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: azad.hussain@nice.org.uk and IPSA@nice.org.uk

Procedure Name:	**Low energy contact X-ray brachytherapy (the Papillon technique) for locally advanced, inoperable, rectal cancer**
Name of Specialist Advisor:	Arthur Sun Myint
Specialist Society:	Association of Coloproctology of Great Britain and Ireland (ACPGBI)

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?

☐ Yes.

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

Comments:

Better to use in patients not suitable for surgery rather than 'inoperable' as most rectal tumours are now operable by modern surgical techniques.

2 Your involvement in the procedure

2.1 Is this procedure relevant to your specialty?

X☐ Yes.

X☐ 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:

Older surgeons considered CXB as palliative treatment and do not advise patients even when they refused surgery. Most patients were offered external beam chemo-radiotherapy (EBCRT) or radiotherapy (EBRT). Only 10-20 % will achieve clinical complete response (cCR) and they can adopt 'Watch wait 'programme (Smith et al. BMJ.2018). However, 20-30% will develop local regrowth which required salvage surgery (See also section 4.7 answer).
This is gradually changing and younger surgeons are keen to avoid major surgery especially in older patients (to avoid surgical harm) and are referring more patients for CXB and reserve surgery as a salvage procedure. Referrals for CXB have increased from less than 80 patients to over 300 patients in the past 5 years).

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.

X☐ I do this procedure regularly.

Comments:

I have treated 142 patients personally in the past 12 months and over 1600 patients in the past 25 years (since 1993).

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

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

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

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

Comments:

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

☐ I have done bibliographic research on this procedure.

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

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

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

☐ Other (please comment)

Comments:

I have published a number of research papers related to this procedure since 2003 (see list of publications). I am also PI of the European phase 3 randomised trial OPERA for operable patients with rectal cancer.

3 Status of the procedure

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

☐ Established practice and no longer new.

X☐ 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:

NICE has published (IPG 532) in September 2015 for early rectal cancer in patients not suitable for surgery. This includes safety and efficacy for early rectal cancer but not for advanced rectal cancer.

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

The standard of care for advanced rectal cancer is preoperative EBCRT or EBRT followed by surgery (NICE guidance 2011, 2014).

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:

There are 4 centres in the UK offering CXB at present. There is interest from clinicians in other centres that are keen to set up CXB facilities in their centres.

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)

NICE has reviewed the potential harms of CXB in the IPG 543 and had published their findings. The main adverse events are:-

1.1 Bleeding occurs in 20-38% of patients following CXB (Grade 1-2). This is due to telangiectasia caused by radiation. Argon plasma coagulation (APC) is necessary in 10% of these patients for trouble some bleeding (Grade 3). Most of these are patients on anticoagulants or antiplatelet therapy. No hospital admission needed for surgery to stop the bleeding or blood transfusion necessary in our patients.

1.2 Rectal ulceration caused by radiation (Radiation ulcer) can occur in 27% of cases but this usually healed within 3-6 months without any late sequelae (IPG 532).

1.3 Slight proctitis (10%).

1.4 Moderate tenesmus 15% after treating very low rectal cancer (<6cm from anal verge). Respond well to steroid suppositories.

2. Anecdotal adverse events (known from experience)

Unusual anecdotal adverse events

2.1 Recto vaginal fistula. Can occur after CXB in less than 1% of cases following TEMS (Trans-anal Endoscopic Micro surgery). We now avoid doing TEMS on very low rectal tumour and avoid CXB after TEMS when very low rectal tumours are treated.

2.2 Rectal stenosis. This can occur in less than 1% of cases when TEMS procedure was done for circumferential rectal cancer. We do not recommend doing CXB post-operative in such cases now.

3. Theoretical adverse events

3.1 Rectal perforation. We have never encounter rectal perforation in over 1600 patients treated at Clatterbridge over the past 25 years (Sun Myint et al. BJR 2017).

