NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

MULTIPLE TECHNOLOGY APPRAISAL

Intrabeam radiotherapy system for adjuvant treatment of early breast cancer [ID618]

The following documents are made available to the consultees and commentators:

1. **Response to consultee, commentator and public comments on the Appraisal Consultation Document (ACD)**

2. **Consultee and commentator comments on the Appraisal Consultation Document** from:
   - Carl Zeiss (Company)
   - Association of Breast Surgery
   - Breast Cancer Now (Former Breakthrough Breast Cancer and Breast Cancer campaign)
     Department of Health sent a 'no comment' response
   - Health Improvement Scotland
   - Independent Cancer Patients Voice
   - Institute of Physics and Engineering Medicine (IPEM)
   - NHS England
   - Royal College of Physicians
   - Royal College of Radiologists
   - Society and College of Radiographers

3. **Comments on the Appraisal Consultation Document from experts:**
   - Professor Michel Douek Clinical expert, nominated by Association of Breast Cancer Surgery
   - Dr Charlotte Coles Clinical expert, nominated by NCRI/RCP/ACP/JCCO
   - NHS England Expert

4. **Comments on the Appraisal Consultation Document received through the NICE website**

Any information supplied to NICE which has been marked as confidential has been redacted. All personal information has also been redacted.

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Multiple Technology Appraisal

Intrabeam targeted intraoperative radiotherapy for the treatment of early or locally advanced breast cancer

Response to consultee, commentator and public comments on the second Appraisal Consultation Document (ACD)

Definitions:

Consultees – Organisations that accept an invitation to participate in the appraisal including the companies, national professional organisations, national patient organisations, the Department of Health and the Welsh Government and relevant NHS organisations in England. Consultees can make a submission and participate in the consultation on the appraisal consultation document (ACD; if produced). All non-company consultees can nominate clinical experts and/or patient experts to verbally present their personal views to the Appraisal Committee. Company consultees can also nominate clinical experts. Representatives from NHS England and clinical commissioning groups invited to participate in the appraisal may also attend the Appraisal Committee as NHS commissioning experts. All consultees have the opportunity to consider an appeal against the final recommendations, or report any factual errors, within the final appraisal determination (FAD).

Clinical and patient experts and NHS commissioning experts – The Chair of the Appraisal Committee and the NICE project team select clinical experts and patient experts from nominations by consultees and commentators. They attend the Appraisal Committee meeting as individuals to answer questions to help clarify issues about the submitted evidence and to provide their views and experiences of the technology and/or condition. Before they attend the meeting, all experts must either submit a written statement (using a template) or indicate they agree with the submission made by their nominating organisation..

Commentators – Commentators can participate in the consultation on the ACD (if produced), but NICE does not ask them to make any submission for the appraisal. Non-company commentator organisations can nominate clinical experts and patient experts to verbally present their personal views to the Appraisal Committee. Commentator organisations representing relevant comparator technology companies can also nominate clinical experts. These organisations receive the FAD and have opportunity to report any factual errors. These organisations include comparator technology companies, Healthcare Improvement Scotland any relevant National Collaborating Centre (a group commissioned by NICE to develop clinical guidelines), other related research groups where appropriate (for example, the Medical Research Council and National Cancer Research Institute); other groups such as the NHS Confederation, the NHS Commercial Medicines Unit, the Scottish Medicines Consortium, the Medicines and Healthcare Products Regulatory Agency, the Department of Health, Social Services and Public Safety for Northern Ireland).

Public – Members of the public have the opportunity to comment on the ACD when it is posted on the Institute's web site 5 days after it is sent to consultees and commentators. These comments are usually presented to the appraisal committee in full, but NICE reserves the right to summarise and edit comments received during consultations, or not to publish them at all, where in the reasonable opinion of NICE, the comments are voluminous, publication would be unlawful or publication would be otherwise inappropriate.

Please note: Comments received in the course of consultations carried out by NICE are published in the interests of openness and transparency, and to promote understanding of how recommendations are developed. The comments are published as a record of the submissions that NICE has received, and are not endorsed by NICE, its officers or advisory committees.

Comments received from consultees

Consultee	Comment [sic]	Response
Carl Zeiss	Dear Appraisal Committee, pursuant to the invitation to comment on the Appraisal Consultation Document (ACD) and evaluation report for the above appraisal we (manufacturer) would like to comment on the following: • Has all of the relevant evidence been taken into account? Yes, except some **newer additional recent publications as cited below** • Are the summaries of clinical and cost effectiveness reasonable interpretations of the evidence? **Yes, with some comments as stated below** • Are the recommendations sound and a suitable basis for guidance to the NHS? **Yes, with a minor changes suggested below** • Are there any aspects of the recommendations that need particular consideration to ensure we avoid unlawful discrimination against any group of people on the grounds of race, gender, disability, religion or belief, sexual orientation, age, gender reassignment, pregnancy and maternity? **No** **We suggest the following minor addition to the draft guidance:** …. • with managed evidence collection developing a national data set of all patients with early invasive breast cancer having adjuvant treatment with the Intrabeam radiotherapy system in the NHS **using existing UK routine cancer registries.** This should … **We suggest to consider the following points for the interpretations of the evidence:** Page 5: The committee also heard from the clinical experts that in some radiotherapy centres in the NHS intensity modulated radiotherapy is used, which has the potential to reduce local adverse effects. • **The studies with IMRT machines are not fully published yet and with newer techniques (IMRT, Gating, SIB) the costs are higher than calculated**	Comments noted. Comment noted. This has been deleted from section 4.1 of the FAD.

Consultee	Comment [sic]	Response
	in the available cost-efficiency models for EBRT. IMRT machines would significantly change the ICERs for EBRT. Therefore these techniques cannot be included in the current technology appraisal. The committee noted comments from professional groups and also heard from the clinical experts that radiotherapy is constantly evolving, and that there are several ongoing trials investigating, for example, whether the course of radiotherapy could be reduced from 3 weeks to 1 week … • **These trials are still ongoing, the outcome is not clear and e. g. the Rapid trial interim late toxicity results showed worse toxicity at 3 years in the APBI arm (1).**	Comment noted. No change to FAD required.
	Page 6: … or whether radiotherapy is needed at all for patients considered to be at low risk of recurrence. • **The current evidence suggests that despite having worse prognosis cancers in the TARGIT-A trial, local control with TARGIT during lumpectomy was excellent and clearly better than 'no-radiotherapy' as compared to CALGB, BASO II, PRIME II (2; 3; 4).**	Comment noted. No change to FAD required.
	Page 6: If adverse histological features were identified in the cancer cells at final pathology after treatment with Intrabeam, and subsequent EBRT was recommended, a further external boost dose would not be needed. • **This is true. The immediate irradiation with Intrabeam as a boost has the advantage of no geographical miss and no time delay after surgery. The IORT boost treatment can kill remaining tumor cells directly after tumor excision and has demonstrated better outcomes regarding local recurrence and survival (5; 6). Furthermore the abscopal effects and the inhibition of tumor proliferating cytokines with the irradiation directly after surgery should be considered as further advantage of Intrabeam treatment when it is applied as a boost (7; 8).**	Comment noted. No change to FAD required.
	Page 6: Although there is a risk of clips moving within the cavity, EBRT has evolved and is generally considered to be accurate for targeting the tumour site. • **Since nowadays oncoplastic techniques are implemented more widely, the EBRT (despite evolving) is accepted as less accurate compared to IORT with Intrabeam (9)**	Comment noted. No change to FAD required.

Consultee	Comment [sic]	Response
	Page 6: However for some patients, brachytherapy may be a suitable breast-conserving treatment instead of mastectomy. • **Also IORT has been shown as suitable breast-conserving treatment after local recurrence and is considered in the German S3 guideline as such treatment (10-13).**	Comment noted.
	Page 8: However, a clinical expert stated that the radiation dose to the heart with modern EBRT is not clinically significant. • **Even with modern EBRT the dose rate to the heart cannot be completely avoided. Every gray of radiation which reaches the cardiovascular system leads to a 16.3 %/Gy increased rate in major coronary events already during the first 4 years after radiation (14). The lower cardiovascular mortality in the in the Targit Intrabeam group can be explained with less side effects compared with EBRT (14; 15) and also with the effect on EGF influencing cardiac disease (7; 8). Still modern EBRT cannot avoid patient's movement uncertainties in radiation planning (16) and increasing additional risk factors in the patient population like obesity, diabetes and cigarette smoking of women.**	Comment noted. It is stated that this was heard at committee. No change to FAD required.
	Page 8: The committee noted that in TARGIT-A, EBRT was delivered in an average of 23 fractions, longer than the 15 fractions delivered in established clinical practice in the NHS. • **A substantial number of patients who were treated in the UK centers received already 15 fractions. Canadian as well as Australian centers have treated at that time their patients with 15 fractions as well (personal communication with trial centers). Comparing the total enrollment number of 3451 patients in the Targit trial with other radiation studies, the number of UK patients in Targit-A should be high enough to be generalizable in NHS clinical practice. In general the high standard of EBRT treatment and clinical practice in the Targit-A study can be compared to NHS quality requirements. Only centers of clinical excellence in Germany, France, Italy, Denmark, US and Australia were included after the center specific treatment practice was audited and verified.**	Comment noted. Section 4.4 of the FAD states the average fractions used in the trial. No change required.

Consultee	Comment [sic]	Response
	Page 9: Median follow-up in the trial was 2 years and 5 months and only 35% of the patients had 5-year follow-up at the time of the analysis. The committee heard from the clinical experts that longer follow-up, usually of at least 5 years, is needed for clinicians to feel confident about data on local recurrence. • **1222 patients were analyzed as sub-group in the Lancet 2014 publication which was as high as the number other radiation oncology trials e. g. Eliot and GEC-ESTRO trials with similar follow up (17; 18).**	Comment noted.
	Page 9: The committee was aware of the large debate in the medical community about TARGIT-A in which opposite views have been raised about the importance of mature follow-up, trial governance and the interpretation of the results • **We were puzzled by the fact that some medical communities expressed opposite and emotional views against the study which was conducted by highly qualified academic investigators in 33 centers in 11 countries and was published two times in the peer reviewed The Lancet. Besides that, the Southhampton AG has confirmed the good quality of the trial. The "quasi-religious debate" is perfectly described by the chief editor of the Red Journal Prof. Anthony Zietmann (19).** [image redacted – see the document, comments on ACD Carl Zeiss]	Comment noted.
	Page 10: It noted that some patients having Intrabeam also had further treatment with EBRT depending on their final pathology report, but that the results were not presented for this group separately. • **The results were presented in the Lancet 2014 publication under attachments (Table 2) however the number is very low (20).**	Comment noted. Section 4.7 of the FAD has been amended and wording has been added to section 4.2.
	Page 11: It considered that the pre-trial estimated 5-year rate of 6% for local recurrence, on which the non-inferiority margin was based, is higher than the current expected rate of local recurrence in people having treatment with EBRT. The committee also noted that patients in the trial had a relatively good prognosis and low risk of local recurrence and heard from the clinical experts that since 2000, when patients were first recruited into the trial, the 5-year local recurrence rate with	

Consultee	Comment [sic]	Response
	EBRT has decreased to much lower than 6%. The committee also noted that when assessing non-inferiority, the point estimate alone is not sufficient. The confidence interval around the point estimate should also be considered and compared with the pre-specified non-inferiority margin. • **The non-inferiority margin was also based on a previous preference trial showing up to which rate the patient is willing to accept a higher risk of local recurrence. In fact, two patient preference studies have suggested that the median additional increase that would be accepted by physicians and patients in exchange for the convenience of a single treatment dose is 2,5% (21). Thus, with a background recurrence rate at 5 years for example of only 1,5% instead of the 6 % (in the START trial, the recurrence rate at 5 years was 2,3%) a trial for testing a noninferiority margin of 2,5% with 80% power and 95% confidence needs a sample size of only 585 patients (21). Consequently the number of 3451 patients was far beyond the needed minimum statistical number. Furthermore the Lancet 2014 results reported 1222 patients with a 5 years follow up.** Page 12: The committee considered that the criterion for non-inferiority was not appropriately defined and the trial was therefore underpowered and the results could not be considered robust enough to determine whether Intrabeam is non-inferior to EBRT in terms of local recurrence. • **See The Lancet 2010: With a background recurrence rate at 5 years for example of only 1,5% instead of the 6 % a trial for testing a non-inferiority margin of 2,5% with 80% power and 95% confidence needs a sample size of only 585 (21). The trial was not underpowered, it was closed after 3451 patients resulting in 9491 women-years of follow-up.** Page 13: It understood that the assessment group had reported that the difference in overall survival was based on a small number of events and that it did not consider that there was an excess of deaths in the EBRT group, but rather a shortfall of deaths in the Intrabeam group occurring by chance. • **Fewer non-breast cancer were probably unmasked in this cohort of excellent prognosis patients (>98% were local-recurrence-free at 5 years) in whom only 36/3451 patients died from breast cancer (vs. 52 died from other causes) as stated above due to unmasked side effects of EBRT and probably due to the inhibition of EGF. Furthermore other effects on**	Comments noted. The committee discussed this see section 4.7 of the FAD. Comments noted. The committee discussed this, see section 4.8 of the FAD. Comments noted.

Consultee	Comment [sic]	Response
	cytokine factors and abscopal effects of immediate irradiation can be considered as explanation (7; 8). Page 13: The committee heard from a clinical expert that the mean radiation dose to the heart was not provided in the TARGIT-A publication and that the mean dose to the heart delivered with EBRT in clinical practice in the NHS is minimal. Therefore it is highly unlikely that the difference in non-breast cancer deaths between treatment groups in TARGIT-A could be explained by an increased risk of cardiovascular death related to EBRT. • **The heart dose is dependent on the position of applicator in the breast tissue and is very low with the Intrabeam radiation due to the steep dose fall off of the photon radiation system. The heart dose can be extrapolated and is published as a mean dose of 0.01 Gy by Aziz et al. (22). A recently published meta-analysis regarding survival of randomized partial breast radiation studies showed that the mortality is lower with APBI (23). The similar effect has been seen in the Start trial. The mortality rate was 108 in the test arm compared to 137 in the conventional arm (24).** Page 15: …the company's model Intrabeam was associated with slightly more QALYs than EBRT, whereas in the assessment group's model Intrabeam was associated with fewer QALYs than EBRT. • **The slightly more QALYs in the company's model included the lower non-breast cancer death and the better progression free survival rate for Intrabeam as a result of the randomized Targit A trial (23). Ongoing research will investigate the utility of IORT compared to EBRT (e. g. Targit-B trial). Additionally better QOL is noted by patients groups: less disruption of daily life, less travel costs, less inconvenience and productivity loss and less radiation exposure to other organs compared EBRT.** Page 15: Section 5.12.6 of the guide states that if savings are anticipated, the extent to which these finances can actually be realised should be specified. The committee debated whether the costs for Intrabeam and linear accelerator equipment should be included in the same way in the economic model (that is, including the capital costs of equipment for both technologies) or using only the tariff cost associated	Comments noted. Comments noted.

Consultee	Comment [sic]	Response
	with each technology. • **We agree that the equipment costs of both technologies should be included to ensure equal comparison since there are no tariffs existing so far for Intrabeam. Unfortunately both models (company's and AG's) did not consider the equipment costs for EBRT. Since Intrabeam can free up capacity for EBRT these savings for the NHS should be considered as stated in Section 5.12.6. In the Lancet 2010 savings of around £15 000 000 were estimated (21). The NHS needs high investments in the near future (£130 million fund) for missing or older radiotherapy equipment. Intrabeam could be an opportunity to reduce the needed EBRT capacity. Additionally Intrabeam is used also in other tumor entities (Glioblastoma, Colorectal Cancer, Spine-Metastasis, Sarcoma), thus freeing up capacity for EBRT as well.** Page 16: The committee considered that, based on the high degree of uncertainty in the cost-effectiveness analysis, it is not possible to state the most plausible ICER for Intrabeam compared with EBRT. It concluded that Intrabeam is associated with slightly lower costs and fewer QALYs than EBRT. • **As stated above including equipment costs for both technologies would reflect a realistic view of cost-comparison or cost-effectiveness and a plausible ICER. The recent HTA publication has shown again cost-effectiveness for Intrabeam as well as higher QALYs for Intrabeam (25). As mentioned above Intrabeam could reduce EBRT capacity and save needed investment in the NHS.** **Final remarks:** **We do appreciate the current recommendation and want to support in full extent the implementation of the technology in the NHS. Intrabeam does not necessarily imply an increase in NHS investment since the rising demand in radiation capacity can be compensated by freeing up needed fractionation schemes for early breast cancer. For the staff training there already exists a standardized training course which is provided by academic centers using the device for many years (London, Heidelberg and Cleveland). Also our clinical application team is supporting the centers to set up the system and workflow and is helping during the first cases in the operating theatre.**	Comments noted. Comments noted. Comments noted. Recommendations have changed see section 1.

Consultee	Comment [sic]	Response
	For the implementation we have the following suggestions: **A patient shared decision making tool can be provided by the manufacturer if needed. Intrabeam centers worldwide have developed already such tools for their patients. The decision making leaflet should be made available for all patients with early breast cancer and the informed consent discussion should be a given procedure in every hospital. In NHS hospitals with no Intrabeam, elderly, disabled and pregnant patients should have the possibility of free transportation to hospitals with existing NHS Intrabeam machines. The managed evidence collection should be made possible for new centres who want to use own funding to acquire/lease Intrabeam. Therefore we suggest to use the excising UK cancer registry for the data collecting.** **Finally we want to emphasize, that current health service research of Intrabeam centres worldwide reflects obviously low recurrence rates in real world settings outside of randomized trials. Cost-effectiveness has also been shown in other health societies showing that the single radiation saves resources in public health care systems.** [references excluded - see the document, Comments on ACD Carl Zeiss]	
Breast Cancer Now	Breast Cancer Now welcomes the opportunity to respond to the Appraisal Consultation Document (ACD) on the Intrabeam radiotherapy system for adjuvant treatment of early breast cancer, published by NICE on 8 February 2017. The Committee has recommend Intrabeam as an option for adjuvant treatment of early invasive breast cancer during breast conserving surgical removal of the tumour using machines that are already available; providing patients with information on the risks and benefits on the range of treatments available and collecting evidence to develop a national data set of all patients receiving this treatment. Has all of the relevant evidence been taken into account? We believe all the relevant evidence has been taken into account. Are the summaries of clinical and cost effectiveness reasonable interpretations of the evidence? We believe that the summaries of clinical and cost effectiveness are reasonable interpretations of the evidence.	Comments noted. See recommendations in section 1 of the FAD.

Consultee	Comment [sic]	Response
	Are the recommendations sound and a suitable basis for guidance to the NHS? We believe these recommendations are sound and a suitable basis for guidance to the NHS. Are there any aspects of the recommendations that need particular consideration to ensure we avoid unlawful discrimination against any group of people on the grounds of race, gender, disability, religion or belief, sexual orientation, age, gender reassignment, pregnancy and maternity? We are not aware of any aspects that require particular consideration to avoid unlawful discrimination.	
Independent cancer patients' voice	We are breast cancer patient members of Independent Cancer Patients' Voice – a patient advocate group run and lead by patients whose aim is to bring the patients' voice to the cancer research community. ICPV members have been involved with radiotherapy research and trials for a number of years. Some of our members have also been involved with CTRad and the Royal College of Radiology Guidelines for Breast Cancer published in 2016 We contributed to the NICE consultation in 2014. We have considered the latest consultation and are entirely unpersuaded that is sensible to issue guidance on this matter before the mature follow-up data is available. The NICE remit is to 'decide whether the technology should be recommended as a clinically-effective and cost-effective use of NHS resources', and the report itself says that ' the clinical and cost-effectiveness evidence for Intrabeam remains uncertain'. It seems to us that relevant evidence so far has been taken into account but this is immature, and the conclusion of uncertainty in clinical and cost-effectiveness is a reasonable interpretation of the current evidence. We therefore strongly believe that there is no sound and suitable evidence for this to be recommended at this stage. We also strongly believe that it is a disservice to patients to consider Intrabeam in isolation, precluding its consideration by the NICE Early Breast Cancer Guideline Update committee which is currently considering the update of CG80, and in	Comments noted. Intrabeam is not recommended for routine commissioning. It is recommended using only machines already available to collect further data. See FAD sections 1, 4.13-4.17.

Consultee	Comment [sic]	Response
	particular the omission of radiotherapy and partial radiotherapy in selected sub-groups of patients. In addition, we have serious concerns relating to • the provision of high-quality information for all patients • the geographic inequity that this recommendation is likely to introduce for patients ICPV patient members have made a number of comments on these matters which we have included below “It is wrong for NICE to go for approval for a procedure when the full follow-up data has not been published. When is this due? They should wait until this and IMPORT-Low data is available. This will give a much clearer picture of its usefulness (or otherwise).” “I thoroughly support your argument and resulting position. I'm horrified by NICE.” “It is unfortunate that there seems to be a conclusion that the trial is underpowered and not necessarily applicable to the NHS. The addition of the managed data collection seems to be to provide extra data to off-set this deficit. However, there is no discussion of the costs involved in doing this collection properly outside of a trial, or whether patients need to consent to this collection. Whilst some of the data points measured are standard, I don't think QOL data collection is. Also, data like OS and DFS, and QOL will take 5 – 10 years to collect. None of this discussion is included. it seems to me that if a treatment is evidenced based then it is reasonable to recommend it and deal with the practicalities of delivery afterwards. However, in this case where the decision is not evidenced-based surely these other issues are pertinent.” “Patients will definitely need written standard information about this if they are to be fully informed. This written information ought to include this, EBRT, and the relevant trial options available to patients, including the biomarker directed PRIMETIME. The committee themselves say ' that, given the difficulty in interpreting the evidence, particularly where specialist clinicians do not agree, special effort would be required	

Consultee	Comment [sic]	Response
	to support shared decision-making'. This disagreement amongst clinicians is likely to be even within the units that have this equipment, isn't it? It is not easy for us as patients to grasp the significance of the low levels of risk and benefit that we are talking about here and very easy to be swayed by whether or not we 'trust' the person who is talking to us at difficult times like these." "I agree that any patient literature must clearly show that there are choices – all with pros & cons. Could this be badged with the College and a charity to give it independence. What is the position of the charity sector e.g. Breast Cancer Now and Breast Cancer Care?" "The patient group that will be eligible for this will be very small and may in part be the exact match for PRIMETIME and this has to be highlighted. Fear of recurrence and being left alone after treatment are common psychological issues for patients and follow-up to pick up any early recurrence should be particularly addressed in studies and evaluations of uncertain treatments. Of course, there may also be a small number of patients with comorbidities that may not be able to have standard RT." "I find it difficult to see how this recommendation can work in practice. The NHS is supposed 'to promote equality through the services it provides', but these machines are mostly in the South of England, mainly London. The patients, most likely to benefit will be the very small group of people with co-morbidities, who need but can't manage EBRT, and those patients could be anywhere in the country. Will all relevant patients need to be informed of this recommended option and offered the option of travelling to London? We also however note that there are other brachytherapy options with a greater evidence base for these women which have not been considered by this committee at all." "I disagree in part with this comment from the 'patient expert'. How often do women have to travel long distances for standard therapy unless they live in very rural areas? Yes, travelling daily can be an issue, but is it that great an issue?? I would like to see more evidence of this. "The patient may need to stop working and face substantial travel costs, which can have a considerable financial and emotional impact on the patient and their family. The committee also heard from the patient expert that some patients who live a long distance from a radiotherapy centre may need to stay away from their home to be able to complete the course of radiotherapy"	

Consultee	Comment [sic]	Response
	"I have concerns that this recommendation is not solving anything but rather continuing with unnecessary confusion for patients. I also detect (maybe wrongly), a subtext that because the absolute risk of local recurrence is very low in this group whatever we do (this is mentioned several times), this justifies a decision made too early without mature evidence." To summarise we have reached the conclusion that this procedure should not be given NICE approval at this time, and any further consideration should be within the NICE Early Breast Cancer Guideline Update committee currently looking at CG80.	

