifocality, portal vein involvement etc.

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

Interventional Radiology training with specific training in this procedure. Nuclear medicine facilities, radiopharmacy etc. Imaging facilities (PET-CT etc.)

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

Not aware

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).

Not aware

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 are 2 companies that make the spheres – one is glass one is resin. They have slightly different dosing strategies and technique. It is not clear if there is any difference between the two methods.

5 Audit Criteria
Please suggest a minimum dataset of criteria by which this procedure could be audited.
Tumour volume
Single or Bilobar
Number of treatments
Overall survival
Complications/Safety
Liver function tests

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:

Overall survival
Liver free progression

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:

Bleeding (within 1 week)
RILD for up to 1 year
Gastritis/Cholecystitis (1 month)

6 Trajectory of the procedure

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

Slowly – the treatment is expensive and there are generally only single centre series in the literature. A good quality multicentre RCT would help.

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

☐ 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.

☒ Minor.

Comments:
Would be for small numbers of patients

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?

n/a

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.

xI 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** ☒ **NO**
Fee-paid work – any work commissioned by the healthcare industry **– this includes income earned in the course of private practice**	☐ **YES** ☒ **NO**
Shareholdings – any shareholding, or other beneficial interest, in shares of the healthcare industry	☐ **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** ☒ **NO**
Investments – any funds that include investments in the healthcare industry	☐ **YES** ☒ **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** ☒ **NO**

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

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[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).

Fellowships endowed by the healthcare industry

☐ **YES**

☒ **NO**

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

☐ **YES**

☒ **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.