3.2 No deaths have been report following CXB procedure.

4.2 What are the key efficacy outcomes for this procedure?

a. Improve local control with reduction in the risk of local regrowth. (11% vs 25-30% following EBRT or EBCRT (Sun Myint et al; Dhadda et al, Gerard JP et al.)
b. Improve chance of cCR (clinical complete response) following CXB boost for residual tumour after EBRT or EBCRT (70-80% vs 10-20%)

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

There are concerns about the efficacy of this procedure. However, there was at least one randomised trial (Lyon 96-02) and several published observational studies.

a. The efficacy of CXB boost has been shown previously in a randomised trial Lyon 96-02 on cT2 cT3 tumours (IPG 532). The drawback of this trial was EBRT was used instead of EBCRT. The main end point was sphincter preservation which most clinician now accept is less important.
b. We have now set up a trial using EBCRT and recruiting patients for a phase 3 randomised trial OPERA (Organ Preservation for Early rectal Adenocarcinoma) in patients fit and suitable for surgery with cT2/cT3 and cN0 or cN1 <5cm. The trial is ongoing and will stop recruiting end of this year (NCT02505750). We aim to publish our results in 2022. Briefly, this trial randomised between EBCRT and EBRT boost (stand of care) against EBCRT and CXB (boost). The difference in primary outcome of organ preservation is an end point (reduce local regrowth needing salvage surgery). We believe the extent of organ preservation will reflect on the efficacy of this procedure. Local regrowth require surgical salvage and reduce the chance of organ preservation (either APER or AR surgical salvage procedures remove the rectum resulting in loss of an organ).

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

Clatterbridge Cancer Centre organises annual CXB (Papillon) training courses since 2010. Several centres in the UK have been trained and currently there are 4 centres offering CXB facility in the UK. I (ASM) provide mentoring scheme and personal hands on training for clinicians wanting some experience in CXB procedure since 2010.

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

a. **OPERA (Organ Preservation for Early Rectal Adenocarcinoma)** is the ongoing European phase 3 randomised trial for operable patients with advance rectal cancer (cT2 cT3 / cN0 or cN1) [NCT02505750].

b. **CONTEM 1** – an observational study on early cT1cN0 rectal tumours. This study was initiated by ICONE (International Contact radiotherapy Network group) to establish the role of CXB in post local excision using TEMS. Data complete due for publication shortly.

c. **CONTEM 2-** In patients fit or suitable with more advance tumour cT2 and above where EBCRT was offered followed by CXB boost. Analysis of data ICONE group (work in progress).

d. **CONTEM 3-** In patients with cT1-cT3 rectal tumours not suitable for surgery where combination of EBCRT or SCRT was given with CXB. Analysis of data ICONE group (Work in progress).

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).

List of publications on CXB (attached)

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 standard of care for advanced rectal cancer is preoperative chemo radiotherapy followed by surgery. However, patients who are not suitable for surgery or refusing surgery only EBRT or EBCRT were offered. The chance of pathological complete response (pCR) following EBCRT or EBRT was only <10% (ESCP group, Colorectal Disease.2018). The majority of patients will have residual disease which will grow within 6-18 months causing local symptoms of pain, bleeding and discharge. Distant metastases (liver, lungs, abdominal lymph nodes, bones and brain) will developed in most if not all and eventually cause demise of the patient. CXB can cure a proportion of these patients (30-50%) and improve local control which in turn control of local symptoms.

The concept of 'Watch and wait' for advanced rectal cancer following EBCRT was initiated by a surgical Professor Angelita Habr Gama from Sao Paulo in Brazil. The chance of cCR after EBCRT is between 20-30% (Habr Gama et al. 2004, 2014). In these patients surgery was not carried out initially and a programme of 'watch and wait' was carried out as in prostate cancer. Salvage surgery is only carried out in the event of local regrowth. The probability of local relapse following EBCRT alone was 25-30%, however, over 90% can be salvage by delayed surgery.
CXB boost after EBCRT can reduced this local regrowth from 30% to less than 11% (Sun Myint et al BJ Radio (2017), Int J Radio Bio and Physicists (2018). Our findings were supported by publications from three other centres (Dhadda Clinical Oncology (2016); Gerard J P et al E J Cancer (2017); Stewart at el Brachytherapy (2018). The outcomes from OPERA trial will support our results. However, in patients not suitable for surgery there is no published data.