Consultee	Comment [sic]	Response
Association of breast surgery	**Response from the Association of Breast Surgery (ABS)** The ABS are pleased that NICE cautiously recommend the commissioning of Intrabeam as an alternative to standard external beam radiotherapy if certain conditions are met. The ABS strongly supports the principle of follow up data collection for newly introduced treatments and of appropriate patient information. ABS notes that there has been clinical expert discord on this topic and within the breast community as a whole. We therefore understand why NICE have to be cautious and not recommend Intrabeam as standard therapy. The clinical trial examining IORT has patients with a mean follow up of 4 years and shows non-inferiority of IORT compared with external beam radiotherapy and has been published in peer reviewed journal. The data is therefore encouraging, if immature, for incorporation into routine practice with the parallel development of a national dataset to gather outcome data. NICE recommend that IORT only be performed in units that already possess the equipment for this treatment. As there are only 6 such units nationally, NICE are, in effect, introducing a new technology which is available only to those patients within the vicinity of these units and not to all patients. The assessment committee conclude that IORT is probably cost effective if compared to 15 fractions of radiotherapy which is the current NHS standard. Partial breast irradiation is now supported, for selected cases, by evidence from a range of strong clinical trials using a number of different delivery systems. We think the patient representative on this NICE committee has done a good job of highlighting patient concerns.	Comments noted.

Institute of Physics and Engineering Medicine (IPEM)	The vision of the Institute of Physics and Engineering in Medicine (IPEM) is to constantly improve human health by the application of physics and engineering to prevention, diagnosis and treatment of disease through research, innovation, education and clinical practice. As such, we support the use of existing equipment (and resources) to further research into the efficacy of intra-operative breast radiotherapy. It is disappointing that the TARGIT trialists have not released long-term follow up data for the patients in this trial, when median five year follow up was achieved in January 2015. We share the concerns of oncologists who have criticised the methodology and presentation of results from this trial, and support the recommendation that the higher risk of recurrence should be explained to patients seeking this treatment option. This discussion should be with an oncologist. At the time of first report, 6 INTRABEAM units were reported to be used in the UK. A recent survey by IPEM suggests 5 NHS units and 3 private units are currently available (Palmer et al Br J Radiol 2016). However, several of these have been moth-balled by restrictions on use, or have changed their radiotherapy physics support centre, and the numbers of patients treated in 2016 was very low. Therefore we strongly recommend: * Centres with obsolete equipment, or those requiring major capital upgrade, are not included in the current recommendations; * A minimum of six months is given to allow re-training of staff and mobilisation of resources (even though the long term resource requirements may be equal to external beam radiotherapy); *No centre is permitted to start treatment unless close involvement of medical physics expertise and clinical scientists has been established; *Tariffs for treatment are set by NHS England, following the economic analysis by the HTA (e.g. £2069 per treatment, table 33, Picot et al SHTAC 2014). The appraisal consultation document (p4) describes the recommended dose as 20Gy at the surface of the tumour bed, which attenuates to 5-7Gy at 1cm depth. The TARGIT trial protocol allows dose prescription either to the surface, or 6Gy at 1cm depth, however modelling studies (Ebert and Carruthers Med Phys 2003, Eaton Med Phys 2012) recommend the prescription at depth approach to minimise variation between units.	Comments noted. See sections 4.13-4.17 of the FAD for discussion of the recommendations. Comment noted. The FAD states the typical dose and schedule.

Consultee	Comment [sic]	Response
	The Xoft Axxent system (NICE MIB76) is almost identical in terms of radiation profile and delivery method (Eaton Br J Radiol 2015), therefore treatments should be allowed with this device also, but only with the same tariff, and when data are collected in the same system. Finally, funding for the data collection both at the recruiting centres and the central registry should be identified before treatments commence, and form part of the tariff used to support this process. We hope that this feedback is helpful to NICE. This response has been prepared by some members of IPEM's Radiotherapy Special Interest Group and approved by IPEM's Science, Research and Innovation Council.	Comments noted. This appraisal only considered the evidence for the Intrabeam radiotherapy system and therefore can only make recommendations on this technology.
Royal college of Physicians	The NCRI-ACP-RCP-RCR is grateful for the opportunity to respond to the above consultation. We have liaised with our experts and would like to make the following comments. Our experts do not feel it is possible to support the Intrabeam Radiotherapy System as a NHS treatment given the following statement: 'The committee noted that the clinical evidence for Intrabeam is immature and associated with considerable uncertainty. It acknowledged that Intrabeam has not been proven to be non-inferior to EBRT and could have a higher risk of local recurrence'. We would like to see the mature results of the Targit trial before this technique is offered as an NHS treatment. Given that it is more than 3 years since the 2013 publication with a median follow up of 2 years 5 months, it is anticipated that an updated analysis would soon be available. We also consider patient choice to be paramount, but have a number of concerns regarding the proposal of offering Intrabeam at existing UK centres: • How will it be ensured that patients will be offered 'impartial information' regarding this treatment and other evidence-based treatments?	Comments noted. See sections 4.13-4.17 of the FAD for discussions on the recommendations in section 1.

Consultee	Comment [sic]	Response
	• How will it be ensured that the national database will collect all the necessary data for all patients for a period of at least 5 years, given the current national trend for early discharge for low risk breast cancer? • How will this database be funded? • What is the time-scale for this 'monitoring' exercise and what is the endpoint? • How will training of radiographers, physicists, oncologists and breast surgeons be carried out and funded? • How will revenue costs of the existing Intrabeam radiotherapy systems be funded? • How will this recommendation affect bio-similar intra-operative radiotherapy techniques? Patient representatives have raised specific queries in addition to strongly supporting the views in this document: • Given that patients tend to trust their own doctors, how will they know if they have been given impartial information? • Will patients be consented for this data collection? • Will the proposed provision of Intrabeam in existing centres result in inequity for patients based on where they live, or will they be given financial assistance to travel/stay at the designated centres? We would also like to highlight the Royal College of Radiologists (RCR) UK Breast Radiotherapy Consensus 2016 document, which has recommendations for partial breast radiotherapy and omission of radiotherapy: https://www.rcr.ac.uk/publication/postoperative-radiotherapy-breast-cancer-uk-consensus-statements https://www.rcr.ac.uk/clinical-oncology/service-delivery/postoperative-radiotherapy-breast-cancer-uk-consensus-statements In summary:	

Consultee	Comment [sic]	Response
	Safe omission of radiotherapy after breast-conserving surgery - avoidance of radiotherapy should be considered: In women deemed to be at very low risk of local recurrence, for example patients ≥70 years out of a research study and ≥60 years in study with T1N0 oestrogen receptor positive (ER+), progesterone receptor positive (PR+), human epidermal growth factor receptor negative (HER2-), Grade 1–2 tumours AND who are willing to take adjuvant endocrine therapy for a minimum of five years AND have regular mammograms for ten years. These criteria are best fulfilled within the UK PRIMETIME bio-marker directed study and participation is recommended. Partial breast radiotherapy after breast-conserving surgery can be considered: For patients ≥50 years, Grade 1–2, ≤3 centimetres (cm), oestrogen receptor positive (ER+), human epidermal growth factor receptor negative (HER2-), N0 with minimum 1 millimetre (mm) radial excision margins for invasive disease, using either (i) external beam radiotherapy with 40 Gray (Gy) in 15 fractions over three weeks* or (ii) multicatheter brachytherapy using fractionation schedules as per the Groupe Européen de Curiethérapie and European Society for Radiotherapy and Oncology (GEC-ESTRO) trial[1,2]. Classical lobular cancer and/or lymphovascular space invasion should be excluded. *UK IMPORT LOW trial: presented at European Breast Cancer Conference 2016 and European Cancer Conference 2017, currently under review with the Lancet [reference excluded – see RCP ACD response]	
Royal college of radiologists	The Royal College of Radiologists (RCR) is re-submitting its original comments from the NICE consultation in 2014 (see annex A) as it does not feel that the question of the unacceptably short median follow up of 2 years and 5 months has been resolved. The additional information provided by the trialists does not address this. As the first analysis was performed over 3 years ago, there must be further patient events which must be looked at. The decision to allow ongoing NHS treatment in existing centres with an aspirational audit without funding is not evidence based, since the Targit-A trial has been completed and needs further analysis of mature data.	Comments noted. See sections 4.13-4.17 of the FAD for committee discussions on the recommendations in section 1.

Consultee	Comment [sic]	Response
	The RCR hosted a UK-wide multi-disciplinary meeting in March last year to establish a consensus view among professionals involved in the treatment of breast cancer on (inter alia) the use of intra-operative radiotherapy[1]. This meeting firmly concluded that the relapse rate data were immature. The RCR feels strongly that a properly evidenced decision should be made only when five-year follow-up data are available. Patients cannot be expected to make an informed choice about the risk of local recurrence without such information. The proposal now put forward by NICE seems to be contrary to evidence and goes against the careful long-term studies in radiotherapy for breast conservation which the UK has led on for many years. The need for caution has been demonstrated through the ELIOT trial which showed a HR of 9.3 for IORT compared with whole breast RT with median follow up of 5.8 years: non-inferiority was not reached[2]. [Annex A excluded from comments table] [Appendix 1-4 excluded from the comments table]	
The Society and College of Radiographers	The Society and College of Radiographers is concerned that this is directed at a single manufacturer (Carl Zeiss) and we would consider there is a need for a serious re-think as to the scope of the appraisal document **1) Has all of the relevant evidence been taken into account?** No. As outlined in (3) there are other trials that need to be taken into account to evaluate IORT, not just via single randomised controlled trial (TARGIT A). The EIIOT Study has a longer follow up (> 5yrs median) and after breast conservation surgery favours EBRT over IORT with respect to ipsilateral breast tumour recurrences and higher mastectomy rate. PRIME 2 Trial with 5yr follow up data needs to be considered. **2) Are the summaries of clinical and cost effectiveness reasonable interpretations of the evidence?** Currently directed at a single manufacturer so, given the lack of follow up data and full evaluation of all the evidence, useful interpretation is challenging. Suggest a more complete evaluation.	Comments noted. See sections 4.13-4.17 of the FAD for committee discussions on the recommendations in section 1.

Consultee	Comment [sic]	Response
	The Society and college of Radiographers is concerned who is responsible for the data collection and this needs be a recommendation. **3) Are the provisional recommendations sound and a suitable basis for guidance to the NHS?** From The Society and College of Radiographers perspective we would certainly say a definite no. It identifies the need to provide patients with information to 'aid shared decision making' but only includes one manufacturer i.e. Carl Zeiss. There are issues with the methodological approach and statistical analysis of the TARGIT A trial and these are well documented: not least that of the length of the lack of 5 year follow up data and therefore it is not possible to state that intrabeam is superior or inferior to EBRT. How can a treatment be suggested as appropriate 'using machines that are already available'? What happens if a centre buys a different unit? Then is that not recommended for use? This has led to mis-representation and misunderstanding and this MTA document does not offer the level of recommendation needed to ensure patients have enough information to enable an informed decision. How can patients be informed and make informed decisions on a treatment modality that has not been fully evaluated or understood by clinicians.	
NHS England	Thank you for your letter regarding the Multiple Technology Appraisal (MTA) of intrabeam radiotherapy for the adjuvant treatment of early breast cancer and the opportunity to both formally participate in the consultation process and work with you about this important matter. I would like to raise two distinct points, our assessment of the clinical evidence base contained within the Appraisal Consultation Document (ACD) and a number of wider system implications associated with the ACD recommendations.	Comments noted. See sections 4.13-4.17 of the FAD for committee discussions on the recommendations in section 1.

Consultee	Comment [sic]	Response
	Assessment of the clinical evidence-base NHS England, having been advised by the Radiotherapy Clinical Reference Group (CRG), does not support the recommendations contained within the ACD. This is because we consider that the evidence within the ACD demonstrates that IORT is clinically inferior compared to conventional External Beam Radiotherapy (EBRT). The challenges for patients associated with conventional radiotherapy treatments are acknowledged, as is the very difficult decision that the MTA committee are faced with in relation to this MTA. However, NHS England does not consider it appropriate for a treatment, which does not meet the thresholds for clinical effectiveness or safety, to be made routinely available in the NHS purely to facilitate greater patient choice. **Wider system implications** The ACD recommends that the treatment be made available in a managed way and from a small number of centres, in part to address the need to continue to build the evidence base and in part to manage the financial impact on the NHS associated with offering this treatment. Whilst the recommendations clearly recognise the financial implications for the NHS, they also raise some profound system concerns. Of paramount importance to NHS England is to ensure that only evidence-based, clinically and cost effective treatments are made available, this is to ensure that value is maximised for both patients and taxpayers. Where treatments meet these criteria, there should be equitable access for patients. If the recommendations contained within ACD were to be approved, the NHS would need to carefully consider what grounds there were for restricting access. In addition, should IORT be supported, there are some practical commissioning considerations for the NHS. The treatment is delivered as part of breast surgery procedures, which are commissioned by Clinical Commissioning Groups (CCGs), who reimburse hospitals through national prices set out within the National Tariff Payment System. Therefore, despite radiotherapy being a wholly nationally commissioned service, it is not clear that the costs of this treatment would in fact pass to NHS England. As a result, we ask for assurance that this issue will be fully considered by the committee, prior to any decision being made. This is because funding flows are often an important element of access arrangements. Finally, I have enclosed the detailed advice provided by the Radiotherapy CRG (Annex 1), as this raises a number of important points. The advice is endorsed by	

Consultee	Comment [sic]	Response
	NHS England and is included as part of our consultation response. Given the range of issues raised, I would like to offer the opportunity for the MTA team to liaise directly with both the Radiotherapy CRG and other members of the Specialised Commissioning team, as this may help to clarify the issues quickly. Annex 1 excluded from table	

Comments received from clinical experts and patient experts

Nominating organisation	Comment [sic]	Response
Specialist commissioning (NHS England)	This statement wholly endorses the response provided by NHS England in relation to this matter, and in doing so highlights the most pertinent issues associated with the Appraisal Consultation Document (ACD), as follows: 1. The Radiotherapy Clinical Reference Group (CRG) has articulated a compelling case that the current evidence base suggests that the treatment is clinically inferior to conventional radiotherapy. 2. Furthermore, the CRG have provided advice that clearly indicating that there is a highly active research programme in this field, the results of which may yield alternative and better options for this patient group: a. A number of studies are exploring the potential of delivering external beam radiotherapy (EBRT) in five rather than 15 fractions; and b. The IMPORT-LOW study is due to be published shortly in the Lancet, this is likely to recommend a focus on using partial breast radiotherapy in the same patient group to limit toxicity, as opposed to intrabeam radiotherapy (IORT). 3. In the context of the clinical advice received from the CRG, a positive recommendation would be premature. This is particularly because the commissioning consequence of such a recommendation would be to require the treatment to be routinely available in the English NHS to every patient meeting the eligibility criteria. 4. At this point, if it is the case that further data collection is required as part of implementing the positive recommendation, the treatment would appear to be better suited to research rather than routine commissioning.	Comments noted. See sections 4.13-4.17 of the FAD for committee discussions on the recommendations in section 1.

Nominating organisation	Comment [sic]	Response
	5. Finally, the practical commissioning considerations are not insignificant. The most challenging of which relates to the rationale for limiting the number of centres able to deliver this treatment. This aspect of the recommendations contained in the ACD risks contradicting the desire to make it easier for patients to accept radiotherapy as part of treatment, which forms part of the rationale underpinning the positive recommendation. Should the ACD progress as it is currently written, the impact of implementing it may result in a perverse outcome for patients that do not live close to one of the centres able to deliver IORT.	
Cancer Research UK	I wish to raise the following points regarding the consultation document: **1. The proposal is not in line with section 6.1.2 of the Guide to the methods of technology appraisal 2013 and the caveats stated cannot be substantiated** The consultation document states the following: "The committee recognised its role of not recommending treatments for routine use if the benefits to patients are unproven, or if the treatments are not cost effective…However, it is understood that some patients are willing to accept a treatment that may have a higher risk of local recurrence in order to have the benefits of Intrabeam, noting several benefits highlighted by the patient expert and clinical experts in terms of improving patients' quality of life, which could not be captured in the QALY calculation. It is also noted that although non-inferiority for Intrabeam compared with EBRT (external beam radiotherapy) is unproven for local recurrence, the rates of recurrence in the Intrabeam group in the pre-pathology group are low." a. The evidence for improved quality of life is based on an anecdotal report by a patient who received Intrabeam treatment and who speculated upon the effects of EBRT, which she did not receive. The Targit trial did not report systematically the long-term side effects of treatment, either as clinician reported or patient reported outcomes. Hence, there is no reliable evidence of the long-term toxicity or quality of life after Intrabeam treatment. A small (N=196) single centre study reporting 3-year cumulative toxicity assessed by clinicians involved in the Targit trial reported rates of moderate-severe of breast fibrosis fully comparable with those following	Comments noted. See sections 4.13-4.17 of the FAD for committee discussions on the recommendations in section 1.

Nominating organisation	Comment [sic]	Response
	current EBRT, as recently reported in the UK IMPORT LOW trial.1-2 It should be noted that 15% of patients in the Targit trial required both Intrabeam and EBRT due to higher risk histology found after surgery. The small study suggested that more than one-third of these patients develop moderate-severe fibrosis, which is substantially higher than rates with current EBRT. b. The low rates of local recurrence in the Intrabeam group in the Targit trial do not justify the use of Intrabeam as an NHS treatment. Firstly, with a median follow up of only 2 years 5 months, the local recurrence risk at 5 years is as yet unknown. As a warning, please note that the ELIOT intraoperative trial showed a 9 times increased in local recurrence compared with EBRT, with a median follow up of 5.8 years3. ELIOT is a very similar technique to Intrabeam, but treats a larger volume of breast and the local recurrence rates were very low with a median follow up of 2.5 years (see figure below courtesy of Profs Orecchio and Yarnold: cumulative incidence of ipsilateral breast tumour recurrence for ELIOT trial). [figure excluded] **2. The process for this technology appraisal conflicts with the on going update of the NICE guidance for early breast cancer** The process is flawed as partial breast radiotherapy recommendations are being made using two separate NICE committees with seemingly differing evidence level requirements. It is incongruous that one advisory committee to NICE can recommend Intrabeam treatment within the NHS, whereas another has excluded data from Targit trial as it is will only make evidence graded recommendations using trials with at least 5 year published outcome data. 3. **A national database to collect efficacy outcomes for patients treated with Intrabeam within the NHS is as expensive and complex as conducting a research trial and will take many years to produce mature data**	The clinical guideline will not consider technologies where there is a technology appraisal in development. The scope for the guideline development mentions no such exclusion criterion.

Nominating organisation	Comment [sic]	Response
	The Targit trial protocol stated that follow up would continue for 10 years. The Targit team intend to report the mature results as shown by their 2016 Health Technology Assessment publication in September 2016: [figure excluded] Given this intention to publish mature results, any decision from Appraisal Committee should be postponed until this new data is available from the Targit trial. This spares the uncertainty for patients and cost for the NHS in delivering and monitoring an unproven treatment. [References excluded]	
King's College London / Guy's & St Thomas' Hospitals	I entirely support the latest recommendations of NICE and would like to find a pragmatic way to implement this in order to ensure suitable NHS patients have access to this treatment option should they wish. Intraoperative radiotherapy using the TARGIT technique was evaluated in a large multinational randomised controlled trial (academically run and HTA funded) run from London and the first patient was randomised in March 2000. After 10 years, the data was published in the Lancet in 2010 (Vaidya et. al). Following a very stringent peerreview process (over 5 reviewers and detailed independent statistical assessment), the Lancet Editorial Team decided that the data, as presented (with 2.4 years median follow-up overall), should be in the public domain. The Lancet published the article as a fast-track publication and graced its cover with the TARGIT-A Trial conclusion, that IORT (Intrabeam) should be considered in suitable patients as an alternative to external beam radiotherapy delivered over several weeks. NICE received the go ahead to consider Intrabeam IORT for the NHS, following a scoping meeting held on the 12/11/2012. Following this, 3 committee meetings took place (in 2013, 2014 and 2015) and public consultations (2014 and 2017). Meanwhile, the TARGIT-A trial was extended to over 33 centres, recruiting over 3,400 patients and the Lancet published the data again in 2014 (Vaidya et al). Clearly, the independent	Comments noted. See sections 4.13-4.17 of the FAD for committee discussions on the recommendations in section 1.

Nominating organisation	Comment [sic]	Response
	reviewers (typically 5-6 experts including statisticians) and the Editorial Board of the Lancet felt, again, that this data was important enough to be in the public domain. Therefore, patients are entitled to know about this option of treatment if they meet the inclusion criteria of this trial. In August 2015, the NICE MTA Committee confirmed that Intrabeam IORT is a costeffective alternative to external beam. In addition, the mortality benefits of Intrabeam IORT observed in the TARGIT-A trial, were confirmed in a large meta-analysis of nearly 4,500 patients with 5 years follow-up (Vaidya et al, 2016) published in the Red Journal (top radiotherapy journal). Also in 2015, the Supreme Court (Montgomery vs Lanarkshire Health, March 2015) decided that patients now have a legal right to be advised of all treatment options available - not just a moral responsibility. Clinicians (and by extension the NHS) now have a legal responsibility to provide evidence-based information to enable patients to make informed decisions about their treatment and care, including information on evidence-based treatment options that they may not, personally, agree with. The judgment went beyond this specifying that when presenting treatment options, the Bolam test of conduct (eg: comparison of practice with opinions from Royal Colleges or NICE guidance), does not apply. This is because patients are entitled to take into account their own values, whatever medical opinion may say. Bearing this in mind, it has been worrying that IORT is currently not yet routinely mentioned to suitable women as a treatment option (potentially exposing the NHS to indefensible litigation, given the above) and the proposed NICE recommendation will rectify this. [References excluded]	

Comments received from commentators

Commentator	Comment [sic]	Response
Healthcare Improvement Scotland	**Has all the relevant evidence been taken into account?** NO If NO, what evidence has been omitted and what are the implications of this omission? There are three major issues that do not seem to have not been considered to support the provisional recommendation of the committee 1) Flawed analysis of the TARGIT A trial 2) Inadequate follow up of the TARGIT A trial. 3) Evidence of non inferiority of brachytherapy after breast conserving surgery compared to postoperative whole breast irradiation with boost and results of other trials of partial breast irradiation that are awaited. 1) The flawed analysis of the TARGIT A trial (Vaidya et al, Lancet 2014; 383:603-13) is a principal concern since there is no other trial of Intrabeam for comparison. Prof Cuzick rightly highlights that dangers of concentrating in reporting the most favourable subgroup (the prepathology group) when the protocol states that the primary analysis includes all randomised patients (Cuzick et al,Lancet 2014;383:1716. He also highlights the misuse of the non-inferiority criterion which requires the upper (90%) CI to be below a predefined value. Professor Cuzick states that this criterion fails when the appropriate Kaplan-Meier estimates are used, which in fact establish a 2% superiority of external beam radiotherapy (p=0.004). The crude rates reported by Vaidya et al, are 'substantially diluted by patients with short follow up (only 611 [18%] had 5 year follow up'. Haviland et al (Int J Rad Oncol Biol Phys 2015; 92:954-5) further express concerns about the TARGIT-A trialists using a non inferiority test based on binomial proportions in which subjects with very short follow up are counted as not having had a local recurrence and that appropriate assessment of non inferiority in the TARGIT A trial should use survival analysis to estimate the absolute differences in 5-year recurrence rates (protocol specified primary endpoint) with a confidence interval. They also point out the error of stating that predefined subgroups are not	See sections 4.13-4.17 of the FAD for committee discussions on the recommendations in section 1.

Commentator	Comment [sic]	Response
	subgroups and the well recognised dangers of limiting results to subgroups (Cuzick et al, Lancet 2005; 365:1308). The NCRI Breast Cancer Studies Group, Chair of the NCRI Clinical and Translational Radiotherapy Research Working Group, Royal College of Physicians, Association of Cancer Physicians and Joint Collegiate Council for Council state in section 1 (iii) of their specific comments that the results are presented by Vaidya et al in the TARGIT A analysis for the 3 cohorts with varying length of follow up and that it is stated by the authors that 'the results illustrated the stability of the treatment effect over time'. The NCRI BCSG et al note that 'this is a flawed approach as the cohorts are nested within each other and so in effect the patients with the longest follow up have been analysed three times'. 2) The substantial weight of the professional advice from the Royal College of Radiologists, the NCRI Breast Cancer Studies Group, Chair of the NCRI Clinical and Translational Radiotherapy Research Working Group, Royal College of Physicians, Association of Cancer Physicians and Joint Collegiate Council for Council and the Society of Radiographers does not seem to have been recognised in the recommendation that Intrabeam should be available outside a research setting in existing UK intrabeam facilities. All of these organisations consider that it is premature to recommend Intrabeam until mature results of the TARGIT-A trial (with a median follow up of at least 5 years are published (by implication) in a peer reviewed journal). 3) There are other options for partial breast irradiation. Postoperative brachytherapy has maturer 5 year evidence of equivalence to whole breast irradiation than Intrabeam. A European phase 3 non inferiority trial of 1184 patients with low risk invasive breast cancer or in situ carcinoma (Strnad et al Lancet 2016;387:229-38) showed cumulative incidence of local recurrence at 5 years of 1.44% (95% CI 0.51-2.38) for accelerated partial breast irradiation with multicatheter brachytherapy to the tumour bed over 4-5 days vs 0.92% (95% CI 0.12-1.75) for whole breast irradiation (50Gy in 25 daily fractions).The authors concluded that adjuvant multicatheter brachytherapy adjuvant accelerated partial breast irradiation is not inferior with respect to 5 year local control, disease free survival and overall survival.	

Commentator	Comment [sic]	Response
	The authors acknowledge the importance of follow up to at least 10 years in the light of the linear rate of recurrence for lower risk patients and the ongoing effect of external beam radiotherapy after 5 years of treatment. In an accompanying editorial to the article, Charlotte Coles and John Yarnold, two leading UK breast radiotherapy trialists, point out that European Strnad et al trial is maturing but that further evidence is needed from 14,000 patients in five as yet unreported trials of accelerated partial breast irradiation (Lancet 2016;387:201-202). The committee will be aware of the UK IMPORT LOW trial of partial breast radiotherapy with external beam vs whole breast radiotherapy due to report its 5 year results in 2016/7. The UK Fast Forward trial (Coles C et al, Clin Oncol published online June 28: DOI 10:1016/jclon, 2015.06.007) is investigating just 5 treatments for whole breast irradiation over 1 week. So the duration of future comparators of external beam after breast conserving surgery, if validated, may well be shorter than the standard arm 50 Gy in 25 fractions over 5 weeks as comparator in the TARGIT A trial. **Has the analysis of clinical and cost effectiveness used an appropriate comparator which reflects Scottish practice?** YES with the comparator as external beam radiotherapy If NO, please explain. **Are the summaries of clinical and cost effectiveness reasonable interpretations of the evidence?** NO If NO, please explain. With concerns about flaws in the analysis of the TARGIT-A trial, I do not think it justifies the committee's conclusion (4.6, last 3 lines) 'that it was reasonable to	

Commentator	Comment [sic]	Response
	consider treatment with intrabeam only at the time of primary surgical removal of the tumour'. I would agree with the conclusion of the committee (4.12 lines 1-3) that 'the clinical effectiveness of Intrabeam compared with EBRT remains uncertain'. Treatments where clinical benefit is uncertain should not be recommended for routine care, even within existing UK centres with intrabeam facilities. I would agree with the committee's comment (4.13, line 3-9) that '…even if the length of follow up in TARGIT-A were longer, the quality of the trial and particularly its generalisability to NHS clinical practice would still not provide conclusive evidence to establish the relative clinical and cost effectiveness of Intrabeam with EBRT as delivered in the NHS'. As the provisional advice stands, there is likely to be inequity of treatment between centres with and without Intrabeam facilities. Enthusiasts for Intrabeam within existing centres potentially may recommend it after breast conserving surgery outside an RCT without adequate evidence of clinical and cost effectiveness, while in other centres without Intrabeam, the option of Intrabeam will not be recommended because it is not considered clinically or cost effective and not available. Assessment of Intrabeam should only be conducted in patients already recruited into the TARGIT A trial. **Are the provisional recommendations of the Appraisal Committee reasonable?** NO If NO, please explain. The recommendations are at variance with the acknowledgement within the report that it is uncertain whether Intrabeam is clinically or cost effective. I would strongly disagree with the committee's provisional recommendation (4.14, lines 10-12) that 'it can only recommend Intrabeam as an option if its use is accompanied by additional information on clinical effectiveness by appropriate data collection'.	

Commentator	Comment [sic]	Response
	I would contend that ethically patients should not be treated with Intrabeam following breast conserving surgery in existing centres with managed national data collection unless Intrabeam is considered to have robust level 1 evidence of clinical effectiveness and cost effectiveness (which it does not). Patients treated in UK centres will not provide robust effectiveness of clinical effectiveness since they do not provide the level 1 evidence needed from an RCT. Patients so recruited may being an exposed to an ineffective treatment. Data collection in existing UK facilities will be from non randomised patients, subject to selection bias and will not contribute meaningfully to the assessment of Intrabeam's clinical effectiveness. No detail is given of the duration of national data collection but the costs could be substantial for little return. I would strongly disagree with the committee's conclusion (4.16,line 10-12) that ' obtaining further information on the clinical effectiveness of Intrabeam from its use in the NHS, added to longer term follow up of TARGIT A would be valuable for decision making' for the reasons outlined above. It is inappropriate to ask clinicians to discuss Intrabeam with patients as a treatment option where it has not be robustly validated to be clinically effective and cost effective. While the views of the patient expert on the impact of many (external beam) radiotherapy sessions and financial and emotional impacts are recognised, the overriding concern of patients with early breast cancer is that the treatment will reduce the risk of local recurrence. I am not sure whether recurrence free patients treated with external beam radiotherapy or no radiotherapy after breast conserving surgery were included in the panel of patient experts to avoid bias towards Intrabeam treatment. Due weight should be given to the comments of the NCRI patients advocates (a larger group of patients) that ''.. Patient choice is important but forcing Trusts to spend money on this sort of equipment up and down the country on as yet insufficient evidence, will affect patient choice somewhere else may result in considerable wastage down the line if the 10 year results show problems". **Are the patient pathways and treatment options described in the NICE assessment applicable to NHS Scotland?**	

Commentator	Comment [sic]	Response
	YES Breast conserving therapy is similar to England and does not include Intrabeam as an option outside a clinical trial. **Is the provisional guidance as valid in Scotland as it is in England and Wales?** NO If NO, please explain. See comments on reservations above and below **Please add any other information which you think would be useful to the Appraisal Committee, or helpful to us in guiding the Scottish response to this assessment.** In the summary discussion from the Intrabeam investigators (p.7) the eligibility criteria of the PRIME2 trial are incorrectly stated: T size was =/<3cm (not =/<2cm), grade 3 tumours were included (if not combined with lymphovascular invasion (rather than grade 1 or 2 as stated) and LV invasion was allowed if not combined with Grade 3 histology. Only peer reviewed published analyses of the trial with a median follow up of 5 years should be admissible to assessing the clinical efficacy of Intrabeam rather than hypothetical scenarios (p.27).	

Summary of comments received from members of the public

Theme	Response
Supporting the provisional recommendations were: • 24 patients • 5 NHS professionals • 2 members of the public	Comments noted. The recommendations in the FAD have been amended, see section 1 and sections 4.13-4.17 for the committee discussions on the recommendations.
Not supporting the provisional recommendations were: • 2 members of the public	Comments noted. The recommendations in the FAD have been amended, see section 1 and sections 4.13-4.17 for the committee discussions on the recommendations.

Multiple Technology Appraisal (MTA)
INTRABEAM Radiotherapy System for the adjuvant treatment of early breast cancer [ID618]

Dear Appraisal Committee,

pursuant to the invitation to comment on the Appraisal Consultation Document (ACD) and evaluation report for the above appraisal we (manufacturer) would like to comment on the following:

- Has all of the relevant evidence been taken into account? **Yes, except some newer additional recent publications as cited below**
- Are the summaries of clinical and cost effectiveness reasonable interpretations of the evidence? **Yes, with some comments as stated below**
- Are the recommendations sound and a suitable basis for guidance to the NHS? **Yes, with a minor changes suggested below**
- Are there any aspects of the recommendations that need particular consideration to ensure we avoid unlawful discrimination against any group of people on the grounds of race, gender, disability, religion or belief, sexual orientation, age, gender reassignment, pregnancy and maternity? **No**

We suggest the following minor addition to the draft guidance:

….

- with managed evidence collection developing a national data set of all patients with early invasive breast cancer having adjuvant treatment with the Intrabeam radiotherapy system in the NHS **using existing UK routine cancer registries.** This should …

We suggest to consider the following points for the interpretations of the evidence:

Page 5:
The committee also heard from the clinical experts that in some radiotherapy centres in the NHS intensity modulated radiotherapy is used, which has the potential to reduce local adverse effects.

- **The studies with IMRT machines are not fully published yet and with newer techniques (IMRT, Gating, SIB) the costs are higher than calculated in the available cost-efficiency models for EBRT. IMRT machines would significantly change the ICERs for EBRT. Therefore these techniques cannot be included in the current technology appraisal.**

The committee noted comments from professional groups and also heard from the clinical experts that radiotherapy is constantly evolving, and that there are several ongoing trials investigating, for example, whether the course of radiotherapy could be reduced from 3 weeks to 1 week …

- **These trials are still ongoing, the outcome is not clear and e. g. the Rapid trial interim late toxicity results showed worse toxicity at 3 years in the APBI arm (1).**

Page 6:
… or whether radiotherapy is needed at all for patients considered to be at low risk of recurrence.

- **The current evidence suggests that despite having worse prognosis cancers in the TARGIT-A trial, local control with TARGIT during lumpectomy was excellent and clearly better than 'no-radiotherapy' as compared to CALGB, BASO II, PRIME II (2; 3; 4).**

Page 6:
If adverse histological features were identified in the cancer cells at final pathology after treatment with Intrabeam, and subsequent EBRT was recommended, a further external boost dose would not be needed.

- **This is true. The immediate irradiation with Intrabeam as a boost has the advantage of no geographical miss and no time delay after surgery. The IORT boost treatment can kill remaining tumor cells directly after tumor excision and has demonstrated better outcomes regarding local recurrence and survival (5; 6). Furthermore the abscopal effects and the inhibition of tumor proliferating cytokines with the irradiation directly after surgery should be considered as further advantage of Intrabeam treatment when it is applied as a boost (7; 8).**

Page 6:
Although there is a risk of clips moving within the cavity, EBRT has evolved and is generally considered to be accurate for targeting the tumour site.

- **Since nowadays oncoplastic techniques are implemented more widely, the EBRT (despite evolving) is accepted as less accurate compared to IORT with Intrabeam (9)**

Page 6:
However for some patients, brachytherapy may be a suitable breast-conserving treatment instead of mastectomy.

- **Also IORT has been shown as suitable breast-conserving treatment after local recurrence and is considered in the German S3 guideline as such treatment (10-13).**

Page 8:
However, a clinical expert stated that the radiation dose to the heart with modern EBRT is not clinically significant.

- **Even with modern EBRT the dose rate to the heart cannot be completely avoided. Every gray of radiation which reaches the cardiovascular system leads to a 16.3 %/Gy increased rate in major coronary events already during the first 4 years after radiation (14). The lower cardiovascular mortality in the in the Targit Intrabeam group can be explained with less side effects compared with EBRT (14; 15) and also with the effect on EGF influencing cardiac**

disease (7; 8). Still modern EBRT cannot avoid patient's movement uncertainties in radiation planning (16) and increasing additional risk factors in the patient population like obesity, diabetes and cigarette smoking of women.

Page 8:
The committee noted that in TARGIT-A, EBRT was delivered in an average of 23 fractions, longer than the 15 fractions delivered in established clinical practice in the NHS.

- **A substantial number of patients who were treated in the UK centers received already 15 fractions. Canadian as well as Australian centers have treated at that time their patients with 15 fractions as well (personal communication with trial centers). Comparing the total enrollment number of 3451 patients in the Targit trial with other radiation studies, the number of UK patients in Targit-A should be high enough to be generalizable in NHS clinical practice. In general the high standard of EBRT treatment and clinical practice in the Targit-A study can be compared to NHS quality requirements. Only centers of clinical excellence in Germany, France, Italy, Denmark, US and Australia were included after the center specific treatment practice was audited and verified.**

Page 9:
Median follow-up in the trial was 2 years and 5 months and only 35% of the patients had 5-year follow-up at the time of the analysis. The committee heard from the clinical experts that longer follow-up, usually of at least 5 years, is needed for clinicians to feel confident about data on local recurrence.

- **1222 patients were analyzed as sub-group in the Lancet 2014 publication which was as high as the number other radiation oncology trials e. g. Eliot and GEC-ESTRO trials with similar follow up (17; 18).**

Page 9:
The committee was aware of the large debate in the medical community about TARGIT-A in which opposite views have been raised about the importance of mature follow-up, trial governance and the interpretation of the results

- **We were puzzled by the fact that some medical communities expressed opposite and emotional views against the study which was conducted by highly qualified academic investigators in 33 centers in 11 countries and was published two times in the peer reviewed The Lancet. Besides that, the Southhampton AG has confirmed the good quality of the trial. The "quasi-religious debate" is perfectly described by the chief editor of the Red Journal Prof. Anthony Zietmann (19).**

THE TARGIT-A DEBATE

Letters Regarding the TARGIT-A Trial: The Editor's Introduction

Anthony Zietman, MD, FASTRO, *Editor-in-Chief*

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be another way to achieve it. Many careers have been built around fractionated radiation therapy for breast cancer, and it comprises a substantial proportion of the practice of the average contemporary radiation oncologist. Depending on your perspective, intraoperative radiation therapy is thus either a very serious threat or a quantum leap forward. Data will ultimately resolve this debate as TARGIT-A matures

in the eye of the beholder. There are some subjects for which the stakes are so high that scientific discourse can cross a line into irresolvable ideological or quasi-religious debate, and it is in this third category that we come closest to this. "My God is better than your God" is an irresolvable argument. In medicine, however, data and a common desire to benefit our patients should act as a compass to guide resolution. As you will read, both sides powerfully invoke the breast cancer patient to illuminate their case, and it will take a moral philosopher to separate them.

Page 10:
It noted that some patients having Intrabeam also had further treatment with EBRT depending on their final pathology report, but that the results were not presented for this group separately.

- **The results were presented in the Lancet 2014 publication under attachments (Table 2) however the number is very low (20).**

Page 11:
It considered that the pre-trial estimated 5-year rate of 6% for local recurrence, on which the non-inferiority margin was based, is higher than the current expected rate of local recurrence in people having treatment with EBRT. The committee also noted that patients in the trial had a relatively good prognosis and low risk of local recurrence and heard from the clinical experts that since 2000, when patients were first recruited into the trial, the 5-year local recurrence rate with EBRT has decreased to much lower than 6%. The committee also noted that when assessing non-inferiority, the point estimate alone is not sufficient. The confidence interval around the point estimate should also be considered and compared with the pre-specified non-inferiority margin.

- **The non-inferiority margin was also based on a previous preference trial showing up to which rate the patient is willing to accept a higher risk of**

local recurrence. In fact, two patient preference studies have suggested that the median additional increase that would be accepted by physicians and patients in exchange for the convenience of a single treatment dose is 2,5% (21). Thus, with a background recurrence rate at 5 years for example of only 1,5% instead of the 6 % (in the START trial, the recurrence rate at 5 years was 2,3%) a trial for testing a non-inferiority margin of 2,5% with 80% power and 95% confidence needs a sample size of only 585 patients (21). Consequently the number of 3451 patients was far beyond the needed minimum statistical number. Furthermore the Lancet 2014 results reported 1222 patients with a 5 years follow up.

Page 12:
The committee considered that the criterion for non-inferiority was not appropriately defined and the trial was therefore underpowered and the results could not be considered robust enough to determine whether Intrabeam is non-inferior to EBRT in terms of local recurrence.

- **See The Lancet 2010: With a background recurrence rate at 5 years for example of only 1,5% instead of the 6 % a trial for testing a non-inferiority margin of 2,5% with 80% power and 95% confidence needs a sample size of only 585 (21). The trial was not underpowered, it was closed after 3451 patients resulting in 9491 women-years of follow-up.**

Page 13:
It understood that the assessment group had reported that the difference in overall survival was based on a small number of events and that it did not consider that there was an excess of deaths in the EBRT group, but rather a shortfall of deaths in the Intrabeam group occurring by chance.

- **Fewer non-breast cancer were probably unmasked in this cohort of excellent prognosis patients (>98% were local-recurrence-free at 5 years) in whom only 36/3451 patients died from breast cancer (vs. 52 died from other causes) as stated above due to unmasked side effects of EBRT and probably due to the inhibition of EGF. Furthermore other effects on cytokine factors and abscopal effects of immediate irradiation can be considered as explanation (7; 8).**

Page 13:
The committee heard from a clinical expert that the mean radiation dose to the heart was not provided in the TARGIT-A publication and that the mean dose to the heart delivered with EBRT in clinical practice in the NHS is minimal. Therefore it is highly unlikely that the difference in non-breast cancer deaths between treatment groups in TARGIT-A could be explained by an increased risk of cardiovascular death related to EBRT.

- **The heart dose is dependent on the position of applicator in the breast tissue and is very low with the Intrabeam radiation due to the steep dose fall off of the photon radiation system. The heart dose can be extrapolated and is published as a mean dose of 0.01 Gy by Aziz et al. (22). A recently published meta-analysis regarding survival of randomized partial breast radiation studies showed that the mortality is lower with APBI (23). The similar effect has been seen in the Start trial.**

The mortality rate was 108 in the test arm compared to 137 in the conventional arm (24).

Page 15:
…the company's model Intrabeam was associated with slightly more QALYs than EBRT, whereas in the assessment group's model Intrabeam was associated with fewer QALYs than EBRT.

- **The slightly more QALYs in the company's model included the lower non-breast cancer death and the better progression free survival rate for Intrabeam as a result of the randomized Targit A trial (23). Ongoing research will investigate the utility of IORT compared to EBRT (e. g. Targit-B trial). Additionally better QOL is noted by patients groups: less disruption of daily life, less travel costs, less inconvenience and productivity loss and less radiation exposure to other organs compared EBRT.**

Page 15:
Section 5.12.6 of the guide states that if savings are anticipated, the extent to which these finances can actually be realised should be specified. The committee debated whether the costs for Intrabeam and linear accelerator equipment should be included in the same way in the economic model (that is, including the capital costs of equipment for both technologies) or using only the tariff cost associated with each technology.

- **We agree that the equipment costs of both technologies should be included to ensure equal comparison since there are no tariffs existing so far for Intrabeam. Unfortunately both models (company's and AG's) did not consider the equipment costs for EBRT. Since Intrabeam can free up capacity for EBRT these savings for the NHS should be considered as stated in Section 5.12.6. In the Lancet 2010 savings of around £15 000 000 were estimated (21). The NHS needs high investments in the near future (£130 million fund) for missing or older radiotherapy equipment. Intrabeam could be an opportunity to reduce the needed EBRT capacity. Additionally Intrabeam is used also in other tumor entities (Glioblastoma, Colorectal Cancer, Spine-Metastasis, Sarcoma), thus freeing up capacity for EBRT as well.**

Page 16:
The committee considered that, based on the high degree of uncertainty in the cost-effectiveness analysis, it is not possible to state the most plausible ICER for Intrabeam compared with EBRT. It concluded that Intrabeam is associated with slightly lower costs and fewer QALYs than EBRT.

- **As stated above including equipment costs for both technologies would reflect a realistic view of cost-comparison or cost-effectiveness and a plausible ICER. The recent HTA publication has shown again cost-effectiveness for Intrabeam as well as higher QALYs for Intrabeam (25). As mentioned above Intrabeam could reduce EBRT capacity and save needed investment in the NHS.**

Final remarks:

We do appreciate the current recommendation and want to support in full extent the implementation of the technology in the NHS. Intrabeam does not necessarily imply an increase in NHS investment since the rising demand in radiation capacity can be compensated by freeing up needed fractionation schemes for early breast cancer. For the staff training there already exists a standardized training course which is provided by academic centers using the device for many years (London, Heidelberg and Cleveland). Also our clinical application team is supporting the centers to set up the system and workflow and is helping during the first cases in the operating theatre.

For the implementation we have the following suggestions:
A patient shared decision making tool can be provided by the manufacturer if needed. Intrabeam centers worldwide have developed already such tools for their patients. The decision making leaflet should be made available for all patients with early breast cancer and the informed consent discussion should be a given procedure in every hospital. In NHS hospitals with no Intrabeam, elderly, disabled and pregnant patients should have the possibility of free transportation to hospitals with existing NHS Intrabeam machines. The managed evidence collection should be made possible for new centres who want to use own funding to acquire/lease Intrabeam. Therefore we suggest to use the excising UK cancer registry for the data collecting.

Finally we want to emphasize, that current health service research of Intrabeam centres worldwide reflects obviously low recurrence rates in real world settings outside of randomized trials. Cost-effectiveness has also been shown in other health societies showing that the single radiation saves resources in public health care systems.

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Response from the Association of Breast Surgery (ABS)

The ABS are pleased that NICE cautiously recommend the commissioning of Intrabeam as an alternative to standard external beam radiotherapy if certain conditions are met. The ABS strongly supports the principle of follow up data collection for newly introduced treatments and of appropriate patient information.

ABS notes that there has been clinical expert discord on this topic and within the breast community as a whole. We therefore understand why NICE have to be cautious and not recommend Intrabeam as standard therapy.

The clinical trial examining IORT has patients with a mean follow up of 4 years and shows non-inferiority of IORT compared with external beam radiotherapy and has been published in peer reviewed journal. The data is therefore encouraging, if immature, for incorporation into routine practice with the parallel development of a national dataset to gather outcome data.

NICE recommend that IORT only be performed in units that already possess the equipment for this treatment. As there are only 6 such units nationally, NICE are, in effect, introducing a new technology which is available only to those patients within the vicinity of these units and not to all patients.

The assessment committee conclude that IORT is probably cost effective if compared to 15 fractions of radiotherapy which is the current NHS standard. Partial breast irradiation is now supported, for selected cases, by evidence from a range of strong clinical trials using a number of different delivery systems.

We think the patient representative on this NICE committee has done a good job of highlighting patient concerns.

Declaration of Interest

took part in The Targit A trial as a local co-researcher.

Bijal Joshi/Liv Gualda
Project Manager
NICE
10 Spring Gardens
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1 March 2017

Dear Bijal/Liv

Re: Response to Appraisal Consultation Document on Intrabeam radiotherapy system for adjuvant treatment of early breast cancer

Breast Cancer Now welcomes the opportunity to respond to the Appraisal Consultation Document (ACD) on the Intrabeam radiotherapy system for adjuvant treatment of early breast cancer, published by NICE on 8 February 2017.

The Committee has recommend Intrabeam as an option for adjuvant treatment of early invasive breast cancer during breast conserving surgical removal of the tumour using machines that are already available; providing patients with information on the risks and benefits on the range of treatments available and collecting evidence to develop a national data set of all patients receiving this treatment.

Has all of the relevant evidence been taken into account?

We believe all the relevant evidence has been taken into account.

Are the summaries of clinical and cost effectiveness reasonable interpretations of the evidence?

We believe that the summaries of clinical and cost effectiveness are reasonable interpretations of the evidence.

Are the recommendations sound and a suitable basis for guidance to the NHS?

We believe these recommendations are sound and a suitable basis for guidance to the NHS.

Are there any aspects of the recommendations that need particular consideration to ensure we avoid unlawful discrimination against any group of people on the grounds of race, gender, disability, religion or belief, sexual orientation, age, gender reassignment, pregnancy and maternity?

We are not aware of any aspects that require particular consideration to avoid unlawful discrimination.

Yours sincerely.