'Watch and wait' strategy is gaining acceptance among the surgical community (Smith et al. BMJ; 2018) and increase number of referrals has been seen in the past 5 years at our 4 CXB centres. It will be difficult to do a randomised trial on patients not suitable for surgery but data from OPERA trial will certainly help to establish the efficacy of CXB following EBCRT.

5 Audit Criteria

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

There is a national CXB data base at Guilford as suggested by NICE (IPG 532) since 2015. However, this is only for early stage rectal cancers. We could use this data base to include advanced rectal cancers and carry out an audit.

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:

Outcome measures of benefit

1. Local control (reduce local regrowth)
2. Symptom control (Bleeding , pain and discharge)
3. Quality of life
4. Stoma requirement following treatment.

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:

Adverse outcomes

Acute (up to 3 months)

1. Pain
2. Proctitis
3. Incontinence

Late (after 3 months)

1. Bleeding
2. Ulceration
3. Rectal discharge

6 Trajectory of the procedure

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

There are a number of centres in the UK trained up and keen to start this procedure. However, the specialist commissioners have not adopted this procedure for routine commissioning and there is uncertainty whether there will be additional or continued funding for this procedure.

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:

We need minimum of 10 centres to cover the UK population and to address the inequalities of provision of CXB services currently offered by the NHS.

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:
There are 12,000 new cases of rectal cancer diagnosed each year. Less than half of these patients had surgery (NBOCA data. 2015, 2017). It is possible that some patients with advanced inoperable or patients extensive metastatic (20%) and were not eligible for surgery.

1. Through national bowel screening programme which started 10 years ago, a number of patients diagnosed with early rectal cancer can be offered nonsurgical treatment with EBCRT + CXB and adopting a watch & wait programme. It is envisage that up to 30% of early rectal cancer will be detected through NBCSP. Most of the cT1 cN0 will be eligible for local excision or CXB. Patients with cT2 or cT3 cN0 will be eligible for CXB +EBCRT.

2. Patients with advanced rectal cancer cT3cN1or cN2 will refuse surgery if they achieved a clinical complete response after EBCRT or EBRT. However, up to 30% will develop a local regrowth needing salvage surgery. CXB could reduce this local regrowth to less than 11%.

3. There is increase in ageing population in the UK and most will not be suitable for extirpative surgery especially for early stage rectal cancer.

Potentially there are approximately 1000-1500 patients or more from above 3 groups who could be treated by CXB if facilities are widely available within the UK. We have published several papers on Health economics of CXB and affordability by the NHS (Rao et al. Clinical Oncology 2017; 2018). There will be substantial cost savings by NHS on avoiding surgery in these 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?

The cost of setting up CXB facilities (about 10 centres) around the UK is relatively low (unlike Proton facilities) and will be cost effective (Rao et al). Arian is a British company which produces the CXB machines and the initial cost is relatively cheap (£300K per machine). No shielding is necessary as it is a low energy (50KeV) machine and no extra cost for building bunkers (unlike Linear Accelerators and Protons). There are several centres in the UK already trained and ready to set up CXB facility.

8 Data protection and conflicts of interest

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

8.1 Data Protection

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

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

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

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

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

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

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

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

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

Fellowships endowed by the healthcare industry	☐	**YES**
	X ☐	**NO**
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:
No conflict of interest to declare.

Thank you very much for your help.

Dr Tom Clutton-Brock, Interventional **Mark Campbell**
Acting Programme Director

[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).