[redacted]
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Healthcare Improvement Scotland

NICE Health Technology Appraisal
On ACD for

Intrabeam radiotherapy system for adjuvant treatment of early breast cancer - 2nd ACD for consultation

TO: NICE	FROM: Healthcare Improvement Scotland 01 March 2017

Comment provided to HIS by [redacted]

Question	Response
Has all the relevant evidence been taken into account?	NO If NO, what evidence has been omitted and what are the implications of this omission? There are three major issues that do not seem to have not been considered to support the provisional recommendation of the committee 1) Flawed analysis of the TARGIT A trial 2) Inadequate follow up of the TARGIT A trial. 3) Evidence of non inferiority of brachytherapy after breast conserving surgery compared to postoperative whole breast irradiation with boost and results of other trials of partial breast irradiation that are awaited. 1) The flawed analysis of the TARGIT A trial (Vaidya et al, Lancet 2014; 383:603-13) is a principal concern since there is no other trial of Intrabeam for comparison. Prof Cuzick rightly highlights that dangers of concentrating in reporting the most favourable subgroup (the prepathology group) when the protocol states that the primary analysis includes all randomised patients (Cuzick et al,Lancet 2014;383:1716. He also highlights the misuse of the non-inferiority criterion which requires the upper (90%) CI to be below a predefined value. Professor Cuzick states that this criterion fails when the appropriate Kaplan-Meier estimates are used, which in fact establish a 2% superiority of external beam radiotherapy (p=0.004). The crude rates reported by Vaidya et al, are 'substantially diluted by patients with short follow up (only 611 [18%] had 5 year follow up'. Haviland et al (Int J Rad Oncol Biol Phys 2015; 92:954-5) further express concerns about the TARGIT-A trialists using a non inferiority test based on binomial proportions in which subjects with very short follow up are counted as not having had a local recurrence and that appropriate assessment of non inferiority in the TARGIT A trial should use survival analysis to estimate the absolute differences in 5-year recurrence rates

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	(protocol specified primary endpoint) with a confidence interval. They also point out the error of stating that predefined subgroups are not subgroups and the well recognised dangers of limiting results to subgroups (Cuzick et al, Lancet 2005; 365:1308). The NCRI Breast Cancer Studies Group, Chair of the NCRI Clinical and Translational Radiotherapy Research Working Group, Royal College of Physicians, Association of Cancer Physicians and Joint Collegiate Council for Council state in section 1 (iii) of their specific comments that the results are presented by Vaidya et al in the TARGIT A analysis for the 3 cohorts with varying length of follow up and that it is stated by the authors that 'the results illustrated the stability of the treatment effect over time'. The NCRI BCSG et al note that 'this is a flawed approach as the cohorts are nested within each other and so in effect the patients with the longest follow up have been analysed three times'. 2) The substantial weight of the professional advice from the Royal College of Radiologists, the NCRI Breast Cancer Studies Group, Chair of the NCRI Clinical and Translational Radiotherapy Research Working Group, Royal College of Physicians, Association of Cancer Physicians and Joint Collegiate Council for Council and the Society of Radiographers does not seem to have been recognised in the recommendation that Intrabeam should be available outside a research setting in existing UK intrabeam facilities. All of these organisations consider that it is premature to recommend Intrabeam until mature results of the TARGIT-A trial (with a median follow up of at least 5 years are published (by implication) in a peer reviewed journal). 3) There are other options for partial breast irradiation. Postoperative brachytherapy has maturer 5 year evidence of equivalence to whole breast irradiation than Intrabeam. A European phase 3 non inferiority trial of 1184 patients with low risk invasive breast cancer or in situ

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	carcinoma (Strnad et al Lancet 2016;387:229-38) showed cumulative incidence of local recurrence at 5 years of 1.44% (95% CI 0.51-2.38) for accelerated partial breast irradiation with multicatheter brachytherapy to the tumour bed over 4-5 days vs 0.92% (95% CI 0.12-1.75) for whole breast irradiation (50Gy in 25 daily fractions).The authors concluded that adjuvant multicatheter brachytherapy adjuvant accelerated partial breast irradiation is not inferior with respect to 5 year local control, disease free survival and overall survival. The authors acknowledge the importance of follow up to at least 10 years in the light of the linear rate of recurrence for lower risk patients and the ongoing effect of external beam radiotherapy after 5 years of treatment. In an accompanying editorial to the article, Charlotte Coles and John Yarnold, two leading UK breast radiotherapy trialists, point out that European Strnad et al trial is maturing but that further evidence is needed from 14,000 patients in five as yet unreported trials of accelerated partial breast irradiation (Lancet 2016;387:201-202). The committee will be aware of the UK IMPORT LOW trial of partial breast radiotherapy with external beam vs whole breast radiotherapy due to report its 5 year results in 2016/7. The UK Fast Forward trial (Coles C et al, Clin Oncol published online June 28: DOI 10:1016/jclon, 2015.06.007) is investigating just 5 treatments for whole breast irradiation over 1 week. So the duration of future comparators of external beam after breast conserving surgery, if validated, may well be shorter than the standard arm 50 Gy in 25 fractions over 5 weeks as comparator in the TARGIT A trial.
Has the analysis of clinical and cost effectiveness used an appropriate comparator which reflects Scottish practice?	YES with the comparator as external beam radiotherapy If NO, please explain.

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TO: NICE	**FROM: Healthcare Improvement Scotland** **01 March 2017**

Are the summaries of clinical and cost effectiveness reasonable interpretations of the evidence?	NO If NO, please explain. With concerns about flaws in the analysis of the TARGIT-A trial, I do not think it justifies the committee's conclusion (4.6, last 3 lines) 'that it was reasonable to consider treatment with intrabeam only at the time of primary surgical removal of the tumour'. I would agree with the conclusion of the committee (4.12 lines 1-3) that 'the clinical effectiveness of Intrabeam compared with EBRT remains uncertain'. Treatments where clinical benefit is uncertain should not be recommended for routine care, even within existing UK centres with intrabeam facilities. I would agree with the committee's comment (4.13, line 3-9) that '…even if the length of follow up in TARGIT-A were longer, the quality of the trial and particularly its generalisability to NHS clinical practice would still not provide conclusive evidence to establish the relative clinical and cost effectiveness of Intrabeam with EBRT as delivered in the NHS'. As the provisional advice stands, there is likely to be inequity of treatment between centres with and without Intrabeam facilities. Enthusiasts for Intrabeam within existing centres potentially may recommend it after breast conserving surgery outside an RCT without adequate evidence of clinical and cost effectiveness, while in other centres without Intrabeam, the option of Intrabeam will not be recommended because it is not considered clinically or cost effective and not available. Assessment of Intrabeam should only be conducted in patients already recruited into the TARGIT A trial.
Are the provisional recommendations of the Appraisal Committee reasonable?	NO If NO, please explain. The recommendations are at variance with the acknowledgement within the report that it is uncertain whether Intrabeam is clinically or cost effective.

Healthcare Improvement Scotland

NICE Health Technology Appraisal
On ACD for

Intrabeam radiotherapy system for adjuvant treatment of early breast cancer - 2nd ACD for consultation

TO: NICE	FROM: Healthcare Improvement Scotland 01 March 2017
	I would strongly disagree with the committee's provisional recommendation (4.14, lines 10-12) that 'it can only recommend Intrabeam as an option if its use is accompanied by additional information on clinical effectiveness by appropriate data collection'. I would contend that ethically patients should not be treated with Intrabeam following breast conserving surgery in existing centres with managed national data collection unless Intrabeam is considered to have robust level 1 evidence of clinical effectiveness and cost effectiveness (which it does not). Patients treated in UK centres will not provide robust effectiveness of clinical effectiveness since they do not provide the level 1 evidence needed from an RCT. Patients so recruited may being an exposed to an ineffective treatment. Data collection in existing UK facilities will be from non randomised patients, subject to selection bias and will not contribute meaningfully to the assessment of Intrabeam's clinical effectiveness. No detail is given of the duration of national data collection but the costs could be substantial for little return. I would strongly disagree with the committee's conclusion (4.16,line 10-12) that ' obtaining further information on the clinical effectiveness of Intrabeam from its use in the NHS, added to longer term follow up of TARGIT A would be valuable for decision making' for the reasons outlined above. It is inappropriate to ask clinicians to discuss Intrabeam with patients as a treatment option where it has not be robustly validated to be clinically effective and cost effective. While the views of the patient expert on the impact of many (external beam) radiotherapy sessions and financial and emotional impacts are recognised, the overriding concern of patients with early breast cancer is that the treatment will reduce the risk of local recurrence. I am not sure whether recurrence free patients treated with external beam radiotherapy or no radiotherapy after breast conserving surgery were included in the panel of patient experts to avoid bias towards Intrabeam treatment.

Healthcare Improvement Scotland

NICE Health Technology Appraisal On ACD for Intrabeam radiotherapy system for adjuvant treatment of early breast cancer - 2nd ACD for consultation	
TO: NICE	**FROM: Healthcare Improvement Scotland** **01 March 2017**

	Due weight should be given to the comments of the NCRI patients advocates (a larger group of patients) that ".. Patient choice is important but forcing Trusts to spend money on this sort of equipment up and down the country on as yet insufficient evidence, will affect patient choice somewhere else may result in considerable wastage down the line if the 10 year results show problems".
Are the patient pathways and treatment options described in the NICE assessment applicable to NHS Scotland?	YES Breast conserving therapy is similar to England and does not include Intrabeam as an option outside a clinical trial.
Is the provisional guidance as valid in Scotland as it is in England and Wales?	NO If NO, please explain. See comments on reservations above and below
Please add any other information which you think would be useful to the Appraisal Committee, or helpful to us in guiding the Scottish response to this assessment.	In the summary discussion from the Intrabeam investigators (p.7) the eligibility criteria of the PRIME2 trial are incorrectly stated: T size was =/<3cm (not =/<2cm), grade 3 tumours were included (if not combined with lymphovascular invasion (rather than grade 1 or 2 as stated) and LV invasion was allowed if not combined with Grade 3 histology. Only peer reviewed published analyses of the trial with a median follow up of 5 years should be admissible to assessing the clinical efficacy of Intrabeam rather than hypothetical scenarios (p.27).

We are breast cancer patient members of Independent Cancer Patients' Voice – a patient advocate group run and lead by patients whose aim is to bring the patients' voice to the cancer research community.

ICPV members have been involved with radiotherapy research and trials for a number of years. Some of our members have also been involved with CTRad and the Royal College of Radiology Guidelines for Breast Cancer published in 2016

We contributed to the NICE consultation in 2014.

We have considered the latest consultation and are entirely unpersuaded that is sensible to issue guidance on this matter before the mature follow-up data is available. The NICE remit is to *'decide whether the technology should be recommended as a clinically-effective and cost-effective use of NHS resources*', and the report itself says that *' the clinical and cost-effectiveness evidence for Intrabeam remains uncertain'*. It seems to us that relevant evidence so far has been taken into account but this is immature, and the conclusion of uncertainty in clinical and cost-effectiveness is a reasonable interpretation of the current evidence. We therefore strongly believe that there is no sound and suitable evidence for this to be recommended at this stage.

We also strongly believe that it is a disservice to patients to consider Intrabeam in isolation, precluding its consideration by the NICE Early Breast Cancer Guideline Update committee which is currently considering the update of CG80, and in particular the omission of radiotherapy and partial radiotherapy in selected sub-groups of patients.

In addition, we have serious concerns relating to

- the provision of high-quality information for all patients
- the geographic inequity that this recommendation is likely to introduce for patients

ICPV patient members have made a number of comments on these matters which we have included below

"It is wrong for NICE to go for approval for a procedure when the full follow-up data has not been published. When is this due? They should wait until this and IMPORT-Low data is available. This will give a much clearer picture of its usefulness (or otherwise)."

"I thoroughly support your argument and resulting position. I'm horrified by NICE."

"It is unfortunate that there seems to be a conclusion that the trial is underpowered and not necessarily applicable to the NHS. The addition of the managed data collection seems to be to provide extra data to off-set this deficit. However, there is no discussion of the costs involved in doing this collection properly outside of a trial, or whether patients need to consent to this collection. Whilst some of the data points measured are standard, I don't think QOL data collection is. Also, data like OS and DFS, and QOL will take 5 – 10 years to collect. None of this discussion is included. it seems to me that if a treatment is evidenced based then it is reasonable to recommend it and deal with the practicalities of delivery afterwards. However, in this case where the decision is not evidenced-based surely these other issues are pertinent."

"Patients will definitely need written standard information about this if they are to be fully informed. This written information ought to include this, EBRT, and the relevant trial options available to patients, including the biomarker directed PRIMETIME. The committee themselves say ' that, given

the difficulty in interpreting the evidence, particularly where specialist clinicians do not agree, special effort would be required to support shared decision-making'. This disagreement amongst clinicians is likely to be even within the units that have this equipment, isn't it? It is not easy for us as patients to grasp the significance of the low levels of risk and benefit that we are talking about here and very easy to be swayed by whether or not we 'trust' the person who is talking to us at difficult times like these."

"I agree that any patient literature must clearly show that there are choices – all with pros & cons. Could this be badged with the College and a charity to give it independence. What is the position of the charity sector e.g. Breast Cancer Now and Breast Cancer Care?"

"The patient group that will be eligible for this will be very small and may in part be the exact match for PRIMETIME and this has to be highlighted. Fear of recurrence and being left alone after treatment are common psychological issues for patients and follow-up to pick up any early recurrence should be particularly addressed in studies and evaluations of uncertain treatments. Of course, there may also be a small number of patients with comorbidities that may not be able to have standard RT."

"I find it difficult to see how this recommendation can work in practice. The NHS is supposed 'to promote equality through the services it provides', but these machines are mostly in the South of England, mainly London. The patients, most likely to benefit will be the very small group of people with co-morbidities, who need but can't manage EBRT, and those patients could be anywhere in the country. Will all relevant patients need to be informed of this recommended option and offered the option of travelling to London? We also however note that there are other brachytherapy options with a greater evidence base for these women which have not been considered by this committee at all."

"I disagree in part with this comment from the 'patient expert'. How often do women have to travel long distances for standard therapy unless they live in very rural areas? Yes, travelling daily can be an issue, but is it that great an issue?? I would like to see more evidence of this. ***"The patient may need to stop working and face substantial travel costs, which can have a considerable financial and emotional impact on the patient and their family. The committee also heard from the patient expert that some patients who live a long distance from a radiotherapy centre may need to stay away from their home to be able to complete the course of radiotherapy"'***

"I have concerns that this recommendation is not solving anything but rather continuing with unnecessary confusion for patients. I also detect (maybe wrongly), a subtext that because the absolute risk of local recurrence is very low in this group whatever we do (this is mentioned several times), this justifies a decision made too early without mature evidence."

To summarise we have reached the conclusion that this procedure should not be given NICE approval at this time, and any further consideration should be within the NICE Early Breast Cancer Guideline Update committee currently looking at CG80.

on behalf of Independent Cancer Patients' Voice

10 February 2017

Response to 2nd Appraisal Consultation Document (ACD) for

Multiple Technology Appraisal of INTRABEAM Radiotherapy System for Adjuvant Treatment of Early Breast Cancer

from the Institute of Physics and Engineering in Medicine (IPEM)

- Has all of the relevant evidence been taken into account?
- Are the summaries of clinical and cost effectiveness reasonable interpretations of the evidence?
- Are the provisional recommendations sound and a suitable basis for guidance to the NHS?

The vision of the Institute of Physics and Engineering in Medicine (IPEM) is to constantly improve human health by the application of physics and engineering to prevention, diagnosis and treatment of disease through research, innovation, education and clinical practice. As such, we support the use of existing equipment (and resources) to further research into the efficacy of intra-operative breast radiotherapy.

It is disappointing that the TARGIT trialists have not released long-term follow up data for the patients in this trial, when median five year follow up was achieved in January 2015. We share the concerns of oncologists who have criticised the methodology and presentation of results from this trial, and support the recommendation that the higher risk of recurrence should be explained to patients seeking this treatment option. This discussion should be with an oncologist.

At the time of first report, 6 INTRABEAM units were reported to be used in the UK. A recent survey by IPEM suggests 5 NHS units and 3 private units are currently available (Palmer et al Br J Radiol 2016). However, several of these have been moth-balled by restrictions on use, or have changed their radiotherapy physics support centre, and the numbers of patients treated in 2016 was very low. Therefore we strongly recommend:

* Centres with obsolete equipment, or those requiring major capital upgrade, are not included in the current recommendations;
* A minimum of six months is given to allow re-training of staff and mobilisation of resources (even though the long term resource requirements may be equal to external beam radiotherapy);
*No centre is permitted to start treatment unless close involvement of medical physics expertise and clinical scientists has been established;
*Tariffs for treatment are set by NHS England, following the economic analysis by the HTA (e.g. £2069 per treatment, table 33, Picot et al SHTAC 2014).

The appraisal consultation document (p4) describes the recommended dose as 20Gy at the surface of the tumour bed, which attenuates to 5-7Gy at 1cm depth. The TARGIT trial protocol allows dose prescription either to the surface, or 6Gy at 1cm depth, however modelling studies (Ebert and Carruthers Med Phys 2003, Eaton Med Phys 2012) recommend the prescription at depth approach to minimise variation between units.

The Xoft Axxent system (NICE MIB76) is almost identical in terms of radiation profile and delivery method (Eaton Br J Radiol 2015), therefore treatments should be allowed with this device also, but only with the same tariff, and when data are collected in the same system.

Finally, funding for the data collection both at the recruiting centres and the central registry should be identified before treatments commence, and form part of the tariff used to support this process.

We hope that this feedback is helpful to NICE.

This response has been prepared by some members of IPEM's Radiotherapy Special Interest Group and approved by IPEM's Science, Research and Innovation Council.

NHS England

Specialised Commissioning
Quarry House
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Professor Carole Longson,
Executive Director
Centre for Health Technology Evaluation

By email

01 March 2017

Dear Carole,

Re: ID 618 Intrabeam radiotherapy system for adjuvant treatment of early breast cancer

Thank you for your letter regarding the Multiple Technology Appraisal (MTA) of intrabeam radiotherapy for the adjuvant treatment of early breast cancer and the opportunity to both formally participate in the consultation process and work with you about this important matter. I would like to raise two distinct points, our assessment of the clinical evidence base contained within the Appraisal Consultation Document (ACD) and a number of wider system implications associated with the ACD recommendations.

Assessment of the clinical evidence-base

NHS England, having been advised by the Radiotherapy Clinical Reference Group (CRG), does not support the recommendations contained within the ACD. This is because we consider that the evidence within the ACD demonstrates that IORT is clinically inferior compared to conventional External Beam Radiotherapy (EBRT).

The challenges for patients associated with conventional radiotherapy treatments are acknowledged, as is the very difficult decision that the MTA committee are faced with in relation to this MTA. However, NHS England does not consider it appropriate for a treatment, which does not meet the thresholds for clinical effectiveness or safety, to be made routinely available in the NHS purely to facilitate greater patient choice.

Wider system implications

The ACD recommends that the treatment be made available in a managed way and from a small number of centres, in part to address the need to continue to build the evidence base and in part to manage the financial impact on the NHS associated with offering this treatment. Whilst the recommendations clearly recognise the financial implications for the NHS, they also raise some profound system concerns.

Of paramount importance to NHS England is to ensure that only evidence-based, clinically and cost effective treatments are made available, this is to ensure that value is maximised for both patients and taxpayers. Where treatments meet these criteria, there should be equitable access for patients. If the recommendations contained within ACD were to be approved, the NHS would need to carefully consider what grounds there were for restricting access.

In addition, should IORT be supported, there are some practical commissioning considerations for the NHS. The treatment is delivered as part of breast surgery procedures, which are commissioned by Clinical Commissioning Groups (CCGs), who reimburse hospitals through national prices set out within the National Tariff Payment System. Therefore, despite radiotherapy being a wholly nationally commissioned service, it is not clear that the costs of this treatment would in fact pass to NHS England. As a result, we ask for assurance that this issue will be fully considered by the committee, prior to any decision being made. This is because funding flows are often an important element of access arrangements.

Finally, I have enclosed the detailed advice provided by the Radiotherapy CRG (Annex 1), as this raises a number of important points. The advice is endorsed by NHS England and is included as part of our consultation response. Given the range of issues raised, I would like to offer the opportunity for the MTA team to liaise directly with both the Radiotherapy CRG and other members of the Specialised Commissioning team, as this may help to clarify the issues quickly.

Yours sincerely

Operational Delivery Director (National)
Specialised Commissioning & Chair of the Cancer Programme of Care Board

Annex 1: Advice received from the Radiotherapy CRG

1. The Radiotherapy CRG agrees that informed patient choice should be paramount. Information used in shared decision making should be based on mature, peer-reviewed evidence so that the risks and benefits of a treatment can be fully considered.

2. The ACD proposes the availability of a technology which, during the NICE evidence review process, did not meet threshold requirements for evidence of clinical effectiveness or safety.

3. The ACD does not consider published data from TARGIT A on the risks of increased fibrosis (approximately 30%) in those who require additional external beam whole breast following IORT because of high risk pathological features (15% of patients).

4. The ACD proposes the availability of a technology which, during the NICE evidence review process, did not demonstrate cost benefit to the NHS.

5. The clinical effectiveness/cost effectiveness analyses do not reflect developments in UK breast radiotherapy practice in the timescale of the MTA. For example data from IMPORT LOW (whole breast versus partial breast irradiation using external beam radiotherapy) is available in abstract form and the full publication with 5-year outcome data is expected shortly. The PRIMETIME trial of biomarker driven omission of radiotherapy in women at very low risk for recurrence will be opening imminently in many UK radiotherapy centres.

6. Mature 5-year outcome data regarding the effectiveness of the Intrabeam system should now available to the TARGIT trial investigators. The Radiotherapy CRG believe that this mature data should be published and subject to peer review. Published 5 year outcome data should form the basis for any definitive NICE recommendation.

7. The NICE guidance directly conflicts with Royal College of Radiologist national consensus guidance on Partial Breast Irradiation (PBI) developed March 2016.

8. Other forms of PBI and the omission of radiotherapy in women at low/very low risk for local recurrence are the subject of an in-progress update of the NICE Clinical Guideline CG80. As an MTA, Intrabeam is specifically excluded from the scope of the Clinical Guideline. As a consequence, different management options for the population of women with early breast cancer at low risk for local recurrence will be evaluated by separate NICE processes with different required thresholds of clinical evidence and relative weighting given to patient choice.

9. The Radiotherapy CRG recommends that the Intrabeam MTA should become part of the wider update of NICE Clinical Guideline CG80 with immediate effect:

    - Technologies with proven clinical effectiveness and cost benefit should be implemented in the NHS in a way that ensures equitable access for suitable patients. The ACD recommendation that Intrabeam should be an option for

adjuvant treatment of early invasive breast cancer using only machines that are already available will create inequity of access and variation in clinical practice driven largely by clinician bias.

10. The training costs and capital required to implement the guidance as it stands have been underestimated and would be a costly financial risk for the NHS and divert funding for existing services.

11. The recommendation for mandated clinical outcome data collection does not have clarity on governance and oversight of this data. There is no underpinning resource for collection of the data or its quality assurance. The proposal does not have a formal Commissioning through Evaluation structure with predefined clinical endpoints, patient numbers or data collection period.

12. The Radiotherapy CRG's view remains that any further evaluation of Intrabeam should be within well designed and conducted clinical trials.

13. The Radiotherapy CRG does not consider the current NICE recommendations to be a suitable basis for guidance to the NHS.

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9 February 2017

Dear Liv and Marcia

Re: ACD2 - Consultees & Commentators: Breast cancer (early) - Intrabeam targeted intraoperative radiotherapy [ID618]

The Royal College of Physicians (RCP) plays a leading role in the delivery of high quality patient care by setting standards of medical practice and promoting clinical excellence. We provide physicians in the United Kingdom and overseas with education, training and support throughout their careers. As an independent body representing over 33,000 Fellows and Members worldwide, we advise and work with government, the public, patients and other professions to improve health and healthcare.

The NCRI-ACP-RCP-RCR is grateful for the opportunity to respond to the above consultation. We have liaised with our experts and would like to make the following comments.

Our experts do not feel it is possible to support the Intrabeam Radiotherapy System as a NHS treatment given the following statement: 'The committee noted that the clinical evidence for Intrabeam is immature and associated with considerable uncertainty. It acknowledged that Intrabeam has not been proven to be non-inferior to EBRT and could have a higher risk of local recurrence'. We would like to see the mature results of the Targit trial before this technique is offered as an NHS treatment. Given that it is more than 3 years since the 2013 publication with a median follow up of 2 years 5 months, it is anticipated that an updated analysis would soon be available.

We also consider patient choice to be paramount, but have a number of concerns regarding the proposal of offering Intrabeam at existing UK centres:

- How will it be ensured that patients will be offered 'impartial information' regarding this treatment and other evidence-based treatments?
- How will it be ensured that the national database will collect all the necessary data for all patients for a period of at least 5 years, given the current national trend for early discharge for low risk breast cancer?
- How will this database be funded?
- What is the time-scale for this 'monitoring' exercise and what is the endpoint?
- How will training of radiographers, physicists, oncologists and breast surgeons be carried out and funded?

- How will revenue costs of the existing Intrabeam radiotherapy systems be funded?
- How will this recommendation affect bio-similar intra-operative radiotherapy techniques?

Patient representatives have raised specific queries in addition to strongly supporting the views in this document:

- Given that patients tend to trust their own doctors, how will they know if they have been given impartial information?
- Will patients be consented for this data collection?
- Will the proposed provision of Intrabeam in existing centres result in inequity for patients based on where they live, or will they be given financial assistance to travel/stay at the designated centres?

We would also like to highlight the Royal College of Radiologists (RCR) UK Breast Radiotherapy Consensus 2016 document, which has recommendations for partial breast radiotherapy and omission of radiotherapy:

https://www.rcr.ac.uk/publication/postoperative-radiotherapy-breast-cancer-uk-consensus-statements

https://www.rcr.ac.uk/clinical-oncology/service-delivery/postoperative-radiotherapy-breast-cancer-uk-consensus-statements

In summary:

Safe omission of radiotherapy after breast-conserving surgery - avoidance of radiotherapy should be considered:
In women deemed to be at very low risk of local recurrence, for example patients ≥70 years out of a research study and ≥60 years in study with T1N0 oestrogen receptor positive (ER+), progesterone receptor positive (PR+), human epidermal growth factor receptor negative (HER2-), Grade 1–2 tumours AND who are willing to take adjuvant endocrine therapy for a minimum of five years AND have regular mammograms for ten years. These criteria are best fulfilled within the UK PRIMETIME bio-marker directed study and participation is recommended.

Partial breast radiotherapy after breast-conserving surgery can be considered:
For patients ≥50 years, Grade 1–2, ≤3 centimetres (cm), oestrogen receptor positive (ER+), human epidermal growth factor receptor negative (HER2-), N0 with minimum 1 millimetre (mm) radial excision margins for invasive disease, using either (i) external beam radiotherapy with 40 Gray (Gy) in 15 fractions over three weeks* or (ii) multicatheter brachytherapy using fractionation schedules as per the Groupe Européen de Curiethérapie and European Society for Radiotherapy and Oncology (GEC-ESTRO) trial[1,2].
Classical lobular cancer and/or lymphovascular space invasion should be excluded.

*UK IMPORT LOW trial: presented at European Breast Cancer Conference 2016 and European Cancer Conference 2017, currently under review with the Lancet

References

1. Strnad V, Ott OJ, Hildebrandt G, Kauer-Dorner D, Knauerhase H, Major T, Lyczek J, Guinot JL, Dunst J, Gutierrez Miguelez C, Slampa P, Allgäuer M, Lössl K, Polat B, Kovács G, Fischedick AR, Wendt TG, Fietkau R, Hindemith M, Resch A, Kulik A, Arribas L, Niehoff P, Guedea F, Schlamann A, Pötter R, Gall C, Malzer M, Uter W, Polgár C; Groupe Européen de Curiethérapie of European Society for Radiotherapy and Oncology (**GEC**-**ESTRO**). 5-year results of accelerated partial breast irradiation using sole interstitial multicatheter brachytherapy versus whole-breast irradiation with boost after breast-conserving surgery for low-risk invasive and in-situ carcinoma of the female breast: a randomised, phase 3, non-inferiority trial. Lancet. 2016 Jan 16;387(10015):229-38
2. Polgár C, Ott OJ, Hildebrandt G, Kauer-Dorner D, Knauerhase H, Major T, Lyczek J, Guinot JL, Dunst J, Miguelez CG, Slampa P, Allgäuer M, Lössl K, Polat B, Kovács G, Fischedick AR, Fietkau R, Resch A, Kulik A, Arribas L, Niehoff P, Guedea F, Schlamann A, Pötter R, Gall C, Uter W, Strnad V; Groupe Européen de Curiethérapie of European Society for Radiotherapy and Oncology (**GEC**-**ESTRO**). Late side-effects and

cosmetic results of accelerated partial breast irradiation with interstitial brachytherapy versus whole-breast irradiation after breast-conserving surgery for low-risk invasive and in-situ carcinoma of the female breast: 5-year results of a randomised, controlled, phase 3 trial Lancet Oncol. 2017 Jan 13. pii: S1470-2045(17)30011-6.

Finally, not only does this sit outside the RCR consensus, but conflicts with the ongoing update of Early Breast Cancer (EBC) NICE Clinical guidance update, where evidence graded recommendations on the omission of radiotherapy and partial breast radiotherapy will be made only on studies with at least 5 year published outcome data. As such, Intrabeam is excluded from the EBC Clinical Guideline update. Partial breast radiotherapy recommendations are therefore being made using two separate NICE processes with seemingly differing evidence level requirements.

Yours sincerely

[redacted]

THE ROYAL COLLEGE OF RADIOLOGISTS

Response to:

NICE consultation
Intrabeam radiotherapy system for adjuvant treatment of early breast cancer

The Royal College of Radiologists (RCR) is re-submitting its original comments from the NICE consultation in 2014 (see **annex A**) as it does not feel that the question of the unacceptably short median follow up of 2 years and 5 months has been resolved. The additional information provided by the trialists does not address this. As the first analysis was performed over 3 years ago, there must be further patient events which must be looked at.

The decision to allow ongoing NHS treatment in existing centres with an aspirational audit without funding is not evidence based, since the Targit-A trial has been completed and needs further analysis of mature data.

The RCR hosted a UK-wide multi-disciplinary meeting in March last year to establish a consensus view among professionals involved in the treatment of breast cancer on (inter alia) the use of intra-operative radiotherapy[1]. This meeting firmly concluded that the relapse rate data were immature. The RCR feels strongly that a properly evidenced decision should be made only when five-year follow-up data are available. Patients cannot be expected to make an informed choice about the risk of local recurrence without such information. The proposal now put forward by NICE seems to be contrary to evidence and goes against the careful long-term studies in radiotherapy for breast conservation which the UK has led on for many years. The need for caution has been demonstrated through the ELIOT trial which showed a HR of 9.3 for IORT compared with whole breast RT with median follow up of 5.8 years: non-inferiority was not reached[2].

The Royal College of Radiologists
March 2017

[1] Postoperative radiotherapy for breast cancer: UK consensus statements
[2] Veronesi U et al. Intraoperative radiotherapy versus external radiotherapy for early breast cancer (ELIOT): a randomised controlled equivalence trial. Lancet Oncol. 2013 Dec;14(13):1269-77

Annex A

Multiple Technology Appraisal (MTA) INTRABEAM Photon Radiosurgery System for Adjuvant Treatment of Early Breast Cancer

Response by The Royal College of Radiologists (Faculty of Clinical Oncology) – 2014

The Royal College of Radiologists' (RCR's) role in oncology is to advance the science and practice of all aspects of oncology, educate the public on these issues and to set professional standards of practice. The RCR's Clinical Oncology members and Fellows are the only medical professional group responsible for the delivery of radiotherapy to breast cancer patients in the UK and therefore wish to respond to this consultation and to express concerns under three main headings.

1. Recommendations drawn from a single trial (TARGIT A) reviewed in this MTA and confining the appraisal/recommendations to a single IORT facility (Zeiss Intrabeam device).

2. Concerns around the methodological flaws of this single study (TARGIT A trial).

3. The misrepresentation to/by the media of preliminary recommendations from the NICE appraisal findings at the start of the consultation period.

Background to External Beam Radiotherapy (EBRT) for breast cancer patients

Breast cancer radiotherapy has been one of the most thoroughly researched areas in oncology over the past 30 years. During this time sequential high-quality clinical trials, based on appropriate hypothesis generation, have been conducted and led to the evolution of an evidence-based practice which incorporates science, clinical probity, health economics and, additionally, has given high priority to patient acceptability and outcomes. Thousands of women have contributed to this programme of oncology research which embodies trial design advances and in which quality assurance is integral. This programme continues and assures patients that they are receiving the highest quality of care with proven clinical effectiveness, both in terms of cancer control and normal tissue effects, including cosmesis.

Against this background of high quality research the Clinical Oncology community, represented by the RCR, is concerned that the recommendations of this TA may facilitate patients being offered a treatment that has not been subject to the same rigorous scientific approach and that this may also destabilise and threaten the integrity of breast cancer research in the UK.

Areas of Concern regarding the Consultation document:

1. Recommendations drawn from a single trial (TARGIT A) reviewed in this MTA and confirming the appraisal/recommendations to a single IORT facility (Zeiss Intrabeam device).

- The wording of the preliminary recommendation is tortuous and ambiguous, and its ability to cause confusion has been demonstrated by inappropriate media statements at the start of the consultation period.

- As the Committee is aware of, and has acknowledged, criticisms of the TARGIT A trial, the RCR seeks explanation as to why any recommendation for the use of IORT should be confined to the Zeiss intrabeam device. There are other devices which can deliver IORT in this setting and which are available in many centres without the investment in this specific equipment.

- The appraisal is based on a single RCT (TARGIT A) which does not meet the internationally recognised standard of five-year follow up for breast cancer trials addressing local recurrence. The TARGIT A trial reported with a median follow up of only two years and five months.

- The trial was designed on the premise that local recurrence rates were in the order of 6 per cent and this provided the basis for establishing a non-inferiority threshold of 2.5 per cent. This level of local recurrence is no longer accepted as appropriate and is more likely to be in the order of 2 per cent for the patient group in the trial. As a consequence, within the current parameters of the TARGIT A trial, and in the setting of inadequate follow up, this could allow a doubling of local recurrences, a doubling of the salvage mastectomy rate and a significant increase in reconstructive surgery procedures. This is well-described in the correspondence that followed in *The Lancet* following the TARGIT publication (Appendix 1).

- There are other published randomised trial data (ELIOT study[3]) which report higher ipsilateral breast tumour recurrences and a higher mastectomy rate for patients treated with intraoperative rather than external beam radiotherapy after conservative breast surgery. There is over five years' median follow-up and the five-year event rate favours EBRT by 0.4 per cent to 4.4 per cent.

- The PRIME II trial[4] provides further relevant randomised data in the setting of good prognosis breast cancer, in terms of evaluating IORT. Again, reporting with the standard five years follow up, there was a local relapse rate of 1.3 per cent for patients treated with adjuvant radiotherapy (external beam) and 4.1 per cent for the no radiotherapy arm of the trial. Patients included in this trial had good prognosis breast cancer, similar to those included in the TARGIT A trial, and this raises the possibility that the Intrabeam technique may offer an outcome similar to avoiding radiotherapy altogether.

- The appraisal acknowledges that the risk of recurrence carries with it a burden to patients and their families who want to ensure they have the best chance of a future free from breast cancer. In the same section of the document, this statement is immediately followed by a patient group commenting on the frequency of hospital visits and potentially disruptive treatments, in terms of EBRT. Although the latter are very important issues, the former statement regarding concern of risk of recurrence and being offered the best chance of a future free from cancer would seem likely to dominate any argument for most patients, particularly in the modern era of delivering EBRT over a three week period. Furthermore, radiotherapy departments now offer increasing flexibility in terms of times of attendance which allows patients to incorporate their personal and professional activities.

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[3] Veronesi U, Orecchia R, Maisonneuve P, Viale G, Rotmensz N, Sangalli C, Luini A, Veronesi P, Galimberti V, Zurrida S, Leonardi MC, Lazzari R, Cattani F, Gentilini O, Intra M, Caldarella P, Ballardini B. Intraoperative radiotherapy versus external radiotherapy for early breast cancer (ELIOT): a randomised controlled equivalence trial. Lancet Oncol. 2013 Dec;14(13):1269-77.

[4] Kunkler IH, Williams LW, Jack W, et al: The PRIME II trial: Wide local excision and adjuvant hormonal therapy ± postoperative whole breast irradiation in women ≥ 65 years with early breast cancer managed by breast conservation.2013 San Antonio Breast Cancer Symposium. Abstract S2-01. Presented December 11, 2013.

2. Concerns around the methodological flaws of this single study (TARGIT A trial)

- The Consultation document acknowledges most of the concerns held by the scientific and clinical community over the methodology and governance of the TARGIT A trial, but does not then seem to have given these issues full credence in the recommendations.

- The main criticism of the TARGIT A trial lies in the statistical analyses and it is of major concern that Professor Jack Cuzick has commented on these issues and voiced his opinion publicly in a *Lancet* publication (Appendix 2), also commenting that he had resigned from his position as Chair of the independent Data Monitoring Committee for the trial. The main statistical analyses criticisms can be summarised as follows:

    i. The median follow up of the trial is only two years and five months, which is inadequate for ensuring the estimate of risk recurrence is robust.

    ii. The analysis includes the presentation of results from three cohorts of patients with varying median follow-up. This flawed approach allows triple counting.

    iii. There is a linear risk of local recurrence for patients with tumours of the type entered into the TARGIT A trial - i.e. those with good prognosis tumour and a lower risk of recurrence. This means that there can be a year-on-year rise in local recurrence which necessitates the application of five-year follow-up (absolute minimum) to any recommendation for use of this approach.

    iv. There are errors in the analysis in terms of attributing causes of excess non-breast cancer mortality and the authors of the TARGIT study have made basic errors which are particularly apparent in the estimate of cardiac damage. These areas could lead to an estimate of standard breast RT risk to the heart being represented as approximately ten times the actual incidence. Again this is well explained in the correspondence in *The Lancet* (Appendix 3,4).

3. Misrepresentation to/by the media of preliminary recommendations from the NICE appraisal findings at the start of the consultation period.

- The RCR is concerned that the preliminary recommendations and findings of this appraisal were widely represented in the media at the start of the consultation period. This has obviously had an impact on patients who are currently approaching radiotherapy as part of their treatment for breast cancer, currently undergoing external beam radiotherapy or having had it in the past. It has also caused disquiet among professionals, both in terms of dealing with patient queries and in assessing the consequence of such a recommendation on the services they are able to offer patients.

- The release of this information at this inappropriate time makes it difficult to ensure that the remainder of the appraisal process is carried out without prejudice. The RCR is concerned that NICE does not appear to have taken steps publicly to deal with this situation, to provide assurance that the appraisal process will consider these events and ensure that the process retains credibility.

- The misrepresentation is explained by the response of an official body to the premature release of NICE findings in the media:

    NICE writes that:

    "...the criterion for non-inferiority was not appropriately defined and the trial was therefore underpowered and the results could not be considered robust enough to determine whether Intrabeam was non-inferior to EBRT in terms of local recurrence. The Committee therefore

concluded that the non-inferiority of Intrabeam compared with EBRT in terms of local recurrence was unproven."

On the CRUK website[5] this is translated into:

"A clinical trial in 2013 suggested it [i.e. Intrabeam] was likely to be as effective as conventional radiotherapy".

In summary the RCR wishes to express its strongest concerns about both the conduct of, and preliminary recommendations from, this MTA, as detailed above. It urges NICE to reconsider its preliminary recommendations in keeping with the large body of expert clinical opinion, as expressed through the RCR's Clinical Oncology community.

[5] http://www.cancerresearchuk.org/about-us/cancer-news/news-report/nice-set-to-recommend-single-dose-radiotherapy-during-breast-surgery

Appendix 1

The Lancet, Volume 383, Issue 9930, Pages 1716 - 1717, 17 May 2014
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Radiotherapy for breast cancer, the TARGIT-A trial

Joanne S Haviland a, Roger A'Hern b, Soeren M Bentzen c, Timothy Whelan d, Judith M Bliss b

The investigators from the TARGIT-A trial[1] claim to have established non-inferiority of intraoperative radiotherapy relative to external beam radiotherapy (EBRT) for breast cancer in terms of 5-year local recurrence. Assessment of local recurrence at 5 years by comparison of binomial proportions is appropriate only if 5-year follow-up is available for all patients, whereas only 611 of 3451 patients have reached this point.

This analysis, including the non-inferiority test statistic, is therefore unreliable. The most appropriate measure of non-inferiority given available data uses the survival analysis of local recurrence rates. Based on the 5-year estimates for local recurrence of 3·3% (95% CI 2·1—5·1) after intra-operative radiotherapy and 1·3% (0·7—2·5) after EBRT, the estimated hazard ratio (HR) is 2·56. The standard error of the HR can also be estimated,[2] suggesting an upper limit of 5·47 for its one-sided 95% CI. In view of the 1·3% local recurrence rate after EBRT, the local recurrence rate after intraoperative radiotherapy could therefore be as high as 7·1%, far exceeding the predefined non-inferiority limit.

The investigators present results for three cohorts of patients with varying lengths of median follow-up, claiming to portray the apparent stability of treatment effect estimates over time. The cohorts are nested within each other, thus patients with longest follow-up (who contribute most events) are analysed three times, generating a result of questionable validity.
Median follow-up is only 2·4 years, and a substantial increase in observed duration of follow-up is needed before any analysis of non-inferiority of local recurrence risk can reliably inform clinical practice. The TARGIT-A trial[1] remains inconclusive, and intraoperative radiotherapy using TARGIT remains an experimental treatment.

We declare that we have no competing interests.

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1 Vaidya JS, Wenz F, Bulsara M, et alon behalf of the TARGIT trialists' group. Risk-adapted targeted intraoperative radiotherapy versus whole-breast radiotherapy for breast cancer: 5-year results for local control and overall survival from the TARGIT-A randomised trial. Lancet 2014; 383: 603-613. Summary | Full Text | PDF(448KB) | PubMed
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Appendix 2

The Lancet, Volume 383, Issue 9930, Page 1716, 17 May 2014
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Radiotherapy for breast cancer, the TARGIT-A trial

Jack Cuzick a

The TARGIT-A trial (Feb 15, p 603)1 is a good example of trying to make data fit a pre-existing hypothesis; there are several major deficiencies in the analysis. Paramount among these deficiencies is the misuse of the non-inferiority criterion,2 which requires the upper (90%) CI to be below a predefined value (here 2·5%). This criterion clearly fails when the appropriate 5-year Kaplan-Meier estimates are used, which in fact establish a 2% superiority of external beam radiotherapy (p=0·04) and a CI extending beyond 2·5%. Table 3 of the Article1 uses crude rates that are substantially diluted by patients with short follow-up (only 611 [18%] patients had a 5-year follow-up). The effect is even clearer if locoregional recurrence or all recurrence is used, as in previous radiotherapy trials.3

Another common but well known danger is to focus attention on the most favourable subgroup.4, 5 The protocol clearly states that the primary analysis population includes all randomised patients. However, the report concentrates on the prepathology group. No correction for multiple comparisons or test for heterogeneity between groups is provided, and the data available suggest that it would not be significant. More should be said about all randomised patients.

Although a small increase in recurrence with a simpler therapy might well be acceptable in many circumstances, the present attempt to argue for virtually no difference by misuse of the non-inferiority criteria, focusing on the most favourable subgroup and not including all events affected by external beam radiotherapy does not give an objective assessment of this treatment modality.

I was chairman of the Data Monitoring Committee for the TARGIT trial previously but have resigned.

Appendix 3

The Lancet, Volume 383, Issue 9930, Pages 1717 - 1718, 17 May 2014
doi:10.1016/S0140-6736(14)60828-X

Radiotherapy for breast cancer, the TARGIT-A trial

John Yarnold [a], Birgitte Vrou Offersen [b], Ivo Olivotto [c], Philip Poortmans [d], Rajiv Sarin [e]

In reporting the testing of intraoperative radiotherapy against standard whole breast radiotherapy (WBRT), the investigators of the TARGIT trial[1] claim an excess of non-breast cancer deaths are "almost certainly" due to the adverse effects of WBRT.[2]

We argue that causation is very unlikely. The risk of a major cardiac event increases by 7% per Gy of mean heart dose.[3] Based on expected mean heart doses in the WBRT group of 1—5 Gy, radiotherapy cannot explain more than one of the 11 cardiovascular deaths. This is the case even if all eight cardiac deaths occurred in patients with left-sided cancers. Neither is it credible to attribute an excess of eight other, non-breast, cancer deaths in the WBRT group to radiotherapy. The NSABP B-04 trial[4] followed 1665 patients for a median of 21·4 years after randomisation with or without locoregional radiotherapy after mastectomy, confirming a small excess (n=6) of primary lung cancer that took more than 10 years to emerge. The excess was attributed to large anterior axillary radiotherapy beams. No excess of lung cancers was noted in 1261 patients in the B-06 trial[4] at a median of 19 years after randomisation with or without WBRT after lumpectomy. Lung cancer is the most common cause of death from other cancers in this context, but the TARGIT[1] investigators provide no information about tumour site in relation to randomisation.

The difference in non-breast cancer deaths between randomised groups in the TARGIT trial is explained either by imbalances in risk factors or by under-reporting of non-breast cancer deaths in the test group.

We declare that we have no competing interests.

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[1] Vaidya JS, Wenz F, Bulsara M, et al on behalf of the TARGIT trialists' group. Risk-adapted targeted intraoperative radiotherapy versus whole-breast radiotherapy for breast cancer: 5-year results for local control and overall survival from the TARGIT-A randomised trial. Lancet 2014; 383: 603-613. Summary | Full Text | PDF(448KB) | PubMed
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Appendix 4

The Lancet, Volume 383, Issue 9930, Pages 1718 - 1719, 17 May 2014
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Radiotherapy for breast cancer, the TARGIT-A trial

Jay K Harness a, Melvin J Silverstein b c, David E Wazer d, Adam I Riker e f

Jayant Vaidya and colleagues1 claim that TARGIT treatment results in increased survival since the number of non-breast cancer deaths are higher in the external beam radiotherapy (EBRT) cohort. The investigators cite higher incidences of cardiac toxic effects and deaths from non-breast cancers in the EBRT group as the major cause for the difference in overall survival, even though the TARGIT group currently has a higher, although not significantly breast cancer death rate (2·6% *vs* 1·9%, p=0·56).

The data, with a 29-month median follow-up, show a total of 37 deaths in the TARGIT group, from all causes, and 51 deaths in the EBRT group, from all causes. The authors included deaths from stroke and ischaemic bowel disease as cardiac toxic effects. However, these diseases are caused by narrowing of the arteries (arteriosclerosis) or clot formation, which are unlikely to result from any purported radiation damage to cardiac vessels or valves caused by the EBRT breast treatment. Moreover, deaths from other cancers are not credible to attribute to the breast EBRT treatment. The latency period for induced cancers from breast treatment is well established to be at least 15—20 years. Even after developing a radiation-induced cancer, treatments should prolong survival for several further years, even if cure is not affected. Thus, it is impossible for the 12-year old TARGIT-A study1 to affect other cancer deaths. If you include only cardiac deaths and breast cancer deaths, the difference between TARGIT and EBRT is only two patients, and is thus hardly significant.

The authors state that although cardiac deaths from radiotherapy typically do not manifest until 7—10 years after treatment (well outside the median follow-up of this study), a recent study2 that included patients treated as late as 2001 shows that significant cardiac toxic effects are apparent within the first 4 years. Since 35% of the trial patients (1222 patients) had a median follow-up of 5 years, they claim that the study2 supports the increased toxic effects with EBRT noted in the TARGIT trial.1 This statement is supported neither by the science nor by any evidence the investigators present.

Darby's study2 began in 1958 and ended in 2001, so most of their patients were treated with outdated radiotherapy techniques and equipment, and before the era when cardiac toxic effects from breast irradiation were fully appreciated. Furthermore, 76% of the patients in Darby's study2 had radiation after mastectomy, which is known to result in higher doses to the heart, especially for left breast irradiation. The consensus is that modern radiation techniques should limit the cardiac dose to less than 2 Gy for left-breasted tumours, and to less than 1 Gy for right-breasted tumours. These small doses result in very low cardiac toxic effects. In Darby's study,2 the median heart dose for a cardiac event was 4·9 Gy, with heart doses as high as 25 Gy. The risk of cardiac toxic effects rose with increasing dose. All modern radiation treatment planning systems have constraints that limit the cardiac dose, so it is unlikely that any centre participating in the study would deliver high cardiac doses, and any EBRT breast radiation study should surely include the requirement to limit the dose to the heart for EBRT radiation. Furthermore, even with data from Darby's study, for doses limited to 3 Gy, the increased risk of death from ischaemic heart disease over 30 years is less than 1%—data that hardly support the TARGIT investigators' assertions. Although the authors state that data for comorbidities were not collected at the time of randomisation, the exclusion criteria listed on ClinicalTrials.gov excludes “Patients with any severe concomitant disease that may limit their life expectancy.” It should have been the responsibility of the participating centre to undertake such screening.