Procedures Advisory Committee Chair Devices and Diagnostics

June 2018

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: azad.hussain@nice.org.uk and IPSA@nice.org.uk

Procedure Name:	**Low energy contact X-ray brachytherapy (the Papillon technique) for locally advanced, inoperable, rectal cancer.**
Name of Specialist Advisor:	Amanndeep Dhadda
Specialist Society:	Association of Coloproctology of Great Britain and Ireland (ACPGBI)

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

x Yes.

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

1.1 Does the title used above describe the procedure adequately?

x Yes.

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

Comments:

2 Your involvement in the procedure

2.1 Is this procedure relevant to your specialty?

x Yes.

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

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

Comments:

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

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

☐ I have never done this procedure.

☐ I have done this procedure at least once.

x I do this procedure regularly.

Comments:

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

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

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

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

Comments:

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

x I have done bibliographic research on this procedure.

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

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

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

☐ Other (please comment)

Comments:

3 Status of the procedure

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

x Established practice and no longer new.

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

☐ Definitely novel and of uncertain safety and efficacy.

☐ The first in a new class of procedure.

Comments:

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

TME surgery

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)

Rectal bleeding – mostly grade 1-2 in 30% of patients

Altered bowel function – 35%

Ulceration of rectal wall - usually asymptomatic if above level of dentate line

Dhadda et al. Organ preservation using contact radiotherapy for early rectal cancer: outcomes of patients treated at a single centre in the United Kingdom. Clin Oncol 2017; 29(3); 198-204.

2. Anecdotal adverse events (known from experience)

Rectal stenosis (<5% risk)

3. Theoretical adverse events

Rectal fistula

4.2 What are the key efficacy outcomes for this procedure?

Local recurrence free survival
Overall survival

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

This is not a treatment for all locally advanced/inoperable patients. It can be used as a boost treatment in patients who have had an excellent response to initial external beam chemo/radiotherapy and who do not wish to proceed down the standard route of radical surgery due to stoma aversion or are unfit for surgery. Radical surgery remains the gold standard approach for these patients if suitable. It is for only selected patients in the overall group.

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

Contact brachytherapy machine
Training at contact radiotherapy centre – Clatterbridge have run a training course for many years.

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

There is a national database hosted by the Royal Surrey Hospital of patients receiving contact brachytherapy but it does not cover this indication alone (ie also will contain much earlier cancers and also patients who have had a local excision and

adjuvant contact brachytherapy). There is a randomised trial called OPERA but not in this setting per se.

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).

Sun Myint et al. Dose Escalation Using Contact X-ray Brachytherapy After External Beam Radiotherapy as Nonsurgical Treatment Option for Rectal Cancer: Outcomes From a Single-Center Experience. Int J Radiat Oncol Biol Phys. 2018 Mar 1;100(3):565-573.

There was a recent paper for planned organ preservation using contact brachytherapy in T2/T3 cancers by Gerard et al (Int J Radiat Oncol Biol Phys. 2019 Mar 1;103(3):565-573)

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 procedure is only available currently in 4 centres in the UK. It is also for very selected patients with regards to locally advanced/inoperable disease who have shown an excellent response to external beam radiotherapy.

5 Audit Criteria

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

Patient age/sex
MRI stage
CRM involved – yes/no
Medically fit for surgery (ASA grade)
Reasons for not having radical surgery
Dose of external beam radiotherapy
Concurrent chemotherapy - yes/no
Dose of contact brachytherapy
Local recurrence
Distant recurrence

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:

Local recurrence free survival (months)
Overall survival (months)

LARS score at 3, 6, 9 , 12 months

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:

Rectal bleeding – CTC grading
30 day mortality

6 Trajectory of the procedure

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

Very slowly. I think more published work will be required before it is accepted.

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.

x 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:
There are more patients who would benefit from this procedure than we know about – I fear a lot at the moment are simply being offered palliative radiotherapy if not fit for surgery and inoperable on medical grounds. No thought is given to assessing response to external beam radiotherapy and contemplating a contact brachytherapy boost if they've had a good response.

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.

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 ☐ **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).

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

Mark Campbell
Acting Programme Director
Devices and Diagnostics

June 2018

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.