To prove their contention of reduced cardiac toxic effects with TARGIT, the authors should have taken four things into account. First, they should have calculated the heart dose for those patients who had a cardiac event. (There are only a total of eight EBRT patients so this would not be too burdensome). Second, they should have identified and presented in the paper whether the left or right breast was irradiated in those patients that died from cardiac toxic effects. Third, the authors should have identified the time after the completion of EBRT that the cardiac events occurred. Finally, they should have indicated whether deaths occurred in those who actually received the prescribed treatment since they used the intention-to-treat population to establish non-breast cancer deaths. 26 patients assigned to EBRT actually received TARGIT; were any of the eight deaths in the EBRT group in these 26 patients?

Clinicians, on the basis of the existing immature TARGIT-A data, would be well advised not to suggest that TARGIT treatment can result in improved non-breast cancer survival.

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2 Darby SC, Ewertz M, McGale P, et al. Risk of ischemic heart disease in women after radiotherapy for breast cancer. N Engl J Med 2013; 368: 987-998. PubMed
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f Department of Surgery, University of Illinois, Chicago, IL, USA

The Society and College of Radiographers is concerned that this is directed at a single manufacturer (Carl Zeiss) and we would consider there is a need for a serious re-think as to the scope of the appraisal document

1) **Has all of the relevant evidence been taken into account?**

No. As outlined in (3) there are other trials that need to be taken into account to evaluate IORT, not just via single randomised controlled trial (TARGIT A).

The ElIOT Study has a longer follow up (> 5yrs median) and after breast conservation surgery favours EBRT over IORT with respect to ipsilateral breast tumour recurrences and higher mastectomy rate.

PRIME 2 Trial with 5yr follow up data needs to be considered.

2) **Are the summaries of clinical and cost effectiveness reasonable interpretations of the evidence?**

Currently directed at a single manufacturer so, given the lack of follow up data and full evaluation of all the evidence, useful interpretation is challenging. Suggest a more complete evaluation.

The Society and college of Radiographers is concerned who is responsible for the data collection and this needs be a recommendation.

3) **Are the provisional recommendations sound and a suitable basis for guidance to the NHS?**

From The Society and College of Radiographers perspective we would certainly say a definite no.

It identifies the need to provide patients with information to ‘aid shared decision making’ but only includes one manufacturer i.e. Carl Zeiss.

There are issues with the methodological approach and statistical analysis of the TARGIT A trial and these are well documented: not least that of the length of the lack of 5 year follow up data and therefore it is not possible to state that intrabeam is superior or inferior to EBRT.

How can a treatment be suggested as appropriate ‘using machines that are already available’? What happens if a centre buys a different unit? Then is that not recommended for use?

This has led to mis-representation and misunderstanding and this MTA document does not offer the level of recommendation needed to ensure patients have enough information to enable an informed decision.

How can patients be informed and make informed decisions on a treatment modality that has not been fully evaluated or understood by clinicians.

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE
MULTIPLE TECHNOLOGY APPRAISAL (MTA)

Intrabeam targeted intraoperative radiotherapy for the treatment of early or locally advanced breast cancer [ID618]

Appraisal Committee Meeting – Thursday 9th March 2017

Expert Statement: Professor Michael Douek

Professor of Surgical Oncology

King's College London / Guy's & St Thomas' Hospitals

I entirely support the latest recommendations of NICE and would like to find a pragmatic way to implement this in order to ensure suitable NHS patients have access to this treatment option should they wish.

Intraoperative radiotherapy using the TARGIT technique was evaluated in a large multinational randomised controlled trial (academically run and HTA funded) run from London and the first patient was randomised in March 2000. After 10 years, the data was published in the Lancet in 2010 (Vaidya et. al). Following a very stringent peer-review process (over 5 reviewers and detailed independent statistical assessment), the Lancet Editorial Team decided that the data, as presented (with 2.4 years median follow-up overall), should be in the public domain. The Lancet published the article as a fast-track publication and graced its cover with the TARGIT-A Trial conclusion, that IORT (Intrabeam) should be considered in suitable patients as an alternative to external beam radiotherapy delivered over several weeks.

NICE received the go ahead to consider Intrabeam IORT for the NHS, following a scoping meeting held on the 12/11/2012. Following this, 3 committee meetings took place (in 2013, 2014 and 2015) and public consultations (2014 and 2017). Meanwhile, the TARGIT-A trial was extended to over 33 centres, recruiting over 3,400 patients and the Lancet published the data again in 2014 (Vaidya et al). Clearly, the independent reviewers (typically 5-6 experts including statisticians) and the Editorial Board of the Lancet felt, again, that this data was important enough to be in the public domain. Therefore, patients are entitled to know about this option of treatment if they meet the inclusion criteria of this trial.

In August 2015, the NICE MTA Committee confirmed that Intrabeam IORT is a cost-effective alternative to external beam. In addition, the mortality benefits of Intrabeam IORT observed in the TARGIT-A trial, were confirmed in a large meta-analysis of nearly 4,500 patients with 5 years follow-up (Vaidya et al, 2016) published in the Red Journal (top radiotherapy journal).

Also in 2015, the Supreme Court (Montgomery vs Lanarkshire Health, March 2015) decided that patients now have a legal right to be advised of all treatment options available - not just a moral responsibility. Clinicians (and by extension the NHS) now have a legal responsibility to provide evidence-based information to enable patients to make informed decisions about their treatment and care, including information on evidence-based treatment options that they may not, personally, agree with. The judgment went beyond this specifying that when presenting treatment options, the Bolam test of conduct (eg: comparison of practice with opinions from Royal Colleges or

NICE guidance), does not apply. This is because patients are entitled to take into account their own values, whatever medical opinion may say.

Bearing this in mind, it has been worrying that IORT is currently not yet routinely mentioned to suitable women as a treatment option (potentially exposing the NHS to indefensible litigation, given the above) and the proposed NICE recommendation will rectify this.

Comments on Consultation Document and Stakeholder submissions.

There were 49 submissions in the current consultation of which 41 were in favour (including the Association of Breast Surgery, Breast Cancer Now – the largest breast cancer charity). Of the critical submissions I would like to raise the following points:

1. *Royal College Radiologists:* Re-submitted their 2014 statement, without updating it, and without including the published authors responses to the Lancet letters (Vaidya et al, 2014) providing a very biased view of the published exchange. They justify their opposition using data from the ELIOT trial which is not relevant to this MTA – it involves a different radiation dose, different and more disruptive surgical technique, different patient population (higher risk) and different device (NOVAC-7). They report that they held a multidisciplinary meeting in March last year but their position stands against the peer-review literature and against the supportive position of the Association of Breast Surgery. They also do not declare their clear conflict of interest since the introduction of IORT will negatively impact on their workload (both NHS and private); and they support the IMPORT LOW protocol (despite the fact the data is unpublished) which will increase their workload without a demonstrable patient benefit, and likely to prove significantly more expensive.
2. *Independent Cancer Patient Voice (ICPV):* This submission is signed by 2 patients but does not include their patient representative who sat on the TARGIT-A Steering Committee, is not signed by the Chair and does not include comments from patients who received IORT. They limit their comments to misinterpretation of the published literature.
3. *Society of Radiographers:* This is unsigned and may not represent the society as a whole - a past-President has welcomed the likely extended role of diagnostic radiographers with IORT, in the recent past.
4. *Dr Charlotte Cole, Reader in Breast Radiotherapy Oncology:* As PI of several radiotherapy fractionation trials and competing technologies (including IMPORT-LOW & HIGH, IMRT, Mammosite trial, FAST-FORWARD), this MTA process competes with her research interests. I disagree with her view that the benefits of Intrabeam IORT remain unproven and this does not sit comfortably with the publication of 2 articles in the Lancet and an HTA publication (Vaidya et al, 2016). Also the QOL data supporting Intrabeam IORT is not anecdotal as there are at least 2 published articles supporting this (Welzel et al. 2013; Corica et al, 2016). Contrary to her statement about fibrosis, the fibrosis risk is similar between the randomised Intrabeam IORT and EBRT arms of the TARGIT-A trial (Sperk et al, 2012). She also uses the ELIOT trial data as evidence against Intrabeam IORT, without mentioning it uses a completely different technology (NOVAC-7) and not Intrabeam.
5. *Specialised Commissioning (NHS England) & personal statement by Nicola MacCulloch:* Both disclose that their opposition is entirely based on advice from the Radiotherapy Clinical Reference Group (CRG). They clearly suffer from misinterpretation of the level of evidence of the TARGIT-A trial, patients' right to be offered IORT and the fact that Intrabeam IORT is not clinically inferior to EBRT. Both promote IMPORT LOW which, contrary to Intrabeam, is not supported by published

evidence and there is no evidence that it will be less expensive (it requires 3 weeks of daily treatment with IMRT and more complex radiotherapy planning).

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NICE appraisal consultation document for Intrabeam radiotherapy system for adjuvant treatment of breast cancer: response from Dr Charlotte Coles, Reader in Breast Radiotherapy Oncology, Cancer Research UK Cambridge Centre

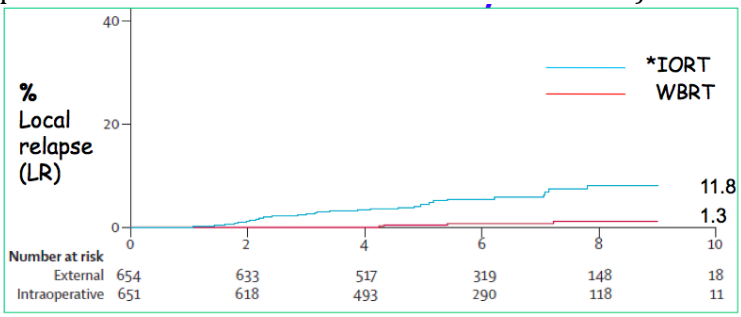
I wish to raise the following points regarding the consultation document:

1. **The proposal is not in line with section 6.1.2 of the Guide to the methods of technology appraisal 2013 and the caveats stated cannot be substantiated**

The consultation document states the following: "The committee recognised its role of not recommending treatments for routine use if the benefits to patients are unproven, or if the treatments are not cost effective…However, it is understood that some patients are willing to accept a treatment that may have a higher risk of local recurrence in order to have the benefits of Intrabeam, noting several benefits highlighted by the patient expert and clinical experts in terms of improving patients' quality of life, which could not be captured in the QALY calculation. It is also noted that although non-inferiority for Intrabeam compared with EBRT (external beam radiotherapy) is unproven for local recurrence, the rates of recurrence in the Intrabeam group in the pre-pathology group are low."

a. The evidence for improved quality of life is based on an anecdotal report by a patient who received Intrabeam treatment and who speculated upon the effects of EBRT, which she did not receive. The Targit trial did not report systematically the long-term side effects of treatment, either as clinician reported or patient reported outcomes. Hence, there is no reliable evidence of the long-term toxicity or quality of life after Intrabeam treatment. A small (N=196) single centre study reporting 3-year cumulative toxicity assessed by clinicians involved in the Targit trial reported rates of moderate-severe of breast fibrosis fully comparable with those following current EBRT, as recently reported in the UK IMPORT LOW trial.[1-2] It should be noted that 15% of patients in the Targit trial required both Intrabeam and EBRT due to higher risk histology found *after* surgery. The small study suggested that more than one-third of these patients develop moderate-severe fibrosis, which is substantially higher than rates with current EBRT.

b. The low rates of local recurrence in the Intrabeam group in the Targit trial do not justify the use of Intrabeam as an NHS treatment. Firstly, with a median follow up of only 2 years 5 months, the local recurrence risk at 5 years is as yet unknown. As a warning, please note that the ELIOT intraoperative trial showed a 9 times increased in local recurrence compared with EBRT, with a median follow up of 5.8 years[3]. ELIOT is a very similar technique to Intrabeam, but treats a larger volume of breast and the local recurrence rates were very low with a median follow up of 2.5 years (see figure below courtesy of Profs Orecchio and Yarnold: cumulative incidence of ipsilateral breast tumour recurrence for ELIOT trial).



Cumulative LR (%)						
Ext RT	0	0	0	0.8	1.3	1.3
ELIOT	0	1.0	3.7	5.9	9.1	11.8

2. **The process for this technology appraisal conflicts with the on going update of the NICE guidance for early breast cancer**

   The process is flawed as partial breast radiotherapy recommendations are being made using two separate NICE committees with seemingly differing evidence level requirements. It is incongruous that one advisory committee to NICE can recommend Intrabeam treatment within the NHS, whereas another has excluded data from Targit trial as it is will only make evidence graded recommendations using trials with at least 5 year published outcome data.

3. **A national database to collect efficacy outcomes for patients treated with Intrabeam within the NHS is as expensive and complex as conducting a research trial and will take many years to produce mature data**

   The Targit trial protocol stated that follow up would continue for 10 years. The Targit team intend to report the mature results as shown by their 2016 Health Technology Assessment publication in September 2016:

> **Work package 1: continue to gather efficacy, safety and follow-up data to year 10, all centres, using the current case report forms as per protocol**
>
> *Aim and rationale*
>
> The latest analysis of the TARGIT-A trial includes a very large number of patients ($n = 1222$) with a median follow-up of 5 years and our analysis suggests that the results remain stable for cohorts of patients with increasing periods of follow-up up to 5 years. However, for the whole trial, the median follow-up is 2.6 years and one of the barriers to widespread adaptations of the new treatment appears to be the perception that we should undertake 5-year follow-up of all of the patients in the trial. This will mean that a substantial number will also have 10-year follow-up, a milestone that is now considered essential in many trials. Importantly, follow-up up to 10 years was stipulated in the original protocol.
>
> Work package 1 will deliver this.

   Given this intention to publish mature results, any decision from Appraisal Committee should be postponed until this new data is available from the Targit trial. This spares the uncertainty for patients and cost for the NHS in delivering and monitoring an unproven treatment.

References

1. Sperk E, Welzel G, Keller A, Kraus-Tiefenbacher U, Gerhardt A, Sütterlin M, Wenz F. Late radiation toxicity after intraoperative radiotherapy (IORT) for breast cancer: results from the randomized phase III trial TARGIT A. Breast Cancer Res Treat. 2012 Aug;135(1):253-60.
2. The IMPORT LOW trial 5 year results (median follow up 72.2 months) have been presented at the European Breast Cancer Conference in 2018 and European Cancer Conference in 2018 and a revised submission has been requested by The Lancet.
3. Veronesi U, Orecchia R, Maisonneuve P, Viale G, Rotmensz N, Sangalli C, Luini A, Veronesi P, Galimberti V, Zurrida S, Leonardi MC, Lazzari R, Cattani F, Gentilini O, Intra M, Caldarella P, Ballardini B. Intraoperative radiotherapy versus external radiotherapy for early breast cancer (ELIOT): a randomised controlled equivalence trial. Lancet Oncol. 2013 Dec;14(13):1269-77.

NICE MULTIPLE TECHNOLOGY APPRAISAL – INTRABEAM FOR EARLY BREAST CANCER

PERSONAL STATEMENT

This statement wholly endorses the response provided by NHS England in relation to this matter, and in doing so highlights the most pertinent issues associated with the Appraisal Consultation Document (ACD), as follows:

1. The Radiotherapy Clinical Reference Group (CRG) has articulated a compelling case that the current evidence base suggests that the treatment is clinically inferior to conventional radiotherapy.

2. Furthermore, the CRG have provided advice that clearly indicating that there is a highly active research programme in this field, the results of which may yield alternative and better options for this patient group:

    a. A number of studies are exploring the potential of delivering external beam radiotherapy (EBRT) in five rather than 15 fractions; and
    b. The IMPORT-LOW study is due to be published shortly in the Lancet, this is likely to recommend a focus on using partial breast radiotherapy in the same patient group to limit toxicity, as opposed to intrabeam radiotherapy (IORT).

3. In the context of the clinical advice received from the CRG, a positive recommendation would be premature. This is particularly because the commissioning consequence of such a recommendation would be to require the treatment to be routinely available in the English NHS to every patient meeting the eligibility criteria.

4. At this point, if it is the case that further data collection is required as part of implementing the positive recommendation, the treatment would appear to be better suited to research rather than routine commissioning.

5. Finally, the practical commissioning considerations are not insignificant. The most challenging of which relates to the rationale for limiting the number of centres able to deliver this treatment. This aspect of the recommendations contained in the ACD risks contradicting the desire to make it easier for patients to accept radiotherapy as part of treatment, which forms part of the rationale underpinning the positive recommendation. Should the ACD progress as it is currently written, the impact of implementing it may result in a perverse outcome for patients that do not live close to one of the centres able to deliver IORT.

Author name	Role	Organisation	Comment	Job Title	Location	Disclosure
[redacted]	NHS Professional		I welcome the NICE guidance as this Intrabeam treatment has the potential to allow me to treat about one quarter of my breast cancer patients locally in Swindon, saving each of them approximately 1000 miles of travelling to receive traditional radiotherapy. Most women comment to me that the stress and anxiety of this daily commute is considerably worse than the surgical process. It has a significant impact on their quality of life, eating into several hours each day in the weeks following surgery, time that they could be spending with their grandchildren, or even working. For those older women who are still in employment the loss of about 40-50 hours (due to travel) is a concern about their job security having already taken time off because of surgery. Coupled with the cost of fuel and parking it s not uncommon for women to ask if there is an alternative to traditional radiotherapy. As a surgeon I have a moral and ethical duty to offer he patient treatment options and allow the patient to make an informed and educated decision - one that is right for them, rather than a one-size-fits-all strategy. Patients are happy to make informed decisions when presented with clear the facts. They are comfortable making decisions for treatments (such as whether or not to have chemotherapy) based on risks and statistics and welcome the honesty of a specialist in presenting different treatments that may be suitable. Intrabeam allows patients to make that decision for themselves about radiotherapy. Failure to implement Intrabeam IORT to selected breast cancer patients would mean that our cancer treatment options are more limited than those available to citizens in Australia, Europe and many US cancer centres. This seems ridiculous considering that the technology was developed here in the UK, yet is still not able to be given to UK patients. As a practicing breast surgeon I know that he effects of radio-sensitivity, skin oedema and skin discolouration are considerably under reported and not seen by clinical oncologists as most effects described are late effects and most clinical oncologists will discharge their radiotherapy patients	Consultant Breast Surgeon	England	No

Author name	Role	Organisation	Comment	Job Title	Location	Disclosure
			shortly after treatment. If a breast cancer patient has a breast problem it is to the surgeons that they turn first. Therefore for the clinical oncology expert to state that "only a few patients have radiosensitivity, which can cause swelling and weeping of the breast" is to under-estimate the pain and problems of EBRT. These problems are seen more frequently in the larger breasted patient too. The committee should note that although six Intrabeam machines were used in the UK as part of the TARGIT - A trial, a seventh NHS hospital, the Great Western Hospital in Swindon acquired an Intrabeam device in June 2014. It is in use with fully trained staff and has been treating patients regularly. As the senior breast clinician I would consider that Swindon is one of the hospitals where a machine is available, having shown already that Intrabeam IORT can be delivered safely to patients.			
[redacted]		Prince of Wales Medical Centre	I have nothing but positive feedback. I was offered ORT and I was so pleased to hear that I had picked. Everyone should be given the opportunity to have ORT this avoids costs, travelling as you are already stressed by being diagnosed with breast cancer. I felt so well after surgery and ORT, I had no side affects, in fact I looked so well I was asked if I had been away. I definitely would recommend this is offered national wide patients would definitely feel the benefits. I was diagnosed 7 years ago and I feel well in myself and had excellent service from all the team. ORT should be recommended.	Deputy Practice Manager	England	No
[redacted]	Patient	UCL	I urge NICE to complete the process of approving this technology and making the treatment available on the NHS as soon as possible. I am one of the lucky breast cancer patients who was able to access it as part of a trial conducted by Prof. Jayant Vaidya two and a half years ago, when the only alternative to the lumpectomy I had would have been total mastectomy. This was because standard radiation therapy was precluded in my case, as my entire chest area and neck had already been exposed to intense radiation two years previously, following surgery as part of the treatment for another cancer. My last two annual breast checkups have shown no indication that the cancer was back, and - on the basis of much reading on the subject - I believe that the chances are as good that this would continue to be the case as they would have been had I been treated with conventional radiotherapy after surgery.	Professor (Emerita) of Jewish History	England	No

Author name	Role	Organisation	Comment	Job Title	Location	Disclosure
[redacted]	Patient		I completely endorse all the positive comments. Conventional radiotherapy would have meant four hours driving each day to Cheltenham.I ver felt ill or unwell. I left hospital the same day, spent the night with family in London before going home, where I continued life as normal.		Wales	No
[redacted]	Patient		I was diagnosed with breast cancer in September 2014, apart from the shock my immediate panic was how on earth I could manage weeks of daily radiotherapy. I would have had to travel at least one and a half hours each way to my nearest hospital for treatment. I am a widow, my family would not have been able to help due to old age and babies, my friends work, therefore I would have had to live in London for several weeks which would have been very difficult due to responsibilities at home. I was so lucky and relieved when the very helpful nurse explaining my options mentioned IORT, which I had not heard of. Having had the procedure explained to me, it only took half a second to realise what a wonderful procedure this was. I was very lucky in being able to have IORT, I was in hospital for twenty four hours, apart from slight tenderness the only after effects were from the anaesthetic which I would have anyway for a lumpectomy. I was able to carry on with my busy life immediately instead of having weeks of tiredness and feeling unwell. I have regular check ups and thankfully all is well. The huge benefit of IORT is not only the convenience but the fact it is localised as compared to traditional radiotherapy which can cause severe damage to other organs, I am well aware of this damage due to treatment received by a family member. I spread the word of IORT as much as I can to doctors, friends, in fact everyone. I am so thankful and strongly believe IORT should be available to all.		England	N/A
[redacted]			It has been 2 years since I had IORT for early stage breast cancer at the age of 66, I am to date cancer free and very healthy. When considering treatment options I was given more than adequate information on both EBRT and IORT, I had every confidence in Professor Vaidya and was delighted to find that I was eligible for IORT. Post op the lumpectomy sites healed quickly and I have no problem wearing swimwear or lightweight summer tops. The scars are negligible. I have had excellent care throughout, and psychologically the best thing was knowing that once the lumps had been removed, the treatment (apart from Letrozole) was		England	No

Author name	Role	Organisation	Comment	Job Title	Location	Disclosure
			finished. 3 weeks of EBRT was traumatising for 2 women I know who did not have IORT.			
[redacted]			As a patient who has chosen to self fund my Intrabeam treatment in preference to EBRT, I am amazed at the negativity expressed against IORT. At my age(71) convenience and few side effects mean so much. A 100 mile daily round trip on the M6 would have badly affected my precarious health and as I live alone my life would have fallen apart. Come on NICE! PLEASE SHOW SOME COMPASSION TO THE ELDERLY! At our age quality is more important than quantity.		England	No
[redacted]			The advantage of intra-operative radiotherapy for early stage breast cancer, from my view point as a patient, is that the process would remove the indecision and fear of submitting to protracted treatment with the likelihood of damaging and painful side effects, (as detailed on the consent form for External Beam Radio Therapy). This prospect poses a dilemma for patients who wish to take every precaution against recurrence of breast cancer, as I'm sure most do. Furthermore, advice as to the effectiveness of EBRT 12 weeks or more post-op. is variable or vague, increasing the sense of conflict for patients who have had treatment delayed for any reason. The inconvenience of multiple visits to hospital and the ultimate reduction of costs must also be significant. Breast surgery is surprisingly painful, frightening and uncertain. IORT would, I think, significantly reduce the physical and emotional trauma of early stage breast cancer treatment for the patient.		England	N/A
[redacted]			On behalf of my wife [redacted] who was diagnosed with brest cancer of the right brest in 2012. On advice of professor Vadia who surgested Intrabeam Radiotheropy. It has been a very affective and positive reaction. Inspite of having her six monthly checks it has been a very rewarding experience. Many thanks to Professor Vadia for the introduction of Intrabeam Radiotheropy which has been a trendous successes.	Retired	England	No

Author name	Role	Organisation	Comment	Job Title	Location	Disclosure
[redacted]			As a patient who has received IORT, I am absolutely delighted that NICE are recommending adding it to the portfolio of adjuvant treatments available to treat early stage breast cancer. I was equally delighted to read that the patient point of view has been taken into consideration and made reference to throughout this document, and for me, the sections that deal with the financial effects and the potential risks of EBRT in particular ring true. As an interim resource in the technology sector, simply being diagnosed and treated without adjuvant therapy was costly enough, but to then be faced with a possible 3-6 weeks of daily EBRT would have had introduced further and significant financial losses. Also, at the time of my diagnosis (being unaware of IORT), I was adamant that mastectomy was to be my preferred choice of treatment as my sister, who had been diagnosed with breast cancer 10 years earlier, had suffered a damaged heart as a result of the EBRT she had received â€“ and I was not prepared to put myself at that risk. It goes without saying that had I not the choice of IORT, I would be in a psychologically very different place today.	IT Director	England	No
[redacted]			Two years ago I was diagnosed with breast cancer at the West Suffolk Hospital. Through a friend I was told of Prof.Vaidya's procedure, which this hospital did not provide. I pursued the possibilities of having IORT because it made absolute sense to me and also offered an alternative to the standard treatment. This would have involved a prolonged course of radiotherapy and many miles of travel. I am lucky - I had people available to drive me the miles involved, I did not have family commitments (children), or a job that made the demands of the conventional treatment difficult. In the end I was extremely fortunate to undergo the Professor's treatment at Swindon's Great Western Hospital, under Mr Coombs where the excitement, dedication and utter belief in the procedure was palpable. It was again a hospital that under the established procedure had no alternative but to subject its patients to miles of travel and prolonging of the treatment. I spent one day in the hospital, and took two paracetamol as a precaution that evening. I had no reaction, no real discomfort, and most importantly no further treatment other than quarterly check ups and annual mammograms. For me IORT made absolute sense both medically and emotionally, and above all it gave me choice, a choice that should be made available to all women.	Patient	England	no

Author name	Role	Organisation	Comment	Job Title	Location	Disclosure
[redacted]	Patient		I was lucky to receive target treatment for my breast cancer in January 2014. I was given information about the new treatment compared to traditional treatments which I read & decided 'target' was definitely for me. I believe women should be given the choice of treatment & most would choose target. Friends with similar cancers have been very disappointed that they have been denied the treatment. Long journeys to hospital for weeks is avoided & life returns to normal as soon as the wound has healed. This is very important to women with busy lives.	Retired	England	No

Author name	Role	Organisation	Comment	Job Title	Location	Disclosure
[redacted]	NHS Professional		As a Consultant Clinical Oncologist with special interest in treating breast cancer patients and being local principal investigator in several Breast Radiotherapy trials (including PRIME, PRIME II and IMPORT Low and High amongst others), I welcome the appraisal consultation document Intrabeam radiotherapy system for adjuvant treatment of early breast cancer released for consultation. Having offered and treated several patients with IORT, I have a special interest in this aspect of treatment. The consultation document and the associated comments and papers bring out the point clearly that those in favour of incorporating this find the available data reasonably justified to be confident regarding non-inferiority of IORT compared to whole breast radiotherapy whilst others have ongoing issues with the short follow-up, some statistical concerns and other aspects including cost-effectiveness. Despite these differences, one aspect is clear that patient preference and choice of treatment with full understanding of the available data and its weaknesses and strengths has been acknowledged by all. Therefore, keeping all this in perspective and having had the privilege of treating more than 7000 breast cancer patients in my professional career so far and having had the opportunity to discuss and address their concerns related to conventional whole breast radiotherapy, I welcome the recommendations made.	Consultant clinican		

Author name	Role	Organisation	Comment	Job Title	Location	Disclosure
[redacted]	NHS Professional		We welcome NICEâ€™s recommendation of Intrabeam intraoperative radiotherapy for suitable patients within the NHS, and fully agree with the suggested summary recommendations. However, we would like to draw the committeeâ€™s attention to new evidence which we believe supports the use of Intrabeam and which we submitted to you in September 2016. http://bit.ly/2mkhqLA In addition, there are some important errors of fact that should be corrected before final publication given in the comments below: Professor Jayant S Vaidya, Professor of Surgery and Oncology, University College London Professor Jeffrey S Tobias, Professor of Cancer Medicine, Consultant Radiation Oncologist, University College London Hospitals Professor Max Bulsara, Professor of Biostatistics, University of Notre Dame, Australia and Visiting Professor of Biostatistics, University College London Professor Michael Baum, Emeritus Professor of Surgery and Professor of Medical Humanities, University College London			

Author name	Role	Organisation	Comment	Job Title	Location	Disclosure
			We have prepared a model patient information leaflet that can be used to help shared decision making. This is available in A4 format as well. It can be downloaded from: http://bit.ly/2lagiVE Number of fractions of radiotherapy: Although the average number of fractions of EBRT received in the TARGIT-A trial was 23, it was mainly due to the patients recruited in other centres who received 5-6 weeks of radiation rather than 3-4 weeks. It should be recognised that the great majority of UK patients (over 85%) who participated in the TARGIT-A trial received the modern 3-4 weeksâ€™ course of radiation, because the 3-4 week (START) regimen was already standard practice for EBRT in the UK during the course of the TARGIT-A trial. Number of patients with 5-year follow up: With regard to the number of patients in the TARGIT-A trial who had a longer follow up, it may be considered misleading to only state a percentage figure (of 35%) because this percentage refers to a large number (n=1222) of patients that had a median follow up of 5 years. The absolute number is important because it is similar to or larger than most other trials testing radiotherapy for breast cancer. Furthermore, an analysis of the two randomised arms in this earliest cohort of 1222 patients as well as the first 817 patients randomised in the pre-pathology stratum(ref 2, page 43-44 and figure 15 on page 45) gives the same results as the whole trial â€“ no difference in breast cancer control and a lower non-breast-cancer mortality with TARGIT-IORT.			

Author name	Role	Organisation	Comment	Job Title	Location	Disclosure
			Ref 2. Vaidya JS, Wenz F, Bulsara M, et al. An international randomised controlled trial to compare targeted intra-operative radiotherapy (TARGIT) with conventional post-operative radiotherapy after conservative breast surgery for women with early stage breast cancer (The TARGIT-A trial). Health technology assessment. 2016;20(73). (page 43-44 and fig 15 on page 45) https://njl-admin.nihr.ac.uk/document/download/2003454 Strata not subgroups: The title of section 4.6 should be corrected â€“ it should say â€˜strataâ€™ rather than â€˜subgroupsâ€™ because the two strata were separately randomised from the outset. Use of 5-year Kaplan Meier point estimates: The method of testing for non-inferiority using 5 year Kaplanâ€“Meier point estimates is greatly limited because in the presence of censoring, the KM point estimate at a particular time point, for example 5 years, is not a simple binomial proportion. In the presence of non-proportionality the parameter estimate for between group differences may not be meaningful. The precision of an estimator depends on the observed number of events and when event rates are small very large confidence interval for the estimator will arise. Furthermore, when looking at Kaplanâ€“Meier curves, the right-hand end of the curve is the one with the most uncertainty and with the widest CIs. Therefore, it is inappropriate to apply the usual formula normally used to calculate the SE (and CI) of a difference between binomial proportions, namely square root of sum of squares of the two standard errors, to calculate differences between such point estimates. These values, that is, 5-year point estimates, should not be used to calculate the CI of the difference or for testing non-inferiority. Using the other three appropriate methods as already			

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			published(ref 2)Â non-inferiority is established particularly for the pre-pathology stratum. Thus, the statements that â€˜non-inferiority has not been proven in the TARGIT-A trialâ€™, are contrary to peer-reviewed published evidence(Ref1, 2). Furthermore, the difference in local recurrence between TARGIT and EBRT was not even statistically significant; the 95% CI of the difference between the two straddled the zero value. (âˆ’0.68 to 2.68). Even if we disregard the above concerns and use the difference in Kaplanâ€“Meier to assess the difference between treatments, then the measure needs to be applied fairly and equally to both local recurrence and mortality. Therefore, while the upper confidence limit of the 95% CI of the difference in local recurrence is 2.68%, the confidence limit of the 95% CI for overall mortality is â€“5.48, favouring TARGIT IORT. Not only is 5.48% a much larger value favouring TARGIT IORT but it is also for a much more important outcome - death. Therefore, the full interpretation of the data is that at worst TARGIT might have 2.68% higher local recurrence rate, and by the same token, TARGIT might also have 5.48% improved survival. One cannot consider one and ignore the other(Ref 2) While these statistical nuances need to be corrected for the record, the committee wisely acknowledges that ultimately, the risk of local recurrence with TARGIT IORT is very low and therefore they would recommend its use in suitable patients, with a full and comprehensive discussion about the available evidence along with			

Author name	Role	Organisation	Comment	Job Title	Location	Disclosure
			continued collection of national data. We strongly support this recommendation, and it is very straightforward to implement Ref 1. Vaidya JS, Wenz F, Bulsara M, et al. Risk-adapted targeted intraoperative radiotherapy versus whole-breast radiotherapy for breast cancer: 5-year results for local control and overall survival from the TARGIT-A randomised trial. Lancet. 2014;383(9917):603-613. http://www.thelancet.com/journals/lancet/article/PIIS0140-6736(13)61950-9/abstract Ref 2. Vaidya JS, Wenz F, Bulsara M, et al. An international randomised controlled trial to compare targeted intra-operative radiotherapy (TARGIT) with conventional post-operative radiotherapy after conservative breast surgery for women with early stage breast cancer (The TARGIT-A trial). Health technology assessment. 2016;20(73). https://njl-admin.nihr.ac.uk/document/download/2003454 Health Economic Analysis: We believe that the document should include the new evidence published in the HTA Journals (Ref 2- Chapter 6) that demonstrated that the cost of TARGIT IORT was less than that of EBRT. Therefore, if TARGIT were given instead of EBRT in suitable patients, it might potentially reduce costs to the health-care providers in the UK by Â£8â€“9.1 million each year. This does not include environmental, patient and societal costs.(ref 4). Ref 2. Vaidya JS, Wenz F, Bulsara M, et al. An international randomised controlled trial to compare targeted intra-operative			

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			radiotherapy (TARGIT) with conventional post-operative radiotherapy after conservative breast surgery for women with early stage breast cancer (The TARGIT-A trial). Health technology assessment. 2016;20(73). https://njl-admin.nihr.ac.uk/document/download/2003454 Ref 4. Coombs NJ, Coombs JM, Vaidya UJ, et al. Environmental and social benefits of the targeted intraoperative radiotherapy for breast cancer: data from UK TARGIT-A trial centres and two UK NHS hospitals offering TARGIT IORT. BMJ open. 2016;6(5):e010703. http://bmjopen.bmj.com/content/6/5/e010703			

Author name	Role	Organisation	Comment	Job Title	Location	Disclosure

Author name	Role	Organisation	Comment	Job Title	Location	Disclosure

Author name	Role	Organisation	Comment	Job Title	Location	Disclosure
			We reject any suggestion that the quality of the TARGIT-A trial was in some way inadequate. The trial was funded by HTA, NIHR, DoH and was peer-reviewed and published in several peer-reviewed journals as well as a peer-reviewed 226-page full report (ref 3). The trial was conducted to the highest quality standards and governance. Therefore, we believe that the two sentences about the quality of the trial that are not based on fact should be deleted from the final document (i.e. the 2nd and 3rd sentences in section 4.13). Also, the doubt about generalisability of the trial couldnâ€™t be more inappropriate because this was the most pragmatic of trials and the external beam radiotherapy given in the control arm of the trial was a true reflection of current practice in the UK. The fourth sentence should ideally include a phrase about mortality: The committee also noted that the rate of local recurrence with Intrabeam may be higher than with EBRT although the mortality could be lower.			

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			The National Cancer Registration Service systematically collects the data about patient and tumour characteristics requested by NICE, and routinely follows up patients for date of death through their links with the death certification process. These data can be used for health care studies with appropriate information governance. Local centres will collect additional fields, primarily the Quality of Life data, which will be linked to the cancer registry data. Data collection form that includes all the data requested by NICE and that will be used by clinicians can be downloaded from http://bit.ly/2mvJebJ Ref 2. Vaidya JS, Wenz F, Bulsara M, et al. An international randomised controlled trial to compare targeted intra-operative radiotherapy (TARGIT) with conventional post-operative radiotherapy after conservative breast surgery for women with early stage breast cancer (The TARGIT-A trial). Health technology assessment. 2016;20(73). https://njl-admin.nihr.ac.uk/document/download/2003454 -- Appendix 6			

Author name	Role	Organisation	Comment	Job Title	Location	Disclosure

Author name	Role	Organisation	Comment	Job Title	Location	Disclosure
			In addition, there are some important errors of fact that should be corrected before final publication given in the comments below: Professor Jayant S Vaidya, Professor of Surgery and Oncology, University College London Professor Jeffrey S Tobias, Professor of Cancer Medicine, Consultant Radiation Oncologist, University College London Hospitals Professor Max Bulsara, Professor of Biostatistics, University of Notre Dame, Australia and Visiting Professor of Biostatistics, University College London Professor Michael Baum, Emeritus Professor of Surgery and Professor of Medical Humanities, University College London			

Author name	Role	Organisation	Comment	Job Title	Location	Disclosure

Author name	Role	Organisation	Comment	Job Title	Location	Disclosure

Author name	Role	Organisation	Comment	Job Title	Location	Disclosure
[redacted]	Patient		The importance of choice from a patient perspective cannot be under estimated, and Inatrabeam offers this. There are multiple DISbenefits of EBRT which should be factored in more strongly: practical (logistical and economic), physical (long lasting pain and discomfort, and potential damage to organs), and psychological (repeated and intensive hospital visits post surgery; skin damage / sun protection) compared with Intrabeam.			
[redacted]	NHS Professional		We are writing as clinicians who use the Intrabeam system in the delivery of targeted intra-operative radiotherapy. Between us, we have counselled, examined and treated many women with early breast cancer with Intrabeam. We see many advantages for the patient of offering this treatment as a single dose of radiotherapy. Our patients often ask if this treatment may be suitable for them. Our enthusiasm to embrace this technique is balanced by the fact that we want to ensure that patients are counselled properly, given accurate information and allowed time to reflect on their options before being given the freedom to make informed decisions that are right for their personal situation. We would want to continue to review patients treated with Intrabeam and use our information leaflets, data collection and quality of life forms (http://bit.ly/2lagiVE and http://bit.ly/2mvJebJ). We represent a spectrum of hospitals. Some in large regional hospitals with on-site radiotherapy centres while others provide Intrabeam in district general hospitals. When given the option, along with all the available evidence, our patients have been grateful to have been able to choose and have usually chosen to IORT rather than the longer course of daily radiation. They have told us that psychologically it is so much better for them, knowing that in the space of one day their breast cancer has been removed			

Author name	Role	Organisation	Comment	Job Title	Location	Disclosure
			and that (in most cases) no further treatment with radiotherapy is required. They also appreciate that they do not need to spend out of pocket on fuel or parking when travelling to receive radiotherapy. This is true for patients from DGHâ€™s as well as teaching hospitals. Many of our patients are carers for grandchildren or children or are in employment. For them the chance of receiving all of their treatment in one day has meant that there was minimal disruption to family or work life. The older patients also feel happier that they donâ€™t need to be obliged to a friend or family to accompany them to the radiotherapy centre every day. As clinicians caring for our cancer patients, we see other benefits of allowing IORT to be used within the NHS. The delivery of the radiotherapy into the cavity means that we can be confident that the treatment is accurately sited to the very place within the breast at greatest risk of disease recurrence. Also, the introduction of IORT will free some of the capacity in existing radiotherapy departments so that other patients may receive treatment in a more timely fashion as well as with longer time slots that may allow higher quality radiation. Similarly, the development of IORT in district general hospitals has allowed a broadening of the role of existing staff with a significant improvement in staff morale with extended skills and responsibilities. With these arguments in mind we welcome the decision of NICE to recommend Intrabeam when chosen as the preferred treatment option by fully informed patients with early breast cancer. Yours sincerely Mr Nathan Coombs, Consultant Breast Surgeon, Great Western Hospital, Swindon.			

Author name	Role	Organisation	Comment	Job Title	Location	Disclosure
			Mr Dick Rainsbury, Consultant Breast Surgeon, Royal Hampshire Hospital, Winchester. Mr Ashraf Patel, Clinical Lead and Breast Surgeon, Princess Alexandra Hospital, Harlow. Dr Shiroma De Silva-Minor, Consultant Clinical Oncologist, Oxford University Hospital.			
[redacted]	Patient		This process is a no brainer. Theres just no downside to a quicker, less invasive, time saving procedure.			
[redacted]		Healthcare Other	To Whom It May Concern: We became aware that the United Kingdomâ€™s NHS is again considering approval of reimbursement for breast IORT treatments. We are quite pleased to learn of the continued acceptance of breast IORT in the United Kingdom, but are disappointed and surprised to learn that only a single IORT technology, the Zeiss Intrabeam System, has been specified even though at least ten hospitals in the United Kingdom are using the Xoft Axxent Electronic Brachytherapy System for exactly the same treatment. We suggest that the reimbursement be offered for similar IORT technologies, independent of vendor, in order to stimulate competition and offer medical providers a range of treatment options. We also strongly request that the procedure be given a generic description such as â€œIntraoperative radiation treatment for early stage breast cancerâ€ or â€œIntraoperative breast irradiationâ€ which does NOT specifically include reference to a single vendor or treatment system.			

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			The Xoft Axxent System has been used to treat breast IORT, breast APBI, and skin and gynecological cancers in over 125 facilities in the United States, and 30 facilities outside of the U.S. The product received US FDA clearance in 2005, and received a CE Mark in 2009. Other details: â€¢ Like the Zeiss Intrabeam, the Xoft Axxent System is a 50 kV X-ray system that delivers 20 Gy of radiation to the applicator surface for Breast IORT treatments. â€¢ The Axxent product, in our opinion, offers certain advantages (reduced treatment time, mobility, multiple additional treatment indications) that may reduce costs and improve access to critical cancer treatments for a broader range of the population. â€¢ Over 16000 patients have been treated with the Axxent System as of January 2017, including over 3100 breast IORT patients. â€¢ Over 40 U.S. hospitals and 10 private UK hospitals have used the Axxent System for breast IORT treatments. â€¢ Axxent is in use in over 125 facilities in the United States, including UCLA, UCSD, City of Hope Hospital, Vanderbilt, Hoag Hospital, Florida Hospital Celebration Health, Long Beach Memorial, Rush University Medical Center and Virginia Mason Medical Center. â€¢ Initial results have been published for 702 breast cancer patients receiving intraoperative radiation therapy with the Xoft Axxent System at Hoag Hospital from June 2010 to February 2016. After 20 months median follow-up, results for complications and recurrence are comparable to patients treated in the TARGIT-A trial.1 â€¢ A comparison of relative biological effectiveness (RBE) between the Xoft Axxent System and the Zeiss Intrabeam System has also been published which shows that RBE differences between the two systems are			

Author name	Role	Organisation	Comment	Job Title	Location	Disclosure
			â€˜insignificantâ€™.2 â€¢ Over 50 scientific and clinical publications on the Xoft Axxent System have been published over the last several years. â€¢ In 2012 the Center for Medicaid and Medicare services in the United States approved a CPT1-level reimbursement code for IORT. Code 77424 is specific to 50 kV X-ray treatments and applies to both the Xoft Axxent System and the Zeiss Intrabeam System. Again, we were distressed to learn that NICE is continuing to recommend a single companyâ€™s product for breast IORT as opposed to endorsing the treatment modality. Excluding similar products unfairly limits competition and treatment choices for both physicians and patients. We urge you to reconsider and expand this decision. Sincerely, Thomas W. Rusch, Ph. D Technical Advisor, Xoft Co-founder Xoft, Inc. â€“ a subsidiary of iCAD, Inc. 1 M. Epstein, M. Silverstein, et al, â€œAcute and Chronic Complications in Breast Cancer Patients Treated with Intraoperative Radiation Therapyâ€, Ann Surg Oncol 23, 3304-3309 (2016).			

Author name	Role	Organisation	Comment	Job Title	Location	Disclosure
			2 S.A. White, B. Reniers et al, â€œA Comparison of the Relative Biological Effectiveness of Low Energy Electronic Brachytherapy Sources in Breast Tissue: A Monte Carlo Studyâ€, Phys Med Biol 61, 383-399 (2016).			
[redacted]	Patient		I feel that the Consultation Document covers all the possible issues/concerns about the Intrabeam treatment, but it does not cover the huge benefits to patients. I had the IORT Intrabeam treatment for breast cancer at the NHS Great Western Hospital, Swindon in March 2015. I would like to explain why this procedure has made such a difference to me and why I feel it is so important that it should be available to as many women as possible. I was 57 years old and was diagnosed with a small Grade 1 invasive ductal tumour, the cancer was thought not to have spread. I put off having treatment for 4 months until my local hospital was able to offer the Intrabeam treatment because I was convinced it was by far the best option for me. Although there are many advantages with the IORT procedure, it is the fact that there is no need for a course of radiotherapy which makes such a difference. There are very few people who can easily arrange to attend up to 30 daily radiotherapy sessions. In my case I look after my partner who is severely disabled. A course of radiotherapy would have involved, having to arrange specialist care for him for around 3 hours per day, plus the cost of a lengthy journey and car parking at the hospital and arranging a rota of people willing to do the driving. Traumatic for my partner (who is brain damaged) and expensive, stressful and tiring for me too. The Intrabeam surgery meant that instead of my treatment lasting between two and a half to four months, it was over in ONE DAY, and two weeks later I had the 'all clear' and was able to live my life normally again.	Patient	England	No

Author name	Role	Organisation	Comment	Job Title	Location	Disclosure
[redacted]	Patient		I have read the Committee papers, and whilst I am not qualified to give an opinion on the technology or clinical effectiveness of the method, I fully concur with the sentiments expressed in the letter addressed to Dr. Jane Adam Chair of the Appraisal Committee (January 2017) pages 39-45. Specifically, that in all the criticism directed at the method and the practical and economic considerations, the wellbeing (of the patient) and patient choice are completely neglected. I am encouraged to read in the Appraisal Consultation Document that it has been understood that some patients are willing to accept a treatment that may have a higher risk of local recurrence in order to have the benefits of Intra-beam and that quality of life is very important. What is also very important for patients and should not be underestimated is the need to be fully involved in their own treatment and to be provided with all the treatment options available in order to enable them to make an informed choice. The Committee seems to have accepted that individual patient preference is important. I had IORT in July of 2014 and I am well. When I was diagnosed it came as a shock but I was even more upset when later in the evening talking to a family member who lives abroad I found out that an innovative method of radiotherapy which was far less toxic and far less taxing on the patient, called IORT, existed; I immediately made some searches and found out that it could be an option for me. At no time did my consultant at the time ask me for instance whether I had access to private health insurance or inform me that IORT existed and could be an option. When I asked to be referred to be considered for IORT, there was initial surprise that I had found out about IORT, then some resistance and attempts to dissuade me. I was eventually referred. I am very glad that I had IORT in the end, as I was adamant I was not going to submit to EBRT, especially with a history of fibromyalgia and chronic fatigue, having also read about all the potential serious side effects to lung and heart, oesophageal tissues in the future. I was even less receptive to the subtle suggestion (threat?) of a mastectomy or chemotherapy as an alternative if I declined EBRT.		England	N/A

Author name	Role	Organisation	Comment	Job Title	Location	Disclosure
[redacted]	Patient		Having read the documents and committee papers, I believe it's important to contribute my own experience, as others could definitely benefit from more accessible information about Intrabeam radiotherapy than was available when I needed it, and from the potential to debate and choose this treatment as an alternative to traditional EBRT. When I was diagnosed with early breast cancer in Sept 2015, I researched alternatives to EBRT for various reasons, including, but not limited to, the potential risks to otherwise healthy organs and the disruption to my work life (we run a family business which needs my active involvement). I fairly easily came across various references to IORT, but it was not something that my local hospital mentioned until I brought it up - and even then it was remarkably difficult to get any information on where it might be available in the UK. My hospital had no more knowledge of this than I did, although they were supportive of my search, as they felt I I was a good candidate for this treatment. Neither of the key breast cancer websites that I was directed to by them mentioned it even in a research context, and we ended up having to ring round likely hospitals to ask. There were no suitable clinical trials running at that time, and although there was the potential under the existing NICE advice for the Health Commissioners to agree to my having it on the NHS, the process for getting this permission became too protracted. Finally, in December 2015, my Consultant advised me that I shouldn't delay things any further, and I was therefore obliged to pay for private treatment, if I wished to go ahead with IORT. Due to the cost of this in the UK, I went to Italy for the operation / Intrabeam radiotherapy. Having to make this trip was far from ideal, and I would have much preferred to stay in the UK. It seemed such a waste of the equipment that I knew was already available in 6 locations. But I felt sufficiently strongly that this was the right option for me, and was therefore prepared to make the journey and foot the cost. I fully understand that this treatment is not suitable for all, and may not be something that everyone would necessarily choose even if they are suitable candidates. However, I strongly believe that patients should be made aware		England	N/A

Author name	Role	Organisation	Comment	Job Title	Location	Disclosure
			of the option, even if they are diagnosed at hospitals where the equipment is not currently available. Patients should not be penalised if they are not located near hospitals that have the Intrabeam system, and should therefore have the option to travel to a centre that does have the equipment, if they wish. I see this as an integral part of the principle of Choices that the NHS supports and promotes. I also believe it's important to continue to document and add to the body of evidence around the use of Intrabeam radiotherapy, and that using the existing equipment in the first instance makes sense. I would have preferred that the data about my recovery and ongoing progress could have contributed to the UK's evidence. I am VERY glad to have had the Intrabeam radiotherapy, and am a firm advocate of its benefits for others in my position with early breast cancer. For me it was a huge relief to go this route (despite the difficulties I encountered in accessing the treatment). I would more than welcome it becoming available on the NHS, so that it can be presented as a real option for those in my situation.			
[redacted]			My mother had TARGIT and it was so fast and so successful that it seems as if she never had breast cancer at all, She holds down a teaching job and cares for my father - who was seriously unwell at the time - and was back on her feet looking after all of us straight after! The implications for other patients, their jobs and families is extraordinary and I can only hope that if ever I have to deal with such a devastating disease, to have such an efficient and speedy process available to me.	PR Manager	England	No
[redacted]	Patient		My mother had TARGIT and it was so fast and so successful that it seems as if she never had breast cancer at all, She holds down a teaching job and cares for my father - who was seriously unwell at the time - and was back on her feet looking after all of us straight after! The implications for other patients, their jobs and families is extraordinary and I can only hope that if ever I have to deal with such a devastating disease, to have such an efficient and speedy process available to me.	Managing Editor	England	No

Author name	Role	Organisation	Comment	Job Title	Location	Disclosure
[redacted]	Patient		I was a cancer patient in November 2009 within Targit A and received Intrabeam as opposed to standard EBRT on the left side. In early 2012 I was again diagnosed with cancer, this time on the right side. In view of my earlier very positive experience I had no hesitation in requesting/demanding interoperative radio therapy which thankfully was approved.	Retired	England	No
[redacted]			I understand that Intrabeam is a type of targeted radiotherapy and only requires one 30 minute dose given at the same time as surgery to remove the tumour, so there is no need for repeated hospital visits for most patients. Therefore, the patients should recover better and with less stress, which must be an excellent way forward. Radiotherapist's would not be out of work as could retrain further. Surely patients welfare is paramount. Approval, support and encouragement must be given for such invention, commitment, enthusiasm and charity fundraising, etc., for this excellent project. Thank you			
[redacted]			I feel this treatment should be available to as many suitable patients as possible, and if only it had been available when I went through six gruelling weeks of treatment. My disabled husband was nearing the end of his life. I had a 50 mile round trip spending many hours in traffic jams, and I had to leave him for four hours everyday for six weeks, and come home so tired that I just fell asleep all evening, and was no company for him in his final months. I depended on friends driving me to the hospital when I became too tired to drive safely,			

Author name	Role	Organisation	Comment	Job Title	Location	Disclosure
			So please take into consideration these issues as there is so much involved for many patients at what is already a difficult time for them, and anything that will make life easier should be done.			
[redacted]	NHS Professional		I am an Oncology Nurse at The Royal Marsden Hospital in Sutton, and I am writing to you in support of Mr Nathan Coombs new treatment that he has pioneered at The Great Western Hospital in Swindon, delivering a one off dose of intra operative Radiotherapy to women with a diagnosis of Breast Cancer. Having worked for 12 years with women with this disease, I believe this treatment is so important . At present, women are not only having to wait several weeks after surgery to start treatment to ensure wound healing, but they are having to make daily trips for up to 30 days to receive their treatment, this is not only a physical drain, but a costly one in terms of staffing resources. Mr Nathan Coombs treatment however, is given at the time of surgery, thus reducing the delay in treatment and providing a much less stressful approach. I believe this treatment is being presented to NICE sometime in March, and I would like to offer my support for this to be approved so more women are able to benefit from this.			
[redacted]	Patient		I have read about the above form of radiotherapy and am writing to say that if it is possible to do this instead of the daily doses of radiotherapy that go on for weeks, I fully support it. I have experienced breast cancer myself, as has my sister, and although I found radiotherapy not as bad as chemotherapy, getting back to "normal" as quickly as possible is all you want and the trips to hospital for weeks on end and the ensuing side effects just add to the feeling of being ill.			
[redacted]	NHS Professional		With regards to the above technology we are pleased to see that on the draft recommendation, NICE is recommending its use in established centres with emphasis on prospective data collection on outcomes and safety. I would like to pint out that we set up a national TARGIT-Registry (TARGIT-R) that is being run at the Surgical and Interventional Trials Unit			

Author name	Role	Organisation	Comment	Job Title	Location	Disclosure
			(SITU) at UCL (NCT02947425). We have been acquiring prospective data which includes all parameters specified within the draft guidance. The purpose of this e-mail is to bring this to the attention of the committee and outline that we will be happy to provide support to all existing centres within UK through TARGIT-Registry.			
[redacted] [redacted]			Until I retired in June 2010, my last post for seven years was as the Patient Advice and Liaison Service (PALS) Manager at the Walton Centre, Liverpool. In my role on behalf of patients and/or relatives, I was involved objectively in very many cases regarding access to services, second opinions, referrals to other Hospitals, etc for a wide range of neurological and pain services. I became familiar with the pathways for treatment of brain and spinal tumours, including various forms of radiotherapy including standard Radiotherapy, stereotactic radiosurgery (available only in Sheffield at the time) and even proton beam treatment in Switzerland for a patient with chordoma. On retirement I volunteered for the Royal College of Radiologists (RCR) and have taken a keen interest in all aspects of Radiotherapy for the last five years. Amongst my tasks was to design in 2012, the first ever National Patient Experience Survey for people who had recently had Radiotherapy in England – 24,000 patients responded to the survey. I applied to become a member of the Radiotherapy CRG in my own right and this was the source of my interest in IORT. NICE Technical Appraisal of IORT for breast cancer 1. Consent I think the very first question to the patient representative from the Chair of the Appraisal Committee was, 'What they might do now, not what they might do if it comes back?'			

Author name	Role	Organisation	Comment	Job Title	Location	Disclosure
			I think this is somewhat misleading. To give fully informed consent, the patient must know what other treatments might be required and the chances of recurrence and what the probability of this and possible treatments at that time. For example, there was some debate at the meeting about rates of fibrosis. Informed consent would involve, amongst many other considerations, saying:- a) You can have IORT now and the chance of fibrosis is 6% b) If you wait and have conventional EBRT the chance of fibrosis is 18% c) If you have IORT there is a one on five chance you may have to have EBRT also. In this case, your chance of fibrosis happening rises to 32%. (I may have misheard this comment as the paper by Sperk says it is even higher at 37.5%) Hence, it is not just a simple case of IORT now or EBRT later. 2. Patient Information I am really keen on simple, clearly written (and web-based) patient information as part of the dialogue between Doctor and patient. From the dialogue I heard, there are many complex issues to resolve for this new Radiotherapy modality. To pick up on just one topic. I was alarmed by the discussion about cardiac deaths. The claim that deaths are much higher amongst EBRT patients compared to IORT needs to be firmly proven (over a long period) as this could be a significant factor in choice of treatment. I think someone queried if data had been collected on whether the breast cancers where deaths had been reported were left or right sided breast? The investigators were unable to answer this crucial point.			

Author name	Role	Organisation	Comment	Job Title	Location	Disclosure
			3. Evidence-based medicine It is frustrating when a potential treatment that has advantages, eg potential to avoid 3 weeks or more of attending for EBRT, takes so long to prove itself. However, very many areas of cancer (and non-cancer) research take more than ten years to fully evaluate overall survival and late effects, compared to existing, evidence-based treatments. I am firmly of the opinion that an appropriate time lapse should be allowed to ensure that IORT is fully evaluated before it becomes available within the NHS. I think one of the investigators asked for a 'pragmatic solution' but I do not think this is acceptable. 4. Options/choice I think Dr Coles mentioned that EBRT in 15 fractions is becoming the norm but she also mentioned that in some cases of early stage breast cancer, women are not having any Radiotherapy at all, as cancer treatments become increasing targeted to the individual. Do those seeking to introduce IORT accept this and give patients this option? 5. Patient experience I have no doubt about the passion that an individual who has had IORT like [redacted] thinks about her good, personal experience. But this can take away objectivity. Being part of a trial where the risk of recurrence is very low (2%?) and even this possibility is spread over very many years, cannot ignore the long term outcomes of the whole cohort of those involved in the trial compared to existing evidence-based treatments. I was surprised and disappointed that a helpline worker at Breast Cancer Care should advocate for a treatment that is not yet fully evidenced. I hope you will be able to take the above comments into account. I would like to raise some further issues around Patient Information and Consent			

Author name	Role	Organisation	Comment	Job Title	Location	Disclosure
			A Doctor or other health professional taking Consent to treatment is required to explain all possible treatments (including 'wait and see'). I am concerned that there may be a bias towards IORT where this may not be the most appropriate choice for the patient. My suspicion is based on the written information on the University College London web site under 'Participants Corner', regarding IORT for breast cancer. (Note: this is identical to the NIHR 'Plain English Summary' Highlights section of their report. Appendix 2). For example, this patient information refers to 'fewer deaths from heart attacks or other cancers' but does not mention that deaths from breast cancer are higher - no objectivity/consistency there. See below. I think this is potentially a major consent-influencing sentence. Number of deaths Whole study population TARGIT v EBRT TARGIT EBRT Breast Cancer 20 16 Other cancer 8 16 Cardiac 2 8 Other Vascular 0 3 Other 7 8 --- --- Total 37 51			

Author name	Role	Organisation	Comment	Job Title	Location	Disclosure
			There are a number of other words or phrases to the written information within 'Participants Corner' that I think require change. I attach at Appendix 3 a few examples of alternative wording which I think give a more accurate reflection of the research findings to-date. In summary, accurate patient information is key to women making the correct choices when consenting to radiotherapy treatment – or not. I remain concerned that the data is not yet sufficiently mature to recommend IORT for breast cancer and that IORT may be used where alternatives may have given better outcomes.			
[redacted]			I understand that Intrabeam is a type of targeted radiotherapy and only requires one 30 minute dose given at the same time as surgery to remove the tumour, so there is no need for repeated hospital visits for most patients. Therefore, the patients should recover better and with less stress, which must be a excellent way forward. Radiotherapist's would not be out of work as could retrain further. Surely patients welfare is paramount. Approval, support and encouragement must be given for such invention, commitment, enthusiasm and charity fundraising, etc., for this excellent project.			
[redacted]			If the Appraisal Committee proceed with the proposed recommendations it is likely that: 1. NICE will exceed its powers 2. NICE will make recommendations without sufficient evidence to support them			

Author name	Role	Organisation	Comment	Job Title	Location	Disclosure
			1. NICE will exceed its powers 1.1 The recommendation is based on criteria other than those permitted The NICE Technology Appraisal Guidance specifies "We base our recommendations on a review of clinical and economic evidence". Clinical evidence is defined as how well the treatment works, economic evidence is defined as whether it represents value for money. The Appraisal Committee was unable to recommend Intrabeam using evidence for these criteria concluding that "it considered that the clinical and cost-effectiveness evidence for Intrabeam remains uncertain". The Committee also recognised that it is required to "…not recommend treatments for routine use if the benefits to patients are unproven, or if the treatments are not cost-effective". It is surprising, therefore, that despite the lack of clinical and economic evidence, the Appraisal Committee goes on to make a recommendation based on an unsubstantiated premise, provided by a single patient expert, that some patients may like to be offered non-equivalent treatment in order to achieve what the patient expert believes are benefits but "…which could not be captured in the QALY calculation". For the recommendation to be valid the view of the patient expert would need to be sufficiently robust to override the clinical and cost efficacy findings which do not support a recommendation. In addition, the Approval Committee would need to have the authority to deviate from the terms of reference described in their Appraisal Guidance to allow it.			

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			The Appraisal Committee may take account of social value judgments when making decisions about the effectiveness and cost effectiveness of interventions (1.15 of the Guide to the Processes of Technology Appraisal), and they invite written submissions from patient and carer groups because "…they may judge the evidence according to different criteria" (Guide to the Methods of Technology Appraisal). It is stated at 4.3.4 that it is important for the Appraisal Committee to include a range of patient views. In this case, however, no written evidence was provided as a result of the invitation and none was sought to substantiate, qualitatively or quantitatively, the premise made by the expert patient. It seems unlikely, therefore, that the subjective view of the patient expert constitutes evidence which is sufficiently robust for the Committee to rely in terms of it amounting to a sound social value judgment on which to make a recommendation. 2. NICE will make recommendations without sufficient evidence to support them 2.1 Incorrect use of clinical expert evidence is compounded by an insufficient range of patient views 2.1.1 Incorrect use of clinical expert evidence The understanding the Appraisal Committee has of clinical expert evidence, on which it states it relies in section 4.2, that local recurrence is not related to an increased risk of metastatic disease or mortality, is incorrect. The EBCTCG meta-analysis reveals that for every 4 local recurrences one breast cancer death occurs (Effects of radiotherapy and of differences in the extent of surgery for early breast cancer on local recurrence and 15-year survival: an overview of the randomised trials, Lancet 2005; 366: 2087–2106). Evidence provided of low risk patients in trials such as UK PRIME II does not alter the 4 in 1 ratio because the EBCTCG findings apply irrespective of risk and, in any case, recurrence in the TARGIT IORT arm is not in keeping with a 'low risk' group (TARGIT has not defined 'low risk' and patients who go on to have EBRT are included in study results). Failure to			

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			properly apply expert clinical evidence on this point means conclusions drawn by the Appraisal Committee about the relative benefits and risks of Intrabeam later in section 4 are unstable. The perception that some patients are willing to accept a higher risk of local recurrence may, in reality, be very different if patient opinion was assessed in the knowledge that an increased risk of local recurrence could mean an increased risk of death. The view of Patient Groups on this point was that "…people want to ensure they have the best chance of a future free from cancer" (2.7 of the Appraisal Consultation Document). 2.1.2 Insufficient range of patient views Failure by the Appraisal Committee to ensure the range of patient views required has resulted in their failure to take account of any patient views which are not wholly in favour of Intrabeam. That this fails the requirement to include a range of patient views at 4.3.4 of the Guide to the Methods of Technology Appraisal is discussed at Point 1, above. One consequence of the failure is that there is no evidence beyond the subjective perception of the patient expert to substantiate points which are accepted by the Appraisal Committee and on which they base their conclusions. For example, at 4.3 the Appraisal Committee accepts evidence from the patient expert on the cosmetic outcomes of EBRT although she has never experienced it herself and no view from a patient who has experienced EBRT was sought. They also accept that avoiding multiple radiotherapy sessions by having a single treatment with Intrabeam at the same time as surgery would be considered a major advantage by some patients. At 4.10, they accept that many patients make their decisions based on their personal circumstances rather than the possibility of a future event. There is no evidence beyond the subjective perception of the patient expert to			

Author name	Role	Organisation	Comment	Job Title	Location	Disclosure
			substantiate any point, however, the Committee use the views as the basis on which to conclude "…there are benefits of Intrabeam that are very important to patients". That the subjective view of a single patient expert is unlikely to be sufficiently robust for the Committee to rely in order to make a recommendation is discussed under Point 1, above. Another consequence of the failure of the Appraisal Committee to hear a range of patient views is that is has not heard of the extent to which Intrabeam is being promoted by TARGIT team members in the public domain. The biased presentation of multi-media information directed at patients and the public carries the message that IORT is a widely available treatment which has advantages over standard radiotherapy yet is being denied to many patients. The extent of the promotion makes the possibility that patients could achieve the informed view of IORT imagined achievable by the Appraisal Committee with the aid of patient information very slim. Patients do not operate in a clinical bubble – it is well accepted that they seek input from friends and family, often conducting online searches for information. The plethora of biased material about IORT in the public domain prevents any patient achieving a fair and balanced view of the risks and benefits of Intrabeam. The existence of such pervasive yet unbalanced accounts of IORT make it impossible for patients to make informed choices about whether IORT might be a suitable alternative to standard radiotherapy for them. By failing to hear the required range of patient views the Appraisal Committee has failed to take account of this damaging and irreversible factor. Examples of the promotional material include: Patient literature An item entitled 'TARGeted Intraoperative radiotherapy (TARGIT) – A Patient's Guide', which would be better described as marketing material, has been made available to patients on the hospital website at which the Chair of the TARGIT trial works. It was removed following a patient's			

Author name	Role	Organisation	Comment	Job Title	Location	Disclosure
			complaint about its misleading and biased nature but the item is still available online at the Trial Chair's TARGIT website: http://jayantvaidya.org/breast-cancer-surgeon/wp-content/uploads/2014/07/Targeted%20intraoperative%20radiotherapy%20patient%20leaflet.pdf Websites The following have been developed and/or are owned by the Chair of TARGIT. They are all exclusively favourable to IORT : www.targit.org.uk http://jayantvaidya.org/breast-cancer-surgeon/intrabeam-targit-iort-for-breast-cancer/targit-iort-targeted-intraoperative-radiotherapy-for-breast-cancer/ www.targit-research.org Media PR Patients who happen also to be journalists have been encouraged to write favourable, if misinformed articles: www.telegraph.co.uk/women/womens-health/10439775/A-revolution-in-breast-cancer-therapy.html www.theguardian.com/commentisfree/2014/jul/25/breast-cancer-chemotherapy-surgery-escape-radiotherapy http://www.dailymail.co.uk/health/article-4166950/Radiotherapy-new-breast-cancer-blaster.html YouTube Partisan videos have been uploaded to YouTube by the TARGIT Chair:			

Author name	Role	Organisation	Comment	Job Title	Location	Disclosure
			https://m.youtube.com/watch?v=QvDoKZe1WTU https://www.youtube.com/watch?v=3g199iJxfqA https://www.youtube.com/watch?v=ripiKkaJvOE https://www.youtube.com/watch?v=c25YejnAeOk https://www.youtube.com/watch?v=zA6WW2ziyHE https://www.youtube.com/watch?v=0xNmnsDJle0 Press Releases Press releases featuring patient stories and biased towards the benefits of IORT have been created and released for publication: www.dailymail.co.uk/health/article-270 4881/Half-hour-breast-cancer-treatment-replace-weeks-radiotherapy-Thousands-women-benefit-treatment-given-surgery.html www.dailymail.co.uk/health/article-1378267/Me-operation-Targeted-intraoperative-radiotherapy.html www.dailymail.co.uk/health/article-253137/Me-operation-The-one-stop-breast-op-spares-women-weeks-radiotherapy.html Wikipedia A Wikepedia page devoted to IORT is heavily edited by the Chair of TARGIT despite being identified by Wikipedia as a contributor likely to have a conflict of interest and it being contrary to their strong advice that those representing subject matter should not edit it: https://en.wikipedia.org/wiki/Special:Contributions/Jsvaidya			

Author name	Role	Organisation	Comment	Job Title	Location	Disclosure
			2.2 Failure to understand the relevance of Intrabeam machine numbers and availability In accepting the expert patient's view at 4.3 that IORT ameliorates a patient's need to stop working or face substantial travel costs, the Approval Committee has failed to take account of the evidence in Section 2 of the Appraisal Consultation Document that there are only 6 (possibly fewer) Intrabeam machines available, all of which are located in or around London. The travel costs, need to take time off work and likely accommodation costs associated with patients who live in other parts of the country having to go to London for treatment would be significant and possibly more onerous than those associated with receiving EBRT at a local hospital. The potential impact on the hospitals with existing Intrabeam machines having to deal with additional patients from other Trusts has not been considered. The Appraisal Committee appears to have drawn an incorrect conclusion from the statement in Section 2 that "six NHS centres in the UK have used Intrabeam" machines, that six machines are still available for treatment.			

Author name	Role	Organisation	Comment	Job Title	Location	Disclosure
			A Freedom of Information request made to all NHS Trusts and NHS Foundation Trusts in England in February 2016 requested “The number of early breast cancer cases treated at the Trust with TARGeted Intraoperative Radiotherapy (also known as Intrabeam or TARGIT IORT) for each year from January 2000 to the date of this request. Please identify the number which were delivered as part of a clinical trial and the number which were delivered as treatment which was not part of a clinical trial.” The results from this request reveal that IORT is not widely available; of the Trusts that responded only 5 have ever used Intrabeam – University College London Hospitals NHS Foundation Trust, Great Western Hospitals NHS Foundation Trust, Hampshire Hospitals NHS Foundation Trust, Royal Free London NHS Foundation Trust and The Princess Alexandra Hosptial NHS Trust. Since randomisation to the TARGIT trial completed in 2012 only 3 of those 5 Trusts have used the machines to deliver IORT to a total of just 69 patients. The mode of these cases, 36, were at the Royal Free London, the hospital at which the TARGIT Trial Chair practises. The evidence, therefore, is that the use of Intrabeam is contracting. It is unlikely that such low case volumes will be sufficient to develop the national data set prescribed in the Committee’s recommendation.			

Author name	Role	Organisation	Comment	Job Title	Location	Disclosure
			Conclusion For the reasons cited at Point 1 and Point 2, the recommendations being made by NICE are not sound and do not form a suitable basis for guidance to the NHS. Had these errors not been made the recommendations are likely to have been different.			

17 February 2017

National Institute for Health & Care Excellence
10 Spring Gardens
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SW1A 2BU

Intrabeam Radiotherapy System for Adjuvant Treatment of Early Breast Cancer (ID618)

I am a recipient of intra-operative radiotherapy and survivor of breast cancer.

My cancer was diagnosed in June 2008, at the age of 78 and I was referred to Michael Douek and Jeffrey Tobias, at University College Hospital, London. Mr Douek (as he was at the time) thought that I could be a suitable candidate for intra-operative radiotherapy and sent me to Professor Tobias for his review.

I was a widow, my husband having died from cancer less than three months earlier in April 2008 and so, the thought of attending a central London hospital for conventional post-operative radiotherapy over the course of a month, on my own, would have been very difficult, both physically and emotionally.

Under these circumstances and because of the type and location of the tumour, Professor Tobias very kindly confirmed that I should receive the intra-operative radiotherapy and delivered it in collaboration with Mr Douek, who performed a lumpectomy. These procedures were carried out on 10 July 2008.

I recovered very quickly from the surgery and radiotherapy, with no significant after effects. I continue to be reviewed by Professors Douek and Tobias, who always confirm that the surgery and radiotherapy have had no lasting effects. More than eight years on, I continue to be in good health and living testimony to the success of this procedure, as well as the skills, professionalism and expertise of Professors Douek and Tobias.

As I was privately insured, Professor Douek had discussed this treatment with my insurance company and highlighted the fact that this was considerably cheaper than conventional radiotherapy and so not only was it clinically sound, but it was also highly cost-effective.

Far more important for me – and therefore for any other women who receive this devastating diagnosis – the intra-operative radiotherapy was quicker, easier to deal with and considerably less disruptive to my life.

I cannot advocate this treatment too highly and I urge NICE, most strongly, to make the intrabeam radiotherapy readily available to women throughout the country.

Yours sincerely

13th February 2017

Dear Ms.

We have read with interest the article in the Daily Mail regarding "BLAST OF RADIATION YOU GET DURING OP FOR BEAST CANCER"

What a fantastic break-through for women suffering breast cancer!

Thankfully, I've not suffered - but my husband had to have radio-therapy for prostate cancer. The stress and strain we were both under for the 6 weeks of treatment. We had to travel to Poole hospital 7am in the morning - "cold icy" November December days - to try to avoid the traffic jams! then find somewhere to park! and keep this up for 30 times! was horrid, and horrible for me to see my husband, a very ill man, suffer so much. life was just car - hospital - car - then sleep! life was

"on hold" To save women having to go through similar ordeals must be fantastic. Especially young women who are trying to balance family life and possibly working also. Thankfully for us we were retired, and my husband could just sleep! — but for young women how on earth can they find time to rest and recuperate for that horrid thing Breast Cancer.

This treatment sounds excellent! and should be available to all who "qualify medically" I fully endorse Dr Emma Pennery's and Baroness Delyth Morgan remarks, and everything possible should be done to help women with this horrid condition known as breast Cancer - to have a better quality of life.

Yours sincerely